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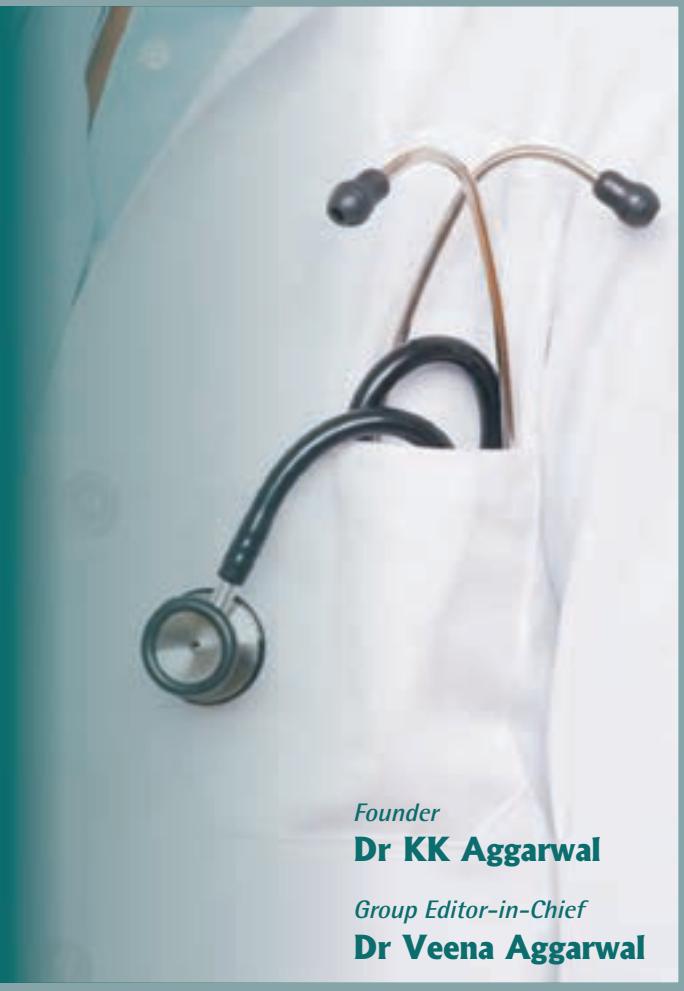

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Coronavirus Updates

COVID-19-RELATED DEATHS RISE AGAIN, SAYS WHO

The number of weekly new COVID cases continues to show a decline, but the weekly deaths have again risen by 4% following 5 weeks of decreasing trend, says the World Health Organization (WHO) in its latest COVID-19 Weekly Epidemiological Update. The new weekly deaths in the Regions of Americas were up by 21% and in the Western Pacific region by 17%, while the new weekly deaths decrease in the other four regions… (*Source: WHO, June 15, 2022*)

COVID-19 VACCINES FOR CHILDREN BELOW 5 YEARS IN THE US MAY START SOON

An FDA panel has unanimously recommended the Pfizer-BioNTech and Moderna COVID-19 vaccines for use in children younger than 5 years beginning from 6 months of age stating that their benefits outweigh the risks in this age group… (*Source: Medscape, June 15, 2022*)

A NEGATIVE COVID-19 TEST NO LONGER MANDATORY TO ENTER THE US

The Centers for Disease Control and Prevention (CDC) has revoked the mandatory requirement of a negative COVID-19 test just prior to traveling or a documentation stating recovery from COVID for international travelers. This will come into effect from June 12, 2022. However, the CDC still recommends travelers to test themselves for COVID nearer to their traveling date and desist from traveling if positive … (*Source: CDC, June 10, 2022*)

DR FAUCI BECOMES COVID-19-POSITIVE

Dr Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases (NIAID) and also the Chief Medical Advisor to the President of the United States, has tested positive for COVID-19 on a rapid antigen test. However, according to the National Institutes of Health (NIH), Dr Fauci has mild symptoms. He is fully vaccinated and has taken two booster doses as well… (*Source: NIH, June 15, 2022*).

PROTECTIVE EFFICACY OF COVAXIN AGAINST DELTA AND OMICRON VARIANTS OF CONCERN

Results of preclinical study conducted on Syrian hamster model show that Covaxin booster dose enhanced the protective efficacy of the vaccine against Delta variant and was also protective against the BA.1.1 and BA.2 subvariants of the Omicron. The viral load in the lungs diminished subsequent to the booster vaccination… (*Source: bioRxiv, June 14, 2022*)

COVID-19 VACCINES PREVENTED 20 MILLION COVID-19 DEATHS FROM 2020 TO 2021

A mathematical modeling study from the Imperial College London published in the *Lancet Infectious Diseases* has described the impact of the COVID-19 vaccines in curbing the onslaught of the pandemic. During the first year of their availability, between December 8, 2020 and December 8, 2021, vaccines prevented 14.4 million deaths from COVID-19 in 185 countries. Addition of excess deaths increased this estimate to nearly

