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IJCP Group and Harm Reduction

Dear Colleague,

Founded in 1990, **IJCP Group is an independent medical communications group** that caters to health awareness, need for policy changes and evidence-based scientific updated information to the health care providers through its publications, journals, books, health information products, online CMEs, advocacy meets, conferences, discussions and consensus statements.

Our purpose and core philosophy has always been to spread medical knowledge to the general public and the medical profession. In order to do this, we work in partnerships with various experts, including industry to bring forward pertinent information that may be helpful to raise public awareness on preventive health and medical advancements.

Our first flagship journal called "The Indian Journal of Clinical Practice" was launched to provide clinicians with evidence-based updated information about a diverse range of common medical topics, including those frequently encountered by Indian physicians. We aim to help our medical practitioners with balanced information to make informed decisions.

Since then, we have grown into a group with various offerings from specialty publications and books (print and online) to consulting, branding and professional medical-related think tank events. IJCP prides itself in its network of various print and online editors who have been or are currently associated with IJCP's growing publications. Some eminent doctors who provide editorial support and contribute to our publications are (not an exhaustive list): Dr Alka Kriplani, Dr Anoop Misra, Dr Rajiv Khosla, Dr Ajay Kumar and Dr Swati Y Bhave. Additionally, we have over 146 contributors who write or provide editorial support to the Group regularly.

With such a wide network of professional medical experts and opinion leaders in their respective fields, IJCP has been effectively enlisting the support of its member contributors towards fulfilling its objectives.

HARM REDUCTION

Of late, IJCP Group, in association with many experts, has been working on the concept of harm reduction.

Harm reduction is multifaceted. It is a public health strategy, which aims to mitigate the dangers or harms associated with a behavior or condition with a goal of cessation of the said behavior. It was first developed and applied to substance abuse disorders as **an alternative to abstinence-only focused interventions for adults,** who were unwilling to accept abstinence to avoid negative consequence of substance abuse.

However, over the years, it has found various other applications including, but not limited to, sexual health education to reduce HIV infection, effective weight management, reducing risks related to tobacco consumption.

In order for us to achieve our mission of advancing public awareness, IJCP Group works with various stakeholders including the industry, Heart Care Foundation of India and Perfect Health Mela in bringing balanced information approach. This network partnership approach helps us bring forth the message of harm reduction and prevention on various issues to a wider audience. We then bring the message to the public by using a multipronged approach.

- We **engage key stakeholders** at different levels of medical fraternity and government to build consensus on pursuing harm reduction as a pan-India public health strategy.
- We **curate conversation** with leading public health practitioners through social and traditional media.
- We run **public health media campaigns** on benefits of harm reduction strategy.
- We are planning **to publish a textbook on Harm Reduction** featuring contributory articles from various public health experts. We are publishing this book because we see the importance of putting together the most prominent voices who champion harm reduction across various public health issues in India.

WHY IS IJCP GROUP FOCUSING ALSO ON TOBACCO HARM REDUCTION?

Apart from IJCP Group's focus on harm reduction across its various public health issues, we also believe that tobacco smoking and tobacco-related diseases and deaths in India are a growing public health concern. It is the #1 cause of preventable death in India and causes 13.5 lakh people to die every year from tobacco or tobacco-related diseases.

Therefore, IJCP has recently taken up a campaign on "Tobacco Harm Reduction" **with a clear-cut policy that we support the total ban or complete cessation of use of tobacco products. Till that goal is achieved, tobacco should be medically replaced by safer nicotine-based non-tobacco products.**

An IJCP expert committee reported that tobacco harm reduction differs from harm reduction as it applies to other issues. While in the case of alcohol, sugar, salt or substance abuse, the harm minimization will be to reduce the dose, the same is not true for tobacco. Reducing tobacco consumption may not reduce the mortality and morbidity and hence the answer lies in replacement or substitution with safer harm minimization-based products including DCGI approved nicotine lozenges and patches and the yet unapproved electronic nicotine delivery products.

In fact, ***a more recent study published in January 2019 in the New England Journal of Medicine also found that Electronic Nicotine Delivery Systems (ENDS) are nearly twice as effective as conventional nicotine replacement products like patches and gum, for quitting.***

Given its mission, IJCP Group is also working, among others, with Juul Labs for compiling and advocating scientific evidence-based literature that addresses issues such as vaping vs. smoking; vaping vs. other nicotine replacement therapies (NRTs) and health effects of vaping.

We, as IJCP Group, will continue with our evidence-based literature research on the subject of Harm Reduction in general and tobacco harm reduction in particular and encourage further research by others on the subject as we believe it has the potential to reduce the burden of tobacco-related chronic diseases in India, particularly lung cancer.

Disclaimer: My association with IJCP Group has nothing to do with my assignments with Indian Medical Association (IMA), Confederation of Medical Associations in Asia and Oceania (CMAAO), Medical Council of India (MCI) or Delhi Medical Council (DMC) with whom I have been associated under many positions.

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GUEST EDITORIAL

FDI Curbs on e-commerce: From Best Deal to Raw Deal

BEJON KUMAR MISRA

It is most unfortunate that consumer organizations are always ignored while framing key policy decisions. The case in hand is on e-commerce, as consumers, the key stakeholders in retail, are never part of any consultations to ensure a robust, inclusive policy framework that protects the consumer's interests.

The sheer array of choices, coupled with better prices and an effortless buying experience offered by e-commerce players, have made the Indian consumer feel truly like a king over the past few years.

Now, if there was a new policy that would not allow the supermarket to offer choice, accessibility and affordability, then these would naturally deny the rights of the consumer to choice, quality, standards, accessibility, safety and redressal. This is exactly what is happening in India's e-commerce space, with the central government implementing a new Foreign Direct Investment (FDI) policy that, among other challenges, artificially limits the growth of Indian manufacturers and dealers working on e-commerce platforms to provide the consumers quality products in a competitive manner - potentially bringing an end to an era of great competition, choice and accessibility to quality products through best deals for consumers. As I always said, "Competition with a robust regulatory oversight is the best friend of the consumer".

CORE CONCERN

Even as the Indian e-commerce industry is on course for a fivefold increase from USD 40-bn today to USD 200-bn by 2025, at the core of the big retail success story is the Indian consumer. Equipped with increasing affluence and armed with improving technologies, the Indian consumer's conscious shifts and changing preferences are the key drivers of the country's organized retail sector. To have a government policy that now strikes at the very core of the consumer's choices, one would have expected the government to hold consultations with the consumer as a key stakeholder in the retail chain before framing a major policy that significantly impacts consumer rights.

POLICY MATTERS

On December 26, the Department of Industrial Policy and Promotion (DIPP) announced broad new restrictions on India's fast-growing e-commerce sector, a sector that is estimated to contribute a good four percent to the country's economy. The government adopted certain new found restrictions, albeit to protect domestic interests in an overenthusiastic manner, which has discouraged healthy competition. The major global players, who popularized the very concept of e-commerce in India and empowered the consumers in true sense for the first time in India, were taken by surprise and so were the consumers. The restrictions imposed by the new policy will not only downgrade quality and choice for the consumers but will also hurt hundreds of thousands of Indian companies that sell on the e-commerce marketplaces.

Over the years, for better inventory management and faster delivery, several of these e-commerce platforms have made huge investments in the interest of customer delight to provide convenience with quality service. If we fail to take appropriate decisions, the consumers will again become victims of cartels and unfair trade practices. Is it fair to suddenly change the script on INVEST INDIA, MAKE IN INDIA after the foreign players have invested billions of dollars to improve India's infrastructure, connect our small businesses to the global marketplace, made our companies more competitive and enabled consumers to access quality products at the most affordable prices? The investments on online marketplaces, in use of technology for good manufacturing and distribution practices, and supply chain infrastructure supporting them, that provide Indian consumers convenient, reliable and fast access to hundreds of millions of products at competitive prices, have gone for a spin at the cost of our resources.

Founder, Consumer Online Foundation, New Delhi
www.jagograhakjago.com

With the new policy, competition will be compromised, which eventually will deny the consumer the choices and access to quality products. This protectionist policy, while destroying the B2B (business-to-business) ecosystem, will also pull down the very structure that ensured the best options to the consumer and protected the consumer's interests from all the dimensions of quality.

THE WAY FORWARD

DIPP seems to have issued the new policy without understanding the consequences as it had a myopic view based on interventions made by certain business interest, undermining the interest of the consumers and use of technology to assure quality, safety and accessibility. The Government has unfortunately failed to notice the harms it may cause to the country in terms of growth and development triggered by restrictions on India's online shoppers. Though the government is well-meaning in its intention, hasty implementation of such a policy can have huge negative fallout for all stakeholders, including the consumer.

The government should always be a neutral and unbiased policy maker and develop policies based on transparent consultations with all the stakeholders including the Indian consumer to encourage free and fair trade rather than restrict investment in the e-commerce sector, which will generate employment for our youth and potential human resource, which we have in abundance and consumers who now have higher disposable income to have quality lifestyle in the most affordable manner based on choice, standards and credible information with prompt redressal mechanism.

An immediate measure would be to push forward the date of implementation and take measures to accommodate the constraints and concerns of all stakeholders. Consulting consumer bodies and organizations working to protect consumer's interests would ensure proper representation of the Indian consumer's apprehensions and expectations before the government, allowing it to take an informed approach to policy-making.

A well-thought, transparent methodology will not only ensure a fair, balanced and robust policy framework for the booming retail sector, but also generate huge confidence among millions of Indian consumers reassured by a responsive government, which the world today recognizes and we are all proud to be part of the NEW INDIA.

■■■■

Another example of nature's illusion.

AMERICAN FAMILY PHYSICIAN

Weighing the Risks and Benefits of Chronic Opioid Therapy

ANNA LEMBKE, KEITH HUMPHREYS, JORDAN NEWMARK

ABSTRACT

Evidence supports the use of opioids for treating acute pain. However, the evidence is limited for the use of chronic opioid therapy for chronic pain. Furthermore, the risks of chronic therapy are significant and may outweigh any potential benefits. When considering chronic opioid therapy, physicians should weigh the risks against any possible benefits throughout the therapy, including assessing for the risks of opioid misuse, opioid use disorder, and overdose. When initiating opioid therapy, physicians should consider buprenorphine for patients at risk of opioid misuse, opioid use disorder, and overdose. If and when opioid misuse is detected, opioids do not necessarily need to be discontinued, but misuse should be noted on the problem list and interventions should be performed to change the patient's behavior. If aberrant behavior continues, opioid use disorder should be diagnosed and treated accordingly. When patients are discontinuing opioid therapy, the dosage should be decreased slowly, especially in those who have intolerable withdrawal. It is not unreasonable for discontinuation of chronic opioid therapy to take many months. Benzodiazepines should not be coprescribed during chronic opioid therapy or when tapering, because some patients may develop cross-dependence. For patients at risk of overdose, naloxone should be offered to the patient and to others who may be in a position to witness and reverse opioid overdose.

Keywords: Opioid therapy, pain, opioid misuse, opioid use disorder, opioid overdose

Opioid analgesics have historically been prescribed for acute trauma, perioperative care, cancer pain, and pain associated with life-limiting illness. Over the past several decades, opioids have been increasingly dispensed chronically for many nonacute conditions. More than one-half of patients who receive continuous opioid therapy for 90 days are still receiving opioids more than four years later.[1] By sheer volume, family physicians prescribe more opioid analgesics than any other subspecialists.[2]

The benefit of short-term opioid therapy is supported by multiple clinical trials.[3] However, the benefit of opioids for managing chronic pain is limited. Chronic visceral or central pain syndromes (e.g., abdominal or pelvic pain, irritable bowel syndrome, fibromyalgia, headache, neuropathic pain) may be especially unresponsive to long-term opioid therapy. Furthermore, the risks associated with chronic opioid therapy increase in a dose-dependent manner.[4]

Nonetheless, chronic opioid therapy benefits some patients with chronic pain. The American Academy of Family Physicians urges physicians "to individualize therapy based on a review of the patient's potential risks, benefits, side effects, and functional assessments, and to monitor ongoing therapy accordingly."[5] This review explores how to assess and mitigate risks when initiating, continuing, and discontinuing chronic opioid therapy. For terms and definitions, see Table 1.[6-8]

RISK ASSESSMENT WHEN INITIATING CHRONIC OPIOID THERAPY

Patients for whom chronic opioid therapy is being considered should be screened for risks and contraindications. Overdose is a key risk. Patients at increased risk of overdose include those with medical comorbidities (e.g., sleep apnea, lung disease, heart failure); those receiving benzodiazepines or other sedative-hypnotics[9,10]; those with problematic alcohol use; and those with psychiatric comorbidities (e.g., depression).

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Source: Adapted from Am Fam Physician. 2016;93(12):982-990.

Opioid Misuse/Opioid Use Disorder

Opioid misuse and opioid use disorder are other key risk factors. Patients for whom chronic opioid therapy is being considered should be evaluated for these conditions.

Opioid misuse is the nontherapeutic use of opioids, including taking opioids in amounts other than prescribed, for indications other than prescribed, or by alternative routes of administration (e.g., crushing and snorting rather than ingesting). Opioid misuse is not always synonymous with an opioid use disorder.

Opioid use disorder (i.e., addiction) is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., (DSM-5) by the presence of the three C's: control loss (out-of-control use), compulsivity (devoting increasing mental and physical resources to obtaining, using, and recovering from substances), and continued use despite adverse consequences. According to the DSM-5, the diagnosis of opioid use disorder excludes tolerance and adverse medical consequences, such as withdrawal symptoms, in patients taking opioids as prescribed.[11] Although tolerance and withdrawal are often present in persons who meet DSM-5 criteria for an opioid use disorder, a person can have an opioid use disorder without tolerance or withdrawal because addiction is also a disease of learning, memory, and psychological compulsion.

Patients at increased risk of opioid misuse and opioid use disorder include those with a history of behaviors such as seeking early refills and "doctor-shopping"; those with a personal or family history of a substance use disorder[12]; those with a preadolescent history of sexual abuse[13]; and those with psychiatric comorbidities.[12] Screening for opioid misuse and opioid use disorder should include checking your state's prescription drug monitoring database[14] (Table 2) and obtaining a urine toxicology screen. Approaches to mitigating risk before initiating chronic opioid therapy are outlined in Table 3.[15-17]

Table 1. Chronic Opioid Therapy: Terms and Definitions

Opiates vs. opioids

Opiate refers to drugs derived from the opium poppy (e.g., morphine, codeine).

Opioid refers to opiates, as well as synthetic and semisynthetic drugs with similar properties (e.g., fentanyl, hydrocodone, oxycodone).

MME

Conversions and comparisons between opioids is typically accomplished by estimating the equivalent dose of oral morphine (i.e., MME). For example, 10 mg of oral oxycodone is approximately equal to 15 mg of oral morphine, or 15 MME.[6]

Online calculators are available to facilitate conversion, but these conversions should never be used without clinical data. Two useful calculators are available at http://www.nyc.gov/html/doh/html/mental/MME.html and http://opioidcalculator.practicalpainmanagement.com/.

Opioids vary greatly in their pharmacokinetic and pharmacodynamic profiles, which in turn are influenced by route of administration and individual tolerability. Comparing dosages across opioids and individuals is challenging.[6] Furthermore, dose conversions for chronic pain may be unreliable, because these equivalents were developed in the context of single-dose, acute pain models in opioid-naïve patients.[7,8]

MME = Morphine milligram equivalents.

Information from references 6 through 8.

Table 2. Interpreting the PDMP

What is a PDMP?

PDMPs collect data from pharmacies on dispensed controlled substance prescriptions, and make those data available to authorized users through a secure, electronic database.

Warning signs for opioid misuse

Early refills

The same or similar prescriptions from multiple physicians simultaneously (doctor-shopping)

Dangerous drug-drug interactions (opioids and benzodiazepines)

Total morphine milligram equivalents exceeding 120 mg per day

False signs of opioid misuse

Patients who are receiving care in a group practice or an academic teaching hospital, where doctors commonly cover for each other, should not be confused with patients who are doctor-shopping.

Patients who are receiving prescriptions for limited quantities (e.g., a two-week prescription as part of an opioid taper) should not be confused with patients who are getting early refills.

PDMP = Prescription drug monitoring program.

Table 3. Strategies for Mitigating Risk Before Initiating Chronic Opioid Therapy

Screen for risks before prescribing, and proceed with caution in at-risk patients by using the lowest possible dose for the shortest duration, and then only if chronic opioid therapy is essential.[15]

Use a controlled substance agreement that defines the terms and expectations of therapy, including allowed circumstances for refills.

Consider transdermal buprenorphine or off-label sublingual buprenorphine/naloxone to treat chronic pain in patients at risk of opioid misuse, opioid use disorder, or overdose.[16]

Avoid methadone use in patients with increased risk of opioid overdose. A retrospective cohort study comparing outpatients with noncancer pain who were receiving methadone or morphine showed an increased risk of death in patients receiving methadone—even at low doses—compared with those receiving morphine.[17]

Information from references 15 through 17.

Patient Education

Before initiating chronic opioid therapy, physicians should take adequate time to inform patients in simple language of the associated risks (Table 4). Patient education can help curb opioid misuse and reduce the risk of developing opioid use disorder. Numerous free continuing medical education options are available online for physicians to learn more about safe opioid prescribing, such as http://www.drugabuse.gov/opioid-pain-management-cmesces and http://www.health.gov/hcq/training-pathways.asp.

RISK ASSESSMENT WHEN CONTINUING CHRONIC OPIOID THERAPY

Risk assessment should not be limited to an evaluation before prescribing chronic opioid therapy. Physicians

Table 4. How to Talk to Patients About the Risks of Chronic Opioid Therapy

Cardiovascular events
"This medicine can cause an irregular heart rhythm. It can also increase the risk of a heart attack. Either of those can lead to sudden death."
Constipation and abdominal pain
"This medicine causes constipation. In severe cases, the constipation can't be helped by laxatives. Rarely, it can result in a hole in the intestines, and you'll need surgery. And even though this medicine is supposed to lessen pain, sometimes it causes stomach pain, even when stomach pain wasn't your original problem."
Depression
"If you use this medicine for a long time, it can make you feel depressed. Some symptoms of depression include getting less pleasure from activities that used to bring you pleasure, and having less energy to get things done. Depression can also affect your ability to think and concentrate. Sometimes when people get depressed, they think about suicide."
Hormonal dysregulation
"This medicine can decrease levels of testosterone and other important hormones in your body. By lowering your hormones, this medicine can make it more difficult to have sex and make a baby. It can also make you feel tired and weak, and can make your bones break more easily."
Opioid-induced hyperalgesia
"This medicine is usually used to relieve pain. But if you take it every day for a long time, it can make your pain worse. It can even cause pain in parts of your body where you didn't have pain before."
Opioid misuse and opioid use disorder (addiction)
"If you are taking more of this medicine than prescribed, saving it up and taking a lot at once, taking it to improve your mood, or taking it to wake yourself up or put yourself to sleep, then you are misusing it. Misusing medicine is a sign that you may be getting addicted. Behaviors that go with addiction include spending a lot of time and effort trying to get more of the medicine, thinking a lot about taking the medicine, and getting into trouble at work or in your personal life because of the way you are taking it. The more you take, the more likely you are to get addicted. Being addicted is nothing to be ashamed of. It can happen to anyone, but it's important to let me know, because it can be treated."
Overdose
"This medicine can kill you by slowing down your breathing and your heart rate until you stop breathing and your heart stops beating. The more you take, the more likely this is to occur, even if you've been taking it the same way for a long time. The risk increases if you take this medicine with alcohol or other drugs that cause sleepiness. Also, if you take high doses of this medicine after you haven't taken it for awhile, you are at increased risk of overdose because your body loses the ability to tolerate high doses."
Physiologic dependence and withdrawal
"Your body may become dependent on this medicine. That means that if you don't take it or you take less than your usual amount, you may experience withdrawal. Withdrawal can feel like a bad case of the flu, including hot and cold sweats, diarrhea, feeling like you need to throw up, not being able to sleep, and feeling down or nervous. You may also have aches all over your body. For some people, withdrawal makes them feel like they might die. But people rarely die from opioid withdrawal."
Suppressed breathing
"This medicine can slow down your breathing. It can also cause breathing problems at night, when you may stop breathing for a few seconds. The result is that you may not get enough oxygen to your lungs, and you will die."
Tolerance
"When you first start taking this medicine, it will probably work well to reduce your pain. But if you take it every day for a long time—weeks to months—it may stop working. You may find that after a while, your pain is as bad as before you started the medicine."

should also perform ongoing risk-benefit assessments throughout the course of therapy because problems can arise at any point. Patients should be reevaluated at least every three months, even when stable and doing well, and more frequently if problems arise.[15] If measures to counteract misuse and adverse effects are not successful, opioids should be decreased or discontinued. Opioids should not be discontinued abruptly; doing so can precipitate acute opioid withdrawal.

Approaches to mitigating risk when continuing chronic opioid therapy are outlined in Table 5.[9,10,15,18-41] Benefit is indicated by improvement in function, not solely by subjective reports of pain relief.

RISKS ASSOCIATED WITH CHRONIC OPIOID THERAPY

Constipation and Abdominal Pain

Constipation is a well-recognized adverse effect of opioid use, with a reported prevalence of 15% to 90%.[42] With chronic opioid use, constipation can become refractory to stool softeners and laxatives,[43] and in some cases can lead to bowel obstruction, perforation, and death.[44]

Chronic opioid therapy can also cause worsened or new-onset abdominal pain, although this is much less common than constipation. This condition is referred to as narcotic bowel syndrome and is characterized by progressive pain despite maintaining or increasing opioid doses. It can occur in patients with no history of gastrointestinal disorders.[45,46] In a study of 146 ambulatory patients with chronic noncancer pain, the prevalence of narcotic bowel syndrome—defined as daily severe to very severe abdominal pain of more than three months' duration requiring more than 100 morphine milligram equivalents (MME) daily—was 6.4% (95% confidence interval, 2.4 to 13.5).[24]

Tolerance

Tolerance is the physiologic adaptation to opioid therapy, as evidenced by the need for increasing doses to get the same effects, or the loss of effectiveness at a given dose. Although the prevalence of tolerance has not been well described, one study found that nearly 28% of persons receiving chronic opioid therapy required increased doses for reasons that could not be explained by progression of their underlying condition or increases in activity level.[47]

Another study reported that patients younger than 50 years had a fourfold dose escalation and older patients had a twofold escalation over two years of opioid therapy.[48]

Physiologic Dependence and Withdrawal

Physiologic dependence is the process whereby the body comes to rely on the drug to maintain biochemical homeostasis. When the drug is not available at expected doses or time intervals, the body becomes biochemically dysregulated, which manifests as signs and symptoms of withdrawal. Opioid withdrawal occurs in patients with physiologic dependence when lowering or discontinuing opioids, but it can also happen when changing the type or method of delivery, or when transitioning from one opioid to another with less bioavailability.

Opioid withdrawal symptoms include arthralgias, myalgias, piloerection, rhinorrhea, diaphoresis, nausea, emesis, muscle cramps/spasms, and diffuse muscle and bone pain. Common behavior and mood changes experienced during withdrawal include insomnia, dysphoria, irritability, and anxiety. Opioid withdrawal can present similarly to influenza. When patients receiving chronic opioid therapy exhibit sudden-onset "flu-like" symptoms, physicians should consider a recent decrease or discontinuation of opioids as the cause.

Opioid Misuse/Opioid Use Disorder

Historically, the risk of opioid use disorder from agents prescribed by a licensed physician for treatment of a medical condition was considered small.[49,50] However, recent reports indicate higher rates of opioid use disorder in this population than previously assumed, with some studies finding prevalence rates as high as 50% in patients receiving chronic opioid therapy.[29-33] The risk of developing new-onset opioid use disorder in opioid-naïve adults increases with the opioid dosage and duration of treatment. Patients receiving opioid therapy for more than 90 days at doses of more than 120 MME are more than 100 times as likely to develop opioid use disorder than patients who do not receive opioids for similar conditions.[34]

Depression

There is a complex relationship between chronic opioid use, worsening of chronic pain, and symptoms of depression. A study of medical record data from 49,770 patients determined that those receiving opioids for 90 to 180 days had a 25% increased risk of depression, and those receiving them for more than 180 days had a greater than 50% increased risk.[51] These data are salient because the population studied was at low risk of depression at baseline, with no recent history of depression before initiation of opioids. The study also adjusted its analysis for symptoms related

Table 5. Strategies for Mitigating Risk in Patients Receiving Chronic Opioid Therapy

Cardiovascular events

Avoid coadministration of methadone and diazepam, which may potentiate the adverse cardiac effects of methadone.[9]

Avoid coadministration with other drugs that prolong the corrected QT interval.

Constipation and abdominal pain

With severe and chronic constipation that is unresponsive to the usual remedies, consider methylnaltrexone, an opioid-receptor antagonist that has limited ability to cross the blood-brain barrier and can reverse opioid-induced constipation without precipitating withdrawal or increasing pain.[18]

Decrease or taper opioids. In one study, opioid weaning after a four- to 11-day protocol was associated with improvements in abdominal and nonabdominal pain, as well as pain scores.[19]

Depression

Treat with antidepressants and/or psychotherapy (but avoid tricyclics because they also have overdose risk).

Limit take-home doses and other central nervous system depressants to decrease the risk of suicide.[20]

Encourage use of mental health services, and monitor for aggression and impulsivity, which have been associated with an increased risk of suicide in patients with chronic pain.[21]

Hormonal dysregulation

Consider measuring hormone levels and using hormone replacement when indicated.

Consider buprenorphine over methadone.[22]

Decrease or slowly discontinue opioid therapy.[23]

Opioid-induced hyperalgesia[24-28]

Taper the dosage and see if pain improves.

During tapering, inform the patient that opioid withdrawal is associated with physical pain, and does not necessarily represent progression of the underlying disease.

Do not reassess pain until acute opioid withdrawal is complete (usually two to four weeks).

Opioid misuse and opioid use disorder (addiction)

When opioid misuse is detected, do not discharge the patient from your practice or refuse to prescribe opioids. Instead, add opioid misuse to the problem list and intervene to change the behavior: educate the patient about the risks of misuse, schedule visits at shorter intervals, prescribe smaller drug quantities without refills (e.g., a two-week rather than a four-week supply), and perform urine drug screening. If aberrant behavior resolves, reward course correction (e.g., resume original prescribing and visit pattern). If aberrant behavior continues, assess for the presence of an opioid use disorder and treat accordingly.[29-34]

Opioid misuse and opioid use disorder (addiction) *(continued)*

Switch to buprenorphine/naloxone to treat addiction and chronic pain. This requires special training and a license waiver, and the therapy can be initiated only when the patient is in active opioid withdrawal.

Refer to a methadone maintenance treatment clinic.

Taper opioids and prescribe naltrexone, an opioid-receptor blocker.

Refer for specialized addiction treatment.

Offer naloxone, an opioid-receptor antagonist that can reverse overdose, to patients at risk of overdose and, where allowed by state law, to individuals (Good Samaritans) who may be in a position to witness and reverse opioid overdose.[35-37]

Physiologic dependence and withdrawal (Table 6)

Taper opioid therapy gradually. Provide nonaddictive medications to lessen symptoms of withdrawal, including antinausea and antidiarrheal agents, muscle relaxants, and alpha-adrenergic receptor agonists (clonidine).

Suppressed breathing and overdose

Consider a sleep study to evaluate for apnea.

Avoid coprescribing with benzodiazepines and other sedatives, especially in patients with opioid misuse or opioid use disorder.[10,15,35,36,38-41]

Monitor for concurrent alcohol consumption, especially binge drinking, with a one-question screen: "Have you had six or more drinks on one occasion any time in the past year?" If the patient screens positive, evaluate for an alcohol use disorder, and consider lowering or discontinuing opioid therapy if the patient has signs and symptoms of an alcohol use disorder.

Advise patients to take precautions with opioids (e.g., never crush or chew long-acting opioids; never cut patches [unless advised by a physician] or expose them to heat, which may change the delivery mechanism; never use patches in any way other than applying them to the skin).

Offer naloxone to patients and, where allowed by state law, to Good Samaritans who may be in a position to witness and reverse opioid overdose.

Tolerance

Total dosages should not exceed a morphine equivalent of 120 mg per day, at which point consider referral to a pain management subspecialist.

Switch to another opioid, but beware of difficulties in doing so, because dose conversion is challenging (Table 1).

Acknowledge that because of tolerance, effective pain relief is not achievable, then taper off opioid.

Information from references 9, 10, 15, and 18 through 41.

to several chronic pain states, an important confounder to consider because progression of pain symptoms that are unresponsive to opioids can lead to depressive symptoms as well.

Opioids are often discovered in a person's possession at the time of suicide-related drug overdoses. Data collected from the National Violent Death Reporting System in 16 states revealed that in 23% of deaths (most

of which are suicide-related), the deceased person tested positive for antidepressants, and 20.8% tested positive for opioids.[52] However, understanding the exact role of opioids is often complex, as is the determination of whether an overdose was accidental or intentional.[20]

Hormonal Dysregulation

Chronic opioid therapy can cause increased prolactin levels and decreased levels of cortisol, testosterone, estrogen, luteinizing hormone, and follicle-stimulating hormone. These hormonal changes contribute to sexual dysfunction,[53] infertility, fatigue, osteoporosis, oligomenorrhea, and galactorrhea.[54]

Opioid-induced Hyperalgesia

Opioid-induced hyperalgesia is the development of increased pain in response to protracted opioid exposure. Whereas opioids have powerful short-term analgesic effects, animal and human studies show that prolonged use can cause heightened pain sensitivity and result in pain syndromes that did not previously exist.[25] The prevalence of opioid-induced hyperalgesia has not been determined.[47] One small prospective study of six patients with chronic low back pain who were receiving oral morphine demonstrated that all six developed hyperalgesia to cold pressor pain testing after four weeks.[26]

Clinically differentiating tolerance from opioid-induced hyperalgesia can be difficult. As a general rule, patients who have developed tolerance to opioids will have recurrent pain in the original anatomic location despite initial relief, and the pain is improved by increasing the opioid dose. With opioid-induced hyperalgesia, pain becomes heightened in the same or a new anatomic location and is improved by decreasing the opioid dose.[27,28]

Cardiovascular Events

Chronic opioid therapy has been associated with sudden cardiac death, possibly as a result of torsade de pointes precipitated by prolongation of the corrected QT interval.[55-57] The available evidence most strongly implicates methadone in opioid-induced cardiac arrhythmias.[55,58] Myocardial infarction may also be a contributing factor; a cohort study including patients receiving diverse prescription opioids showed an increased risk of myocardial infarction compared with persons who were not receiving opioids.[59]

Suppressed Breathing and Accidental Overdose

Patients receiving opioid therapy are at increased risk of death from respiratory suppression, bradycardia, and hypotension. In a sample of 9,940 persons who received three or more opioid prescriptions over 90 days, there were 51 overdoses and six deaths, and the risk of overdose was dose dependent.[10] Compared with patients receiving 1 to 20 MME of opioids daily, those receiving 50 to 99 MME per day had a 3.7-fold increased risk of overdose, and those receiving 100 MME or more per day had an 8.9-fold increased risk. Another study of 607,156 persons 15 to 64 years of age who were prescribed an opioid found that an average daily dosage of 200 MME was associated with a nearly threefold increase in opioid-related mortality (odds ratio = 2.88) compared with low daily dosages (less than 20 MME).[38]

The risk of overdose increases when opioids are combined with sedatives such as alcohol, benzodiazepines, muscle relaxants, or sedative-hypnotics.[10] In such cases, overdose can occur at therapeutic analgesic opioid doses, in part because of drug-drug interactions, and because the physiologic tolerance to the analgesic effects of opioids does not

Table 6. Strategies for Mitigating Risk When Discontinuing Chronic Opioid Therapy

Do not abruptly discontinue chronic opioid therapy, because this can precipitate acute opioid withdrawal.
Taper opioid therapy gradually, especially in patients who experience intolerable withdrawal. Standard recommendations[60] to decrease the dosage by 5% to 10% of the starting dosage every one to four weeks may still be too fast for some patients, especially those receiving high doses. Some patients may need to decrease the dosage by 5% or less every two to three months, with even smaller decrements toward the end of the taper. It is not unreasonable to take many months to wean some patients off chronic opioid therapy.
If the patient is unable to taper off short-acting opioids, switch to equianalgesic doses of longer-acting opioids, such as methadone or buprenorphine, and then taper. Beware of problems with morphine milligram equivalent dose conversion (Table 1) and buprenorphine-precipitated withdrawal.
Warn patients about what to expect during each dosage reduction, including a resurgence of pain, which they may mistakenly attribute to an exacerbation of their original injury or condition. Assure them that the pain is withdrawal mediated, time limited, and not usually life threatening. Some patients require intense psychosocial support when tapering off chronic opioid therapy.
Provide nonaddictive medications to lessen symptoms of withdrawal, including antinausea and antidiarrheal agents, muscle relaxants, and alpha-adrenergic receptor agonists (clonidine). Use benzodiazepines sparingly, because they can lead to cross-dependence in some persons. Inform patients that every time they decrease the dose, they will have withdrawal symptoms, including withdrawal-mediated pain.

Information from reference 60.

necessarily coincide with tolerance to the respiratory effects.[35] Furthermore, those who resume opioid therapy after a period of abstinence (e.g., recently released prisoners) are at increased risk of accidental overdose because of the interim loss of tolerance.[36,39]

Even in the absence of overdose, patients receiving chronic opioid therapy can experience breathing problems such as central and/or obstructive sleep apnea, hypoxemia, and ataxic breathing.[40,41]

RISK ASSESSMENT WHEN DISCONTINUING CHRONIC OPIOID THERAPY

When the risks of chronic opioid therapy outweigh the benefits, opioids should be slowly decreased and/or discontinued. This can present a challenging clinical scenario, particularly when patients have become dependent. Except in cases of overtly illegal activity (diversion), chronic opioid therapy should not be discontinued abruptly.[60] This can precipitate intolerable opioid withdrawal, and in some cases lead patients to seek illicit opioids. Table 6 provides strategies to mitigate risks when discontinuing chronic opioid therapy.[60]

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Practice Guidelines

ACCP RELEASES GUIDELINE FOR THE TREATMENT OF UNEXPLAINED CHRONIC COUGH

Persistent cough with an unknown etiology is difficult to treat and can significantly affect quality of life. Although the evidence for the diagnosis and treatment of adults with unexplained chronic cough is limited, the American College of Chest Physicians (ACCP) has released guidelines based on the best available evidence. Further study is needed to establish universal terminology and the optimal method of investigation.

Recommendations

Diagnosis

Unexplained chronic cough should be diagnosed if cough persists for longer than eight weeks with no etiology identified after evaluation and supervised therapeutic trial(s) that follow published best-practice guidelines. Key to the definition of unexplained chronic cough are adequate assessment, investigation, and therapy.

Adults with unexplained chronic cough should undergo a guideline/protocol-based assessment, including objective testing for bronchial hyperresponsiveness and eosinophilic bronchitis, or a therapeutic corticosteroid trial.

Treatment

Multimodality speech pathology therapy (e.g., education, counseling, cough suppression techniques, breathing exercises) is recommended for adults with unexplained chronic cough. A therapeutic trial of gabapentin is also recommended.

However, the evidence is limited, and there is a possibility of adverse effects. The risk-benefits profile should be discussed with the patient before initiating gabapentin and reassessed at six months.

Inhaled corticosteroids should not be used in patients with unexplained chronic cough and negative results on testing for bronchial hyperresponsiveness and eosinophilia (sputum eosinophils, exhaled nitric oxide). Proton pump inhibitors should not be used in patients with a negative workup for acid reflux disease.

Source: Adapted from Am Fam Physician. 2016;93(11):950.

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CHAT WITH DR KK

Woh to Theek Hai Par Heart Attack Hua Kyon?

Photo Quiz

UNUSUAL URINE COLOR DURING CATHETERIZATION

A 50-year-old woman presented for a routine catheter change. The patient was wheelchair-bound because of a history of transverse myelitis. She had urinary incontinence and was dependent on chronic urinary catheterization. The patient had no symptoms beyond discolored urine. There was no dysuria or blood around the catheter. She had no history of trauma to the catheter.

On examination, she was afebrile and well appearing, but the urine in her catheter bag looked purple (Figure 1). She did not know how long her urine had been discolored. Urinalysis showed leukocytes and microscopic hematuria. The urine was sent for culture.

Question

Based on the patient's history and physical examination findings, which one of the following is the most likely diagnosis?

A. Excessive blackberry or beet consumption.

B. Familial benign hypercalcemia.

C. Isoniazid use.

D. Nitrofurantoin use.

E. Purple urine bag syndrome.

Discussion

The answer is E: purple urine bag syndrome. The urine's purple shade (which leads to staining of the catheter's bag and collecting tube) is caused by the accumulation of tryptophan metabolites. Dietary tryptophan is metabolized by gastrointestinal bacteria, which results in indole production. Indole is converted to indole sulfate in the liver. Indole sulfate in turn is acted on by bacterial enzymes, resulting in the production of indirubin (which is red) and indigo (which is blue). These metabolites concentrate in the urine, and the combination of red and blue pigments produces the purple discoloration.[1]

Figure 1.

Purple urine bag syndrome is more common in older women with chronic urinary catheters,[2] and it may be associated with constipation, dehydration, and alkaline urine. The condition has also been associated with intussusception.[3] Most persons with purple urine bag syndrome are not seriously ill, although the condition is associated with several bacterial infections. Causative organisms include *Providencia, Citrobacter, Enterobacter, Klebsiella, Morganella, Staphylococcus,* and *Streptococcus*.[4] It has been suggested that the urine is not purple but brownish-red, and that the urine bag is discolored purple. This may be because of a reaction of the indirubin and indigo pigments with the lining of the bag and catheter.[5]

Many medications, foods, dyes, and medical conditions can cause urine discoloration. A 2012 review details the differential diagnosis of abnormally colored urine and includes more than 75 items. The differential diagnosis for purple urine or a purple urine bag seems to be limited to purple urine bag syndrome, however.[6]

Source: Adapted from Am Fam Physician. 2016;94(7):572-574.

Selected Medical Conditions Resulting in Abnormal Urine Color

Urine color	Medical conditions
Brown	Hemolysis, Metastatic melanoma, Porphyria
Black	Alcaptonuria, Metastatic melanoma, Porphyria
White	Chyluria, Filariasis, Hypercalciuria, Hyperoxaluria, Lipiduria, Lymphatic fistula, Phosphaturia, Proteinuria, Pyuria due to urinary tract infection, Schistosomiasis, Urinary tuberculosis
Blue or green	Biliverdin, Blue diaper syndrome (familial benign hypercalcemia), Hartnup disease, Porphyria, Pseudomonas urinary tract infection
Purple	Purple urine bag syndrome

Note: Red/orange urine is usually related to hematuria. Causes related to medications are not included in this table.

Information from reference 6.

Eating excessive amounts of blackberries, beets, or carrots is associated with red, but not purple, urine. The medication isoniazid often results in orange urine. The medication nitrofurantoin can produce brown or black urine. White, blue, and green urine are also possible. Familial benign hypercalcemia is sometimes termed blue diaper syndrome because this rare condition is associated with blue urine.[6]

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Comparative Evaluation of ACE Inhibitors for their Beneficial Effects in Patients with Ischemic Left Ventricular Systolic Dysfunction and Undergoing Coronary Artery Bypass Surgery

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ABSTRACT

Three angiotensin-converting enzyme (ACE) inhibitors, captopril, perindopril and ramipril were compared for their effectiveness in patients having left ventricular (LV) systolic dysfunction (Left ventricular ejection fraction [LVEF] 30% as revealed by 2D echocardiography) and who underwent coronary artery bypass grafting (CABG). We enrolled 27 patients in captopril, 43 patients in perindopril and 70 patients in ramipril groups. There was about 25-36% rise in LVEF after 3 and 6 months of ACE inhibitor administration in all three groups. Perindopril treatment produced a sustained improvement in LVEF. However, the difference in terms of percent improvement in LV contractility amongst three groups was not statistically significant. After 3 and 6 months of treatment with ACE inhibitor following coronary arterial grafting, the reduction in LV diameters did not differ significantly amongst three groups. There was a significant decrease ($p < 0.05$) in LV end-diastolic diameter from baseline levels in captopril and perindopril groups after 3 months which got increased after 6 months but remained below pretreatment levels in both the groups. In ramipril group, there was not much change in this parameter from baseline levels at 3 and 6 months of treatment. After 6 months of treatment, the percent reduction in LV end-systolic diameter was also sustained in perindopril-treated patients. The percent reduction was greater in the perindopril group (3 and 6 months: 7.39 ± 5.94 and 7.73 ± 3.43, respectively) as compared to that observed in captopril group (3 and 6 months: 5.67 ± 1.05 and 2.52 ± 3.11, respectively) and ramipril group (3 and 6 months: 7.30 ± 2.75 and 4.93 ± 3.22, respectively). Mitral-valve regurgitation was greatly reduced in the captopril group at 3 as well 6 months of ACE inhibitor administration. However, the percent reduction from baseline levels was not statistically significant amongst three groups. The percent improvement in functional status was significantly greater in the ramipril treatment group (36.46 ± 3.14) after 6 months of treatment as compared to that of captopril (6.67 ± 10.64) and perindopril (4.17 ± 2.73) group. In conclusion, our data show equal beneficial effects with all three ACE inhibitors in CABG patients with LV systolic dysfunction, with marginal superiority for perindopril.

Keywords: ACE inhibitor, left ventricular systolic dysfunction, heart failure, coronary artery bypass surgery

About 23 million people worldwide are afflicted with heart failure (HF) and 2 million new cases of HF are diagnosed each year worldwide. As per the heart and stroke statistics update of American Heart Association (AHA), nearly 5 million people in the United States suffer from HF. A large survey namely MONItoring of trends and determinants in CArdiovascular disease (MONICA) survey found that the prevalence of left ventricular (LV) dysfunction in Britain was 2.27%. Indians and other South Asians are less likely to die from HF in comparison to Caucasians. The incidence of HF has been on the rise in past few decades. Since, myocardial infarction (MI) or severe ischemia, resulting from multiple-vessel coronary artery disease (CAD), is the main underlying cause in the LV systolic dysfunction, surgical revascularization of diseased coronary arteries by coronary artery bypass grafting (CABG) is one of the common interventions for the treatment of such patient population. However, post-surgical therapy with pharmacological measures

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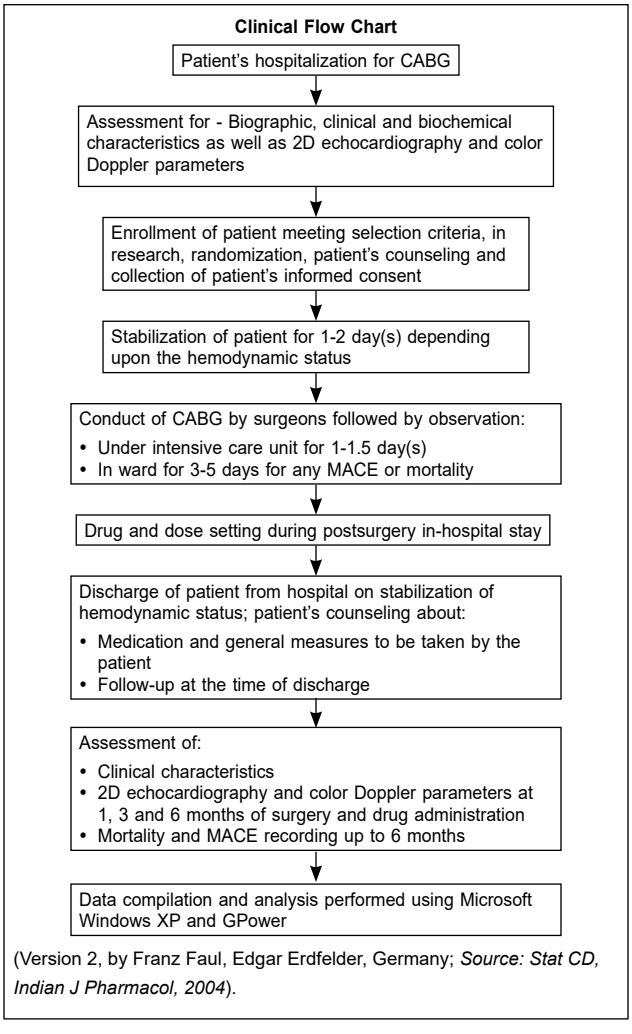
is needed to sustain the beneficial effects of the former. Involvement of neurohormonal system especially sympathetic system and renin-angiotensin-aldosterone system (RAAS) in LV remodeling through direct as well as indirect mechanism is well-documented. Several angiotensin-converting enzyme (ACE) inhibitors and antagonists of angiotensin II receptor subtype-1 (AT_1) have shown a significant reduction in mortality and morbidity in patients having LV systolic dysfunction. Long-term treatment with ACE inhibitors produces absolute increases in LV ejection fraction (LVEF).

Captopril has been found to reverse ventricular dilation caused by MI. Enalapril has also been reported to reverse progression of LV dilation in patients with asymptomatic systolic dysfunction. Thus, many clinical trials and researches are available showing beneficial effects of various ACE inhibitors and American College of Cardiology (ACC)/AHA practice guidelines recommend ACE inhibitors for treatment of LV systolic dysfunction, if not contraindicated. Majority of the reports on beneficial effects of ACE inhibitors in patients with LV dysfunction include placebo-controlled research and do not compare various ACE inhibitors in a single research for their beneficial effects on such patient population. In our earlier report, we found captopril and perindopril more efficient in improving LV contractility as compared to ramipril, lisinopril and losartan.

Captopril and perindopril produced a significant increase in percent LVEF as compared to other ACE inhibitors and losartan. Perindopril also decreased insulin levels significantly. There was a significant correlation between decreases in blood glucose as well as insulin levels with improvements in LVEF. However, the evidence was based on assessment of biochemical parameters to correlate the improvements in LVEF produced by these drugs, while the clinical parameters included echocardiographic evaluation. Hence, we compared various ACE inhibitors in one research for their beneficial effects on patients having ischemic LV systolic dysfunction and undergoing CABG using echocardiographic parameters.

MATERIAL AND METHODS

The study presented here includes the research carried out at SAL Hospital and Sterling Hospital, Ahmedabad. The research was approved by the Ethics Committee of both the hospitals. Written informed consent was taken from all the patients eligible for the investigation, Moreover, all patients were explained about the procedures, the risks and benefits of the interventions.



(Version 2, by Franz Faul, Edgar Erdfelder, Germany; *Source: Stat CD, Indian J Pharmacol, 2004*).

Study Design

It was a prospective, randomized, open-label research. The research did not include a control group since ACE inhibitors have proven absolute beneficial effects on patients with LV systolic dysfunction. Further, as per the ACC/AHA guidelines for management of HF, all the patients with LV systolic dysfunction should be treated with ACE inhibitor, if there is no contraindication. Therefore, the control group was not included and comparison amongst three ACE inhibitors was carried out.

Patient Selection

Inclusion Criteria

Patients presenting with ischemic LV systolic dysfunction (defined as LVEF 30% as revealed from two-dimensional [2D] echocardiography) and undergoing CABG were included.

Exclusion Criteria

Patients of age above 70 years, previous or recent history of second- or third-degree atrioventricular block, renal failure (serum creatinine >2.6 mg%), hepatic dysfunction (serum glutamate pyruvate transaminase [SGPT] >45 IU/L), cerebrovascular events, previous history of revascularization or valve replacement surgery were excluded from the study.

Groups of Patients

Patients meeting the selection criteria were randomized into three groups. Randomization was done using cards indicating '1' designated to captopril, '2' designated to perindopril and '3' designated to ramipril therapy. Group I included patients receiving captopril after CABG. Group II included patients receiving perindopril treatment. In Group III, ramipril was the ACE inhibitor. Patients were evaluated at the time of enrollment a day or 2 before CABG and re-evaluated at 1, 3 and 6 months of CABG and ACE inhibitor administration. We enrolled 27 patients in Group I (captopril group), 43 patients in Group II (perindopril group) and 70 patients in ramipril group (Group III).

TREATMENT

As per the strategy, the drug dose regimen was started with the minimum dose of the drug and allowed to attain the maximum dose. Serial dose titration was carried out depending upon the hemodynamic status of the patients. For captopril, the initial dose was 37.5 mg/day and reached up to maximum of 75 mg/day. Perindopril treatment was begun with the dose of 2 mg/day and reached maximum dose of 4 mg/day. Ramipril administration was started with 2.5 mg/day and the highest dose attained was 20 mg/day. In addition to ACE inhibitor, patients were also receiving other drugs directly affecting cardiac function such as diuretic(s), β-adrenoceptor blocker and digoxin. Other drugs used included amiodarone, isosorbide dinitrate, acetylsalicylic acid, statin, etc., depending upon the requirements. Patients were also advised of general measures about lifestyle modifications, i.e., cessation of smoking or tobacco chewing or alcoholism, regular exercise of low-medium calibre, restricted total salt intake and fluid intake (2-3 liters/day) as well as fat intake.

BIOGRAPHIC CHARACTERISTIC ASSESSMENT

Patient's biographic characteristics, i.e., age and associated risk factors such as habit of smoking, tobacco chewing or alcoholism and family history of ischemic heart disease (IHD) were noted by questioning at the time of enrollment. Body weight was measured with the help of pedal weighing balance. Patient's height was measured in patient's standing position using vertical height-measuring column device.

Clinical Assessment

Clinical assessment included patient's hemodynamic parameters, i.e., pulse rate, systolic and diastolic blood pressure measured in patient's seating position with elbow at the level of heart using sphygmomanometer. They were evaluated for the electrocardiogram (ECG) and CAD characteristics using coronary angiography (CAG) pattern carried out preoperatively. Functional capacity was determined as per New York Heart Association (NYHA) class for HF, assigning patients to 1 of 4 functional classes depending upon the degree of effort needed to elicit symptoms.

2D echocardiography and Color Doppler Assessment

2D echocardiography and color Doppler assessment was performed using CarisPlus (Esaote, USA) machine by a Cardiologist who was unaware of the treatment given. Recommendations of the American Society of Echocardiography were followed by the Cardiologist for measuring various parameters. Images were obtained from the patient lying on the left side in a supine position with the body elevated at about 30°. LVEF was assessed using standard parasternal and apical views. LV end-diastolic diameter (LVEDd) and LV end-systolic diameter (LVEDs) were measured using four-chamber and two-chamber views with apical approach at the level of papillary muscle. Severity of mitral-valve regurgitation (MR) was found out using color Doppler assessment. LVEF, LVEDd, LVEDs and MR-grade were measured a day or 2 before and 1, 3 and 6 months following CABG and ACE inhibitor administration. Mortality and MACE were noted up to 6 months of drug treatment under consideration.

Biochemical Parameter Assessment

Blood samples from patients were collected at the time of enrollment for biochemical parameter testing, which was done in in-hospital pathology laboratory following good laboratory practices. Biochemical parameters assessed included serum glucose, serum urea, serum creatinine, SGPT, serum total cholesterol, serum triglyceride, serum high-density lipoprotein

(HDL) cholesterol, serum low-density lipoprotein (LDL) cholesterol, serum potassium (K^+) and serum sodium (Na^+).

DATA ANALYSIS

The data were analyzed by finding mean ± standard error of mean (SEM) for numerical and ordinal data and percent of number (n) of patients for nominal data. Chi-square test was used to find difference of statistical significance in categorical measurements amongst three groups. For parametric numerical data, results were obtained by applying Student's *t*-test to find the change in characteristics from baseline levels. Analysis of variance (ANOVA) was used for numerical data to find the significant difference amongst three treatment groups. Difference amongst groups and hence treatment, was considered statistically significant if 'p' value was found to be <0.05 ($p < 0.05$). Post-hoc power analysis was done using GPower software. The power of the study (1-β) has been presented along with the respective level of significance.

RESULTS

Baseline biographic characteristics, risk factor association and biochemical variables were similar among three groups (Tables 1-3). There was no significant difference in CAD characteristics, medication affecting cardiac function other than ACE inhibitors, hemodynamics (such as heart rate, systolic and diastolic blood pressure) and baseline 2D echocardiography characteristics amongst three groups (Tables 4-7). After 1, 3 and 6 months of ACE inhibitor administration following CABG, 2D echocardiography showed a significant ($p < 0.05$) improvement in LV contractility from baseline levels (i.e., levels at the time of enrollment) in captopril and ramipril groups. In perindopril treatment group, the increase in LVEF was found to be statistically significant after 1 and 3 months of treatment. Increase in LVEF in terms of percent change from baseline levels in individual patients did not differ significantly amongst three groups; however, the increase was greater and persistent in perindopril group (Table 7 and Fig. 1).

There was a significant decrease in LVEDd from baseline levels in captopril and perindopril groups after 3 months, which increased after 6 months, but remained below pretreatment levels in both the groups. In ramipril group, not much change in this parameter was observed from baseline levels after 3 and 6 months of treatment (Table 7 and Fig. 2). After 3 months of treatment, LVEDs was significantly decreased in captopril and perindopril groups as compared with baseline levels. However, after 6 months, there was an increase in this parameter in both the groups. In ramipril-treated patients, no significant decrease in LVEDs was observed after 3 as well as 6 months of treatment. Decrease in LVEDs in terms of percent change from baseline levels did not differ significantly amongst three groups; however, it was more persistent in perindopril group (Table 7 and Fig. 3). MR grade did not differ significantly from baseline levels within the groups as well as amongst three

Table 1. Baseline Biographic Characteristics of Patients

Parameter	Group I (Captopril) (n = 27)	Group II (Perindopril) (n = 43)	Group III (Ramipril) (n = 70)
Sex males (%)	27 (100%)†	38 (88.37%)	67 (95.71%)
Age (years)*	57.14 ± 1.84	60.25 ± 1.34	56.89 ± 1.07
BMI (kg/m^2)*	26.36 ± 1.53	27.48 ± 1.13	25.31 ± 1.32
Lifestyle (stress)			
Heavy	9 (33.33%)	3 (6.98%)	14 (20.0%)
Moderate	7 (25.92%)	15 (34.88%)	16 (22.86%)
Sedentary	11 (40.74%)	25 (58.14%)	40 (57.14%)
Symptoms			
Dyspnea on exertion	16 (59.26%)	23 (53.49%)	29 (41.43%)
Edema	2 (7.40%)	4 (9.30%)	2 (2.86%)
Chest pain	15 (55.55%)	22 (51.16%)	45 (64.29%)

BMI = Body mass index; kg/m^2 = Kilogram per square meter.

*Mean ± SEM.

†Values in brackets are percent of total *n* in each group.

Table 2. Prevalence of Risk Factors in Patients at the Time of Enrollment

Risk factor	Group I (Captopril) (n = 27)	Group II (Perindopril) (n = 43)	Group III (Ramipril) (n = 70)
Habit			
Alcoholism	1 (3.7%)*	0 (0%)	4 (5.71%)
Smoking	5 (18.52%)	5 (11.63%)	18 (25.71%)
Tobacco chewing	1 (3.7%)	6 (13.95%)	17 (24.28%)
Disease			
DM	10 (37.03%)	21 (48.83%)	36 (51.43%)
HT	7 (25.92%)	17 (39.53%)	29 (41.43%)
DM + HT	3 (11.11%)	10 (23.26%)	17 (24.29%)
Positive family history			
IHD	7 (25.93%)	8 (18.6%)	24 (34.28%)
Past history of MI	18 (66.67%)	21 (48.84%)	42 (60.0%)

DM = Diabetes mellitus; HT = Hypertension; IHD = Ischemic heart disease; MI = Myocardial infarction.

*Values in brackets are percent of total *n* in each group.

Table 3. Biochemical Parameters at Baseline Level

Biochemical parameter	Group I (Captopril) (n = 27)	Group II (Perindopril) (n = 43)	Group III (Ramipril) (n = 70)
RBS (mg%)*	155.59 ± 10.82	149.01 ± 12.43	176.79 ± 7.55
Serum urea (mg%)*	29.59 ± 1.43	32.23 ± 1.39	34.34 ± 1.16
Serum creatinine (mg%)*	1.18 ± 0.08	1.19 ± 0.03	1.15 ± 0.03
SGPT (IU/L)*	28.58 ± 2.52	30.37 ± 1.51	33.4 ± 1.23
Serum K^+ (mEq/L)*	4.47 ± 0.07	4.10 ± 0.08	4.32 ± 0.07
Serum Na^+ (mEq/L)*	135.98 ± 1.47	135.89 ± 0.81	136.56 ± 0.54
Serum TC (mg%)*	112.0 ± 8.54	110.45 ± 4.59	117.65 ± 3.61
Serum TG (mg%)*	75.68 ± 6.46	99.53 ± 8.14	106.17 ± 7.49
Serum LDL-C (mg%)*	59.87 ± 6.55	54.56 ± 4.38	61.61 ± 2.96
Serum HDL-C (mg%)*	31.53 ± 1.52	27.96 ± 1.79	27.71 ± 1.22

HDL-C = High-density lipoprotein cholesterol; IU = International unit; K^+ = Potassium; LDL-C = Low-density lipoprotein cholesterol; mEq = Milliequivalence; mg = Milligram; Na^+ = Sodium; RBS = Random blood sugar; SGPT = Serum glutamate pyruvate transaminase; TC = Total cholesterol; TG = Triglyceride.

*Mean ± SEM.

groups after 3 and 6 months of ACE inhibitor administration. At 6 months of ACE inhibitor administration, the percent improvement in MR-grade was greatest in captopril group as compared to that produced in perindopril and ramipril groups (Table 7 and Fig. 4). The NYHA class was significantly reduced ($p < 0.05$) from baseline levels in all three groups after 3 and 6 months suggesting significant improvement in functional status in all three groups (Fig. 5). Further, in ramipril group, the percent improvement in NYHA class was statistically significant as compared to those observed in other two groups. Two patients died in ramipril treatment group during post-hospital course, one because of sudden fall in heart rate and the other because of recurrent MI. In remaining patients, no major adverse cardiovascular event (MACE) was found in all three groups during 6-month follow-up.

DISCUSSION

Hyperactivated neurohormonal systems responsible for the cardinal effects in patients with LV dysfunction include mainly RAAS and sympathetic system. Amongst various drug therapies, inhibitors of RAAS are at the top of the recommendations. Various components of RAAS play a significant role in the development of LV remodeling; and hence in further deterioration of LV

Table 4. Angiographic Pattern of Stenosed Coronary Arteries as Revealed by Angiography

	Group I (Captopril) (n = 27)	Group II (Perindopril) (n = 43)	Group III (Ramipril) (n = 70)
Single vessel disease	0 (0%)*	1 (2.32%)	0 (0%)
Double vessel disease	4 (14.81%)	7 (16.28%)	8 (11.42%)
Triple vessel disease	23 (85.18%)	35 (81.39%)	62 (88.57%)
Diffusely diseased artery	2 (7.41%)	8 (18.60%)	10 (14.23%)
Diseased artery, lesion severity i.e., percent blockade of diameter			
LMCA (≥50%)	2 (7.41%)	7 (16.28%)	10 (14.23%)
LAD (100%)	17 (62.96%)	7 (39.53%)	30 (42.86%)
LAD (70-99%)	6 (22.22%)	20 (46.51%)	36 (51.43%)
LCx (100%)	3 (11.11%)	9 (20.93%)	7 (10.0%)
LCx (70-99%)	8 (29.63%)	16 (37.21%)	29 (41.43%)
RCA (100%)	9 (33.33%)	17 (39.53%)	28 (40.0%)
RCA (70-99%)	11 (40.74%)	13 (30.23%)	31 (44.29%)

LMCA = Left main coronary artery; LAD = Left anterior descending artery; LCx = Left circumflex artery; RCA = Right coronary artery.

*Values in brackets are percent of total *n* in each group.

Table 5. Medication affecting Cardiac Function other than ACE Inhibitors given to patients following CABG

Medication	Group I (Captopril) (n = 27)	Group II (Perindopril) (n = 43)	Group III (Ramipril) (n = 70)
Digoxin	23 (85.18%)*	29 (67.44%)	49 (70.0%)
Diuretics	25 (92.59%)	37 (86.04%)	62 (88.57%)
β-adrenoceptor blocker	15 (55.55%)	17 (39.53%)	33 (47.14%)

ACE = Angiotensin-converting enzyme; CABG = Coronary artery bypass grafting.

*Values in brackets are percent of total *n* in each group.

Table 6. Hemodynamic Levels in Patients at Baseline (at the Time of Enrollment) and at 1, 3 and 6 Months of Treatment

Parameters	Group I (Captopril) (n = 27)	Group II (Perindopril) (n = 43)	Group III (Ramipril) (n = 70)
HR (beats/min)*			
Baseline	79.60 ± 1.42	85.72 ± 2.49	82.71 ± 2.13
1 month	83.0 ± 1.34	83.92 ± 0.84	83.85 ± 0.99
3 months	81.0 ± 2.45	79.0 ± 1.32	82.4 ± 1.24
6 months	84.0 ± 1.62	82.0 ± 1.12	86.67 ± 1.56
SBP (mmHg)*			
Baseline	125.4 ± 3.69	122.89 ± 2.82	123.75 ± 2.10
1 month	119.0 ± 1.98	125.81 ± 2.74	119.84 ± 1.44
3 months	121.0 ± 3.17	125.67 ± 4.11	127.0 ± 2.86
6 months	126.25 ± 2.45	126.78 ± 3.24	122.0 ± 1.59
DBP (mmHg)*			
Baseline	76.24 ± 1.42	78.19 ± 1.58	79.75 ± 1.16
1 month	76.18 ± 1.59	80.84 ± 1.08	78.01 ± 0.90
3 months	83.0 ± 4.62	83.33 ± 0.83	80.8 ± 1.34
6 months	81.34 ± 2.56	80.0 ± 1.27	83.33 ± 0.70

DBP = Diastolic blood pressure; HR = Heart rate; mmHg = Millimeters of mercury; SBP = Systolic blood pressure.

*Mean ± SEM.

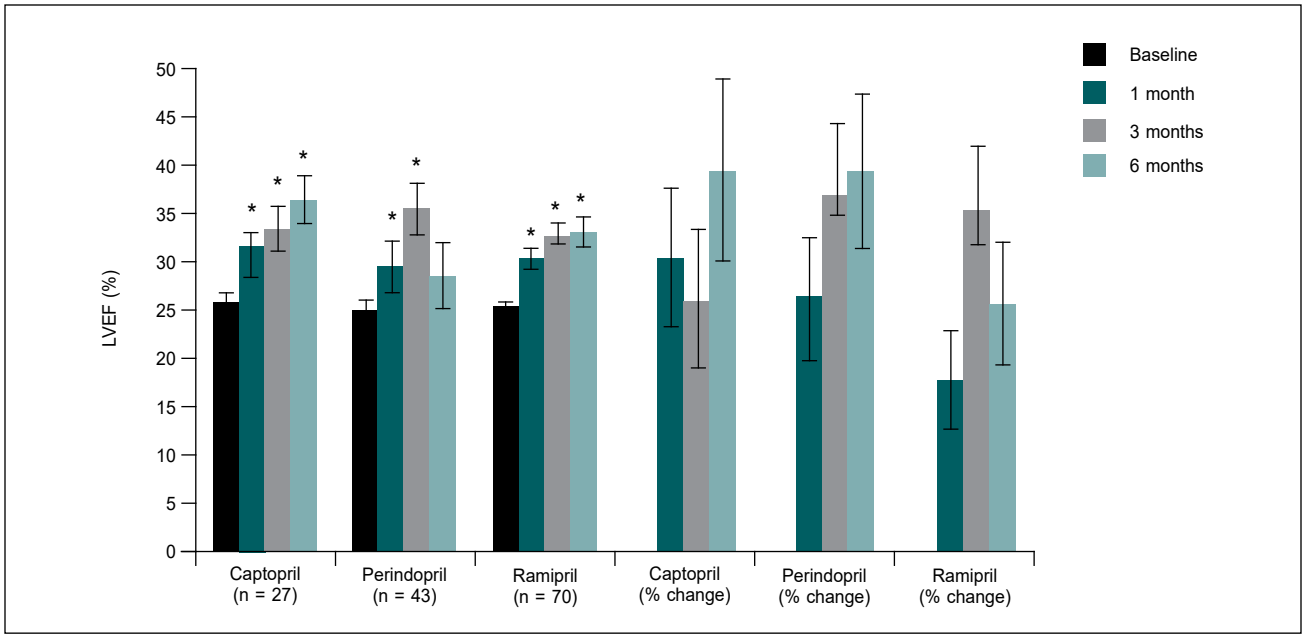


Figure 1. Effect of ACE inhibitors on LV contractility measured as LVEF in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from baseline ($p < 0.05$).