20 million. During the first year, an estimated 60% of people globally had received at least one dose of the vaccine…. (*Source: Medscape, June 23, 2022*)

SURGE IN BA.4 AND BA.5 CASES IN EUROPE

There has been an upsurge of new COVID-19 infections in Europe driven by the BA.4 and BA.5 Omicron subvariants. On 22nd June, France recorded more than 95,000 daily new cases. Cases are also rising in other European countries such as Portugal. These new subvariants, which are more infectious but less virulent, are likely to become the dominant strains in Europe, says the European Centre for Disease Prevention and Control …(*Source: Reuters, June 23, 2022*)

MODERNA SAYS ITS COMBINATION COVID-19 BOOSTER VACCINE IS EFFECTIVENESS AGAINST OMICRON

Moderna says that its combination COVID-19 booster vaccine candidate mRNA-1273.214-induced eightfold increase in the neutralizing antibody titers among seronegative study subjects against the Omicron variant than the original mRNA-1273 vaccine after 1 month of administration. It was also well-tolerated with a side effect profile similar to the mRNA-1273 vaccine. The vaccine candidate contains the original mRNA-1273 vaccine along with a vaccine candidate targeting the Omicron variant… (*Source: Moderna, June 8, 2022*).

WOMEN ARE MORE LIKELY TO DEVELOP LONG COVID THAN MEN

Women are more likely to develop long COVID than men with odds ratio (OR) of 1.22, according to a recently published review in *Current Medical Research and Opinion*. The likelihood of ENT (OR 2.28), gastrointestinal (OR 1.60), mood/psychiatric (OR 1.58), neurological (OR 1.30), dermatological (OR 1.29) sequelae were higher among women, while men were more likely have renal (OR 0.74) and endocrine (OR 0.75) disorders…(*Source: Current Medical Research and Opinion, June 20, 2022*)

SECOND PFIZER BOOSTER DOSE 72% PROTECTIVE AGAINST COVID-RELATED DEATHS DURING OMICRON WAVE

In a study from Israel involving more than 24,000 residents of long-term care facilities, a fourth vaccine dose of the Pfizer-BioNTech vaccine was highly protective against COVID-19 hospitalizations and deaths. It provided 34% protection against infection, 64% to 67% against hospitalizations and 72% against deaths during the Omicron wave. The study was conducted between January 10 through to March 2022… (*Source: JAMA Internal Medicine, June 23, 2022*)

PREVALENCE OF BA.4 AND BA.5 OMICRON SUBVARIANTS RISING IN THE US

The prevalence of BA.4 and BA.5 sublineages of the Omicron severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant is increasing in the United States. Together the two strains now constitute 13% of new infections compared to 7.5% in the previous week, as per latest CDC data; 7.6% are BA.5 and 5.4% are BA.4 cases. BA.2.12.1 is the predominant circulating strain at 62.2%, while BA.2 accounts for 24.8% of cases… (*Source: Medscape, June 9, 2022*).

HIGHER IMMUNE EVADING PROPERTIES OF BA.4 AND BA.5

The BA.4 and BA.5 Omicron subvariants show 4.2 times higher immune escape potential in persons who are fully vaccinated and also boosted vis-à-vis BA.2, thereby increasing the chances of breakthrough infections. The immune escape potential was less with BA.2.12.1 (1.8-fold). Bebtelovimab was the only monoclonal antibody with robust activity against BA.4 and BA.5 and also BA.2.12.1… (*Source: bioRxiv, May 26, 2022*)

INTRAUTERINE EXPOSURE TO SARS-COV-2 INCREASE RISK OF NEURODEVELOPMENTAL DEFICITS IN INFANTS

Babies born to COVID-positive mothers are at risk of neurodevelopmental deficits, according to preliminary results of a small study presented at the virtual meeting of the European Psychiatric Association (EPA) 2022 Congress. At 6 weeks of age, the infants showed significantly low scores on the social interactive dimension of the Brazelton Neonatal Behavioral Assessment Scale (NBAS) if the mother became infected before 20 weeks of gestation…(*Source: Medscape, June 8, 2022*).

COVID-19 VACCINE PROTECT AGAINST SEVERE OUTCOMES IN HEART FAILURE PATIENTS

Heart failure patients who are fully vaccinated and boosted as well are at lower risk of all-cause mortality with hazard ratio (HR) of 0.33 compared to those who were fully vaccinated but had not taken the booster dose (HR 0.36) and those who were unvaccinated. They also had a lower probability of hospitalization (incidence rate ratio [IRR] 0.68) including ICU admission (IRR 0.63) than those who are partially vaccinated or unvaccinated … (*Source: Journal of Cardiac Failure, June 9, 2022*).