Power (1-β) = 0.546 at α = 0.4.

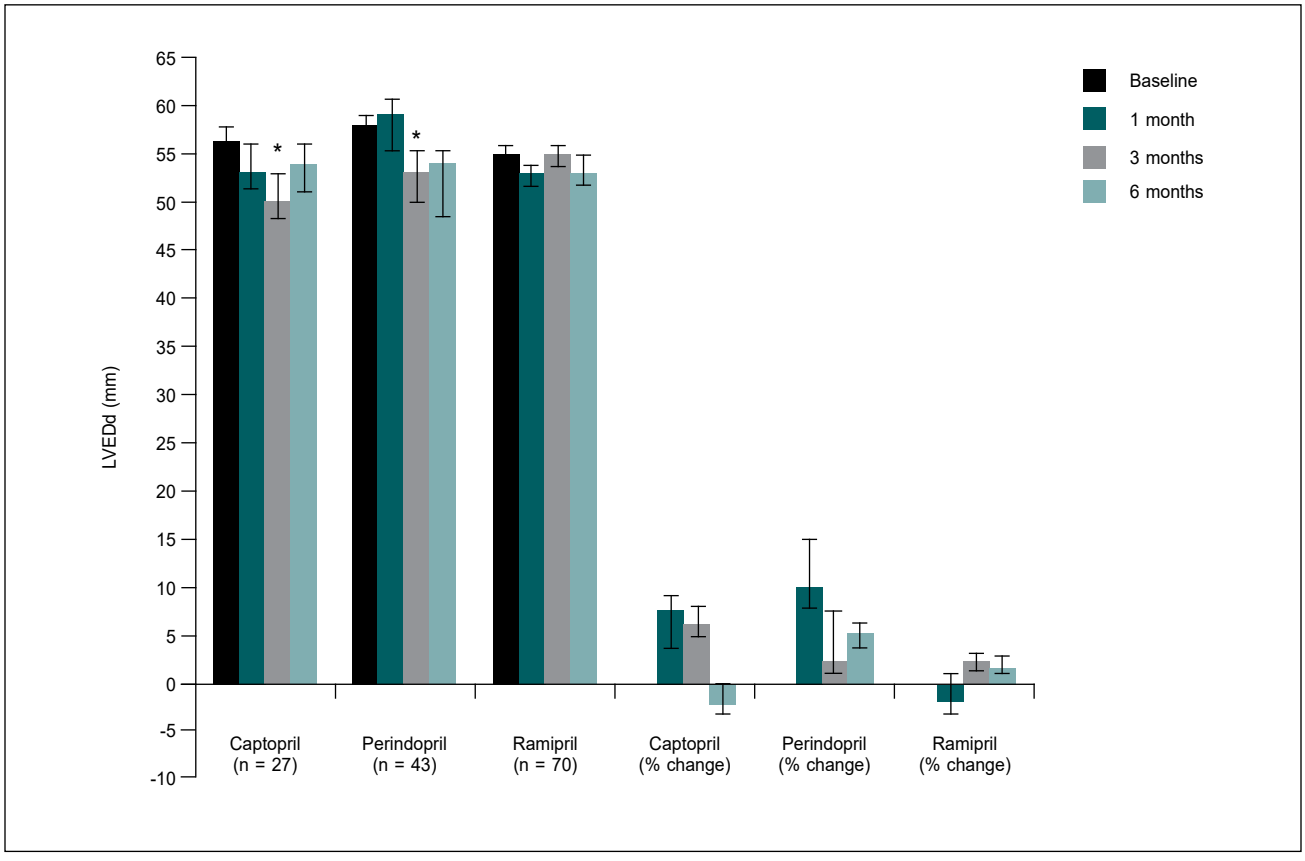


Figure 2. Effect of ACE inhibitors on LVEDd in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from baseline ($p < 0.05$).

Table 7. 2D Echocardiography and Color Doppler Characteristics and NYHA Class for HF in Patients at the Time of Enrollment (Baseline) and at 1, 3 and 6 Months of ACE Inhibitor Treatment

Parameters	Group I (Captopril)		Group II (Perindopril)		Group III (Ramipril)	
2D echocardiography and color Doppler	**(n = 27)**	**% change from baseline in individual patients**	**(n = 43)**	**% change from baseline in individual patients**	**(n = 70)**	**% change from baseline in individual patients**
LVEF (%)*						
Baseline	25.89 ± 0.84		24.91 ± 1.07		25.21 ± 0.57	
1 month	31.68 ± 1.95‡	30.38 ± 7.23	29.44 ± 2.65‡	26.12 ± 6.44	30.29 ± 1.14‡	17.74 ± 5.09
3 months	33.25 ± 2.36‡	26.11 ± 7.22	35.43 ± 2.60‡	36.61 ± 7.68	32.59 ± 1.49‡	35.28 ± 6.72
6 months	36.25 ± 2.51‡	39.42 ± 9.49	28.5 ± 3.42	39.2 ± 7.92	33.03 ± 1.58‡	25.61 ± 6.34
LVEDd (mm)*						
Baseline	55.86 ± 1.60		57.25 ± 1.23		54.82 ± 0.90	
1 month	52.18 ± 2.80	7.67 ± 3.99	58.56 ± 2.06	10.97 ± 9.49	52.28 ± 1.53	-1.9 ± 2.81
3 months	50.5 ± 2.03‡	6.3 ± 3.84	53.83 ± 2.01‡	3.18 ± 3.86	55.39 ± 1.96	2.99 ± 1.32
6 months	53.98 ± 1.47	-2.55 ± 2.07	54.93 ± 2.65	4.81 ± 1.16	54.14 ± 1.07	2.87 ± 2.05
LVEDs (mm)*						
Baseline	44.17 ± 1.57		44.37 ± 1.40		43.18 ± 1.07	
1 month	41.35 ± 2.72	6.37 ± 4.85	47.02 ± 2.32	-2.62 ± 4.36	39.93 ± 1.64	-0.7 ± 4.01
3 months	38.28 ± 2.31‡	5.67 ± 1.05	38.18 ± 1.86‡	7.39 ± 5.94	41.83 ± 2.00	7.30 ± 2.75
6 months	39.91 ± 1.28‡	2.52 ± 3.11	44.3 ± 2.87	7.73 ± 3.43	40.28 ± 1.37	4.93 ± 3.22
MR-grade*						
Baseline	0.77 ± 0.11		0.46 ± 0.08†		0.7 ± 0.08	
1 month	0.82 ± 0.1	-24.55 ± 38.41	0.49 ± 0.16	41.67 ± 13.14	0.6 ± 0.16	-77.14 ± 58.04
3 months	0.6 ± 0.15	50.0 ± 13.87	0.36 ± 0.12	-2.22 ± 41.87	0.7 ± 0.11	-48.75 ± 53.27
6 months	0.5 ± 0.16	50.0 ± 17.41	0.73 ± 0.2	-68.0 ± 53.4	0.68 ± 0.12	-89.09 ± 64.3
NYHA class for HF*						
Baseline	2.91 ± 0.18		2.94 ± 0.15		3.0 ± 0.15	
1 month	2.18 ± 0.22‡	5.0 ± 13.41	1.89 ± 0.26‡	25.0 ± 10.8	2.0 ± 0.24‡	28.7 ± 6.07
3 months	2.0 ± 0.17‡	34.72 ± 13.14	1.95 ± 0.14‡	27.45 ± 4.89	2.17 ± 0.15‡	17.86 ± 5.65
6 months	2.67 ± 0.16	6.67 ± 10.64	2.43 ± 0.20‡	4.17 ± 2.73	2.25 ± 0.15‡	36.46 ± 3.14†

2D = Two-dimensional; HF = Heart failure; LVEDd = Left ventricular end-diastolic diameter; LVEDs = Left ventricular end-systolic diameter; LVEF = Left ventricular ejection fraction; MR = Mitral-valve regurgitation; NYHA = New York Heart Association.

*Mean ± SEM.

†Significantly different as compared with other two groups ($p < 0.05$); ‡Significantly different from baseline ($p < 0.05$).

dysfunction caused by ischemia and/or infarction. Thus, suppression of these components has potential-absolute and synergistic in sustaining the beneficial effects brought about by surgical revascularization. It is recommended that all HF patients with established LV systolic dysfunction should be treated with ACE inhibitor, until there are contraindications to these agents. By inhibiting ACE, systemic and tissue as well, ACE inhibitors reduce afterload and systolic stress too.

These subsequently increase stroke volume due to facilitated stroke work. By improving renal hemodynamics and by reducing aldosterone secretion, ACE inhibitors prevent blood volume overload. Consequently, preload and diastolic wall stresses are diminished. However, different ACE inhibitors may vary in their activity and thus superiority.

Pfeffer et al (1992) found captopril treatment (at about 3.5 years of captopril administration) to be more beneficial, as compared with placebo, in

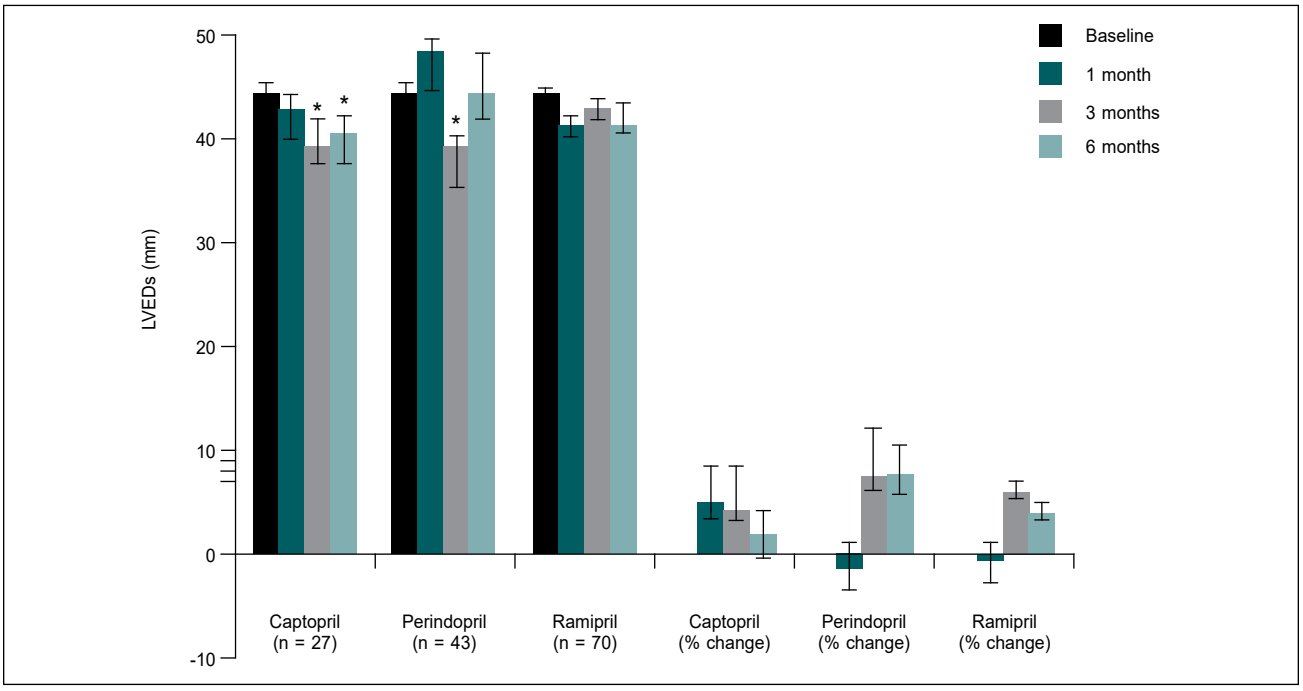


Figure 3. Effect of ACE inhibitors on LVEDs in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from baseline ($p < 0.05$).

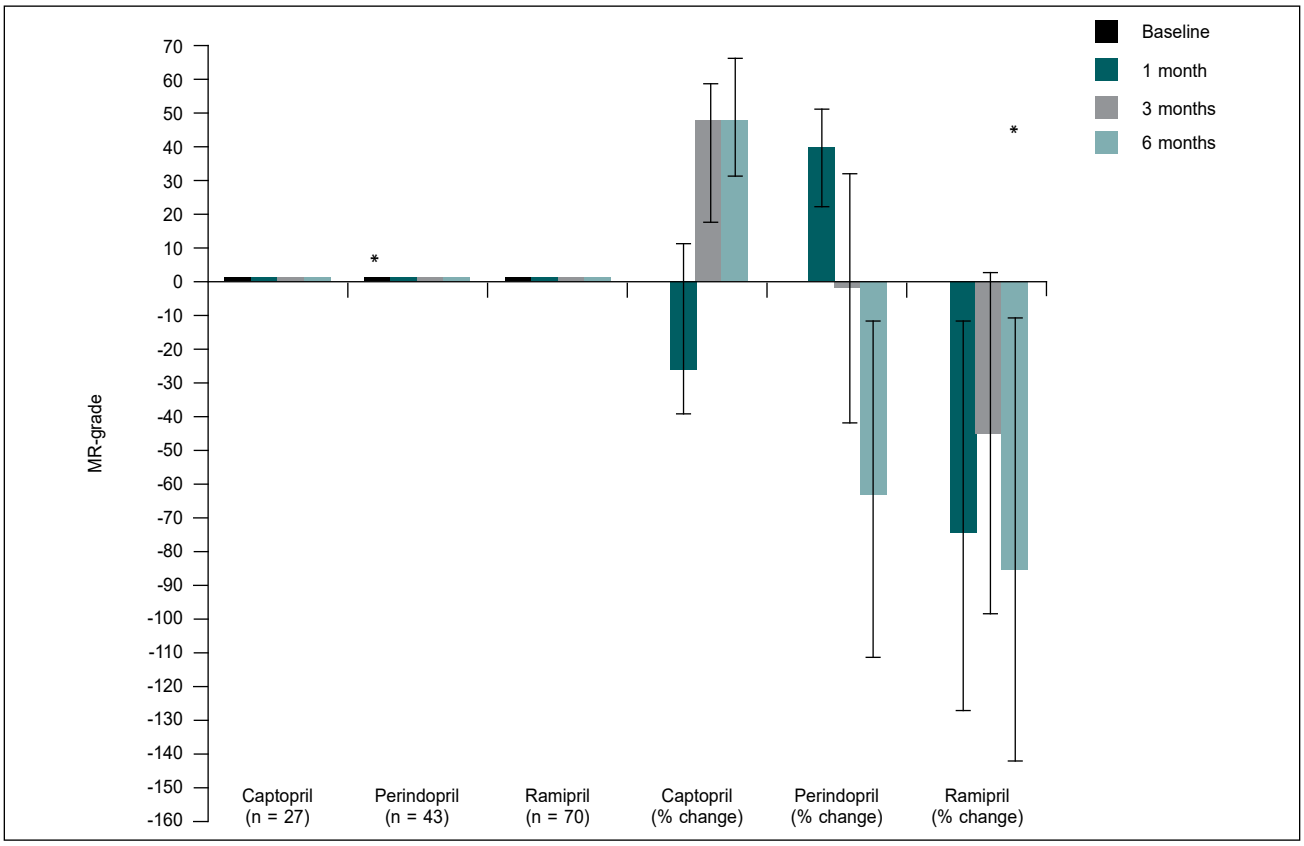


Figure 4. Effect of ACE inhibitors on mitral-valve regurgitation in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from other groups ($p < 0.05$).

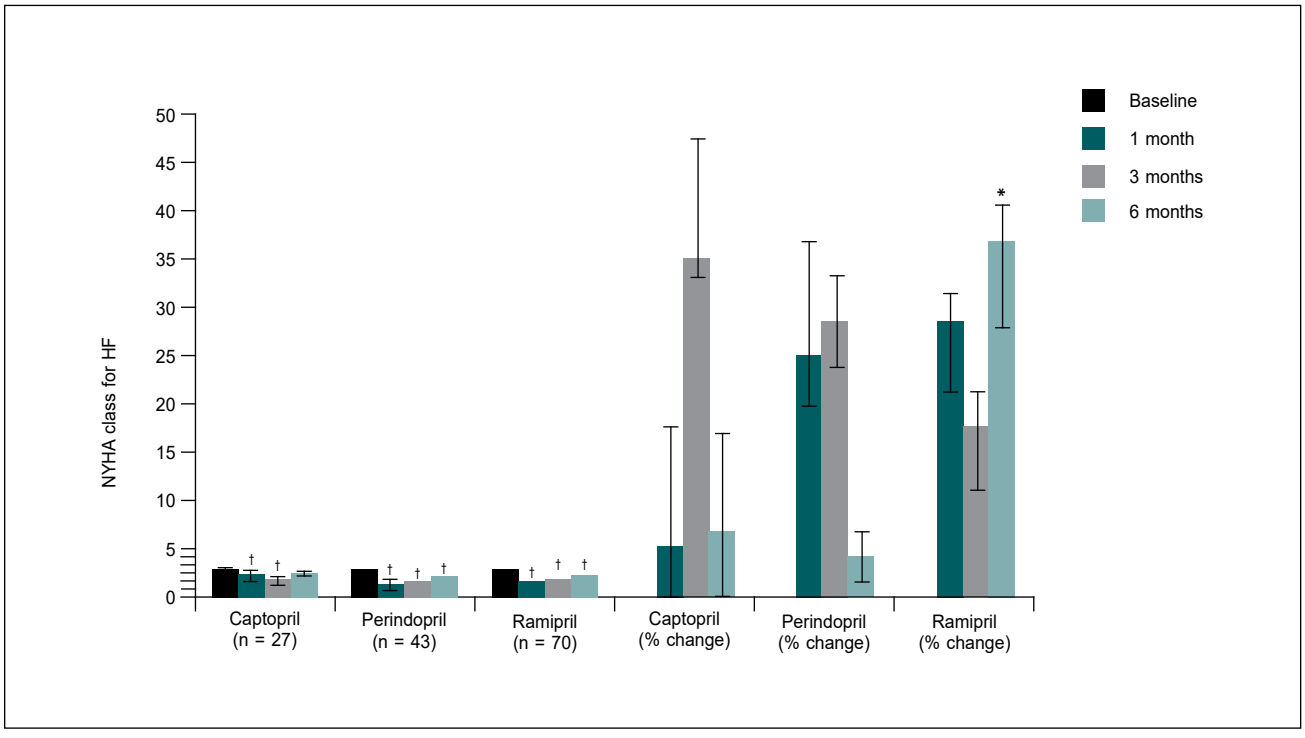


Figure 5. Effect of ACE inhibitors on functional status as per NYHA class for HF in patients with LV systolic dysfunction and undergoing CABG.

*Significantly different from other groups ($p < 0.05$);

†Significantly different from baseline ($p < 0.05$).

patients having LV dysfunction after an MI. They found captopril to significantly reduce mortality from cardiovascular cause with 21% risk reduction and also the incidence of major cardiovascular events, defined in terms of development of severe HF (37% reduction), congestive HF (CHF) requiring hospitalization (22% reduction) and recurrent MI (25% reduction). In EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease), perindopril was compared with placebo in patients with stable CAD. At average follow-up of 4 years, perindopril was found to produce a 20% relative risk reduction in primary endpoints viz. cardiovascular death, MI or cardiac arrest. The Heart Outcomes Prevention Evaluation (HOPE) trial reported that ramipril, when compared with placebo at 5 years of administration, significantly reduced the incidences of MI (relative risk 0.8), stroke (relative risk 0.68) or death from cardiovascular causes (relative risk 0.74). In this trial, the patient group included those having vascular diseases or diabetes *plus* another cardiovascular risk factor but low EF or HF. Thus, various large randomized placebo-controlled clinical trials have shown the absolute beneficial effects of chronic administration of ACE inhibitors on mortality and major cardiovascular events in patients having CAD with or without LV dysfunction.

Captopril, as compared with enalapril in patients with acute MI (AMI), is comparable in terms of improving LV function and survival. Ramipril and captopril are also similar for their effects on serum creatinine, serum K^+, cardiac events such as arrhythmias and mortality as well in patients with CHF, though ramipril significantly controls the blood pressure with longer duration of action. Three-month treatments with captopril and perindopril have been reported to produce similar effects on heart rate, systolic function and LV mass, although less number of patients in perindopril group as compared with captopril group required add-on therapy with thiazides to normalize the blood pressure. Chu-Pak et al (2002) reported no difference in mortality rates after 6 months of treatment with captopril and perindopril in patients with AMI, though perindopril treatment showed better short-term tolerance than captopril treatment did, with significantly less acute hemodynamic changes and fewer withdrawals. Pilote et al (2008) found a possible 10-15% increase in mortality with captopril and enalapril compared with ramipril among patients with CHF. However, following

adjustment for differences in used dosages, all ACE inhibitors had similar clinical efficacy administered in patients after MI. Thus, ours is probably the only research that has compared, in one subset of patient-population, the effects of captopril, perindopril and ramipril in patients with LV systolic dysfunction and who were undergoing CABG.

We found an improvement in LV contractility in all three groups treated with different ACE inhibitors. There was an increase in LVEF at 1, 3 and 6 months of ACE inhibitor administration. The beneficial effects on LV performance observed after 1 month of CABG may be mainly due to revascularization. It is possible that at 3 and 6 months, the observed improvements may be an influence of ACE inhibitor. In the presented research, the percent improvement in LVEF from baseline levels was not statistically significant among three groups, though it was slightly greater in perindopril and ramipril groups after 3 months as compared to captopril group and in captopril and perindopril groups at 6 months as compared to ramipril group. The improvement in overall cardiac function could be because of better coronary blood flow due to inhibition of sympathetic coronary vasoconstriction by ACE inhibitors and due to inhibition of endothelial as well as adventitial ACE providing better hemodynamic control by ACE inhibitors. This property of ACE inhibitors helps enhance coronary circulation and myocardial perfusion through newly placed grafts too.

In our earlier findings, we reported captopril and perindopril to be more efficient for improving LV contractility as compared to ramipril, lisinopril and losartan. Captopril and perindopril were found to produce a significant increase in percent LVEF as compared to other ACE inhibitors and losartan. There was a significant correlation between decreases in blood glucose as well as insulin levels with improvements in LVEF. In the presented work, the sustained and greater improvements observed in perindopril group could be secondary to improved glucose utilization by cardiac myocytes. Moreover, greater improvement in arterial compliance and thus reduction in afterload by perindopril might be responsible for the improvement in LV contractility. Afterload inversely affects LV contractility and has direct correlationship with peripheral vascular resistance which is a measure of arterial compliance. Various ACE inhibitors viz. captopril, lisinopril and perindopril have been shown to increase arterial compliance. However, perindopril is the ACE inhibitor that has been reported to reduce media to lumen ratio of small arteries with significantly correlated LV mass reduction. Increasing the compliance (elasticity) of even larger arteries, in addition to reduction in peripheral resistance, is also an important documented property of perindopril. Perindopril has also been reported to improve patient's hemodynamic status by improving the elasticity of resistance vessels in heart disease patients too. Furthermore, the improved compliance of conduits (by significant improvement in endothelial nitric oxide synthase expression and activity) and repair of coronary arterioles by perindopril could also be the contributing factor for greater improvement in LVEF.

Besides indirect effects, direct effects of ACE inhibitors are of significance in patients with LV systolic dysfunction. ACE inhibitors prevent ventricular dilation and thereby reduce work load of heart with further improvement in its function. In our findings, the reduction in LV systolic and diastolic diameters was observed in all three groups without any significant difference at 3 and 6 months of ACE inhibitor administration. Evidences have shown that ACE inhibitors attenuate LV remodeling. The greater beneficial effects of perindopril on both diastolic and systolic diameters as compared to captopril and ramipril group is consistent with earlier report of Masuelli et al (2002), which reported that perindopril reversed LV remodeling and improved functional status significantly in HF patients who had been switched over from enalapril treatment. The significant reduction in LVEDs by perindopril might be due to its direct effect on Tei index. Perindopril has a distinguished characteristic of suppressing cardiac aldosterone production, which is activated in failing ventricles, by suppressing cardiac ACE activity.

We found perindopril and ramipril treatments to produce negative effects on MR-grade after 3 and 6 months while captopril treatment showed favorable effects on this parameter after both 3 and 6 months of ACE inhibitor administration. Captopril is efficacious in reducing functional MR in dilated left ventricles; however, the doses used are high. MR results from a complex interaction of very small geometric and temporal changes and can occur as a result of multiple mechanisms which can not be simply overcome by inhibiting ACE.

All the ACE inhibitors used in our research (captopril, perindopril and ramipril) were found to be effective in improving functional status. There was reduction in NYHA class in all three groups from baseline levels. However, percent improvement in NYHA class at 6 months of ACE inhibitor treatment was significant

in ramipril group only. This might be because of an increase in skeletal muscle perfusion during exercise and ability of ACE inhibitors to enhance endurance performance and muscle energy metabolism. Further, various ACE inhibitors have been proved to significantly improve NYHA class for HF in patients with moderate-to-severe LV systolic dysfunction.

CONCLUSIONS

Our findings show that all three ACE inhibitors (i.e., captopril, perindopril and ramipril) produce statistically comparable effects on heart in patients with LV systolic dysfunction undergoing CABG.

While perindopril clinically produces a marginal superiority in cardiac function, ramipril produces the greatest improvement in functional capacity.

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■■■■

Primary PCI

- Treatment strategy: Coronary artery reperfusion with percutaneous coronary intervention (PCI) or fibrinolytic therapy to all patients with an acute ST-segment elevation myocardial infarction (STEMI) who present within 12 hours of onset of symptoms.
- Primary PCI should be done within 90 minutes (door-to-balloon time) for patients who arrive at or who are transported by an emergency medical service to a PCI-capable hospital. Patients who arrive at or who are transported to a non-PCI-capable hospital should be transported urgently to a PCI-capable hospital if they can receive primary PCI within 120 minutes of first medical contact.
- For STEMI patients who present within 12 hours of symptom onset, prefer primary PCI rather than fibrinolysis as the reperfusion strategy if PCI can be delivered within 120 minutes of first medical contact by skilled practitioners.
- For patients who cannot receive timely primary PCI, fibrinolytic therapy should be given and should be administered within 30 minutes of first medical contact, and sooner if possible.
- For patients who present after 12 hours (and up to 24 hours) of symptom onset who have evidence of ongoing ischemia, prefer PCI as opposed to no reperfusion therapy.
- Do coronary angiography and possible PCI for all patients who receive fibrinolytic therapy within 3-24 hours in most of these patients.

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A Randomized Clinical End Point Study to Evaluate the Safety and Efficacy of Polyherbal Tablets in Patients with Alcoholic Liver Disease

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ABSTRACT

Objective: To evaluate and compare the hepatoprotective effect of herbal tablets with silymarin in patients with alcoholic liver disease. **Material and methods:** This was a prospective, randomized, multicenter, open-label, parallel group, interventional clinical end point study (Phase IIa). Patients attending General Medicine outpatient department were screened for alcoholic liver disease by using the serum biochemical liver function test, ultrasonogram (USG) abdomen. Investigators tested whether they satisfied the selection criteria and 24 patients were then enrolled in the study. The study drug was administered to Group A and tablet silymarin was administered to Group B from Day 1 to Day 56. Patients were reviewed once in 2 weeks. Liver function test was repeated, and patients were enquired of their well-being and any adverse events. **Results:** The demographic characters and body weight of the subjects showed no significant difference between the groups. There was a significant improvement ($p < 0.05$) in the aspartate transaminase (AST), alanine transaminase (ALT) and total bilirubin (TB) levels on 28th day and 56th day in both silymarin and herbal tablet groups. Out of the two groups, there was higher significance of improvement in herbal tablet group ($p < 0.001$), compared to silymarin group. The herbal tablet group started showing a significant reduction in AST and ALT levels in the first 14 days of study period. On comparing the mean percentage reduction in the levels of AST (35.7% vs. 35%), ALT (26.7% vs. 24.3%) and TB (26.7% vs. 25%), it was found that the herbal tablets showed a better percentage of reduction of the above parameters compared to silymarin. There were reports of adverse effects like loss of appetite and gastritis in both the groups. **Conclusion:** This clinical study proves that the herbal tablets used functioned as a hepatoprotective drug. They offered better hepatoprotection compared to silymarin. These tablets can be indicated for the management of liver dysfunction, which occurs due to alcoholic liver damage. It may also be used in similar manner in cases of viral hepatitis, drug-induced liver damage, as well as acute and chronic hepatitis.

Keywords: Alcoholic liver disease, hepatoprotective, herbal medicine, silymarin

In the year 2010, the global burden of alcoholic liver diseases was large and resulted in 4,93,000 deaths and 14,544,000 disability-adjusted life years. This burden represented 0.9% of all deaths and 0.6% of all disability-adjusted life years in 2010.[1] Alcoholic liver disease encompasses a clinical-histologic spectrum including fatty liver, alcoholic hepatitis and cirrhosis with its complications.[2] The World Health Organization (WHO) estimates that alcohol is now the third highest risk factor for premature mortality, disability and loss of health worldwide.[3] There is a growing incidence of hepatocellular carcinoma (HCC) worldwide. The annual global incidence of HCC is over 5,00,000 cases. The highest incidence of HCC is observed in Asia and Africa, associated with the high prevalence of hepatitis in these regions.[4] The hallmark of therapy in alcoholic liver diseases has been abstinence from alcohol and nutritional therapy. Role of steroids has been accepted in the treatment; however, the effectiveness of therapy should be assessed after 1 week of treatment. Pentoxifylline has been equally effective, especially in patients with renal dysfunction or hepatorenal syndrome. The use of biologics has been disappointing in the treatment of alcoholic liver diseases.[5]

India is the largest producer of medicinal plants. Medicinal plants have a very important role in the

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health of human beings as well as animals. According to the WHO estimates, about three-quarters of the world's population currently use herbs and other traditional medicines to cure various diseases, including liver disorders.[6]

The herbal medicine used in this study is a research product Polyherbal Formulation* developed by Apex Laboratories Limited for hepatoprotection. It is composed of: *Ricinus communis* - 42.85 mg, *Phyllanthus niruri* - 25 mg, *Eclipta alba* - 15 mg, *Boerhavia diffusa* - 12.5 mg, *Tinospora cordifolia* - 10 mg, *Tribulus terrestris* - 14.28 mg, *Tephrosia purpurea* - 11.11 mg, *Indigofera tinctoria* - 9.37 mg, *Andrographis paniculata* - 6.25 mg, *Rubia cordifolia* - 5 mg, *Terminalia chebula* - 12.5 mg, *Curcuma longa* - 3.5 mg and *Aconitum heterophyllum* - 10 mg. The formulation has been validated scientifically and traditional claims have been supported by scientific data. Standardization of all the extracts has been established without losing the essence of the Ayurvedic tradition. In an animal study conducted by Kumar et al, it was shown that this herbal medicine, in doses of 800 and 1,000 mg/kg, has a significant hepatoprotective action against various hepatotoxicant-induced liver necrosis and injury.[7] These tablets are formulated in such a way that it offers three clear benefits in liver care, i.e., conserves the liver, controls the liver damage and corrects the liver function. This tablet is indicated for the management of liver dysfunction which may occur due to alcoholic liver damage, viral hepatitis, drug-induced liver damage and acute and chronic hepatitis. This tablet can also be prescribed during pregnancy for intrahepatic cholestasis (ICP) and associated constipation.

Herbal medicines have been used in the treatment of liver diseases for a long time; however, standardization of herbal medicines has been a problem. Hence, the rationale behind this study is that we have standardized an herbal medicine for liver disease and if it is efficacious without any side effects, then it can be useful for the population suffering from liver disease at a cheaper cost, compared to the current treatments available. Prospective, randomized, controlled clinical trials are also lacking to support their efficacy.[8] Hence, with an aim to evaluate the efficacy and safety of these herbal tablets in patients with liver dysfunction like alcoholic liver disease in comparison with standard drug like silymarin, the present study was conducted.

MATERIAL AND METHODS

This was a prospective, randomized, multicenter, open-label, parallel group interventional clinical end point study (Phase IIa). The study was conducted at two centers in India - Mahatma Gandhi College and Hospital, Pondicherry and PM Medical Centre, Walajapet, Tamil Nadu, according to Good Clinical Practice. The study was initiated after obtaining proper ethical committee approvals. The study was registered in Clinical Trial Registry of India (No: CTRI/2018/03/012644) and Drug Control General of India (DCGI) (AYUSH) was notified (Notification No: 2730). Informed written consent was obtained from the patients attending General Medicine outpatient department. They underwent general and systemic examination followed by laboratory tests for hematology, blood biochemistry, blood microbiology, urine analysis, electrocardiogram and chest X-ray for initial evaluation and were screened for alcoholic liver disease by using serum biochemical liver function test, and ultrasonogram (USG) abdomen. Investigators tested whether they satisfied the selection criteria and 24 patients were then enrolled in the study. The following patients were recruited in the study:

- Patients of either sex, 18-70 years of age, with chronic alcohol intake.
- Patients in whom serum aspartate transaminase (AST) and alanine transaminase (ALT) were typically elevated to a level of 2-6 times the upper limit of normal, patients who tested negative for human immunodeficiency virus (HIV), hepatitis B and C.
- Female patients who tested negative for pregnancy (up to 2 weeks prior to the study), were included.

Patients who were excluded from the study included:

- Those who had liver disease with a cause different from that of alcohol-induced liver disease.
- Patients who were suffering with hepatic failure, hepatic cirrhosis, Wilson's disease, malignant tumor, serious metabolic disease, severe renal disease, severe pulmonary disease, severe cardiovascular disease, severe nervous disease/psychiatric disorder and muscular disorders.
- Pregnant or lactating women.
- Patients with comorbidities, reduced life expectancy, patients known to be dependent on drugs and patients with any known hypersensitivity or allergy to any component of the drugs involved in the study.
- Patients who were on medications that may affect treatment such as colchicine, penicillamine, corticosteroids, ursodeoxycholic acid, pentoxifylline, long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), statins, neuroleptics, anticonvulsant medications, high-dose acetaminophen (>2.5 g/day).

- Patients who may have participated in recent past (past 3 months) in a clinical trial.

Eligible subjects were randomly selected via computer-generated randomization using simple randomization and were divided into Groups A and B. The study drug, polyherbal tablet (2 tablets twice-daily postprandial), was administered to Group A and silymarin tablet (70 mg twice-daily postprandial) was administered to Group B from Day 1 to Day 56 at the specified time of the day. The drugs were provided to the patients at each visit (once in 2 weeks) along with a patient diary to monitor the compliance. The patients were reviewed on Days 14, 28, 42 and 56. Liver function test was repeated, patients were enquired of their well-being, adverse events and compliance. Patients were strictly advised not to consume alcohol throughout the study period. Counseling for alcohol abstinence was given at each visit. Further course of the treatment for the test subjects was based upon the discretion of the investigator. The reports were compiled. Continuous data was reported using the descriptive statistics using mean and standard deviation. For analyzing continuous data, Student's *t*-test followed by Mann-Whitney 'U' test and two-way analysis of variance (ANOVA) was applied. P value <0.05 was considered as statistically significant. All the statistical analysis was performed using SPSS 23.0 software.

RESULTS

All the 24 patients selected for completed the study. There were no dropouts. Complete disposition of the study participants is given in Table 1.

The efficacy of both control and test drugs was found to be similar and there was no statistically significant difference observed between the two. The efficacy was observed as an improvement in AST, ALT and TB levels from the baseline as a result of the treatment with the two drugs. Table 2 enumerates the comparison of mean percentage improvement between the control and the test group (Figs. 1 and 2).

Gastritis and loss of appetite were the two adverse events observed during the study period. None of the patients experienced nausea, vomiting, diarrhea, cardiovascular side effects or neurological side effects. Among 12 subjects in the treatment group, 4 subjects reported loss of appetite and 5 subjects reported symptoms of gastritis, which resolved on their own. Among the 12 subjects in the control group, 6 reported decrease in appetite and 8 subjects reported symptoms of gastritis, which resolved on their own. No other

Table 1. Baseline Demographic Parameters

Parameter*	Silymarin group (Control group) (n = 12)	Herbal tablet group (Test group) (n = 12)
Gender (%) male	100	100
Age	39.08 ± 7.76	36.3 ± 4.3
Body weight	76.8 ± 7.87	78.03 ± 7.04
AST level (IU)	141 ± 19.04	142.58 ± 22.73
ALT level (IU)	68.2 ± 11.09	69 ± 12.22
Total bilirubin (mg/dL)	1.8 ± 0.48	1.87 ± 0.30

*Two-way ANOVA followed by Bonferroni post-test. P value was not significant for baseline parameters.

Table 2. Comparison of Percentage Reduction in AST, ALT and Total Bilirubin Levels at Various Follow-up Visits

Parameter*	Mean (%) Improvement		P value	Significance
	Control group	Test group		
AST				
Day 14	28	34	P > 0.05	NS
Day 28	39	38	P > 0.05	NS
Day 56	38	35	P > 0.05	NS
ALT				
Day 14	28	30	P > 0.05	NS
Day 28	18	20	P > 0.05	NS
Day 56	27	30	P > 0.05	NS
TB				
Day 14	45	45	P > 0.05	NS
Day 28	10	9	P > 0.05	NS
Day 56	20	26	P > 0.05	NS

*Two-tailed student *t*-test followed by Mann-Whitney 'U' test was performed. P value < 0.05 is considered statistically significant.

NS = Not significant.

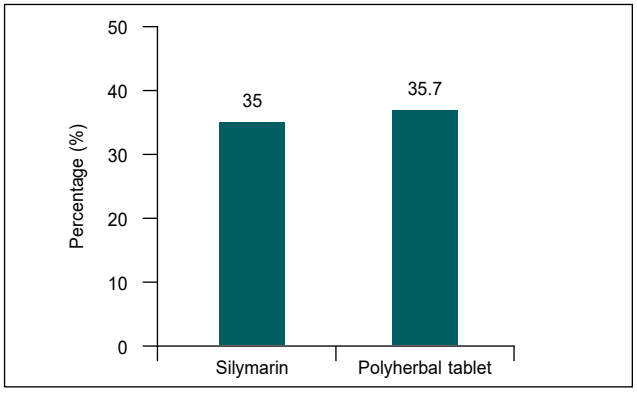

Figure 1. Comparison of mean percentage reduction in AST levels (n = 12 subjects per group).

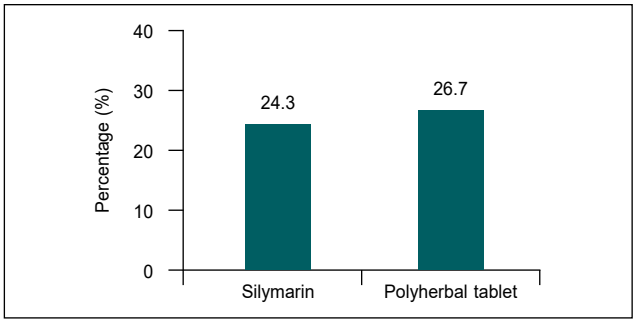

Figure 2. Comparison of mean percentage reduction in ALT levels (n = 12 subjects per group).

Table 3. Adverse Events during the Study Period

Type of adverse events	Number of subjects in control group (n = 12)	Number of subjects in test group (n = 12)
Gastritis	8	5
Nausea	0	0
Vomiting	0	0
Diarrhea	0	0
Loss of appetite	6	4
Cardiovascular side effects	0	0
Neurological side effects	0	0

serious adverse events were reported during the study period. Table 3 enumerates the adverse events recorded during the study period.

DISCUSSION

There was no significant difference between the demographic characteristics of the two groups. None of the patients showed any discomfort in the usage of the herbal tablet. As is observed from the measurement of primary outcome, there is an extremely significant improvement in the AST, ALT and TB levels on 28th day and 56th day of the treatment, both in the silymarin and herbal tablet groups. However, it is noticeable that the patients in the herbal tablet group started showing a significant reduction in AST and ALT levels in the first 14 days of the study period, which was not seen in the silymarin (control) group. A comparison of the percentage reduction in the levels of AST, ALT and TB (Table 2) showed that both silymarin and herbal tablet were equally effective, but herbal tablet demonstrated a better overall reduction in percentage values of these parameters. There was a remarkable overall improvement in the well-being of the study subjects, both in the test and the control group. But the improvement was better in the test group.

Thus, the polyherbal tablet showed a hepatoprotective action. The main component of this formulation, *R. communis* or castor plant, has shown hepatoprotective activity in previous studies done by Pingale et al[9] and Visen et al,[10] where the extract of *R. communis* leaves was used against hepatosuppression induced by carbon tetrachloride and galactosamine-induced hepatic damage, respectively. The hepatoprotective activity may be due to the important phytochemical constituents like flavonoids, saponins, glycosides, alkaloids and steroids in this herb. It was also found out that there were two active intermediate products from the herb namely, ricinine and N-demethyl-ricinine, which showed hepatoprotective activity.

The other major component, namely *P. niruri*, which originated in India, usually occurring as a winter weed throughout the hotter parts, has been shown to have hepatoprotective properties because of the presence of active phytochemicals, flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins and saponins. Extracts of this herb have been proven to have therapeutic effects in many clinical studies.[11,12] The hepatoprotective effects of other components namely *E. alba*, *A. paniculata*, *T. cordifolia*, *T. purpurea*, etc., have been proved in previous studies, by doing biochemical and histopathological assay of liver specimens.[13-15]

All the herbs included in this polyherbal formulation* have antioxidant property. The hepatoprotective activity of this polyherbal formulation* is evident from the normalization of AST, ALT and bilirubin levels. Hence, it can be postulated, that the hepatoprotective effect of these polyherbal tablets is due to the inhibitory effect of the active phytochemicals of each herb upon the free radical formation.

CONCLUSION

The results of the clinical study have shown that this polyherbal formulation* is an effective hepatoprotective drug offering comparatively better hepatoprotection as compared to silymarin. A significant reduction in the AST, ALT and TB levels was observed from 14th day onwards in the polyherbal formulation* treated group. Both the polyherbal formulation* and silymarin treatment groups showed a better reduction in the above parameters from baseline at 28th and 56th days of the treatment.

Hence, it can be concluded that these polyherbal tablets can be indicated for the management of liver dysfunction, which occurs due to alcoholic liver damage. It may also be used effectively in case of viral

hepatitis, drug-induced liver damage, as well as acute and chronic hepatitis. We can clearly say that this polyherbal formulation* is not only an effective but also a safe drug to be used in patients with alcoholic liver disease, which may be evaluated further by doing large-scale clinical studies on liver dysfunction caused due to factors other than alcoholic liver disease.

*Clearliv

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"If you have zest and enthusiasm you attract zest and enthusiasm.
Life does give back in kind."

—*Norman Vincent Peale*

"One resolution I have made, and try always to keep, is this:
To rise above the little things."

—*John Burroughs*

Fecal Calprotectin: A Novel Biomarker in the Management of Inflammatory Bowel Disease

MAYANK JAIN

ABSTRACT

Fecal calprotectin (FC) is extensively used in Gastroenterology practice as a noninvasive marker to differentiate between inflammatory bowel disease (IBD) and functional disorders. It has been found to be useful in noninvasively assessing mucosal healing, monitoring treatment and predicting relapse, though, the optimal cut-offs are yet unclear. FC may help in predicting the postoperative recurrence and pouchitis. The role of FC in other colonic disorders is unclear and needs to be explored further. The present review highlights the literature regarding the use of FC in the management of IBD.

Keywords: Fecal calprotectin, inflammatory bowel disease, noninvasive marker

Fecal calprotectin (FC) is extensively used in Gastroenterology practice as a noninvasive marker to differentiate between inflammatory bowel disease (IBD) and functional disorders. Calprotectin is a 36 kDa calcium- and zinc-binding protein, constituting nearly 60% of soluble proteins in the cytoplasm of granulocytes. It is resistant to heat and proteolysis. The functions of this protein include competitive inhibition of zinc-dependent enzymes, biostatic activity against microbes by means of chelation of zinc ions, induction of apoptosis in malignant cells and regulation of inflammatory process.

METHODS OF ESTIMATION OF FC

FC can be measured qualitatively as well as quantitatively. It has been noted that the qualitative correlation among the methods from different manufacturers is good, whereas, quantitative agreement is poor, which means that the result of one method cannot be replaced by the result of another. Different methods like enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassays (CLIA), fluoro enzyme immunoassays (FEIA) and particle-enhanced turbidimetric immunoassays (PETIA) have been used for quantitative measurement of FC. Based on the variety of tests available, varied cut-offs have been suggested in literature. Initially, a cut-off value of 50 μg/g of FC was adopted for adults and children over 4 years to differentiate IBD from other forms of inflammation. Lin et al also suggested that 50 μg/g may be considered as a screening cut-off value for further endoscopy examination, with specificity of 60% and sensitivity of 92%.

However, an expert panel pointed out that values 100 μg/g would lead to greater diagnostic precision. D'Haens et al proposed a FC cut-off of 250 μg/g for indicating IBD remission and this has been further recommended in a meta-analysis. A cut-off of 1,000 μg/g has been proposed for monitoring response to therapy in patients with severe active IBD. In pediatric patients, the optimal FC cut-offs to differentiate active from inactive IBD have been reported to range from 400 to 800 μg/g, based on the method used for estimation. A study from Mumbai noted that in patients with ulcerative colitis (UC) with inflammation, FC >200 μg/g is more often positive than raised erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and it correlates with clinical and endoscopic activity but not with disease extent. FC level >800 μg/g can be used to differentiate active from inactive UC.

FACTORS INFLUENCING THE LEVELS OF FC

Factors likely to influence the levels of FC include colonic cleansing, age, diet, exercise and the fecal

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amount of mucus or blood in stools. FC remains stable up to 7 days and hence, the test should be done within 7 days, preferably within 3 days. Moreover, day-to-day variation has been reported. Hence, decision-making based on single quantitative FC levels, and without clinical and endoscopic correlation is not advisable. In a country like India, where gastrointestinal infections are rampant, one needs to be cautious in using FC for diagnostic purposes.

USES OF FC IN CLINICAL PRACTICE IN IBD

Diagnostic

FC has adequate sensitivity and specificity to identify patients most likely to have organic bowel disease. FC is currently the most widely used fecal marker for the same as it is highly accurate in ruling out intestinal inflammation both in primary and secondary care. Waugh et al undertook a systematic study to evaluate the role of FC testing for distinguishing between IBDs and non-IBDs. In adults, at a cut-off level of 50 μg/g, FC showed sensitivity of 93% (83-100%), while the specificity ranged between 60% and 100% with a pooled value of 94%. In pediatric patients, at the same cut-off, sensitivity and specificity ranged from 95% to 100% and from 44% to 93%, respectively. Chang et al reported significantly higher FC values in IBD than in irritable bowel syndrome (IBS) and healthy controls. Caviglia et al found sensitivity and negative predictive value (NPV) of 100% and specificity and positive predictive value (PPV) of 52.4% and 70.6%, respectively for differentiating between patients with and without intestinal inflammation. Similar results were reported by Banerjee et al.

Assessing Disease Activity and Response to Treatment

The aim of the treatment of IBD is to achieve mucosal healing. FC helps to noninvasively identify the same. Though most gastroenterologists managing IBD cases follow clinical and symptom-based approach in treating these cases, it has been documented that many IBD patients in clinical remission still have subclinical mucosal inflammation. FC correlates with clinical activity evaluated either by Sutherland criteria or Partial Mayo Score. Studies have shown that FC concentrations of >50 μg/g are useful to discriminate patients with active UC, inactive UC and controls. Moreover, FC assessment after 3 months of the initial treatment can predict the clinical course of UC patients after 3 years of follow-up.

FC is the most promising noninvasive marker for assessing mucosal inflammation. D'Haens et al reported that FC had a significant correlation with endoscopic disease scores in both Crohn's disease (CD) and UC. In UC, FC levels reflect the degree of inflammation rather than the disease extent. However, FC has been significantly related to symptom scores in UC, but not in CD. In CD, a significant correlation with endoscopic activity has been reported both in colonic and in small bowel CD, as well as with capsule endoscopy. In a prospective study on 58 pediatric patients, FC proved to be the most accurate tool to detect active mucosal inflammation compared to clinical scores and serum markers. Zittan et al confirmed that FC could predict histological remission with a cut-off of 100 μg/g. It has been reported that low FC levels are closely linked with mucosal healing.

In clinical practice, "Treat-to-Target" represents the most important strategy for therapy adjustment. Monitoring of treatment thus assumes great importance. A study by Wagner et al noted that in patients with complete response to therapy, there was a significant decline in FC levels after 4 weeks. The same was not observed in partial or nonresponders. In children with active disease treated with steroids, FC levels showed a decline with clinical improvement. FC also has a role in assessing the response to biologic therapy. Molander et al demonstrated that FC <100 μg/g after induction therapy with anti-TNF-α predicted sustained clinical remission in the majority of patients. De Vos et al reported that two consecutive FC measurements >300 μg/g are more specific than a single assessment for predicting relapse in UC patients under maintenance treatment with infliximab.

The diagnostic accuracy of FC seems to be higher in predicting persistence of endoscopic lesions than clinical remission. Both in monitoring of therapy and in prediction of relapses, FC seems to be more effective in UC than in CD. In severe acute colitis, FC evaluation could be helpful in timely prediction of clinical course. FC has been reported to be higher in patients requiring colectomy, suggesting that FC in patients with severe acute colitis should be included as a prognostic criteria. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) recommendations and control management on Crohn's disease (CALM) study have defined FC as an adjunctive target in IBD patients. It may be used to define remission with clinical and endoscopic response and may also guide to escalation of therapy if levels are higher than 250.

Postoperative Disease Recurrence

FC has also been evaluated as an easy, quick and cheap tool for the early diagnosis of postoperative recurrence or pouchitis. Orlando et al prospectively evaluated 50 CD patients who had undergone surgery. FC value >200 μg/g within 3 months showed 63% sensitivity and 75% specificity in predicting endoscopic recurrence at 1 year. However, the optimal cut-off value of FC as a surrogate marker of postoperative recurrence needs to be standardized.

Pouchitis

Thomas et al reported significantly increased FC levels in all patients with endoscopic and histologic evidence of pouch inflammation compared with those without it. The findings were confirmed in adults and pediatric patients.

Prognostic Significance

A rising FC can predict an imminent clinical relapse of IBD allowing prompt initiation of treatment. FC has been used to determine relapse of IBD as well. Tibble et al suggested that a high FC concentration could identify those IBD patients in remission who were at risk of early relapse. This was validated in another study which showed 14-fold increase in the relapse risk in patients with UC and a twofold increase in CD patients in clinical remission with FC concentration >150 μg/g. In asymptomatic patients with IBD, Heida et al found that increase of FC levels correlated with increased probability of relapse within 3 months. In patients under maintenance therapy with infliximab, levels >160 μg/g were related to probability of relapse higher than 60% over the following 8 weeks. The ideal FC threshold for monitoring disease relapse is still waiting to be defined.

Other Diseases where FC may have a Role

Gastrointestinal tract malignancy especially colorectal cancer may have high FC levels. Similar higher levels have been noted in nonsteroidal anti-inflammatory drug (NSAID) enteropathy, infectious gastroenteritis, diverticular diseases and necrotizing enterocolitis in neonates.

CONCLUSION

FC is a novel biomarker that helps to differentiate IBD from functional diseases. It has been found to be useful in noninvasively assessing mucosal healing, monitoring treatment and predicting relapse; though, the optimal cut-offs are yet unclear. FC may help in predicting the postoperative recurrence and pouchitis. The role of FC in other colonic disorders is unclear and needs to be explored further.

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■■■■

Abnormal SpO_2

- At sea level, resting oxygen saturation ≤95% or exercise desaturation of ≥5% is abnormal.
- Resting oxygen saturation of 95% could be abnormal if a patient previously had a resting oxygen saturation of 99%.
- SpO_2 should stay >92% on exercise.
- Oxygen desaturation is a frequent consequence of apnea and hypopnea.
- Oxygen desaturation index (ODI) is the number of times that the oxygen saturation drops from baseline by more than 3% points (ODI 3%) or, more commonly, 4% points (ODI 4%) per hour of sleep or percent time and/or number of minutes less than 90% saturation during sleep or during the entire recording.

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Role of Neutrophil/Lymphocyte Ratio as a Severity Indicator in Patients with Acute Ischemic Stroke and Comparison with National Institutes of Health Stroke Scale

MONIKA MAHESHWARI*, SONAM GUPTA†

ABSTRACT

Introduction: Stroke is one of the leading causes of disability in the world. There is no simple laboratory marker available for assessing the severity of stroke. We studied neutrophil/lymphocyte (N/L) ratio as an indicator of stroke severity and compared it with National Institutes of Health Stroke Scale (NIHSS), used as the gold standard marker for assessing severity of stroke. **Material and methods:** A cross-sectional study was conducted taking 100 subjects fulfilling inclusion and exclusion criteria of the study. N/L ratio was calculated using standard techniques. **Observations:** Patients with moderate stroke had higher N/L ratio than those with mild stroke (p = 0.004). **Conclusion:** N/L ratio can be used as a simple, calculative laboratory marker for assessing the severity of stroke.

Keywords: Stroke, N/L ratio, severity, ischemic stroke

The World Health Organization (WHO) defines stroke as a clinical syndrome consisting of rapidly developing signs of focal or global (in case of coma) disturbance of cerebral functions lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin.

Stroke is more disabling than fatal. Approximately 20 million people each year suffer from stroke and out of these, 5 million will not survive after stroke. Projections show that by 2030, stroke prevalence will increase by more than 20% than in 2012. There is no simple laboratory maker to predict stroke severity.

AIMS AND OBJECTIVE

To study the changes in neutrophil/lymphocyte (N/L) ratio in patients of acute ischemic stroke and to compare the efficacy of N/L ratio as a marker of severity in comparison with National Institutes of Health Stroke Scale (NIHSS).

OBSERVATIONS AND RESULTS

A total of 100 subjects were included in our study, out of which 70% were females and 30% were males. Nearly 51% were >60 years of age and 49% were <60 years of age (Table 1). Severity of stroke according to NIHSS score was mild (0-7) in 24% patients, moderate (8-14) in 41% patients and severe (>14) in 35% patients (Table 2). A significant difference in N/L ratio was found in studied stroke patients. Patients with moderate stroke had higher N/L ratio than those with mild stroke (p = 0.004). P value for mild vs. moderate was 0.463, for mild vs. severe was 0.001 (significant) and moderate vs. severe was 0.025 (significant) (Table 3 and Fig. 1).

Table 1. Age and Sex Distribution of Study Subjects

Age group (years)	Male		Female		Total	
	N	%	N	%	N	%
21-40	2	6.7	6	8.6	8	8
41-60	2	6.7	39	55.7	41	41
>60	26	86.6	25	35.7	51	51
Total	**30**	**30**	**70**	**70**	**100**	**100**

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Table 2. Severity of Stroke According to NIHSS Score

Severity	NIHSS	N	Percentage (%)
Mild	0-7	24	24
Moderate	8-14	41	41
Severe	>14	35	35
Total		**100**	**100**

Table 3. N/L Ratio in Relation to Severity of Stroke

Severity	N	Mean	SD	P value
Mild	24	6.5	3.8	
Moderate	41	7.2	5.1	0.004 (S)
Severe	35	10.5	5.6	
Multiple comparison	**Mild vs. moderate**		**Mild vs. severe**	**Moderate vs. severe**
P value	0.463		0.001 (S)	0.025 (S)

SD = Standard deviation; S = Significant

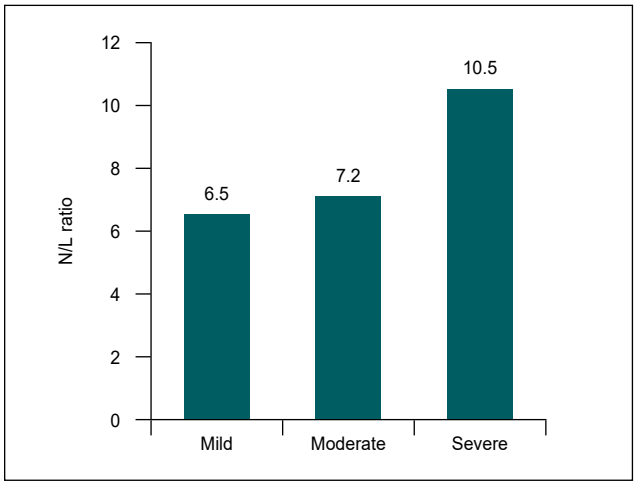

Figure 1. N/L ratio in relation to severity of stroke.

DISCUSSION

The NIHSS (Table 4) which measures neurological function in stroke patients, has been well validated and is commonly used in both the clinical and research settings. However, this score involves use of 15 different individual clinical parameters for patient's clinical status assessment, which is cumbersome and time consuming especially in emergent situations. Secondly, being subjective, it is entirely a clinical parameter based score, and it's validity and objectivity is further limited.

In stroke patients, a rise in total peripheral leukocyte count in the first 72 hours after stroke onset is associated with larger final infarct volumes on computed tomography (CT) and magnetic resonance imaging (MRI) and increase stroke severity. Experimental models of stroke have shown that within minutes of the onset of focal ischemia, there is activation of microglia followed by increased trafficking of leukocytes into the ischemic territory. Neutrophils are the earliest leukocyte subtype to show substantial upregulation in gene expression and to infiltrate areas of brain ischemia. Early neutrophil activation has been implicated in the potentiation of post-ischemic brain injury, and animal stroke models have suggested that depleting circulating neutrophils either before or at the onset of stroke reduces the size of infarction. Hence, N/L ratio could be an alternative and easy, approachable and calculative option in comparison to several other cumbersome scoring systems used to quantify the degree of severity of stroke like Glasgow Coma Scale, Canadian Neurological Scale, Scandinavian Stroke Scale and NIHSS.

In our study, a significant association was found between severity of stroke according to NIHSS criteria and N/L ratio (p = 0.004). Xue et al conducted a study which aimed to assess N/L ratio as a prognostic marker in acute ischemic stroke. A total of 280 patients with acute ischemic stroke were included in the study. Patients were divided into 3 groups according to the N/L ratio value (<2, 2-3 and >3). Demographic, clinical and laboratory data were accumulated for all patients. After adjustment for potential confounders, N/L ratio was associated with an increased risk of stroke severity on admission (odds ratio [OR] 1.364, 95% confidence interval [CI] 1.101-1.690, p = 0.005) and primary unfavorable outcome (OR 1.455, 95% CI 1.083-1.956, p = 0.013). After a median of 1.13 years (interquartile range 0.91-1.42) of follow-up, N/L ratio was associated with recurrent ischemic stroke after adjustment (hazard ratio 1.499, 95% CI 1.161-1.935, p = 0.002). The findings were in corroboration with our study. Yu et al also conducted a study to investigate whether N/L ratio is associated with early clinical outcomes in patients with acute ischemic stroke. Data were collected from a tertiary hospital's stroke registry including admitted patients with a first-ever acute ischemic stroke within 72 hours of onset. White blood cell counts and peripheral differential counts were measured on admission. Early clinical outcomes were in-hospital mortality and disability at discharge assessed by the modified Rankin Scale (mRS). Among 1,131 stroke patients, 454 patients were included and classified into tertile groups based on N/L ratio on admission. Patients in higher tertiles of N/L ratio were likely to have severe neurologic deficit

Table 4. National Institutes of Health Stroke Scale

Response	Score	Response	Score
Level of consciousness	Alert = 0	**Motor arm (Left and Right)**	No drift = 0
	Drowsy = 1		Drift before 10 sec = 1
	Stuporous = 2		Falls before 10 sec = 2
	Coma = 3		No effort against gravity = 3
			No movement = 4
Level of consciousness questions	Answers both correctly = 0	**Motor leg (Left and Right)**	No drift = 0
How old are you?	Answers one correctly = 1		Drift before 5-10 sec = 1
What month is this?	Answers both incorrect = 2		Falls before 5-10 sec = 2
			No effort against gravity = 3
			No movement = 4
Level of consciousness commands	Performs both correctly = 0	**Limb ataxia**	Absent = 0
Squeeze my hand (using nonparetic hand)	Performs one correctly = 1		Present in one limb = 1
Close your eyes	Performs neither = 2		Present in two limbs = 2
Pupillary response	Both reactive = 0	**Sensory**	Normal = 0
	One reactive = 1		Mild = 1
	Neither reactive = 2		Severe loss = 2
Gaze	Normal = 0	**Language**	Normal = 0
	Partial gaze palsy = 1		Mild aphasia = 1
	Total gaze palsy = 2		Severe aphasia = 2
			Mute/Global aphasia = 3
Visual field	No visual loss = 0	**Facial palsy**	Normal = 0
	Partial hemianopsia = 1		Minor = 1
	Complete hemianopsia = 2		Partial = 2
	Bilateral hemianopsia = 3		Complete = 3
Dysarthria	Normal = 0	**Extinction and inattention**	Normal = 0
	Mild = 1		Mild = 1
	Severe = 2		Severe = 2

Maximum score - 42.

Source: Goldszmidt AJ, Caplan LR. Thrombolytic therapy for acute ischemic stroke (Chap. 3). In: Stroke Essentials. 2 nd Edition, Jones and Bartlett Publishers; Sudbury, Massachusetts; 2010. p. 33.

at discharge. Higher N/L ratio tertiles were associated with an unfavorable shift of mRS score ($p < 0.0001$). This association remained significant after adjustment for clinical and laboratory variables including age, sex, hypertension, hypercholesterolemia, atrial fibrillation, stroke severity and glucose level ($p = 0.032$ for trend). Celikbilek et al conducted a study which aimed to analyze the predictive ability of N/L ratio in acute ischemic cerebrovascular disease. In all, 190 patients including 70 patients with first-ever atherothrombotic acute ischemic stroke (AAIS), 50 patients with transient ischemic attack and 70 healthy subjects were enrolled in this study. N/L ratio was found to increase significantly in AAIS patients than the controls ($p < 0.001$). In addition, N/L ratio values were found to increase significantly in dead patients ($p = 0.029$). A cut-off value of 4.1 for N/L ratio was detected in predicting mortality with a sensitivity of 66.7% and a specificity of 74.1% ($\kappa = 0.299$, $p = 0.006$). These findings also support the role of N/L ratio as a simple, inexpensive and readily available marker of prognosis in acute ischemic stroke, as we found in our study.

CONCLUSION

Our study indicates that N/L ratio can be used as a simple laboratory marker for assessing the severity of stroke and prognosis in patients with acute ischemic stroke.

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Every citizen of India should have the right to accessible, affordable, quality and safe heart care irrespective of his/her economical background

HEART CARE FOUNDATION OF INDIA
A Not-For-Profit Organisation

Sameer Malik Heart Care Foundation Fund

An Initiative of Heart Care Foundation of India

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"No one should die of heart disease just because he/she cannot afford it"

About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

Donate Now...

About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

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This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.

http://heartcarefoundationfund.heartcarefoundation.org

Protein S Deficiency in a Patient with Bad Obstetric History

VANASHRI UDAY KARGAR*, UDAY M KARGAR†

ABSTRACT

Protein S deficiency is uncommon. It may cause recurrent thrombosis and may complicate pregnancy. A patient with protein S deficiency presented with bad obstetric history of two blighted ovum and then had a successful pregnancy, managed with anticoagulation and close fetal monitoring. Anticoagulation therapy is the cornerstone in the management of patients with inherited coagulation defects.