With inputs from Dr Monica Vasudev

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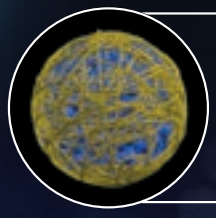

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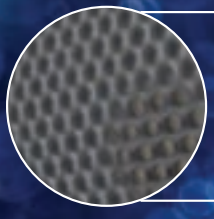

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Dr Sanjay Kalra
President Elect IPATH (Indian Professional Association)
Dept. of Endocrinology, Bharti Hospital, Karnal, Haryana, India

Transgender Health Issues: Children of a Lesser God

ABSTRACT

The transgender community is a distinct population, with its unique health care needs, wishes and preferences. This calls for an enhanced focus on transgender health issues, as an integral part of the health care system, and also through specialized multidisciplinary centers of excellence. The authors call for sensitization of the health care profession, and request for sensitivity while managing transgender and gender diverse individuals. If this is accomplished, transgender health issues will become normalized as part of the wider spectrum of health care, just as being a transgender person is normal.

Keywords: Gender-affirmative therapy, inclusive care, person-centered care, patient-centered care, transgender health care

The transgender community is a well-recognized minority in India, and across the globe. Along with other members of the LGBTQAI+ (Lesbian, Gay, Bisexual, Transgender, Queer, Asexual, Intersex, The plus sign denoting all other identities) spectrum, transgender individuals are gradually acknowledging and appreciating their rights, as well as responsibilities.[1] Major successes in legal and political acceptance have meant that transgender persons are now allowed to choose "other" non-binary gender in legal documents in some countries, and fight (and win) elections in others.

Within the health care system as well on social front, however, transgender persons still face challenges and concerns.[2] Current medical and nursing curricula do not address the needs of transgender and gender diverse people.[3] Neither do they make any attempt to sensitize health care professionals regarding how to use gender friendly language and behavior. This, coupled with a heavy burden on existing health services, leads to a situation where health care providers feel inadequately prepared to handle trangender patients, and transgender persons remain dissatisfied with the quality of care they receive. There are committed health care professionals who do provide gender friendly support as well as advice but there number is very few, and are woefully inadequate for the huge number of transgender and gender diverse individuals in our society. Besides a poor referral system and lack of awareness in primary health care provider further aggravates the management of transgender and gender diverse individuals.

Being gender incongruent is not a disease, but transgender persons do face more than their fair share of health challenges.[4] Some of these issues are listed in Table 1. This list conveys an idea of the various health care services needed by members of the transgender community. It is not always necessary that each individual will require help or assistance for all the domains enumerated. It is also not always possible to have all services under one roof. At the same time, transgender persons should not always have to seek specialist advice for routine medical and metabolic issues. Primary health needs should be resolved at the primary care level, while ensuring that the health care providers are sensitive to the needs, wishes and preferences of transgender individuals.[5]

Secondary and tertiary care needs may need to be handled by specialists. A multimodal approach should be followed, in which all relevant specialties, such as mental health,[1] endocrinology/metabolism[6,7] internal medicine/pediatrics, surgery and urology/gynecology,

Table 1. Some Domains of Transgender Health

The health care ecosystem
• Trans*-sensitive communication
• Trans*-friendly infrastructure
• Trans*-facilitatory medicolegal rules and regulations
Pediatrics and adolescent health
• Early supportive care
• Puberty suppression till final affirmative care
• Support and affirmative intervention before, during and after puberty
• Social support, including within family, at school
Endocrine health
• Gender affirmative interventions
• Metabolic support, e.g., for bone health
Mental health
• Psychological counseling
• Psychiatric intervention, if needed
Medical health
• Prevention of commonly encountered infections, e.g., STDs, blood-borne infections
• Mitigation of medical concerns noted with endocrine/surgical intervention
• Facial feminization/masculinization interventions
Surgical aspects
• Top surgery, if required
• Bottom surgery, if required
Fertility medicine
• Preservation of ova/sperms
• Pregnancy/fatherhood, if required
Non-medical gender-affirmative interventions
• Tucking and binding practices and related issues
• Skin, hair, nail health
• Voice and communication

*Person/Individual

should integrate transgender health into their academics and practice. Concurrently, multidisciplinary centers of excellence should be created to offer state-of-the-art transgender health services under one roof. This will help transgender health emerge as a distinct discipline, serving a particular segment of population, akin to pediatrics, geriatrics, gynecology or urology. It will also facilitate the nesting and growth of transgender health issues within relevant specialties, like psychology, psychiatry, surgery and fertility management.