Keywords: Protein S deficiency, blighted ovum, thromboprophylaxis, anticoagulation, thrombophilia

Acquired or hereditary thrombophilia occurs in almost two-thirds of women presenting with recurrent miscarriages, pre-eclampsia, intrauterine growth retardation, abruptio placentae or stillbirth, which are associated with microvascular thrombosis in placental blood vessels. Protein S deficiency is associated with a variably increased risk of thrombosis and is inherited independently in an autosomal dominant trait. Here we report such a case with protein S deficiency with a successful maternal and fetal outcome.

CASE REPORT

A 27-year-old woman, Gravida 3, with history of two blighted ovum in the past, presented in April 2016 for preconceptional counseling. Her first pregnancy in 2015 was spontaneous conception that ended in blighted ovum (8-9 weeks). She underwent curettage. Her second pregnancy in January 2016 was again spontaneous conception that again ended in blighted ovum (9-10 weeks), where yolk sac was seen but fetal pole was not developed. In both instances, patient had no other intra- or postoperative complications and was discharged on contraceptive advice. Investigations carried out on her during interval period revealed cytomegalovirus (CMV), herpes simplex virus (HSV) and Rubella IgG positivity in nonsignificant titers, and deficient protein S activity of 32%. Other thrombophilia screening, protein C, antithrombin III, factor V leiden levels were normal. Lupus anticoagulant (LA), anticardiolipin antibody (ACLA), antinuclear antibody (ANA), anti-double stranded DNA antibody (anti-ds-DNA), sugars, Venereal Disease Research Laboratory (VDRL) were negative, including normal parental karyotyping. The couple was advised to take hematological opinion and was counseled about autosomal dominant nature of protein S deficiency. The patient was advised periconceptional folic acid and early antenatal care (ANC) registration and thromboprophylaxis in next pregnancy.

She conceived in September 2016 and registered at the antenatal clinic where I was consulting. Her baseline complete blood count and coagulation profile were within normal limits. In view of protein S deficiency, the patient was started with low molecular weight heparin (LMWH) 60 units subcutaneous once-daily from same day when her urine pregnancy test (UPT) was found positive and aspirin 75 mg once a day after dinner, once cardiac activity was confirmed in her first scan around 6-7 weeks. The patient was monitored for symptoms of bleeding during pregnancy. Her nuchal translucency (NT) scan, combined test, anomaly scan all were normal. She was given two doses of betamethasone intramuscular around 28 weeks. Color Doppler at 32 weeks showed good interval growth with normal Doppler flows. She underwent weekly nonstress test (NST) and biophysical profile from 32 weeks onwards for antepartam fetal surveillance.

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Aspirin was stopped around 34 weeks. Doppler was again repeated around 36-37 weeks, and was normal. Elective lower segment cesarean section (LSCS) was planned at 38 weeks, and LMWH was stopped 12 hours before surgery. She delivered a male child of 3 kg with good Apgar score on 10th May 2017.

Neonate was evaluated by pediatrician and was found to be normal. Injection LMWH was restarted on the day after surgery. Warfarin 1 mg o.d. was also started. Warfarin doses were stepped up and adjusted up to 5 mg o.d. with daily monitoring of prothrombin time/international normalized ratio (PT/INR) values. Heparin was discontinued once INR levels were in the range of 2-3. The patient was advised to continue warfarin for 6 weeks after discharge.

DISCUSSION

Protein S deficiency is associated with a variably increased risk of thrombosis and is inherited independently in an autosomal dominant trait. The protein S gene is located on chromosome 3. Over 90 different mutations in protein S gene have been found.

Incidence of symptomatic protein S deficiency is 1:20000. Anticoagulant therapy is the cornerstone in the management of these patients.

The cerebrovascular system may be primarily involved in young adults suffering from anticoagulants deficiency. Considering the importance of prothrombotic state, especially caused by deficiency of protein S, any patient presenting with features of cerebrovascular accidents should be thoroughly investigated for any natural anticoagulant deficiency, in whom no other etiological factors can be determined. Hence, thrombophilia screening might be justified in women with pregnancy loss and treatment with LMWH might be considered for those with pregnancy loss and thrombophilia. Women with thrombophilia are also prone to venous thromboembolism in pregnancy and puerperium.

Many women with a history of recurrent miscarriage are at greater risk of pre-eclampsia, intrauterine growth retardation and intrauterine fetal death, which suggests that these adverse pregnancy outcomes represent a spectrum of disorders which share a common origin. Special care and precautions should be taken in postoperative period to prevent the catastrophic event of venous thromboembolism, which could lead not only to major morbidity, but also mortality.

CONCLUSION

Patients with protein S deficiency may remain asymptomatic or present with thromboembolic incidents and bad obstetric history. Anticoagulant prophylaxis should be considered weighing the risk of bleeding to thromboembolic recurrence.

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Anterior Abdominal Wall Leiomyoma

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ABSTRACT

Extrauterine leiomyomas are uncommon, generally benign and occasionally cause diagnostic dilemmas as they can mimic malignancy. Anterior abdominal wall leiomyoma is a rare finding and there are very few reported cases of primary abdominal wall leiomyoma without previous uterine surgeries or concomitant presence of uterine fibroids. We present a case report of a 24-year-old female, parity 2 live birth 2, both normal vaginal deliveries. She presented to the Gynecology OPD with history of lump in left lower abdomen for the last 1½ months. Patient underwent exploratory laparotomy. Intraoperatively, a huge anterior abdominal wall fibroid was seen on incising anterior rectus sheath. The mass was removed and dead space was closed primarily. Abdominal wall fibroid is a good differential diagnosis to be considered in any woman of reproductive age with an anterior abdominal wall mass even without any history of previous uterine surgery.

Keywords: Leiomyoma, anterior abdominal wall, surgery, fibroid

Leiomyoma is the commonest benign tumor of the reproductive tract and is found in 20% of women of reproductive age.[1] The commonest site is the uterus, but they are also found in the broad ligament, ovaries, vagina and rarely in the anterior abdominal wall.[1-5] Abdominal wall fibroids are an uncommon finding and are thought to follow seeding following surgical resection of uterine fibroids.[4,6,7] With the advent of laparoscopic myomectomies, more cases of abdominal wall fibroids are now being reported. Anterior abdominal wall leiomyomas are a rare finding and there are very few reported cases of primary abdominal wall leiomyoma without previous uterine surgeries or concomitant presence of uterine fibroids.[8]

The common primary diseases of the rectus muscle sheath are desmoid tumor and hematoma. Secondary disorders of the rectus muscle sheath are abscesses from diverticulitis, perforated sigmoid carcinoma, gallbladder empyema and disseminated actinomycosis.[9] Leiomyoma of rectus muscle sheath is extremely rare. We present an interesting case of primary solitary leiomyoma of the anterior abdominal wall in a 24-year-old patient with no previous history of any uterine surgery.

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CASE REPORT

We present a case report of a 24-year-old female, parity 2 live birth 2. She presented to the Gynecology OPD with history of lump in left lower abdomen, which she noticed for the last 1½ months after her last child birth. It was not associated with pain and any menstrual disturbances. Her both live births were by normal vaginal delivery and there was no history of any previous surgeries. Her general physical and systemic examinations were within normal limits.

On local per abdomen examination, a lump of 20 × 20 cm occupying upper left half of abdomen was found. It was firm, nontender, oval, smooth, with well-defined margins and slightly restricted mobility. Her hematological and routine investigations were within normal limits. Ultrasound examination showed that the uterus was bulky with large fibroid of 10 × 9 cm arising from fundus of uterus and bilateral ovaries were normal. A working provisional diagnosis of broad ligament fibroid or ovarian mass was made. The patient was taken for exploratory laparotomy with all risks explained. The patient was opened by a left paramedian incision, which was extended above umbilicus. On incising the anterior rectus sheath, the tumor was found adhered below it and in fact the incision of rectus sheath could be seen incising the tumor capsule. It was meticulously enucleated along its entire surface. A fibroma of around 18 × 18 cm size, firm well-circumscribed was seen (Fig. 1). The tumor

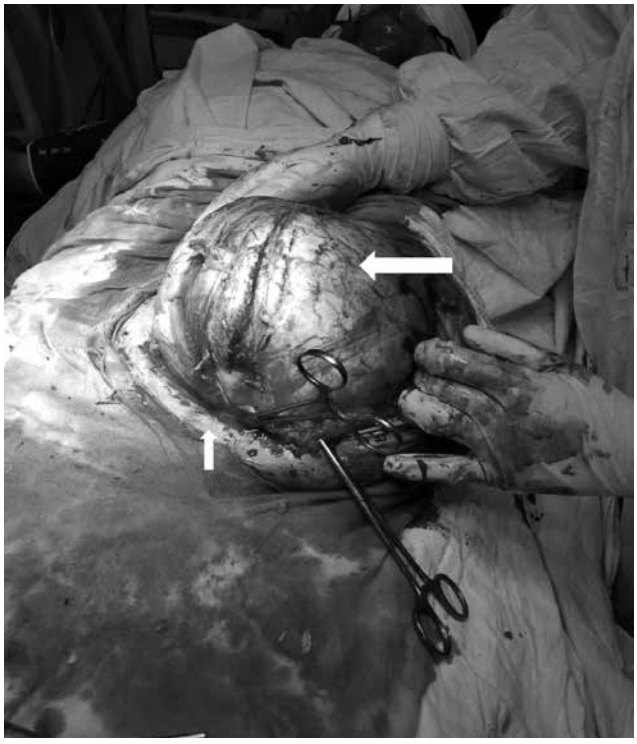

Figure 1. Intraoperative picture showing leiomyoma with large arrow and anterior abdominal wall with small arrow.

had extended into left lateral wall, flattening the rectus abdominis muscle beneath and into subcutaneous plane. A huge dead space was left after excising the tumor and hemostasis was achieved. Surprisingly, the amount of bleeding was very less as compared to fibroid. The mass was excised completely and the defect was closed primarily. The peritoneal cavity was carefully inspected. There was no intra-abdominal collection and no other mass. Uterus and bilateral ovaries were normal. The mass was not connected to any intraperitoneal contents. Layered closure of dead space was done with an intra-abdominal drain *in situ*. Abdominal wall was closed in layers. The mass weighed 3 kg, the cut section resembled whorled appearance, typical of fibroid with hemorrhage in between (Fig. 2).

A diagnosis of primary abdominal wall leiomyoma below anterior rectus sheath was made. Sample was sent for histopathological examination. Her postoperative period was uneventful. She was doing well on 3-month follow-up. Histopathology report of the section examined showed a well-encapsulated tissue i.e., leiomyoma with secondary changes.

DISCUSSION

The common primary diseases of the rectus muscle sheath are desmoids tumor and hematoma. Secondary

Figure 2. Gross sample showing leiomyoma of anterior abdominal wall.

disorders of the rectus muscle sheath are abscesses from diverticulitis, perforated sigmoid carcinoma and disseminated actinomycosis. Leiomyoma of rectus muscle sheath is extremely rare. There can be primary or parasitic leiomyoma. Parasitic leiomyomas have been reported in the retro- or pre-peritoneum. The uterine leiomyoma becomes adherent to these structures, develops its own blood supply from the surrounding structures and gradually loses its attachment with the uterus, thus developing as a parasite at the new location.[10] However, the exact origin of primary leiomyoma is not clear. Leiomyomas originate from smooth muscle cells of the uterus and from intestine or vessel wall rarely. It has been postulated that transformation of these cells in anterior abdominal layer to leiomyoma occurs probably due to somatic mutations and interplay of hormonal and growth factors.[10] The diagnosis of primary leiomyoma of the anterior abdominal wall can be made only when there is no antecedent history of abdominal surgery, open or laparoscopic, ever.[10] Primary anterior wall leiomyoma has been reported without any concomitant tumors elsewhere in the abdomen or any antecedent history of abdominal or pelvic surgery.[11]

On histopathology, somatic leiomyomas present as localized masses, and tend to be much larger than those of skin. Since they present few symptoms, they are discovered relatively late. On gross examination, they are well defined with a fibrous pseudo-capsule. Histologically, they lack atypia, necrosis and are mitotically inactive (<1 mitosis/50 high power field).[12] The tumor must be carefully removed en bloc while

minimizing spillage of tumor cells to prevent recurrence. Synthetic mesh can be used to cover large defects following tumor extrication.[11]

This case is remarkable as there is no history of any previous surgery, no menstrual irregularities and the patient is of young age group, i.e., <30 years with no history of hormonal intake or contraceptive use.

CONCLUSION

Anterior abdominal wall fibroid is a good differential diagnosis to be considered in any woman of reproductive age group with anterior abdominal mass with no history of previous surgery. It can occur without any concomitant tumor elsewhere in the abdomen.

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Prophylactic Effect of Topical Besifloxacin and Moxifloxacin on the Bacterial Conjunctival Flora Before and After Intraocular Surgery

SHAIK MOHAMMAD ZAKIR*, ABHISHEK AGRAWAL†, SAIYID N ASKARI‡, SHAMIM AHMAD§

ABSTRACT

Aim: To study bacterial conjunctival flora before and after topical moxifloxacin or besifloxacin used as prophylactic agent in intraocular surgeries. **Settings and design:** Prospective randomized study. **Material and methods:** Conjunctival swabs of 100 patients undergoing intraocular surgeries were collected 2 days before the surgery without prior antibiotic use and inoculated on culture media for culture and antibiotic sensitivity tests. Patients were randomized into two groups (50 each). Patients of Group A and Group B received topical moxifloxacin 0.5% and besifloxacin 0.6% eye drop, respectively, to the assigned eye 6 hourly. Postoperatively, antibiotic eye drops were instilled 4 hourly for 10 days and then stopped. Topical anti-inflammatory and steroid drugs were continued for 6 weeks. Conjunctival swabs were repeated from operated eyes 20 and 40 days postoperatively. Statistical analysis was done using Chi-square and McNemar's tests. **Results:** Bacterial growth appeared in 27 cases (most commonly *Staphylococcus epidermidis* 51.85%) - 16 in Group A and 11 in Group B - and none of the isolate showed resistance to the assigned antibiotic. **Conclusions:** The antibacterial efficacy of topical moxifloxacin and besifloxacin in preventing postoperative infections is similar; hence, both may be equally effective for prophylaxis in intraocular surgeries.

Keywords: Conjunctival flora, moxifloxacin, besifloxacin, intraocular surgeries, prophylaxis

The term "normal conjunctival flora" refers to microorganisms that dwell within the eyes of healthy individuals. Predominant isolates recovered from the normal adult conjunctiva are *Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus* nonhemolytic and *Propionibacterium acnes*.

The knowledge of these organisms and their antibiotic sensitivity/resistance provides a better guide in choosing an appropriate antibiotic for prophylaxis of postoperative infections for which topical fluoroquinolones are commonly used. Due to antibiotic resistance, proper selection of antibiotic remains a challenge for ophthalmologists.

The present study was planned to ascertain normal conjunctival flora and its sensitivity/resistance to the new fourth-generation fluoroquinolones viz. moxifloxacin and besifloxacin.

MATERIAL AND METHODS

This prospective randomized study was conducted on 100 eyes of 100 patients who presented at Eye OPD in our institution from February 2014 to August 2015 for treatment of diseases requiring intraocular surgeries. The details of the procedures were explained to all the patients in their language and written consent was obtained. Ethical clearance for the study was granted by the Institutional Ethics Committee.

Patients with hypersensitivity to moxifloxacin and besifloxacin or any of the ingredients in the study medications were excluded from this study. Patients who had used any topical antibiotic drops 3 months prior to culture, taken systemic antibiotics 1 month before and during the study period, neonates, infants, pregnant and lactating females were also excluded.

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Moxifloxacin ophthalmic solution and besifloxacin ophthalmic suspension were used for the study.

After taking first preoperative conjunctival swab from the study eye, patients were randomly divided in two groups, A and B, with 50 patients each. Patients of Group A (Moxifloxacin Group) received topical moxifloxacin 0.5% eye drops and patients of Group B (Besifloxacin Group) received topical besifloxacin 0.6% eye drops to the assigned eye 6 hourly for 2 days preoperatively and continued postoperatively every 4 hours for 10 days, and then stopped. Topical anti-inflammatory and steroid eye drops were started from first postoperative day for 6 weeks. Conjunctival swabs were repeated from the operated eyes 20 and 40 days postoperatively and inoculated on culture media to look for bacterial growth.

Sterile cotton swabs with polypropylene stick were used for obtaining conjunctival swab from the eyes of patients. The swabs were inoculated on Blood Agar and Chocolate Agar and incubated at 37°C overnight. Positive cultures were processed for identification of organisms by studying Gram-staining, colony characteristics and several biochemical tests. Later on, antibiotic sensitivity was assessed for moxifloxacin using the commercially available disc containing 5 μg of the drug. Antibiotic discs of besifloxacin are not available commercially, and the sensitivity was assessed using self-made discs of sterile Whatman No. 41 filter paper of 5 mm diameter and eye drop besifloxacin 0.6%, finally achieving a concentration of 10 μg/disc. Antibiotic sensitivity testing was done by the Standard Disc Diffusion method described by Bauer et al (1966).

The results were analyzed statistically using Chi-square and McNemar's tests.

RESULTS

A total of 100 eyes of 100 patients (62 males and 38 females) were included in the study; majority (68%) were between the ages of 51 and 70 years. Maximum number of patients (85/100) underwent manual small incision cataract surgery (MSICS) with posterior chamber intraocular lens (PCIOL) implantation. Nine patients underwent trabeculectomy and 6 patients had combined trabeculectomy with MSICS with PCIOL implantation. Conjunctival swabs were obtained from 100 eyes (50 in moxifloxacin and 50 in besifloxacin group) and inoculated on bacterial culture media. Twenty-seven swabs yielded growth of bacteria (positive cultures) with no statistically significant difference between males and females as shown in Table 1.

The results of the study indicated higher positive cultures occurring in early summer season and also slightly higher in older patients (more than 50 years of age), although the difference was statistically insignificant. Out of 27 positive cultures, 23 (85.2%) cases were patients with mature and immature age-related cataract, 2 (7.4%) cases were with primary open-angle glaucoma and other 2 (7.4%) with co-existing cataract and glaucoma. The association of various diagnoses with positive conjunctival culture was statistically insignificant (p = 0.893). In our study, the most common organisms isolated were *S. epidermidis* (51.85%), *S. aureus* (29.63%), followed by *Streptococcus pyogenes* (11.11%) and *Corynebacterium xerosis* (7.41%) as shown in Table 2.

The intraocular surgery of the patients showing bacterial growth on culture plates was postponed and the designated antibiotic was continued for 5 days. Conjunctival swabs were obtained after a week of drug-free period and at this time, there was no bacterial growth in any of the 27 patients as the organisms were sensitive and therefore eliminated from the conjunctival sac. The same antibiotics were restarted 2 days before the surgery and rest of the procedure was followed as described for other patients. None of the patients included in the study developed postoperative endophthalmitis. The inhibition of bacterial growth was 100% in both the groups viz. moxifloxacin and besifloxacin and all the laboratory cultures showed no bacterial growth on second and third visits, revealing the sensitivity of organisms to be almost similar to both the test antibiotic eye drops as shown in Tables 3 and 4.

Table 1. Gender-wise Distribution of Positive Cultures among Patients

Gender	Positive culture n (%)	Negative culture n (%)	Total n (%)
Male	16 (25.81)	46 (74.19)	**62 (100)**
Female	11 (28.95)	27 (71.05)	**38 (100)**
Total	**27 (27)**	**73 (73)**	**100 (100)**
	$\chi^2 = 0.118$, df = 1, p = 0.731		

Table 2. Occurrence and Distribution of Isolated Organisms

Operated eyes	Total No. of eyes	Positive culture	Organisms isolated							
			SE		SA		SP		CX	
			No.	%	No.	%	No.	%	No.	%
RE	56	15	07	46.67	05	33.33	02	13.33	01	6.67
LE	44	12	07	58.33	03	25	01	8.33	01	8.33
Total	**100**	**27**	**14**	**51.85**	**08**	**29.63**	**03**	**11.11**	**02**	**7.41**

$\chi^2 = 0.506$, df = 3, p = 0.918

SE: *Staphylococcus epidermidis*; SA: *Staphylococcus aureus*; SP: *Streptococcus pyogenes;* CX: *Corynebacterium xerosis;* RE: Right eye; LE: Left eye.

Table 3. Group A: Effect of Topical Moxifloxacin on Bacterial Conjunctival Flora

Before use		After use			
1st Conjunctival swab (Preoperative)		2nd Conjunctival swab (Postoperative Day 20)		3rd Conjunctival swab (Postoperative Day 40)	
Positive	Negative	Positive	Negative	Positive	Negative
16	34	00	50	00	50

McNemar's $\chi^2 = 5.78$, df = 1, p = 0.016

Table 4. Group B: Effect of Topical Besifloxacin on Bacterial Conjunctival Flora

Before use		After use			
1st Conjunctival swab (Preoperative)		2nd Conjunctival swab (Postoperative Day 20)		3rd Conjunctival swab (Postoperative Day 40)	
Positive	Negative	Positive	Negative	Positive	Negative
11	39	00	50	00	50

McNemar's $\chi^2 = 14.58$, df = 1, p < 0.001

DISCUSSION

Prevention of infections following intraocular surgeries is one of the areas of maximum concern to all ophthalmic surgeons. This is especially true because recent reports suggested that though the incidence of postoperative endophthalmitis has decreased significantly in present era, the emergence of resistance among bacterial isolates to routinely used prophylactic antibiotics is a matter of great concern for eye specialists world over. In view of the possible role of conjunctival flora in the causation of any postoperative infections following intraocular surgeries along with an emergence of multidrug-resistant organisms, an understanding of the sensitivity of such flora to appropriate antibiotics is of fundamental importance. Certainly, such type of studies might guide the ophthalmologists when using a prophylactic antibiotic before performing a surgery.

Therefore, the present study aims to assess the normal conjunctival flora and possible role of two newer fourth-generation fluoroquinolones (moxifloxacin and besifloxacin) as one of the preventive measures against postoperative infections. The study was done on 100 patients admitted for various intraocular surgeries; majority of them comprised of age-related cataract (85/100), 11 being mature and 74 being immature age-related cataracts. This is because of the fact that cataract continues to be the leading cause of ocular morbidities requiring intraocular surgeries. In the present series, majority of the admitted patients (85 out of 100) underwent MSICS with PCIOL implantation followed by trabeculectomy and combined trabeculectomy with MSICS with PCIOL implantation.

McNatt et al (1978) reported that out of the 184 eye cultures, 112 (60.9%) contained at least one microorganism. Herde et al (1996) reported that out of 686 conjunctival swab cultures, 126 (18.4%) showed bacterial growth. Our study demonstrated only 27 positive bacterial growths out of 100 cases (27%) as shown in Table 1. This variable incidence could be due to variable environmental and individual factors.

In the present study, the bacterial conjunctival flora observed was almost the same in either sex (25.81% in males and 28.95% in females) as shown in Table 1. Rao and Rao (1972) also did not observe any difference in conjunctival bacterial flora of either sex (22.5% in males and 18.2% in females). They also studied the variation of conjunctival bacterial flora in relation to weather and observed a higher rate of positive bacterial cultures during summer season. Our results too indicated higher positive cultures occurring in early summer season, highest being in the month of April. The incidence of positive bacterial culture was observed to be slightly higher in older patients (>50 years of age), although the difference was statistically insignificant. Singer et al (1988) reported similar results in their study.

There was no association of various diagnoses with positive conjunctival culture. de Kaspar et al (2004) also found no relationship between the conjunctival flora and the ocular morbidities (83% positive in eyes undergoing cataract surgery and 77% in those undergoing glaucoma surgery; p = 0.2246).

Many researchers have studied the composition of normal conjunctival flora. Nema et al (1964) found coagulase-negative staphylococci as the most common organism isolated from conjunctiva. The other isolated organisms included Diphtheroids, coagulase-positive staphylococci, streptococci, pneumococci, Gram-positive spore bearing bacilli and various Gram-negative coliform bacilli. Gritz et al (1997) isolated *S. epidermidis* in 54.8% and Diptheroids in 9.5% subjects in conjunctival swabs. In our study, we noticed *S. epidermidis* (51.85%) as the most common organism isolated from conjunctiva, followed by *S. aureus* (29.63%), *S. pyogenes* (11.11%) and *C. xerosis* (7.41%) as shown in Table 2.

A number of other studies have revealed *S. epidermidis* to be the most frequently isolated organism from the conjunctival sac. This organism, being a part of normal bacterial flora of conjunctiva remains nonpathogenic among healthy individuals but can cause severe infections in the eye, including endophthalmitis, in altered conditions. Therefore, all the conjunctival organisms, including staphylococci harbored by human conjunctiva, need attention before performing any intraocular surgery in order to prevent any postoperative infection.

O'Brien et al (2007) found that moxifloxacin had potent and rapid bactericidal activity against most of the Gram-positive pathogens causing postoperative endophthalmitis, and had excellent ocular penetration after topical administration. Scoper (2008) also reported that fourth-generation fluoroquinolones (moxifloxacin and gatifloxacin) had increased potency against Gram-positive bacteria compared with third-generation fluoroquinolones (levofloxacin), while maintaining similar potency against Gram-negative bacteria.

In our study, bacterial growth was seen in 16 preoperative conjunctival swabs in moxifloxacin group and all of these isolates were found to be sensitive to moxifloxacin on performing *in vitro* antibiotic sensitivity tests and complete eradication of bacteria, as evidenced by conjunctival swab culture, was obtained after pre- and postoperative use of this antibiotic as depicted in Table 3.

Moshirfar et al (2006) first reported 2 cases of bacterial keratitis-resistant to fourth-generation fluoroquinolones after laser *in situ* keratomileusis (LASIK) and photorefractive keratectomy (PRK). Yin et al (2013) also found that repeated use of topical moxifloxacin after intravitreal injection significantly increased antibiotic resistance of ocular surface flora and recommended not to use prophylactic antibiotics routinely after intravitreal injections. Oldenburg et al (2013) isolated 89 *Pseudomonas aeruginosa* isolates during 2007, 2008 and 2009 in "The Steroids for Corneal Ulcers Trial" (SCUT) and reported an increase in the proportion of resistant isolates to moxifloxacin from 19% in 2007 to 52% in 2009. An increase in resistance to the fourth-generation fluoroquinolones was detected for both methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) by Chang et al (2015).

In spite of reports of emergence of resistance against widely used moxifloxacin, no bacterial strain isolated in our study showed resistance to the drug. Similarly, it remained effective in the moxifloxacin receiving group as suggested by negative bacterial cultures taken 20 and 40 days postoperatively. One of the reasons for not detecting resistance to the drug might be attributed to the low prevalence of organisms with resistance to moxifloxacin in the studied population.

The other group of patients, comprising of 50 subjects undergoing various intraocular surgeries, received topical besifloxacin eye drop (0.6%). In May 2009, besifloxacin, a fluoroquinolone, was approved by the Food and Drug Administration (FDA) as a topical agent for the treatment of bacterial conjunctivitis. The results of a study conducted by Haas et al (2010) have confirmed that besifloxacin has potent *in vitro* activity against bacterial isolates including *S. aureus, S. epidermidis* and *S. pneumoniae.* Similar type of antibacterial activity against some of the isolates resistant to other fluoroquinolones was also evident

in a study that evaluated the antibacterial spectrum of besifloxacin against as much as 40 Gram-positive and Gram-negative species (Haas et al, 2009).

In our study, the prophylactic potential of besifloxacin was examined *in vitro* against only Gram-positive organisms as no Gram-negative organism could be recovered in the bacterial conjunctival flora of the patients included. All the organisms isolated from Group B patients were sensitive to besifloxacin because no bacterial growth was seen in postoperative microbiological examination as shown in Table 4. Sanders et al (2009) also demonstrated that besifloxacin was significantly more effective than gatifloxacin and moxifloxacin in reducing the number of MRSA in the rabbit cornea 16 hours after infection.

Both the fluoroquinolones under study (moxifloxacin and besifloxacin) seemed to be highly effective in *in vitro* sensitivity test conducted against all the bacterial isolates recovered from the patients undergoing various intraocular surgeries. Further, the *in vivo* use in pre- and postoperative period in the eyes of as much as 100 patients before undertaking intraocular surgeries and postoperatively at Day 20 and Day 40 revealed their effective potential as possible prophylactic agents in ophthalmic surgeries (Table 3 and 4).

CONCLUSION

On comparing the activity against the bacterial isolates, no significant difference was observed and both the antibiotics (moxifloxacin and besifloxacin) showed an effective antibacterial potential. Thus, these antibiotics can be used in ophthalmology as effective antibacterial prophylactic agents among the patients undergoing various intraocular surgeries.

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Make sure

DURING MEDICAL PRACTICE

SITUATION: A hypertensive patient at high cardiovascular risk was ACEI-intolerant.

LESSON: Make sure to remember that telmisartan significantly reduces the number of myocardial infarction (MI) in high risk hypertensive patients. Results of the TRANSCEND (Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease) trial suggest that MI may be less frequent in hypertensive patients treated with telmisartan (3.8% vs. 5.1%; $p < 0.05$). Telmisartan may also reduce new-onset of LVH and new-onset of micro- and macroalbuminuria in hypertensive patients.

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Maintaining High Quality Services and Enhancing Patient Care: Result of a Symbiotic Relationship Between MGH and TRS

The partnership between Massachusetts General Hospital (MGH) and Teleradiology Solutions is not the stereotypical overseas outsourcing business case of moving jobs to save expense. Rather, the motivation was to enhance patient care and maintain quality of service, says Gordon J Harris, PhD, Director of the MGH (Massachusetts General Hospital) 3D Imaging Service in an interview with IJCP.

PLEASE PROVIDE AN OVERVIEW OF YOUR ONGOING ENGAGEMENT WITH TELERADIOLOGY SOLUTIONS

We opened the 3D Imaging Service in the Radiology Department at Massachusetts General Hospital (MGH) in 1999 to provide image post-processing as a service for aiding radiologists and referring physicians in diagnosis and treatment planning. Our lab was one of the first of its kind and has grown to be one of the largest, processing over 130 exams per day for MGH, our affiliated imaging centers, and our Tele3D client hospitals around the country.

Our growth was in parallel with the adoption of multi-slice CT and its expanding use for procedures requiring 3D post-processing, such as CT angiography (CTA). As we grew, it became difficult to keep up with our growth in volume, and increasing needs for extended hours of coverage. In 2003, in order to provide overnight 3D post-processing, we established a collaboration with a team of radiologists and IT support staff in Bangalore, India, through an agreement with Manipal Hospital and Wipro. Together, we created a 3D lab extension to support our overnight and weekend 3D needs. We went live with the India team in 2004 after 6-9 months of extensive daily training and review of cases led by our 3D Operations Manager, Jennifer McGowan, before we were comfortable that the quality was consistent with our internally processed exams.

One of our MGH 3D lab-trained research fellows, Dr Roy D'Souza, joined the Bangalore team in 2004, and helped train other radiologists to process our exams, and continues to lead a team of three radiologists and support staff in Bangalore. In 2016, we moved the team from Wipro to work under the umbrella of Teleradiology Solutions (TRS) as we felt that alignment with a company focused on radiology remote services would be a better fit for the team there.

WHY HAVE YOU CHOSEN INDIA - WHAT IS THE BUSINESS CASE?

After a few years of rapid growth, we faced challenges in meeting our radiologists' and referring physicians' demand for clinical image post-processing in terms of turnaround time, hours of coverage, and growing clinical volume while maintaining our high standards for quality, consistency, and expertise. It takes us about 9-12 months to train new 3D Technologists in our 40-50 clinical 3D protocols, and our staff were not enthusiastic about the growing demands for them to take night and weekend calls.

We were fortunate in having developed this collaboration that enabled us to have a highly skilled team of India-based radiologists perform our 3D exams during our overnight hours in their daytime. We established this to address needs for clinical care. We have radiologists in India performing work that we have 3D Technologists doing at MGH to ensure that the quality is maintained, and it costs us more as an outsourced service on a per case basis than it would to have overnight full-time staff on site. However, given the difficulty in finding and training qualified candidates who want to work overnight, we were unable to solve our issues through staffing on site.

Thus, this is not the stereotypical overseas outsourcing business case of moving jobs to save expense, but rather, our motivation is to enhance patient care and maintain quality of service. The team in Bangalore is truly an extension of our 3D Lab team. We have bi-weekly calls and daily quality checks, as well as ongoing feedback and training in new protocols. The team has been amazingly cohesive, and most of the India staff have been there for over a decade with little turnover. Our MGH 3D Operations Manager and I visited the team in Bangalore this summer, which was my third visit to meet with the team since we started the India service.

DOWN THE LINE IN A 5-10 YEAR TIMEFRAME, CAN THE PROCESSING BE TAKEN OVER BY AUTOMATION?

We are in the 20th year of operation of our 3D Imaging Service at MGH. Every year, new technology comes along that promises to automate different 3D image processing tasks. While these enhancements have impacted our workflow, and some of the more manual tasks have been replaced by more automated processes, it seems that every time some new technique reduces our work in one area, additional new work is requested. As such, we are now busier than we have ever been and we have trouble keeping up with our workload. Will the advent of new technologies automate some parts of our work and enhance the capabilities of radiologist to provide better diagnosis and quantitative analysis of images?

I certainly hope and expect so. Will this mean less work for our 3D lab? Probably not, but it will mean that some of the more mundane and repetitive tasks will likely be replaced by more automation, enabling us to shift our focus to new areas where our expertise can provide added value.

WHAT IS THE SCOPE FOR PROTOCOL-BASED, TELE3D IMAGING IN INDIA AND IN AREAS SUCH AS MEDICAL TOURISM?

We are exploring ways that we can expand our Tele3D network through our collaboration with our India-based colleagues at Teleradiology Solutions, both in the US and in India and other regions. We have implemented a Tele3D workflow to provide 3D services to teleradiology client sites of TRS and are preparing to launch this at our first pilot site. Once this is operating, we plan to make this service available to TRS' US-based client hospitals and imaging centers.

For India and other regions, we could provide this service in reverse, where daytime cases are processed in India and the MGH team provides coverage during their night-time. While this could be provided for self-pay patients who are either local or traveling for medical tourism, the challenge will be determining how the economics would work for routine clinical 3D exams.

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Sexual Harassment of Women at Workplace

KK AGGARWAL*, IRA GUPTA†

EQUALITY IS FUNDAMENTAL RIGHT

As enshrined in the Preamble to the Constitution of India, "equality of status and opportunity" must be secured for all its citizens; equality of every person under the law is guaranteed by Article 14 of the Constitution of India.

A safe workplace is therefore a woman's legal and fundamental right. Indeed, the Constitutional doctrine of equality and personal liberty is contained in Articles 14, 15 and 21 of the Indian Constitution. These articles ensure a person's right to equal protection under the law, to live a life free from discrimination on any ground and to protection of life and personal liberty.

SEXUAL HARASSMENT AT WORKPLACE

Sexual harassment at workplace is an extension of violence in everyday life and is discriminatory and exploitative, as it affects women's right to life and livelihood. Sexual harassment constitutes a gross violation of women's right to equality and dignity. Sexual harassment at workplace is often regarded as 'natural' male behavior or 'harmless flirtation', which women enjoy. Contrary to these perceptions, it causes serious harm and is also a strong manifestation of sex discrimination at the workplace.

FIRST CASE OF SEXUAL HARASSMENT OF WOMEN AT WORKPLACE: VISHAKA AND OTHERS V STATE OF RAJASTHAN

In India, for the first time in 1997, a petition was filed in the Hon'ble Supreme Court to enforce the fundamental rights of working women, after the brutal gang rape of Shamwari Devi, a social worker from Rajasthan. As an outcome of the landmark judgment of the **Vishaka and Others v State of Rajasthan**, the **Hon'ble Supreme Court** had laid down certain guidelines for the prevention of sexual harassment of women at workplace.

SEXUAL HARASSMENT OF WOMEN AT WORKPLACE (PREVENTION, PROHIBITION AND REDRESSAL) ACT, 2013

The Sexual Harassment of Women at Workplace (Prevention, Prohibition and Redressal) Act, 2013 (hereinafter referred to as SHWW Act, 2013), was enacted wherein it was made mandatory for every employer to provide a mechanism to redress grievances pertaining to workplace sexual harassment and enforce the right to gender equality of working women.

The Central Government notified and the said Act came into force on December 9, 2013.

With the enactment of the Act, India is now a part of a select group of countries to have prohibited sexual harassment at workplace through national legislation. The Act is unique in its broad coverage which includes all working women from organized and unorganized sectors alike, as also public and private sectors, regardless of hierarchy. Effective implementation of the Act is a challenge.

WHO IS AN AGGRIEVED WOMAN?

The Act recognizes the right of every woman to a safe and secure workplace environment irrespective of her age or employment/work status.

Hence, the right of all women working or visiting any workplace whether in the capacity of regular, temporary, ad hoc, or daily wages basis is protected under the Act. It includes all women whether engaged directly or through an agent including a contractor, with or without the knowledge of the principal employer. They may be working for remuneration, on a voluntary basis or otherwise. Their terms of employment can be express or implied. Further, she could be a co-worker, a contract worker, probationer, trainee, apprentice or called by any other such name. The Act also covers a woman who is working in a dwelling place or house.

WHAT IS A WORKPLACE?

A workplace is defined as "any place visited by the employee arising out of or during the course of

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employment, including transportation provided by the employer for undertaking such a journey." As per this definition, a workplace covers both the organized and unorganized sectors. It also includes all workplaces whether owned by Indian or foreign company having a place of work in India. As per the Act, workplace includes:

- Government organizations, including Government company, corporations and cooperative societies;
- Private sector organizations, venture, society, trust, NGO or service providers, etc. providing services which are commercial, vocational, educational, sports, professional, entertainment, industrial, health related or financial activities, including production, supply, sale, distribution or service;
- Hospitals/Nursing homes;
- Sports institutes/Facilities;
- Places visited by the employee (including while on travel) including transportation provided by employer;
- A dwelling place or house.

The Act defines the unorganized sector as:

- Any enterprise owned by an individual or self-employed worker engaged in the production or sale of goods or providing services of any kind;
- Any enterprise which employs less than 10 workers.

MEANING OF SEXUAL HARASSMENT AT THE WORKPLACE

According to the said SHWW Act, 2013 "Sexual Harassment" includes any one or more of the following unwelcome acts or behavior (whether directly or by implication), namely:

- Physical contact or advances;
- A demand or request for sexual favors;
- Making sexually colored remarks;
- Showing pornography;
- Any other unwelcome physical, verbal or non-verbal conduct of a sexual nature.

Impact of Inappropriate Behavior

The impact of sexual harassment at the workplace is far-reaching and is an injury to the equal right of women. Not only does it impact her, it has a direct bearing on the workplace productivity as well as the development of the society.

Examples of behaviors and scenarios that constitute sexual harassment

- Making sexually suggestive remarks or innuendos.
- Serious or repeated offensive remarks, such as teasing related to a person's body or appearance.
- Offensive comments or jokes.
- Inappropriate questions, suggestions or remarks about a person's sex life.
- Displaying sexist or other offensive pictures, posters, MMS, SMS, WhatsApp, or e-mails.
- Intimidation, threats, blackmail around sexual favors.
- Threats, intimidation or retaliation against an employee who speaks up about unwelcome behavior with sexual overtones.
- Unwelcome social invitations, with sexual overtones commonly understood as flirting.
- Unwelcome sexual advances which may or may not be accompanied by promises or threats, explicit or implicit.
- Physical contact such as touching or pinching.
- Caressing, kissing or fondling someone against her will (could be considered assault).
- Invasion of personal space (getting too close for no reason, brushing against or cornering someone).
- Persistently asking someone out, despite being turned down.
- Stalking an individual.
- Abuse of authority or power to threaten a person's job or undermine her performance against sexual favors.
- Falsely accusing and undermining a person behind closed doors for sexual favors.
- Controlling a person's reputation by rumor-mongering about her private life.

Examples of behaviors and scenarios that may constitute sexual harassment at workplace and merit inquiry

- Criticizing, insulting, blaming, reprimanding or condemning an employee in public.
- Exclusion from group activities or assignments without a valid reason.
- Statements damaging a person's reputation or career.

- Removing areas of responsibility, unjustifiably.
- Inappropriately giving too little or too much work.
- Constantly overruling authority without just cause.
- Unjustifiably monitoring everything that is done.
- Blaming an individual constantly for errors without just cause.
- Repeatedly singling out an employee by assigning her with demeaning and belittling jobs that are not part of her regular duties.
- Insults or humiliations, repeated attempts to exclude or isolate a person.
- Systematically interfering with normal work conditions, sabotaging places or instruments of work.
- Humiliating a person in front of colleagues, engaging in smear campaigns.
- Arbitrarily taking disciplinary action against an employee.
- Controlling the person by withholding resources (time, budget, autonomy and training) necessary to succeed.

Examples of behaviors and scenarios that may not constitute sexual harassment

- Following-up on work absences.
- Requiring performance to job standards.
- The normal exercise of management rights.
- Work-oriented stress e.g., meeting deadlines or quality standards.
- Conditions of work.
- Constructive feedback about the work mistake and not the person.

COMPLAINT MECHANISM

The SHWW Act, 2013 provides for two kinds of complaint mechanisms:

Internal Complaints Committee (ICC)

At every workplace where there are more than 10 employees, it is the responsibility of the employer to constitute Internal Complaints Committee (ICC) in the said workplace as per Section 4 of SHWW Act, 2013 consisting of following members:

- Chairperson - Women working at senior level as employee.
- Two members (minimum) - From amongst employees committed to the cause of women/ having legal knowledge/experience in social work.
- External Member - A person familiar with issues relating to women would mean such persons who have expertise in issues related to sexual harassment and may include any of the following:
  - At least 5 years of experience as a social worker, working towards women's empowerment and in particular, addressing workplace sexual harassment;
  - Familiarity with labor, service, civil or criminal law.

Local Complaints Committee (LCC)

As per Section 6 of SHWW Act, 2013, every District Officer has to constitute a **Local Complaints Committee** in the concerned district so as to enable women in the unorganized sector or small establishments to work in an environment free of sexual harassment. The LCC will receive complaints:

- From women working in an organization having less than 10 workers;
- When the complaint is against the employer himself;
- From domestic workers.

WHO CAN COMPLAIN AND WHERE?

Generally, where there are less than 10 workers, any woman employee can complain to the Local Complaints Committee with the support of the Nodal Officer, when required. It is the responsibility of the District Officer to designate a person as the Nodal Officer in every block, taluka and tehsil in rural or tribal areas and wards or municipalities in the urban areas, to receive the complaints of workplace sexual harassment from women. The Nodal Officer will forward all such complaints within 7 days of its receipt to the concerned Complaints Committee for appropriate action. In most other workplaces, a woman employee can make a complaint to the Internal Complaints Committee.

WHAT SHOULD THE COMPLAINT CONTAIN?

The written complaint should contain a description of each incident(s). It should include relevant dates, timings and locations; name of the respondents; and the working relationship between the parties.

A person designated to manage the workplace sexual harassment complaint is required to provide assistance

in writing the complaint if the complainant seeks it for any reason.

LIMITATION PERIOD FOR FILING COMPLAINT UNDER SHWW ACT, 2013

The limitation period for filing the complaint of sexual harassment at workplace either to the ICC or the LCC is specified in Section 9 of SHWW Act, 2013, which is 3 months from the date of incidence and in case of series of incidents, then within a period of 3 months from the date of the last incident.

However, the complaint can be filed after a period of 3 months provided the complainant gives cogent reason for the delay in filing the complaint but the ICC or LCC can extend the limitation, but not more than 3 months.

INDIAN PENAL CODE, 1860

Apart from the Sexual Harassment At Workplace Act, 2013, the victim can also make a police complaint under various provisions of Indian Penal Code (IPC), 1860 such as:

- Section 294 - Obscene acts and songs
- Section 354 - Assault or criminal force to woman with intent to outrage her modesty
- Section 354A - Sexual harassment
- Section 354B - Assault or use of criminal force to woman with intent to disrobe
- Section 354C - Voyeurism
- Section 354D - Stalking
- Section 370 - Trafficking
- Section 376 - Rape
- Section 376A - Rape resulting in persistent vegetative state
- Section 376AB - Rape on a woman under 12 years of age
- Section 376B - Sexual intercourse by husband upon his wife during separation
- Section 376C - Sexual intercourse by a person in authority
- Section 376D - Gang Rape
- Section 376DA - Woman under the age of 16 years is raped
- Section 376DB - Woman under the age of 12 years is raped by one or more persons
- Section 376E - Repeated offender
- Section 503 - Criminal Intimidation
- Section 509 - Word, gesture or act intended to insult the modesty of woman.

INDECENT REPRESENTATION OF WOMEN

Indecent representation of women is also a punishable Act. "Indecent representation of women" means the depiction in any manner of the figure of a woman, her form or body or any part thereof in such a way as to have the effect of being indecent, or derogatory to, or denigrating women, or is likely to deprave, corrupt or injure the public morality or morals. If an individual harasses another with books, photographs, paintings, films, pamphlets, packages, etc. containing the "indecent representation of women", they are liable for a minimum sentence of 2 years.

SEXUAL HARASSMENT OF WOMEN AT ANY OTHER PLACE

Apart from sexual harassment of woman at workplace, even if the woman is sexually harassed at any other place, then also the woman can lodge a police complaint against the offender under various sections of IPC. If a woman up to the age of 18 years is subjected to any kind of sexual harassment, then the police complaint can be lodged under the provisions of Protection of Children from Sexual Offences Act, 2012.

CONCLUSION

It is well established that ensuring safe working conditions for women leads to a positive impact on their participation in the workforce and increases their productivity, which in turn benefits the nation as a whole. Economically empowered women are key to the nation's overall development and this can only be achieved if it is ensured that women's workspaces across all sectors and all over the country have a safe and secure environment for work.

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Financial Tips for Doctors

WHAT DOCTORS SHOULD KNOW ABOUT PROVIDENT FUND?

Provident Fund (PF) is applicable only to those medical establishments that employ more than 20 people. It is applicable to people drawing salary of less than Rs. 15,000/- per month. PF is a retirement benefit scheme that is available to salaried people. Under this scheme, a stipulated amount (12%) is deducted from the employee's salary and contributed towards the fund. A similar amount is contributed by the employer. The accumulated sum is paid at the time of retirement or resignation by the PF department. After 5 years, withdrawal of PF is not taxable.

On the other hand, Public Provident Fund (PPF) has been established by the Central Government. A PPF account can be opened in any bank or post office. One can deposit a minimum amount of Rs. 500/- up to a maximum of Rs. 1,50,000/- per year. A return of 8% is accumulated every year, which is repayable after 15 years. There is no income tax on maturity. When a new employee joins, every salaried person is supposed to give a declaration on Form 11, which indicates whether or not a person was a PF beneficiary in the past. If he/she was, then he/she will continue to be on PF throughout his/her life. Past PF formalities will be shifted to the new one. Any time a new person is taken on salary, a Form 2 is also required, which includes the name of the nominee to get benefits in case the employee dies suddenly. It is a statutory requirement for the employer to get the Form 2 filled up at the time of service.

PF return needs to be filed by 15th of every month. A 5-day grace period is often given if one fails to file the PF details by that day; there is no penalty. If late by one day, there can be up to 100% penalty. The employer can claim PF under an expense. There is also a dual benefit of 20% extra rebate in income tax, if PF is paid before 15th of the following month. PF is always applicable once the number of employees crosses 20. Even if 10 employees remain, the PF will have to be paid for those 10. Even if the number becomes zero, administrative charges of Rs. 7/- per month need to be deposited, even if the company is closed.

Anybody who is working directly or indirectly comes under PF Act. For example, if we have employed guards or safai karamcharis through an agency, PF will be applicable. Either the service provider (agency) will pay the PF or you will have to pay. If the service provider has less than 20 people, PF may not be applicable to him but it will still be applicable to your organization as you are employing these guards indirectly through an agency.

The various forms that need to be complied with are:

- Form 11 for declaration whether or not the employee was getting PF in the past
- Form 5 at joining
- Form 10 (C) at the time of leaving the company
- Monthly returns to be filled in Form 3 (A).

If a person has resigned or has left the job, it is binding on the part of the employer to fill PF form. Even the Supreme Court cannot touch the PF. This is applicable even if the person has left pending dues. You can claim for the pending dues by filing a case against the employee in a different court. Attestation of the form is compulsory if the person has left the job from your organization.

PLANNING FOR YOUR CHILD'S WELFARE

For the birth of a son, plan money for his education; but, for a daughter, plan both for her education as well as her marriage. All doctors must form Family Trust, which can be 100% specific for a girl child, boy child, minor child, etc. The same needs to be registered. The daughter beneficiary family trust can be controlled by the parents, till the daughter is worldly matured, which usually happens after 5-10 years of marriage. This way, the money given to the girl at the time of marriage can be kept out of control of the husband or in laws at least for a few years.

DAY-TO-DAY TIPS IN MANAGING EXPENSES

- Fringe benefits tax is no more there to any type of concern neither company nor firm or Prop.
- Service tax is not applicable to a doctor's consultation (except plastic surgery).
- One cannot take or give a cash loan of more than Rs. 20,000/- from or to a person. Even a husband cannot give a loan of more than Rs. 20,000 to his wife in cash. The penalty is 100-300%. The classical example is when a person has to pay cash on Saturday evening as part of the hospital bill. If the amount exceeds more than Rs. 20,000/-, then one needs to take loan from two different entries.

- Cash expenses of more than Rs. 20,000 to one party in one day are not allowed in income tax. It can be Rs. 19,900/- but not Rs. 20,000.
- If a medical doctor's income is more than 50 lakhs per year then tax audit is a must. Presumptive Tax Scheme U/S 44AD is extended to doctors also.
- If the gross receipt is below 50 lakhs and the taxable profit is shown 50%, there is no need to maintain books of accounts and no tax audit required.
- Every doctor is supposed to maintain books on records and patient register as prescribed in Income Tax Act Form 6 (F). It is mandatory by law.
- Concealment of income is a crime by up to a penalty of 300% (maximum).
- Income generated from writing articles or appearing in TV or radio is not exempted under Income Tax. But for those who are professionals can claim expenses against them. For example, for travel, research, searching of messages, etc.
- All expenses for conferences and business meetings are fully allowed under the Income Tax Act.
- One can pay salary to the wife, if she is technically and professionally qualified. You can pay salary to her or to her daughter.
- Ask your employer to reduce your salary or professional income and give Rs. 15,000/- as medical reimbursement. The same is exempted under Income Tax.
- It is always better to be on professional fee than on salary as you can claim expenses to any amount.
- You can claim depreciation on your car besides driver salary, car maintenance or petrol expenses.
- If the area you are practicing is not in your name then you can give house rent or clinic rent to your partner, son, daughter. The same will be claimable as full expenses.
- Always show 50% of your house as office or clinic and claim depreciation on it.
- In a partnership both husband and wife can draw salary if they are shown to be professionally working in that organization. The maximum amount paid as salary cannot exceed as specified in section 40b i.e., up to Rs. 3,00,000/- salary allowed 90%. Above 3 lakhs, 60% is allowed as salary.
- Always buy a property in the name of HUF. It gives you an opportunity for one more account to save income tax. Always buy a property in the name of HUF and pay rent for your clinic to your own HUF.
- Always buy a car as you can claim the depreciation on the car and 100% reduction on car allowances.
- It is always better to pay rent to your wife as by this you can claim 100% reduction from your professional income and in addition she will get 30% rebate on rental income.
- Up to Rs. 800/- per month of travel allowance is not taxable. Similarly, expenses for uniform, conveyance and reimbursements of expenses are not part of the taxable income.
- Accordingly modify the salary heads of your employees. One can claim a leave travel allowance two times in 4 years for a visit anywhere in the country.
- If you have taken a housing loan jointly along with your wife, then deduction of interest paid on housing loan can be taken by both @ Rs. 2,00,000 each.

SURCHARGES TO BE KNOWN

- **Surcharge:** The amount of income tax shall be increased by a surcharge at the rate of 12% of such tax, where total income exceeds one crore rupees. However, the surcharge shall be subject to marginal relief (where income exceeds one crore rupees, the total amount payable as income tax and surcharge shall not exceed total amount payable as income tax on total income of one crore rupees by more than the amount of income that exceeds one crore rupees).
- **Education Cess:** The amount of income tax and the applicable surcharge, shall be further increased by education cess calculated at the rate of 2% of such income tax and surcharge.
- **Secondary and Higher Education Cess:** The amount of income tax and the applicable surcharge shall be further increased by secondary and higher education cess calculated at the rate of 1% of such income tax and surcharge.
- **Rebate under Section 87A:** The rebate is available to a resident individual if his total income does not exceed Rs. 5,00,000/-. The amount of rebate shall be 100% of income tax or Rs. 2,000/-, whichever is less.

VARIOUS INVESTMENTS TO KNOW

The investment options are either on equity where you can invest in the shares of a company, the price of which varies.

Another option is to invest in debt funds, which give near fixed returns and the duration of investment varies from a few months to a few years. The examples of debt

funds are fixed deposits (banks and companies), bonds (government and company) and government securities.

National Saving Certificates are an instrument for facilitating long-term savings by the Govt. of India. These forms are available in all post offices in denominations of 100/- , 500/-, 1000/-, 5000/- and 10000/-. The maturity period offers a return of approximately 9.5%. There is no scope of premature withdrawal; but, one can borrow against NSC with the approval of the concerned post master.

Infrastructure Bonds are not same as investment in infrastructure funds. At present, they are issued by ICICI and IDBI (considered to be financially healthy institutions). Income from bonds issued by these institutions is generally assured. They are rated AAA by CARE, CRISIL and FITCH. These bonds can be purchased at Rs. 5,000/- each. One has to apply for a minimum of one bond. There are no upper fillings against purchase of such bonds. These bonds are usually sold for a discount on the face value. It is redeemed at the face value on maturity and the difference becomes the gain.

ELSS is an investment under the equity linked saving scheme with a lock in of 3 years. The money invested is 80-100% on equity and 0-20% in debt.

ULIP is unit linked insurance cum investment plan and gives a dual benefit of life insurance and investment. For example, Bajaj ULIP has a lock in period of 5 years. Withdrawal after 5 years is tax-free. The annualized return for ULIP has been up to 48%.

Fixed Deposits: Investments in fixed deposits are not the best option. They are available for duration starting from 14 days to 5 years and are the most popular modes of investments. The interest offered for a 3-year term by a bank varies from 6% to 7%. For senior citizens, the interest rate may be higher by 0.25-0.5%. Any interest earned from the bank deposits is added to the income and is taxable. Only bank deposits lock in for 5 years are eligible for tax deduction under Section 80C. The returns from fixed deposits usually are less than the inflation rate and, therefore, are not the preferred mode for investment.

Fixed Maturity Plans (FMPs) are equivalent to the fixed deposit in a bank. They have different maturities, from 1 month to 3 years. They are classified under debt investments. Income earned after 1 year from FMP is not added to the taxable income. One can choose while applying for dividend or growth options. For example, you may invest in an FD or an FMP dividend or FMP growth, all at a return of 8%. However, they will have different net returns. In FD, 8% will be the return, 33.3% will be the tax (if the slab is the highest). Therefore, net return will be 5.3%. On FMP dividend, the return will be the same 8%, but the tax will be only 14.28% (DDT) with an annualized net return of 6.8% (DDT). In FMP growth, the annual return may be 8% but the net return again will be 6.8% after 33.3% tax, less inflation.

Low risk investment options are bank deposits, FMPs and treasury bills. The medium risk options are corporate bonds, government debt securities, long-term mortgages, mutual funds and call money. High risk options are equity and properties.

Mutual Funds are funds created by the company and managed by fund managers. The money collected from investors is invested by the fund managers to create returns. And the same is passed back to the investors. The mutual fund managers earn approximately 2.25% income out of it. Mutual funds have an advantage as any money earned after 1 year is not taxable. They are well regulated, less risk with low cost and one can invest in small amount. These are often managed by professionals.

There are different types of mutual funds. These can be equity funds, which are medium to high risk but also give high return. Here 80-100% of the money is invested in equity. The different types of equity mutual funds are large cap, mid cap or small cap (capitalization), depending upon the size of the company in which the fund invests and not the size of the mutual fund itself. Large cap are the ones where the company size is more than 1500 crore and in small cap the company size is less than 500 crore. Equity funds can be simple growth funds, or ELSS funds. Or they can be ***debt funds,*** medium risk with medium returns. These invest 80-100% money in debt funds. MIPs are debt mutual funds where 80% is invested in debt and 20% in equity. They provide an annualized return of 12-13%.

Lastly, there are center-specific funds like banking, infrastructure and energy.

SIPs are also mutual funds with systematic investment plans. They are often used for children and for retirement purposes. Pension plans for mutual funds have a 7-year lock in period and provide a return of 13-14%.

- Private fixed deposits give a 3 years annualized return of 9-10%. Always go for AA or AAA rating like Shriram Finance.
- Tax saving FDs come under 80C with a 5-year lock in period. They give a return of 9% and are available in all banks.
- One can invest 3 lakh per person, 6 lakh joint in post office saving bonds.
- They provide 7.5-8% monthly income and 5% bonus on maturity. It is like a time-tested investment.
- Zero risk investments are MIPs, debt funds, FMPs, guild funds.

IANCON 2018: 26th Annual National Conference of the Indian Academy of Neurology

SEPTEMBER 27-30 | PANDIT DEENDAYAL UPADHYAY AUDITORIUM, SCIENCE COLLEGE CAMPUS, RAIPUR

BILATERAL GREATER OCCIPITAL NERVE BLOCK IN TREATMENT OF CHRONIC MIGRAINE: EXPERIENCE FROM A MULTISPECIALTY HOSPITAL IN NORTH INDIA

Dr Ruby Chopra, Bathinda;
Prof Debashish Chowdhury, New Delhi

Greater occipital nerve (GON) block is the most widely used peripheral nerve block for different primary headache disorders. It is cheap, minimally invasive, has no side effects, is associated with a reasonable duration of pain relief and reduces pill burden and toxicity of abortive and prophylactic medication. There is no Indian data on the use of GON block for treatment of primary headaches.

A study was therefore conducted with patients attending Neurology OPD from December 2016 to April 2018 who were diagnosed with chronic migraine according to ICHD 3β. Response was estimated by reduction in headache days as compared to baseline. It was categorized as complete (100%) if there was no headache in 1 month after GON block, significant (76-99%), moderate (50-75%) and mild (<50%).

At 1-month follow-up, complete response was noted in 42.7% patients, significant in 13.8% patients, moderate in 18% patient, and mild in 4.2% patients. Twenty out of 94 patients (21.3%) did not respond. Average time to develop pain relief after block was 3.5 $\pm$ 3.18 days (range 1-15 days). It was concluded that GON block is an effective treatment option in chronic migraine with or without MOH. Presence or absence of OT does not affect the response to GON block. Severity of pain, duration of migraine history, and presence of comorbid psychiatric disorders do not affect response. Side effects are mild and self-limiting.

STEM CELL THERAPY IN STROKE: A META-ANALYSIS

Dr Amit Kumar, New Delhi

There are limited therapeutic options available for the treatment of stroke, with limited time window. Pre-clinical research suggests that stem cells potentially modulate multiple pathways involved in endogenous neurogenesis, angiogenesis, immune modulation, neural plasticity, secretion of growth factors, etc. Translation of these advances into meaningful therapeutic options is required. A meta-analysis was conducted with the aim to assess the effectiveness and safety of cell therapies, studied as monotherapy in adult patients with stroke and published in English language. Trials investigating the use of stem cell therapy in adult patients who had experienced a stroke and in any phase from acute to chronic phase, were included.

Trials investigating combination therapies including stem cells with other therapies were excluded. This review and meta-analysis provides evidence for the safety, feasibility and preliminary efficacy of cell therapies for stroke. There is substantial heterogeneity due to differences in stroke type, route of intervention, timing of intervention, cell types, dose, etc. Further progress in this field will require execution of well-designed phase 2/3 clinical trials with high quality.

DIFFERENTIATING CLUSTER HEADACHE AND SIDE-LOCKED MIGRAINE: A CLINIC-BASED STUDY FROM NORTH INDIA

Dr Amit Shankar Singh, Chandigarh;
Prof Debashish Chowdhury, New Delhi

- Although migraine and cluster headache (CH) are considered 2 different entities with different features, overlap does exist between them.
- Probably the excessive activity of the trigeminal autonomic reflex in this subset of migraine patients is the cause of overlap.
- It is possible that they both share a common pathophysiological step, probably a functional alteration in hypothalamic or brainstem circuits.
- Similarities between CH and side-locked migraine (SLM): Side-locked headaches; Comparable severity of headaches; Common location of headache (orbito-temporal); Throbbing character of pain.
- Differences in CH and SLM: Male preponderance in CH; Duration of attacks - less in CH, more in

SLM; Restlessness (universal in CH); Differences in CAS - Florid ipsilateral CAS in CH in terms of severity, consistency and number.

COMPARISON OF EFFICACY AND SAFETY OF AMITRIPTYLINE WITH GABAPENTIN IN MIGRAINE PROPHYLAXIS: RANDOMIZED DOUBLE-BLINDED DOUBLE DUMMY TRIAL

Dr Satish J Wagh, Puducherry

Migraine is a chronic incapacitating neurovascular disorder. In the United States, only 1 in 5 (19.6%) eligible patient currently receives migraine specific preventive care. Both amitriptyline (AMT) and gabapentin (GP) are effective in migraine prophylaxis. AMT and GP have similar efficacy and side effect profile. Migraine prophylaxis does not affect adiponectin levels. Higher responder rates of both drugs indicate that: AMT may be re-considered as first-line therapy (presently second-line); GP may be evaluated as a novel migraine prophylactic medication.

TRANSITION FROM CHILDHOOD TO ADULTHOOD IN LENNOX-GASTAUT SYNDROME - COGNITIVE AND THERAPEUTIC OUTCOMES

Dr Nitin K Sethi, New York

- There are very few well-performed studies. Impairments are not always necessarily permanent. The outcomes can vary. Babies who have West syndrome and children who have Dravet syndrome (severe myoclonic epilepsy in infancy) usually will have long-term cognitive and behavioral problems.
- Lennox-Gastaut syndrome (LGS) also often has a poor prognosis. Children with Landau-Kleffner syndrome have a variable prognosis; some regain speech while others have permanent speech impairment. Cognitive and behavioral outcome of at least some children with these syndromes can be influenced greatly by early effective treatment with either antiepileptic medication or surgery.
- Antiepileptic drugs, ketogenic diet, vagus nerve stimulation and epilepsy surgery are effective for seizure control in LGS patients, but not necessarily for improvement in cognitive and behavioral outcomes.
- The cause is more than just seizures (likely underlying genetic causes of cognitive and behavioral deficits). Multidisciplinary treatment is the need: adult neurologist/epileptologist, neuropsychologist, psychiatrist, social workers, special needs school/teachers, family and friends.

N-METHYL-D-ASPARTATE ENCEPHALITIS - OUR EXPERIENCE WITH DIAGNOSTIC DILEMMAS, CLINICAL FEATURES AND OUTCOME

Dr SR Chandra, Bengaluru

A total of 29 cases were observed by the team. Surprisingly, only three were males. Their age group ranged from 3 to 31 years and the mean age was 17 years. Age-wise distribution showed maximum incidence in 12-18 years age group. Referral diagnosis in the patients ranged from viral encephalitis in five, catatonia in six, attention-deficit disorder in two, autism spectrum disorder in three, rheumatic chorea in two, autoimmune encephalitis in five, psychiatric illness unspecified in five, rabies in one and schizophrenia in one.

Of the 29 patients, 20 reported minor respiratory infection preceding the problem by 4-10 days. One patient had global developmental delay with congenital heart disease, one patient had hydronephrosis that was operated 4 years ago, and one patient was bitten by dog and received anti-rabies vaccine 30 days before symptom onset. All patients had psychiatric symptoms.

Severe mania-like features were seen in one and schizophreniform symptoms in one, severe panic in nine, unexplained anxiety in 11, catatonia in six, mutism in one, biting self and others in one, and delusions and hallucinations in seven. Neurological features observed in patients were hemiplegia and aphasia in one, mutism in one, seizures in 21, cognitive decline in 29, and chorea in three.

Two patients had benign ovarian teratoma. EEG showed slowing of background in 23 patients, epileptiform discharges in nine, and extreme delta brush in 11. MRI was normal in seven cases. Though reported normal, signal changes in limbic structures were observed in five cases. All others showed clear-cut features of limbic encephalitis. None had any other tumors.

Cerebrospinal fluid (CSF) test showed moderate antibody titers with less than 10% of transfected cells showing two to three plus granular cytoplasmic fluorescence, and serum test showed very high titers of up to 40-60% in seven cases, reverse in 12 cases, and both were moderately positive in 10 cases.

During follow-up at 6 months, only two patients remained positive in serum test. CSF was not tested during follow-up. N-methyl-D-aspartate (NMDA) antibody-related encephalitis seems to be more commonly present with a rapid-onset neuropsychiatric syndrome in children and young girls. Autonomic

involvement was not seen in this cohort as against the literature. Immunotherapy with a single responsive drug was sufficient in most of the patients. Majority of patients are left with cognitive behavioral sequelae and hence, high-degree of suspicion is essential for early diagnosis and treatment. Some of the aggressive and panicky behavior of the patients can even mimic the potentially fatal diagnosis of rabies and needs caution.

Investigators suggest that to the best of their knowledge, this review is the first to report self-mutilating behavior in NMDA encephalitis.

NEW-ONSET UNPROVOKED SEIZURES

Dr Chaturbhuj Rathore, Vadodara

New-onset unprovoked seizures are common with an incidence of 60/1,00,000 person-years. Nearly 20% of patients with apparent new-onset seizures have other diagnoses. Many of these patients have previously unrecognized minor seizures. Careful assessment of clinical details, EEG and MRI are required to assess the recurrence risk and the need for drug therapy. Symptomatic etiology and abnormal EEG are two most important risk factors for seizure recurrence after the first unprovoked seizure. Early drug treatment reduces the risk of immediate recurrence by 50% without affecting the long-term prognosis. Therapy needs to be individualized and majority of patients do not wish to start drug treatment after proper counseling.

ACUTE ISCHEMIC STROKE

Dr Elavarasi A, Puducherry

- Acute stroke therapy has developed hugely in 22 years since alteplase was approved.
- New kids on the block, like tenecteplase, are promising.
- Mechanical thrombectomy has revolutionized stroke therapy.
- Multimodal imaging has changed the way we look at and treat stroke.
- Aspirin is still the KING.
- Many trials in therapy and rehabilitation are on the way.

NEUROLOGY OF SICKLE CELL ANEMIA

Prof Vijay K Sharma, Singapore

- Sickle cell disease is one of the most common disorders of blood caused by a genetic mutation, causing the production of abnormal hemoglobin within the red blood cells (RBCs). This abnormal hemoglobin (HbS) causes distortion of the RBCs (sickling), making them prone to rupture. This leads to anemia (sickle cell anemia) and blocking of blood vessels causing tissue damage, especially in the brain (stroke) and abdomen (crisis).
- Sickle cell anemia primarily affects Africans and African-Americans. Very limited information is available for this disease in India. It has been reported from certain belts in Tamil Nadu, Kerala and central India. Since most of the complications of this disease are preventable, there is an urgent need to understand the features of Indian sickle cell disease so that locally appropriate models of care may be developed.

OCCURRENCE OF MEMORY DYSFUNCTION AND BRAIN LESIONS IN PATIENTS WITH CHRONIC MIGRAINE

Dr Ashish Kumar Duggal, Dr GA Khwaja, Dr Meena Gupta, Dr Debashish Chowdhury; New Delhi

Previous hospital-based studies have shown that migraineurs perform poorly on tests of attention, verbal and visual memory, executive function and psychomotor speed. According to this study that assessed the occurrence and pattern of memory dysfunction, occurrence and character of brain lesions on neuroimaging in patients with chronic migraine (CM), more than 50% of migraine patients reported impaired daily functioning and cognitive symptoms. Ten percent of CM patients had abnormal cognitive tests and most important factor was overuse of medication. Patients with CM had poor performance on working memory, attention, delayed verbal recall and visual retention. Patients with low CR were more prone to develop MOH. Therefore, patients with migraine must be advised to maintain a healthy lifestyle and avoid other risk factors in order to minimize additional brain insults.

INDIGENOUS DEVELOPMENT OF ECoG ELECTRODES

Dr JK Radhakrishnan, Bengaluru

- Prevalence of epilepsy in India is 5.59-10 per 1,000. For seizures that do not respond to antiepileptic medications, surgery is considered as the established option.
- Electrocorticography (ECoG) electrodes are needed in surgery of refractive epilepsy, for direct recording of electrical activity from cortical surface of the brain. At present, ECoG electrodes are imported, and their cost is prohibitive (one

IJCP SUTRA 704: Other clinical targets include BP control, improvement in vascular function and dyslipidemia and reduction in inflammation.

1 × 4 strip electrode costs Rs. 18-24 thousand). Development of indigenous electrodes, which are accurate and safe, with a far less cost, will enable more patients to afford the surgical procedure. Development of indigenous 1 × 4 strip electrodes has been completed. Its impedance values are comparable to imported ECoG electrodes. All the materials/components used for the electrode fabrication are biocompatibility certified. The cost of indigenous ECoG electrode works out to about one-fifth the cost of imported electrode.

- Novelty claims of this indigenous electrode are:
  - Tear-shaped sensing electrodes, to give a sense of the electrode–array orientation in X-ray images taken pre-surgery and during surgery.
  - Multi-strand, insulated and biocompatible conducting wire ribbon, instead of single strands of conducting wires, for ease of fabrication/assembly of the electrode array.
  - Enhanced electrical contact between the electrode and the conducting wire by using a combination spot-welding and adhesive.

SPECTRUM OF PSYCHIATRIC COMORBIDITIES IN ADULT MIGRAINE PATIENTS: LARGEST SERIES OF 470 PATIENTS FROM INDIA

Dr Dilip Nagarwal,
Dr Debashish Chowdhury; New Delhi

Psychiatric comorbidities, especially depression and anxiety, have been well documented in patients with migraine. Limited data exists on a comparative study of the spectrum and distribution of psychiatric comorbidities (Psy-CoM) in migraine from India. A study was thus conducted with migraine patients diagnosed by ICHD 3β criteria who were evaluated for psychiatric comorbidities. Nearly two-thirds of migraine patients had at least one psychiatric comorbidity. In all, 62.4% patients had Psy-CoM. CM patients had greater occurrence and combinations of Psy-CoM than episodic migraine (EM) patients (1.4 vs. 1). Depression is the commonest psychiatric comorbidity in both episodic and chronic migraine patients. EM and CM patients did not differ when compared for severity scores of depression, anxiety and OCD although CM patients had greater proportion of moderate-to-severe depression than EM (34% vs. 25%). All migraine patients, especially CM patients, must be evaluated and adequately treated for Psy-CoM as these may have great bearing on headache outcome.

SPINAL INTRAMEDULLARY TUMOR AND ITS MIMICKERS: AVOIDING MASLOW'S HAMMER

Dr Suresh Nair, Trivandrum

Differential diagnosis for intramedullary spinal lesions: Demyelinating disorders (MS, TM, NMO, ADEM); tumor (astrocytoma, ependymoma, hemangioblastoma, metastases); vascular (ischemia, spinal AVM); inflammatory (vasculitis, sarcoidosis); infection (herpes-VZV, HIV-VM-TB, bacteria, toxofungus).

According to a study by Lee and coworkers that elucidated characteristics that would identify patients with atypical, non-neoplastic intramedullary spinal cord lesions as harboring non-neoplastic lesions before surgical intervention, the most consistent clue was absent or minimal spinal cord expansion on the preoperative magnetic resonance images. Surgeons must not work with Maslow's hammer. A mind with Crabtrees bludgeon will avoid Maslow's hammer. How to avoid Maslow's hammer? Always consider demyelinating diseases in the differential diagnosis of enhancing intramedullary lesions. Surgeons should never ever have Dunning Kruger effect: A cognitive bias in which unskilled individuals suffer from illusory superiority, mistakenly rating their ability much higher than accurate. This is attributed to a metacognitive inability to recognize own ineptitude.

BREAKTHROUGH SEIZURES: WHAT WE KNOW?

Dr Shyam K Jaiswal, Hyderabad

The UK Driver and Vehicle Licensing Agency defines a breakthrough seizure as the first seizure after a minimum of 12 months seizure freedom while on treatment. The risk of seizure recurrence following breakthrough seizure has been reported to be more likely among the following patients: Those who require polytherapy in comparison to those who need monotherapy; took longer to achieve 12-month remission and increased their dose after breakthrough seizure. Factors related to poor adherence in epileptic patients: Not taking prescribed medicine by choice; forget to take medication; poor tolerance; poor purchasing capacity, especially in developing countries; nonavailability of drugs in pharmacy in the place of domicile. It is important to get it right because breakthrough seizures can have devastating consequences for patients (loss of job or driving license, low self-esteem, loss of independence). A link has been seen between seizure frequency and levels of anxiety and depression, perceived impact of epilepsy, perceived stigma and marital and employment status.

IJCP SUTRA 705: Although a higher BMI is associated with worse prognosis, weight loss is not necessarily a relevant target of exercise training for these patients.

ESICON 2018: 48th Annual Conference of Endocrine Society of India

NOVEMBER 15-18 | MAYFAIR CONVENTION, BHUBANESWAR

INTERESTING CASE SCENARIOS IN ENDOCRINOLOGY

Dr CM Batra, New Delhi

- Pituitary metastasis from thyroid – Only 22 cases had been reported till 2012. From 2013 to 2017, 12 more cases of pituitary metastasis have been reported but none from carcinoma thyroid.
- Pituitary metastasis from follicular carcinoma thyroid – Only 11 reported cases from world literature and none from India.
- In pituitary metastasis from follicular carcinoma thyroid, the tumors are larger, more invasive and anterior pituitary deficiency is rare. Diabetes insipidus does not occur.
- The prognosis of pituitary metastasis is poor and only one case of intrasellar metastasis has been cured so far. There is no neuroradiological imaging which could lead to a sure diagnosis.
- A rare case of pituitary metastasis from follicular carcinoma thyroid was presented.
- The treatment in this case was FNAC thyroid, total thyroidectomy; biopsy of the tissue; whole body RAI scan and ^{131}I therapy. Radiotherapy of residual sellar and suprasellar mass was also done, following which the patient was referred to AIIMS.
- The patient was recommended for Tg, TgAb and TSH every 6 months and MRI brain every year. RAI therapy after rh-TSH was repeated 6 times in 6½ years.
- The treatment was successful and the patient continues to live after 10 years.
- In such cases, the treatment outlined above is probably the best approach.
- Surgical treatment is difficult to perform, increases morbidity and does not increase survival.
- Thyroglobulin and thyroid transcription factor 1 are the tumor markers that confirm a thyroid malignancy, while cytokeratin 7 and focal staining for cytokeratin 19 confirm epithelial malignancy.

APPROACH TO SHORT STATURE

Dr Jayaprakash P, Kochi

- Shortness is defined as, "below 3rd percentile or 2 SD below the mean"; excessively short for MPF or TH; or growth velocity <25th percentile over 1 year.
- Various growth charts are available: Growth standards, growth references, WHO charts, CDC charts, Agarwal charts, Khadilkar charts. Physical examination includes height, weight, height age, weight age, midparental height, target height, US:LS, arm span and examination of head, eyes, neck, mouth, hand, SMR and systems.
- Immediate evaluation is required in following cases - Severe short stature: height >3 SD below the mean; Height >1.5 SD below MPH; Height >2 SD below the mean and a height velocity over 1 year >1 SD below the mean for chronological age; Decrease in height SD of >0.5 over 1 year in children over 2 years of age.
- CDGP: Children born with normal weight and length; growth decelerates in 2nd and 3rd year to reach below 3rd percentile; puberty and growth spurt delayed; bone age delayed; males fail to achieve tanner G2 by 14 years and females B2 by 13 years.
- Pubertal assessment is recommended for all children more than 6 years of age. Bone age gives information about skeletal maturity, correlates closely with SMR, informs about growth potential and helps in prediction of adult height. IGF-I assays are dependent on age, puberty, bone age and nutrition; they have low sensitivity but high specificity in younger age.
- IGFBP3 assays are constant, with higher levels, no BP interference, valuable at young ages and not dependent on nutrition. GH provocation tests exclude hypothyroidism. Long-acting GH preparations comprise of depot formulations, PEGylated formulations, Prodrug formulations, Noncovalent albumin-binding GH compound and GH fusion proteins.

GAMMA CAMERA AND SPECT IMAGING IN ENDOCRINOLOGY

Dr Ishita Sen, Delhi

Conventional nuclear medicine techniques can be tools for problem solving in Endocrinology. Investigations should be tailored to answer specific clinical query. Regular interaction between Nuclear Medicine and Endocrinology departments is essential to develop optimum strategies.

Routine screening of asymptomatic diabetics for silent ischemia is not recommended. Stress myocardial perfusion imaging (MPI) has high sensitivity for detecting silent ischemia. Positron emission tomography (PET) coronary flow rate may be useful to detect nonocclusive coronary artery disease (CAD).

According to the ACCF/AHA guidelines, asymptomatic diabetics over age 40 should be screened for coronary heart disease (CHD) with coronary artery calcium (CAC) scan. For those with CAC score <400, medical therapy can be considered and for those with a score >400, stress imaging study should be considered.

NEURORADIOLOGY: PRACTICAL TIPS FOR ENDOCRINOLOGISTS

Prof Niranjan Khandelwal, Chandigarh

- Sellar dimensions on plain radiograph – Anteroposterior diameter: 17 mm (range 5-16 mm); depth: 13 mm; width: 16 mm (range 10-15 mm); area on lateral view: 130 sq.mm; volume: 1,092 cumm (mean 599 cumm).
- Elster's rule for pituitary gland height on MRI (maximum height in mm) – Infants and children: 6; men and postmenopausal women: 8; women of childbearing age: 10; women in late pregnancy and postpartum: 12.
- Imaging approach – Recognize the normal sellar/parasellar region contents; determine the abnormality/lesion; place the abnormality in the appropriate space (sellar/parasellar) – Lesion epicenter; characterize the lesion based on imaging features (solid, cystic, mixed, calcifications, etc.); make a set of imaging differentials.
- MRI protocol – *Cavernous sinus:* T2WI brain; FLAIR brain; pre and post-contrast 3D T1 SPGR/MPRAGE; 3D heavily T2 weighted (CISS/SPACE); T2 cor (optional); T1 FS cor post gad (optional). *Sella:* T1FS sag pre/post gad; T2 sag; T1 cor pre/post gad; T2 cor; dynamic (microadenomas).
- Arachnoid cyst – Lack of fenestration of Liliequist membrane; may occur secondary to adhesions; asymptomatic/hydrocephalus/hypopituitarism/seizures; smooth cyst, no enhancement.
- Tuber cinereum hamartoma – Slow growing heterotopias; precocious puberty/gelastic seizures; nonenhancing, non-calcified, isointense to grey matter, bright on T2; sessile/pedunculated.
- Pituitary hypoplasia – Absent/thread-like stalk; small adenohypophysis; ectopic posterior pituitary bright spot.
- Persistent craniopharyngeal canal – Congenital skull base defect; Sellar floor to nasopharynx; Associations: hamartomas, duplication of pituitary gland/stalk, callosal dysgenesis, facial dysmorphisms.
- Tolosa Hunt syndrome – Idiopathic steroid responsive inflammation; painful ophthalmoplegia; enhancing soft tissue at orbital apex, may extend along tentorium.

THERANOSTICS IN ENDOCRINOLOGY – CURRENT PERSPECTIVE

Dr CS Bal, New Delhi

- Theranostics refers to the treatment strategies that combine diagnostic testing with targeted therapy, which is the epitome of personalized medicine.
- Radioiodine imaging in Ca thyroid – Post-surgery assessment; post-therapy scanning for confirming staging; assessment of radioiodine ablation after 6-12 months; restaging when there is clinical, biochemical or radiological suspicion of recurrence.
- Theranostic radioiodine imaging (Dx-WBS) can provide detailed biological status for each cancerous lesion and helps in predicting the therapeutic response of every lesion to ^{131}I treatment. Based on the imaging, ineffective ^{131}I treatment can be avoided.
- Theranostic approach – Dx-WBS followed by RAI therapy: Unlike fluorodeoxyglucose (FDG) diagnostic imaging studies, radioiodine imaging can forecast response to therapy. It can also potentially alter the decision to treat or not to treat with ^{131}I.
- In recurrent differentiated thyroid cancer (DTC), empiric therapy with RAI should be reserved for those with significantly elevated Tg (or rapidly rising levels) without a structural target amenable to directed therapy.

- Suspecting recurrence – About 20% patients will have elevated Tg levels up to 1 year after near-total thyroidectomy (NTT). Only one-third will have structural disease, rest will remain disease free and often have a decreasing Tg over time; Measurement of serum Tg coupled with neck ultrasound has become the cornerstone of surveillance strategies; Chest CT scan can detect pulmonary metastases in 80-90% cases, being able to detect lesions between 3 and 6 mm; FDG/PET is usually performed in case of elevated Tg with negative WBS; FDG PET scan can offer additional information in about 10% of these patients.
- Localized radioiodine refractory DTC can be treated with – Surgery; stereotactic external beam therapy; ablation (thermal, laser, alcohol); embolization (chemoembolization, radioembolization).

HYPERPROLACTINEMIA AND INFERTILITY

Dr Muthu Kumaran Jayapaul, Chennai

Pathological hyperprolactinemia may cause defective ovulation and reduced fecundability. Known physiological and pharmacological causes of hyperprolactinemia must be considered and a detailed medical history must be obtained. Abnormal prolactin (PRL) secretion is usually related to an idiopathic hypothalamic dysfunction or to the presence of a pituitary adenoma. Clinical examination and blood biochemistry, including tests for pregnancy and renal and thyroid function, are all important. It is also important to determine the serum FSH in order to pick up an unknown primary ovarian insufficiency in the women seeking pregnancy.

Hyperprolactinemic anovulation – Diagnostic work-up: Measure TSH, T3 and T4 (to exclude hypothyroidism); Among women with menses, measure PRL and progesterone in the supposed luteal phase (during at least 2 cycles); Among women with oligomenorrhea, measure FSH and PRL on two different occasions; MRI to be performed in all hyperprolactinemic women. For a reliable study of the abnormal luteal phase, repeated post-ovulatory plasma progesterone assays and the precise measurement of the luteal phase length are the key to treatment.

ROLE OF PET-CT IMAGING IN ENDOCRINOLOGY

Dr Kanhaiyalal Agrawal, Bhubaneswar

- Radiology vs. Nuclear Medicine – Radiology (X-ray, CT) gives a transmission image and is associated with increased radiation dose. Nuclear Medicine gives an emission image and is associated with decreased radiation dose.
- PET tracers – Differentiated Ca: ^{18}F-FDG, ^{68}Ga-DOTATATE, ^{68}Ga-PSMA; Medullary Ca: ^{18}F-FDG, ^{68}Ga-DOTATATE, ^{18}F-DOPA; Anaplastic Ca: ^{18}F-FDG.
- Flip-flop phenomenon – Tumors with functional differentiation of iodine uptake have low glucose metabolism and low FDG avidity; Tumors without functional differentiation of iodine uptake show high glucose metabolism and high FDG avidity.
- A study revealed that the diagnostic accuracy of FDG PET in radioiodine negative thyroid cancer may vary depending on serum Tg levels at imaging. The sensitivity of PET/CT according to Tg levels was 28.6% when stimulated Tg was 2-5, 57.1% when it was 5-10, 60% when it was 10-20 and 85.7% when Tg was >20 ng/mL.
- High FDG uptake suggests more dedifferentiation, aggressive tumor, poorer prognosis and reduced survival.
- A study evaluated the role of ^{68}Ga-DOTANOC PET-CT in DTC patients with negative ^{131}I-WBS along with serially increasing serum Tg, and compared the same with ^{18}F-FDG PET-CT. Per-patient sensitivity and specificity of ^{68}Ga-DOTANOC PET-CT was 78.4%, 100% and for ^{18}F-FDG PET-CT was 86.3%, 90.9%, respectively.
- FDG PET in disease recurrence – A meta-analysis analyzed data on the diagnostic performance of ^{18}FDG PET, and PET/CT in detecting recurrent medullary thyroid carcinoma. Pooled detection rate (DR) on a per patient-based analysis was 59%. It stated that DR of FDG PET and PET/CT increases in patients with higher calcitonin and carcinoembryonic antigen (CEA) values and lower calcitonin doubling time (CTDT) and CEA doubling time (CEADT) values.
- ^{18}F-DOPA PET in recurrent MTC – Sensitivity of 47-83% depending on calcitonin levels; the sensitivity is higher than FDG and ^{68}Ga-somatostatin analog PET/CT. However, FDG PET is a better indicator of survival.
- Indications of imaging in NET – Staging: Evaluation of metastases and localization of primary tumor; Re-staging: residual tumor, recurrence; Evaluation of receptor status and therapy monitoring. In a systematic review and meta-analysis, somatostatin

PET Radiotracers in Endocrinology

Radio-nuclide	Chemical	Radio-nuclide	Chemical
^{18}F	Fluorodeoxyglucose (FDG)	^{68}Ga	DOTATOC/ DOTATATE/ DOTANOC
^{18}F	Dihydroxy-phenylalanine (DOPA)	^{68}Ga	DOTA-Exendin 4/ NOTA-Exendin 4
^{18}F	Choline	C-11	Hydroxyephedrine
		C-11	Methionine

receptor PET/CT (SMSR PET) was found to have good diagnostic performance for evaluation of NET in the thorax and abdomen. The pooled sensitivity was 93% and specificity 96%.

- Ectopic Cushing syndrome – Pooled detection rates: ^{18}F-FDG 61.1%; ^{68}Ga-peptides 70%; ^{18}F-DOPA 46.7%.

APPROACH TO A PATIENT OF HYPERCALCEMIA

Dr P Velayutham, Coimbatore

- Hypercalcemia is defined as serum calcium levels more than 2 SD above mean. Serum calcium in normal adults is between 8.6 and 10.4 mg/dL. Severe hypercalcemia refers to serum calcium >14 mg/dL. Hypercalcemic crisis refers to serum calcium >14 mg/dL with neuro, cardiac, renal symptoms.
- For every 1 g/dL drop in serum albumin below 4 g/dL, measured serum calcium decreases by 0.8 mg/dL.
- Corrected calcium = Measured Ca + (0.8 × [4 - albumin]).
- Ambient pH influences protein binding to calcium. Metabolic acidosis – Decreased protein binding ---- increased ionized calcium; metabolic alkalosis – increased protein binding ----- decreased ionized calcium.
- Fall in pH by 0.1 increases serum calcium by 0.4 mg/dL.
- Clinical symptoms of hypercalcemia (acute) – General: Fatigue, weight loss; CVS: Short QT, arrhythmia, syncope; GI: Anorexia, nausea and vomiting, constipation, pancreatitis; Renal: Polyuria, dehydration, AKI, renal stones; Others: Bone pain, irritability, psychosis.
- Lab pitfalls in primary hyperparathyroidism (PHPT) – Low Ca and high phosphorus diet can obscure hypercalcemia; Very low vitamin D status can obscure hypercalcemia; Low vitamin D can be a manifestation of PHPT; Hypercalcemia can be masked if presentation is with acute pancreatitis; Intact PTH can be high normal in 10-15% of the people with PHPT; High Ca and high iPTH can be seen in 20% familial hypocalciuric hypercalcemia (FHH).
- Correct calcium levels for prevailing serum albumin. PHPT and malignancy account for most of the cases with hypercalcemia. Use of multiple variables helps in arriving at diagnosis easily.
- Hypercalcemic crisis requires urgent medical intervention.

DIAGNOSIS AND MANAGEMENT OF PHEOCHROMOCYTOMA

Prof Karel Pacak, USA

- Pheochromocytomas (PHEOs) are chromaffin – neural crest cell tumors characterized by catecholamine production and catecholamine metabolites (metanephrines/methoxytyramine) secretion.
- About 23 genes are involved in the pathogenesis of PHEO. Nearly 27-35% are inherited (germline mutations), 30-39% have somatic mutations. About 7% have fusion genes.
- All patients with a catecholamine producing PHEO must receive α/β adrenoceptor blockade. Metanephrines are a gold standard in the biochemical diagnosis of PHEO. Metanephrines are produced and released continuously independent of pulsatile catecholamine secretion.
- Catecholamines cannot be used for PHEOs <7-10 mm. About 30% of PHEOs do not secrete catecholamines. Additionally, some PHEOs produce only dopamine which is not usually measured.
- Clonidine test distinguishes increased sympathetic activity (false-positives) from PHEO (true-positives).
- Methoxytyramine, tumor size and succinate dehydrogenase subunit B (SDHB) are independent predictors of metastatic PHEO. ^{68}Ga-DOTATATE PET/CT has a better performance in patients with PHEOs as compared to other imaging modalities. Metabologenomics has a potential role in PHEO diagnosis and treatment.
- Hypoxia-inducible factor (HIF) signaling seems to play an important role in the development of PHEOs and paragangliomas (PGLs), thus suggesting novel therapeutic approaches for the treatment of these tumors. Precision medicine seems to have a potential role in the management of PHEOs.

News and Views

ICMR to Undertake a Nationwide Surveillance of Fruit Bats to Gauge Nipah Virus Threat

The Indian Council of Medical Research (ICMR)-National Institute of Virology (ICMR-NIV) will undertake a nationwide surveillance of fruit bats to gauge Nipah virus threat. The move follows the presence of Nipah virus in fruit bats (*Pteropus giganteus*) during the recent outbreak in Kerala, following which 17 people succumbed to the pathogen in May-June 2018.

"In the recent outbreak in Kerala, ICMR-NIV had shown 23% positivity of Nipah virus in the Pteropus bats while screening throat and cloacal (rectal) swabs of the mammals captured near the index case's house," scientist Devendra Mourya, Director, ICMR-NIV told TOI. The study also becomes vital as there is no information on the presence of the virus in fruit bats in the country, except West Bengal, Assam and Kerala, which are considered the hotspots of the deadly disease. Experts said the crucial intelligence on the presence of the virus in other areas would help in giving alerts, increase preparedness and contain the human-to-human transmission of the virus to save lives. "About 20 states, including Maharashtra, will be covered in the first phase. The site selection activities have begun in 16 states from January... (*TOI, January 13, 2019*)

Updated Guidelines for Treatment of Migraine

The American Headache Society (AHS) has published an updated position statement for treatment of migraine online December 10, 2018 in the journal *Headache*. The statement recommends use of evidence-based treatments when possible and appropriate; start with a low-dose and titrate slowly; reach a therapeutic dose if possible; allow for adequate treatment trial duration; establish expectations of therapeutic response and adverse events and maximize adherence. Neuromodulation may be useful for patients who prefer nondrug therapies or who respond poorly, cannot tolerate or have contraindications to pharmacotherapy.

Health Hazards from Exposure to Cement Common in Construction Workers

Men and women laborers at construction sites who handle cement or are exposed to it are at high risk of contracting skin infections owing to the harmful chemicals it contains, a new study conducted by the All India Institute of Medical Sciences (AIIMS), New Delhi has found. The study, conducted by the AIIMS Department of Dermatology and Venereology along with Sweden's Lund University, with key researchers being Dr Kaushal Verma and Dr Magnus Bruze, found that major concentrations of chemicals like hexavalent chromium in cement can lead to skin problems like dermatitis, eczema, rashes and burning sensation, among others. (*India Today, January 13, 2019*)

Whole Body Examination not Necessary to Diagnose Scabies

According to a study published December 27, 2018 in the journal *PloS Neglected Tropical Diseases*, compared to a full body examination, examination limited to hands, feet and lower legs had 90% sensitivity for detecting scabies. Body regions with highest yield were the hands (sensitivity compared to whole body examination, 51.2%), feet (49.7%) and lower legs (48.3%).

A Healthy Diet Precludes the Need of Vitamins or Nutritional Supplements for Most People

Most people do not need to take vitamins or nutritional supplements as they can get all the nutrients they need by eating a healthy diet, according to a new patient page "Vitamins and Nutritional Supplements What Do I Need to Know?" published online January 7, 2019 in *JAMA Internal Medicine*. It includes information and answers to questions about vitamins and nutritional supplements that patients often have.

Takotsubo Syndrome not as Benign as Thought to be

A systematic review and meta-regression study has shown relatively high rates of life-threatening complications such as acute heart failure (HF) with shock (19%) and malignant arrhythmias (10%), with in-hospital death occurring in 1.8% of cases of Takotsubo syndrome. One percent of the survivors had a recurrent episode. Long-term total mortality in each study was significantly associated with older age, physical stressor and the atypical ballooning form of Takotsubo syndrome. These findings are published January 3, 2019 in the *Journal of the American College of Cardiology: Heart Failure*.

Romosozumab Approved in Japan for Osteoporosis Patients at High Risk for Fracture

Romosozumab has been granted marketing authorization in Japan for the treatment of osteoporosis in patients at high risk of fracture. Romosozumab is a bone-forming agent that increases bone formation and reduces bone resorption to increase bone mineral density (BMD) and reduce the risk of fracture.

This approval is significant because approval of the agent has been held up in the United States because of safety concerns following the ARCH study, which reported a higher rate of serious adverse cardiovascular events with the drug compared with the bisphosphonate alendronate in May 2017.

New Hope with Ebola Drug Trial

There is no cure for Ebola and the mortality rate in this outbreak is about 60%. However, there is new cause for hope. Since the start of this current outbreak in August 2018 - the tenth to hit the DRC since Ebola was discovered in 1976 - patients have had access to one of four investigational treatments on a compassionate basis. These drugs were offered under an ethical framework developed by the World Health Organization (WHO) known as the Monitored Emergency Use of Unregistered Interventions (MEURI) protocol. By January 1, 248 patients had received one of these four drugs. While some patients seemed to improve, there was no scientific evaluation of the efficacy and safety of these drugs.

So, on November 24, the DRC's Ministry of Public Health announced the start of a randomized control trial (RCT). WHO is coordinating the trial which is led and funded by the DRC's Institut National de Recherche Biomédicale (INRB) and the National Institutes of Health (NIH), a part of the US Department of Health and Human Services. Other partners are MSF and ALIMA.

"This is the first multi-drug trial for Ebola treatments, and the rigorous collection and analysis of data is expected to deliver clarity about which drug works best," says Dr Janet Diaz, WHO's team lead for clinical management of emerging infectious diseases and, in this current outbreak, the team lead for care of patients with Ebola. "This will ultimately save lives in future outbreaks - either in the DRC or in other countries." (*WHO Africa*)

Public Health England Launches New Measles and Rubella Elimination Strategy

Public Health England has published a new strategy for measles and rubella elimination. The strategy focuses on 4 core components required to maintain elimination of measles and rubella:

- Achieve and sustain ≥95% coverage in the routine childhood program.
- Achieve ≥95% coverage with 2 doses of MMR vaccine in older age cohorts through opportunistic and targeted catch-up.
- Strengthen measles and rubella surveillance.
- Ensure easy access to high-quality, evidence-based information.

(Public Health England)

10 Threats to Global Health in 2019: WHO

1. Air pollution and climate change
2. Noncommunicable diseases
3. Global influenza pandemic
4. Fragile and vulnerable settings
5. Antimicrobial resistance
6. Ebola and other high-threat pathogens
7. Weak primary health care
8. Vaccine hesitancy
9. Dengue
10. Human immunodeficiency virus (HIV).

Physical Activity Reduces Mortality in Patients with Diabetes

Patients with type 2 diabetes should be prescribed physical activity to control blood sugar and improve heart health, according to a Position Paper of the European Association of Preventive Cardiology titled "Exercise training for patients with type 2 diabetes and cardiovascular disease: What to pursue and how to do it" published January 15, 2019 in the *European Journal of Preventive Cardiology*.

Women Who Undergo IVF with Frozen Embryos at Higher Risk of Pre-eclampsia

Researchers found that pre-eclampsia rates reached 12.8% in women receiving frozen embryos under a programmed cycle without a corpus luteum compared with 3.9% among women who had frozen embryo transfers under a modified natural cycle with a corpus luteum, in a study reported in the journal *Hypertension*. Women without a corpus luteum lacked relaxin, so their blood vessels may remain stiff as shown in the study, particularly the aorta.

IJCP SUTRA 711: At-risk patients or severely detrained patients should start exercising at low intensity, with each increment to be supervised closely, aiming at integration of regular physical activity into daily routine.

Clinical Trial Testing Fecal Microbiota Transplant for Recurrent Diarrheal Disease Begins

A research consortium recently began enrolling patients in a clinical trial examining whether fecal microbiota transplantation (FMT) by enema—putting stool from a healthy donor in the colon of a recipient—is safe and can prevent recurrent *Clostridium difficile*-associated disease (CDAD), a potentially life-threatening diarrheal illness. Investigators aim to enroll 162 volunteer participants, 18 years or older, who have had two or more episodes of CDAD within the previous 6 months.

Sleeping Less than 6 Hours a Night may Increase Risk of Heart Disease

People who sleep less than 6 hours a night may be at increased risk of cardiovascular disease compared with those who sleep for 7-8 hours, suggests a new study published in the *Journal of the American College of Cardiology* online January 14, 2019. Participants who slept less than 6 hours were 27% more likely to have atherosclerosis versus those who slept 7-8 hours. Those who had a poor quality of sleep were 34% more likely to have atherosclerosis than those who had a good quality of sleep.

Heavy Sweating that Led to an Unexpected Diagnosis

A 60-year-old man struggled with unexplained sweating episodes for 3 years before doctors diagnosed him with temporal lobe seizures, according to a case study published in the *Annals of Internal Medicine*. The man was otherwise healthy but had "an average of 8 discrete episodes of sweating" every 24-32 days, the authors said. These episodes lasted several minutes. He had no other symptoms, and all tests that doctors ran on him returned normal results. Doctors saw one of these sweating episodes while the patient was on an office visit, the case study said. The patient reported that "he felt it coming on; he lowered his head into his hands and had slowed verbal responses for approximately 2 minutes."

The doctors described his sweating as "profuse" and detailed a pool of sweat left on an examination table. The changes in the patient's responsiveness, something that "suggested a seizure," led the doctors to perform an ambulatory electroencephalography (EEG), which led to his diagnosis. The patient has since been prescribed anti-seizure medication and has had only one cluster of sweating episodes in the past 18 months. (*CNN*)

Parents do not Realize Teens have Suicidal Ideation and Thoughts of Death, Says Study

Half of parents surveyed were unaware of their teenagers' thoughts of killing themselves, and more than 75% were unaware of their teens' recurrent thoughts of death, according to a study published online January 14, 2019 in *Pediatrics*. Researchers found a high lack of parental awareness of youth suicidal ideation or thoughts of death, and also a significant number of teens who denied suicidal thoughts reported by parents.

Oral Antibiotics Reduce Intestinal Necrosis in Acute Mesenteric Ischemia

By decreasing luminal bacterial load and translocation, oral antibiotics, in addition to early revascularization, might reduce progression of acute mesenteric ischemia to irreversible transmural intestinal necrosis, suggests a prospective cohort study published online December 11, 2018 in the *American Journal of Gastroenterology*. Use of oral antibiotics was independently linked to reduced irreversible transmural intestinal necrosis risk (hazard ratio, 0.16).

Cabozantinib Approved as Second-line Treatment for Advanced Liver Cancer

The Food and Drug Administration (FDA) approved cabozantinib recently for the second-line treatment of hepatocellular carcinoma (HCC) in patients who progressed or were intolerant of sorafenib.

History of Allergic Reaction is an Important Part of Evaluation of Penicillin Allergy

A review article published in the January 15, 2019 issue of *JAMA* on evaluation and management of penicillin allergy says that many patients report they are allergic to penicillin but few have clinically significant reactions. A comprehensive history of the reaction that led to allergy documentation can help determine the patient's risk level.

- Low-risk history includes patients having isolated nonallergic symptoms, such as gastrointestinal symptoms, or patients solely with a family history of a penicillin allergy, symptoms of pruritus without rash, or remote (>10 years) unknown reactions without features suggestive of an IgE-mediated reaction.
- Moderate-risk history includes urticaria or other pruritic rashes and reactions with features of IgE-mediated reactions.

- High-risk history includes patients who have had anaphylaxis, positive penicillin skin testing, recurrent penicillin reactions or hypersensitivities to multiple β-lactam antibiotics.

USPSTF Recommends Risk-reducing Medications to Women at Increased Risk for Breast Cancer

The US Preventive Services Task Force (USPSTF) has published draft Recommendation Statement on the use of medication to reduce risk for breast cancer. The draft is open for public comment through February 11, 2019.

It recommends that clinicians offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene or aromatase inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects. But, the USPSTF has recommended against the routine use of risk-reducing medications, such as tamoxifen, raloxifene or aromatase inhibitors, in women who are not at increased risk for breast cancer.

Amplatzer PDA Occluder for Premature Babies Approved by the US FDA

The US FDA has approved the Amplatzer Piccolo Occluder, the first medical device to treat patent ductus arteriosus (PDA) in premature babies weighing as little as two pounds (907 g).

Study Finds High Burden of Mental Illness in Young-onset Type 2 Diabetes

People who develop young-onset type 2 diabetes, before 40 years of age, are at increased risk for hospitalizations across their lifespan compared with persons with usual-onset type 2 diabetes, including an unexpectedly large burden of mental illness in young adulthood, according to findings from a study published online January 14, 2019 in the *Annals of Internal Medicine.*

ACP Releases New Edition of its Ethics Manual

The American College of Physicians (ACP) has released the seventh edition of its Ethics Manual, published as a supplement to the current issue of *Annals of Internal Medicine*. New or significantly expanded sections of the ACP Ethics Manual include precision medicine and genetic testing, research and protection of human subjects, telemedicine, electronic communications, social media and online professionalism, electronic health records, and physician volunteerism. The manual also revisits issues that are still very pertinent and in which ACP has maintained long-standing positions, such as on end-of-life care and physician-assisted suicide, physician-industry relations, and complementary and integrative care... (*ACP, January 15, 2019*).

Union Cabinet Approves Draft Bill for National Commission for Homeopathy

The Union Cabinet has approved the draft National Commission for Homeopathy Bill, 2018, which seeks to replace the existing regulator Central Council for Homeopathy (CCH) with a new body to ensure transparency.

The draft bill provides for the Constitution of a National Commission with three autonomous boards entrusted with conducting overall education of Homeopathy by Homeopathy Education Board. The Board of Assessment and Rating to assess and grant permission to educational institutions of Homeopathy and Board of Ethics and Registration of Practitioners of Homeopathy to maintain National Register and ethical issues relating to practice are under the National Commission for Homeopathy.

It also proposes a common entrance exam and an exit exam, which all graduates will have to clear to get practicing licenses. Further, a teacher's eligibility test has been proposed to assess the standard of teachers before appointment and promotions … (*ET Health, January 16, 2019*)

WHO Launches Awareness Campaign on Social Inclusion for People with Mental Disabilities in Turkey

People with mental disabilities can face high levels of discrimination in society if the stigma that surrounds mental illness is not addressed and challenged. WHO is committed to ensuring that such people are socially included. A project, co-funded by the European Union and WHO, is set to break down the barriers against inclusion of people with mental disabilities in Turkey.

The Social Inclusion of Persons with Mental Disabilities project was launched during an official ceremony on December 5, 2018 in Ankara, Turkey. The project aims to enhance the competence of the workforce providing health care services to people with mental disabilities and to improve the community-based healthcare services currently being implemented on a national scale… (*WHO Europe, January 16, 2019*)

New British Nutrition Foundation Portion-size Guidelines

The British Nutrition Foundation has released new portion-size guidelines designed to help people eat the

right amounts of each food group, and possibly help them avoid overeating. The portion sizes are averages for healthy adults, based on a daily calorie allowance of 2,000 kcal - the amount estimated for an average, healthy weight, adult woman. Measures using hands and spoons have been provided to make them easier to follow. For example:

- Two handfuls of dried pasta shapes or rice (75 g)
- A bunch of spaghetti the size of a £1 coin, measured using your finger and thumb (75 g)
- The amount of cooked pasta or rice that would fit in two hands cupped together (180 g)
- A baked potato about the size of your fist (220 g)
- About 3 handfuls of breakfast cereal (40 g)
- A piece of cheddar cheese about the size of two thumbs together (30 g)
- About 1 tablespoon of peanut butter (20 g)
- About 3 teaspoons of soft cheese (30 g).

Air Pollution is the Greatest Environment Risk to Health, Says WHO

Nine out of 10 people breathe polluted air every day. In 2019, air pollution is considered by WHO as the greatest environmental risk to health. Microscopic pollutants in the air can penetrate respiratory and circulatory systems, damaging the lungs, heart and brain, killing 7 million people prematurely every year from diseases such as cancer, stroke, heart and lung disease. Around 90% of these deaths are in low- and middle-income countries, with high volumes of emissions from industry, transport and agriculture, as well as dirty cookstoves and fuels in homes.

The primary cause of air pollution (burning fossil fuels) is also a major contributor to climate change, which impacts people's health in different ways. Between 2030 and 2050, climate change is expected to cause 2,50,000 additional deaths per year, from malnutrition, malaria, diarrhea and heat stress.

In October 2018, WHO held its first ever Global Conference on Air Pollution and Health in Geneva. Countries and organizations made more than 70 commitments to improve air quality. This year, the United Nations Climate Summit in September will aim to strengthen climate action and ambition worldwide. Even if all the commitments made by countries for the Paris Agreement are achieved, the world is still on a course to warm by >3°C this century… (*WHO*)

TAVR Patients on DAPT at Higher Risk of Bleeding Events

Transcatheter aortic valve replacement (TAVR) patients who are discharged with dual antiplatelet therapy (DAPT) may have a significantly higher risk of major bleeding events versus patients who are discharged with antiplatelet monotherapy, according to a study published in the *American Heart Journal*. Rates of death, stroke and myocardial infarction at 1 year were similar between patients on DAPT and those on monotherapy. However, patients on DAPT had a significantly higher risk of major bleeding events.

Vaccine-preventable Infections are Common in Children Post-solid Organ Transplants

In a multicenter cohort study of 6,980 pediatric solid organ transplant recipients at a Pediatric Health Information System center, 16% of individuals had at least 1 hospitalization for a vaccine-preventable infection in the first 5 years after transplant. Children who received transplants when they were younger than 2 years and transplant recipients of lung, intestine, heart and multivisceral organs were at greater risk for hospitalization with a vaccine-preventable infection. These findings were reported in *JAMA Pediatrics* online January 14, 2019. The most common infections were influenza, rotavirus, varicella, pneumococcus and respiratory syncytial virus.

India's First Paperless Government Hospital Opens in Ahmedabad

India's first digital paperless hospital was thrown open to the public when Prime Minister Narendra Modi inaugurated the Sardar Vallabhbhai Patel Institute of Medical Sciences and Research in Ellis Bridge recently. Part of the Ayushman Bharat Program, this hospital will provide free treatment to the poor. Culled from the decades-old VS Hospital, the 18-storeyed state-of-the-art super-specialty hospital was built at a cost of Rs. 750 crore. According to Modi, the 1,500-bed hospital is "the first government hospital with a helipad for the air ambulance"… (*ET Health, January 18, 2019*)

Anti-vaccination Movement as Top Health Threat for 2019, Says WHO

The WHO has listed the anti-vaccination movement among the top health threats globally in 2019.

Vaccine hesitancy - the reluctance or refusal to vaccinate despite the availability of vaccines - threatens to reverse progress made in tackling vaccine-preventable diseases.

Measles, for example, has seen a 30% increase in cases globally. The reasons for this rise are complex, and not all of these cases are due to vaccine hesitancy. However, some countries that were close to eliminating the disease have seen a resurgence.

The reasons why people choose not to vaccinate are complex; a vaccines advisory group to WHO identified complacency, inconvenience in accessing vaccines, and lack of confidence as key reasons underlying hesitancy. Health workers, especially those in communities, remain the most trusted advisor and influencer of vaccination decisions, and they must be supported to provide trusted, credible information on vaccines.

In 2019, WHO will ramp up work to eliminate cervical cancer worldwide by increasing coverage of the HPV vaccine, among other interventions. 2019 may also be the year when transmission of wild poliovirus is stopped in Afghanistan and Pakistan. Last year, less than 30 cases were reported in both countries … (*WHO*)

Ebola Outbreak in Congo Crosses 600 Cases

The Democratic Republic of Congo's Ebola outbreak, which began August 1, is continuing unabated in the new year. The total number of probable patients is now 663, while 407 deaths are likely attributable to the viral illness, the Ministry of Health said recently. An additional 123 people, who doctors suspect may be sick with Ebola, are currently under investigation. The ministry also reported that 237 people have recovered from the life-threatening illness… (*CNN, January 17, 2019*)

First Generic Version of Vigabatrin to Help Treat Seizures Gets FDA Nod

The US FDA has approved the first generic version of vigabatrin 500 mg tablets for treating complex partial seizures, also called focal seizures, as an adjunctive therapy (given with another primary treatment) in patients 10 years and older who have responded inadequately to several alternative (refractory) treatments.

Study Shows Association Between Frailty and Dementia of Alzheimer's Disease

Frailty appeared to modify the association between Alzheimer's disease pathology and Alzheimer's dementia in older adults, according to a cross-sectional analysis of data from the Rush Memory and Aging Project published in *The Lancet Neurology*. As Alzheimer's disease frailty increased, the relationship between pathology and dementia weakened - suggesting that the frailer people are, the less likely they could tolerate a given burden of Alzheimer's disease pathology.

Making Simple Healthy Changes in Lifestyle can Boost Longevity

A study published in the journal *Circulation*, which examined five specific lifestyle factors linked to longevity, found that those who adopted all five had a life expectancy at age 50 of 14 years longer for women and 12 years longer for men than those who adopted none of the healthy steps.

1. Regular physical activity - The American Heart Association (AHA) recommends at least 150 minute/week of moderate-intensity physical activity or 75 minute/week of vigorous aerobic activity. You can also do a combination of the two.
2. Appropriate body weight - Maintain a body mass index (BMI) of 18.5-24.9.
3. A healthy diet - Select plenty of fruits and vegetables, and try to work them into every meal and snack. Other foods to emphasize in a healthy eating pattern are whole grains, low-fat dairy products, skinless poultry and fish, nuts and legumes and nontropical vegetable oils. Try to limit sodium, red meat, saturated fat and sugars, including sugary beverages. Remember to drink plenty of water for hydration.
4. Don't smoke.
5. Drink in moderation - The AHA considers moderate alcohol consumption to be an average of 1-2 drinks/day for men and 1 drink/day for women. (A drink is 12 ounces of beer, 4 ounces of wine, 1.5 ounces 80-proof spirits or 1 ounce 100-proof spirits).

Ultraviolet Disinfection Very Effective in Eliminating Pathogens in Hospital Settings

Using ultraviolet (UV) disinfection technology to reduce the risk of hospital-acquired infections eliminated up to 97.7% of pathogens in operating rooms (ORs), according to a study published January 17, 2019 in the *American Journal of Infection Control*.

Moving More in Old Age may be Linked to Sharper Memory

Older adults who move more, either with daily exercise or even simple routine physical activity like housework, may preserve more of their memory and thinking skills, even if they have brain lesions or biomarkers linked to dementia, according to a study

published in the January 16, 2019, online issue of the journal *Neurology*.

Health Ministry Bans 80 More Fixed-dose Combination Drugs

The Union Health Ministry has banned 80 more fixed-dose combination (FDC) drugs which include antibiotics, painkillers, medicines used for treating fungal and bacterial infections, hypertension and anxiety, officials said recently. A notification was issued by the government, stating that the ban has come into force since January 11, they said.

With this, the total number of banned FDCs now stands at 405. Another 325 drugs were banned in September last year. (*ET Health-PTI, January 18, 2019*)

Heart Patients should Avoid Oral Decongestants and NSAIDs

The AHA has cautioned about the use of oral decongestants like pseudoephedrine or phenylephrine and nonsteroidal anti-inflammatory drugs (NSAIDs). People with uncontrolled high BP or heart disease should avoid taking oral decongestants like pseudoephedrine or phenylephrine. NSAIDs, which carry a warning label about the increased risk for a heart attack or stroke can be especially risky for people with heart disease or heart failure. NSAIDs reduce the amount of sodium excreted through the urine, which increases fluid retention and raises BP.

Gene Sequencing Approach may Help Tailor Treatments for Pediatric Kidney Transplant Recipients

Whole-exome sequencing of blood or saliva revealed a genetic diagnosis of kidney disease in 32.7% of pediatric kidney transplant recipients in a study published online January 17, 2019 in the *Journal of the American Society of Nephrology*. The findings indicate that such a sequencing strategy may help individualize pre- and post-transplant care for many young kidney transplant recipients. The chances of detecting a genetic diagnosis was highest for patients with urinary stone disease, followed by renal cystic ciliopathies, steroid-resistant nephrotic syndrome, congenital anomalies of the kidney and urinary tract, and chronic glomerulonephritis.

Single-dose Tafenoquine Prevents *Plasmodium vivax* Malaria Relapse

Single-dose tafenoquine resulted in a significantly lower risk of *Plasmodium vivax* recurrence than placebo in patients with phenotypically normal G6PD activity in a study published online January 17, 2019 in the *New England Journal of Medicine*. The hazard ratio for the risk of recurrence was 0.30 with tafenoquine as compared with placebo and 0.26 with primaquine as compared with placebo.

Confidentiality Discussions may Help Young Patients Open-up About Sensitive Topics

Fewer than half of young people reported having discussed 10 of 11 specific topics recommended by national medical guidelines at their last visit, in a study published online January 16, 2019 in the journal *Pediatrics*. On average, young women discussed 3.7 of the topics, while males averaged 3.6. Factors independently associated with health discussions were - ever talked with a provider about confidentiality, ever had private time with a provider, use of health checklist and/or screening questionnaire at last visit and time spent with provider during last visit.

Serum Cryptococcal Antigen Titers Predict Mortality in HIV-infected Patients with Cryptococcal Meningitis

Serum cryptococcal antigen (CrAg) titers ≥1:1,024 not only were associated with concurrent cryptococcal meningitis but also predicted mortality, says a study published in the January 2019 issue of *HIV Medicine*. The study further suggests that HIV-infected patients with a positive serum CrAg test during screening should receive lumbar punctures regardless of symptoms to rule out cryptococcal meningitis and patients with serum CrAg titres ≥1:1,024 should be offered immediate care.

New 'Planetary Health Diet' can Save Lives and the Planet

An international team of scientists has developed a diet it says can improve health while ensuring sustainable food production to reduce further damage to the planet. And it can prevent up to 11.6 million premature deaths without harming the planet, says the report published in the medical journal *The Lancet*.

The "planetary health diet" is based on cutting red meat and sugar consumption in half and upping intake of fruits, vegetables and nuts. The authors warn that a global change in diet and food production is needed as 3 billion people across the world are malnourished, which includes those who are under and overnourished and food production is overstepping environmental targets, driving climate change, biodiversity loss and pollution… (*CNN*)

Spiritual Prescription: Meditation vs. Concentration

KK AGGARWAL

Meditation is not concentration. Concentration is holding the mind to something within or outside the body, while meditation is an unbroken flow of thoughts towards the object of concentration. It can be called prolonged concentration. Meditation is like pouring of oil from one vessel to another in a steady unbroken stream.

Samadhi or absorption is when the object of concentration and the mind of the perceiver becomes one. When Concentration, Meditation and Samadhi are brought to bear upon one subject, it is called Samyam.

According to yoga sutras of Patanjali, (3.1-3.6), meditation needs to be learnt and applied step by step. The practice starts by sitting straight with erect spine, preferably in Padmasana (one can also sit on the chair) and concentrate on the breathing or on a primordial sound given by the teacher.

When the mind can be made to flow uninterruptedly towards the same object for 12 seconds, one is said to have learnt the process of concentration.

When the mind can continue in that concentration for 12 times (12 seconds × 12 i.e., 2 minutes 24 seconds), one is said to be practicing meditation.

When the mind can continue in that concentration for 12 times (2 minutes 24 seconds × 12 i.e., 28 minutes 48 seconds), one is said to be in Samadhi. And if this lower Samadhi can be maintained for 12 times, i.e., for 5 hours 45 minutes and 36 seconds, one is said to be in Nirvikalpa Samadhi.

The mind becomes one-pointed when similar thought waves arise in succession without any gap between them.

One should remember that during meditation, the object of concentration may change in form, time and rhythm.

The whole process of meditation, therefore, varies from person to person and day to day. During meditation, some may only concentrate, some may actually meditate and some may go into Samadhi. Most of us wander from concentration to meditation.

Once in meditation or Samadhi, by fixing the mind on various structures, internal or external, one can achieve siddhi powers. For e.g., by concentrating on the tip of nose, one can acquire better smelling powers; by concentrating on the tip of the tongue, one can acquire supranormal tasting powers; by concentrating on the middle part of the tongue, one can acquire supranormal powers of touch; by concentrating on the root of the tongue, one can acquire supranormal hearing; and by concentrating on palate one can acquire supranatural color perceptions (sight). With experience, one can concentrate upon any object of any size, from the atom to the infinity.

Just as pure crystal takes color from the object nearest to it, the mind, when cleared of thoughts, achieves identity with the object of concentration.

Primordial sound (beej mantra) meditation is based on the principle that the initial one-point concentration on a particular sound (seed) over a period of time becomes seedless or thoughtless (yoga sutras of Patanjali 1.51).

Swami Vivekananda correlated it with Raj Yoga and said that our average span of attention on a particular object is only around 3 seconds. He said that if one is able to increase this attention span and concentration at an object of our choice for 12 seconds then we are practicing Patanjali's sixth stage of yoga or 'dharana', which translates as contemplation. And if we can further increase our concentration ability to 12 × 12 seconds or for 144 seconds, then we have reached the mental plateau of meditation or 'dhyana'. Swami Vivekananda further went on to attribute values to the exalted state of samadhi or transcendental conscious mental state which in value is termed as arising from a meditative or concentration span of 12 × 12 × 12 seconds, which is 30 minutes or half an hour.

Vedanta describes it in terms of units. It says that if you can concentrate 12 seconds on a subject uninterrupted, it becomes 1 unit of concentration; 12 such units of concentration make one unit of meditation; 12 units of meditation lead to the first stage of Samadhi and

Group Editor-in-Chief, IJCP Group

12 units of this samadhi lead to the highest samadhi, the supreme realization of Atman. Dharana is concentration; Dhyana is meditation and Samadhi is trance.

Patanjali called them as 'Matra': If you are able to sit, withdraw the mind and fix it upon a focal point within (it may be gross, subtle or anything), and are able to keep the mind fixed like that for a period of 12 Matras - a Matra is approximately a moment or a second - it is counted as 'one concentration'. It says, "If you can keep the mind steady without moving, without any contrary thoughts coming in, and without moving away from the object of concentration for a period of twelve Matras, it is regarded as 'one Dharana or one concentration". It is mentioned that one should go on practicing this Dharana for days and weeks and months so that it becomes longer and longer. By continuous practice, if one is able to keep the mind focused upon one single point without moving here or there, for 144 seconds (a period of 12 Dharanas), then the person is called Dhyani or a Dhyana Yogi.

Yoga sutra of Patanjali (3.6) clearly says that meditation must be learnt in stages. It calls for repeated practice of meditation. The three basic components of meditation are: The subject of meditation, the center of consciousness at which the mind is held, and the method employed to guide the mind to concentration. The subject of meditation may be the non-dual all-pervading self, any specific aspect of the divine, or any divine incarnation. The center of consciousness may be at the heart, or between the eyebrows, or at the crown of the head. The method employed to invoke concentration may be any of the following: Japa, or repetition of a sacred word; discrimination between the real and the unreal; dispassion, which is knowing the evil effect of sense-enjoyment; pranayama or control of breath and ceremonial observances.

But regularity is most important. One can start with looking at any object - flame, idol or picture for 12 seconds with total concentration and without blinking eyelids (concentration). And then one practices 12 concentrations to make one meditation. The proper meditation thus need not last more than 2 minutes 24 seconds.

■■■■

INSPIRATIONAL STORY

The Treasure

The cheerful girl with bouncy golden curls was almost five. Waiting with her mother at the checkout stand, she saw them: a circle of glistening white pearls in a pink foil box.

"Oh please, Mommy. Can I have them? Please, Mommy, please!"

Quickly the mother checked the back of the little foil box and then looked back into the pleading blue eyes of her little girl's upturned face.

"A dollar ninety-five. That's almost $2.00. If you really want them, I'll think of some extra chores for you and in no time you can save enough money to buy them for yourself. Your birthday's only a week away and you might get another crisp dollar bill from Grandma."

As soon as Jenny got home, she emptied her penny bank and counted out 17 pennies. After dinner, she did more than her share of chores and she went to the neighbor and asked Mrs. McJames if she could pick dandelions for ten cents. On her birthday, Grandma did give her another new dollar bill and at last she had enough money to buy the necklace.

Jenny loved her pearls. They made her feel dressed up and grown up. She wore them everywhere - Sunday school, kindergarten, even to bed. The only time she took them off was when she went swimming or had a bubble bath. Mother said if they got wet, they might turn her neck green.

Jenny had a very loving daddy and every night when she was ready for bed, he would stop whatever he was doing and come upstairs to read her a story.

One night when he finished the story, he asked Jenny, "Do you love me?"

"Oh yes, Daddy. You know that I love you."

"Then give me your pearls."

"Oh, Daddy, not my pearls. But you can have Princess - the white horse from my collection. The one with the pink tail. Remember, Daddy? The one you gave me. She's my favorite."

"That's okay, Honey. Daddy loves you. Good night." And he brushed her cheek with a kiss.

About a week later, after the story time, Jenny's daddy asked again, "Do you love me?"

"Daddy, you know I love you."

"Then give me your pearls."

"Oh Daddy, not my pearls. But you can have my babydoll. The brand new one I got for my birthday. She is so beautiful and you can have the yellow blanket that matches her sleeper."

"That's okay. Sleep well. God bless you, little one. Daddy loves you." And as always, he brushed her cheek with a gentle kiss.

A few nights later when her daddy came in, Jenny was sitting on her bed with her legs crossed Indian-style. As he came close, he noticed her chin was trembling and one silent tear rolled down her cheek.

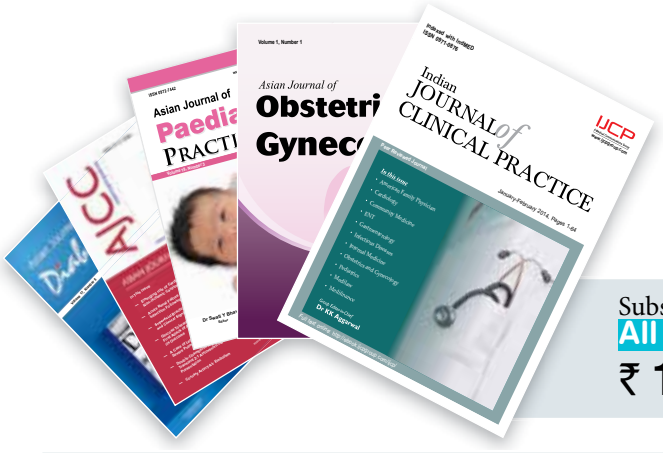
" What is it, Jenny? What's the matter?"

Jenny didn't say anything but lifted her little hand up to her daddy. And when she opened it, there was her little pearl necklace. With a little quiver, she finally said, "Here, Daddy. It's for you."

With tears gathering in his own eyes, Jenny's kind daddy reached out with one hand to take the dime-store necklace, and with the other hand he reached into his pocket and pulled out a blue velvet case with a strand of genuine pearls and gave them to Jenny. He had them all the time. He was just waiting for her to give up the dime-store stuff so he could give her genuine treasure.

So like our heavenly Father. What are you hanging on to?

■■■■



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Lighter Side of Medicine

HUMOR

TROUBLE ON THE ROOF

Mike and Rob were laying tiles on a roof when a sudden gust of wind came and knocked down their ladder.

"I have an idea," said Mike. "We'll throw you down, and then you can pick up the ladder."

"What, do you think I'm stupid?" Rob replied." I have an idea. I'll shine my flashlight, and you can climb down on the beam of light."

"What, do you think I'm stupid?" Mike answers. "You'll just turn off the flashlight when I'm halfway there."

THE SHIPWRECKED MARINER

The shipwrecked mariner had spent several years on a deserted island. Then one morning he was thrilled to see a ship offshore and a smaller vessel pulling out toward him.

When the boat grounded on the beach, the officer in charge handed the marooned sailor a bundle of newspapers and told him, "The captain said to read through these and let us know if you still want to be rescued."

NEW DISEASE

A recent college graduate took a new job in a hilly Eastern city and began commuting each day to work through a tiring array of tunnels, bridges and traffic jams. Thinking it would make the trip more bearable, he invited several coworkers to share the ride. However, the commute actually got more stressful, especially the trips through the tunnels. He consulted the company doctor.

"Doc," the frustrated commuter complained, "I'm fine on the bridges, in the traffic, in the day and at night, and even when Joe forgets to bathe all week. But now, when I get in the tunnels with those four other guys crowded into the car, I get anxious and dizzy, and I feel like I'm going to explode."

Without further analysis, the doctor announced he had diagnosed the ailment. "What is it, Doc? Am I going insane?"

"No, no, no, my boy. You have something that is becoming more and more common." "Tell me! What is it?"

"You have what is known as Carpool Tunnel Syndrome."

HIGH BLOOD PRESSURE

When a physician remarked on a new patient's extraordinarily ruddy complexion, he said, "High blood pressure, Doc. It comes from my family."

"Your mother's side or your father's?" the doctor asked.

"Neither," he replied. "It's from my wife's family."

"Oh, come now," the doctor said. "How could your wife's family give you high blood pressure?"

He sighed. "You oughta meet 'em sometime, Doc!

FIRST DAY AT SCHOOL

A school teacher injured his back and had to wear a plaster cast around the upper part of his body.

It fit under his shirt and was not noticeable at all. On the first day of the term, still with the cast under his shirt, he found himself assigned to the toughest students in school.

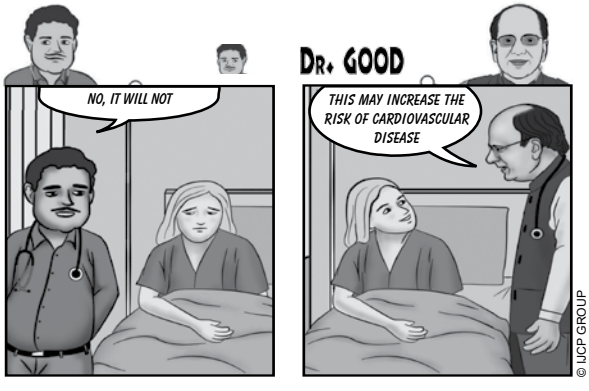
Walking confidently into the rowdy classroom, he opened the window as wide as possible and then busied himself with desk work.

When a strong breeze made his tie flap, he took the desk stapler and stapled the tie to his chest.

He had no trouble with discipline that term.

Dr. Good and Dr. Bad

SITUATION: A female with type 2 diabetes recently had a severe episode of hypoglycemia. She was worried if this could have an impact on her health in the future.



LESSON: The researchers of a study have shown that severe hypoglycemia is suggestive of declining health. In addition, it is a useful marker for determining risk of cardiovascular events and mortality.

Diabetes Care. 2018;41(1):104-11.

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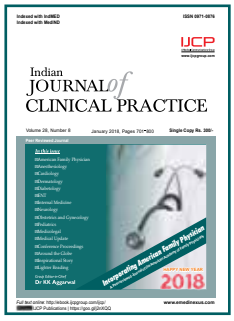

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Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

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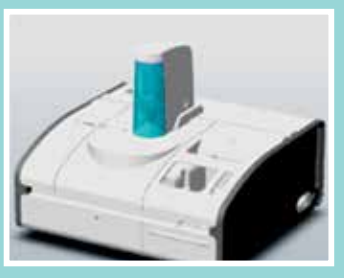

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