Multiple activities are taking place towards achieving this goal of comprehensive transgender care. The IPATH (Indian Professional Association for Transgender Health), supported by WPATH (World Professional Association for Transgender Health), is working to share and spread knowledge about transgender health care amongst doctors, nurses and other health care professionals.[8,9] The Government of India plans to set up a Centre of Excellence for Transgender Health at the All India Institute of Medical Sciences (AIIMS), New Delhi. State governments do not lag behind, and the government of Tamil Nadu has also created two centers of excellence [personal communication, Dr S Sridhar, Madurai]. Yeoman service is being provided at various other public and private hospitals across the country.

What is required, perhaps, is an extra push to sensitize all health care professionals, and all members of the public, to the requirements and rights of the transgender community. All that we request is "listen to the community such that they love to speak to you. Speak with the community such that they love to listen to you".

If we are able to accomplish this, collectively, as a fraternity, as a nation, the title of this editorial will automatically become redundant. Transgender health issues will become a matter of normalcy, just as being a transgender person is normal.

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ORIGINAL ARTICLE

Safety and Efficacy of Nimesulide/Paracetamol Fixed-dose Combination in Acute Pain (SAFE Study)

MANGESH TIWASKAR[*], A MURUGANATHAN[†], DATTATRAY PAWAR[‡]

ABSTRACT

Background: Nimesulide shows preferential inhibition for the cyclooxygenase-2 (COX-2) enzyme, which blocks the formation of prostaglandins critical in pain and inflammatory pathways. Few studies in the past have reported rare and unpredictable hepatic effects with nimesulide. The present study aimed to evaluate the efficacy and safety of nimesulide/paracetamol (100 mg + 325 mg) fixed-dose combination twice a day for 2 weeks in the management of acute pain in Indian population. **Materials and methods:** This was a multicenter study, performed on 500 patients, by 24 experienced physicians across India. The primary outcome assessed clinical safety at 2 weeks for mild/serious adverse effects (AEs), change in liver function tests (LFTs), serum bilirubin and alkaline phosphatase levels. The secondary outcomes assessed the clinical effectiveness in reduction of pain at rest and at movement. **Results:** Analysis of LFT at 2 weeks showed a slight increase (mean change) in the aspartate transaminase {-0.73 [95% confidence interval (CI) -1.54, 0.09; p = 0.081]}, alanine transaminase [-1.73 (95% CI -2.82, -0.64; p = 0.002)], serum bilirubin [-0.02 (95% CI -0.04, -0.001; p = 0.018)] and alkaline phosphatase levels [-1.92 (95% CI -5.84, 2; p = 0.336), not exceeding the normal range. Only one in 500 patients reported AEs. The numerical rating scale (NRS) scores for intensity of pain at rest and at movement at 2 weeks, ≤7 days and >7 days were 68.38%, 68.44% and 68.39%; and 65.43%, 64.60% and 66.02%, respectively. An improvement of 96.6% was observed in patient global assessment scale (GAS) and 97.2% in physician GAS. **Conclusion:** Nimesulide/paracetamol combination was safe, effective and well-tolerated in acute pain conditions and did not lead to clinically significant changes in liver parameters indicating hepatic safety.

Keywords: Nimesulide, paracetamol, acute pain, hepatic safety, COX-2 inhibitor

Pain is among the most frequent complaints encountered in clinical practice.[1] Acute pain is a red flag for a disease or a threat to the body by a noxious insult and is expected to resolve within the normal anticipated healing period.[2] Unrelieved or undertreated acute pain can lead to chronic pain.[2] Nonsteroidal anti-inflammatory drugs (NSAIDs) are the cornerstone of acute pain management.[2] They are a chemically diverse group of drugs that share similar therapeutic anti-inflammatory, analgesic and antipyretic properties, with the exception of the cyclooxygenase (COX)-2-selective agents.[2] The most important property of NSAIDs is the reduction of the biosynthesis and accumulation of prostaglandins at the site of injury or inflammation by inhibition of the cyclooxygenases (COX-1 and the inducible COX-2).[2] Their analgesic and anti-inflammatory properties make NSAIDs, the treatment of choice for relieving pain due to local inflammation.[1] However, treatment with NSAIDs must be short-term and well-tolerated to overcome the painful syndrome at an acute stage leading to a quicker and easier recovery, owing to the tendency for spontaneous remission.[1]

Nimesulide is a unique, nonselective NSAID, which preferentially inhibits the COX-2 enzyme, that blocks the formation of prostaglandins critical in pain and inflammatory pathways.[2] The relative specificity of nimesulide for COX-2 activity, attributes a close association to pain pathways as opposed to COX-1, which has major effects on gastric mucosa cell protection and platelet function.[2] In India, nimesulide has been

[*]Consultant Physician and Diabetologist, Karuna Hospital, Borivali West, Mumbai; Shilpa Medical Research Centre, Mumbai, Maharashtra
[†]AG Hospital, Tirupur, Tamil Nadu
[‡]Medical Affairs Department, Alkem Laboratories Ltd, Mumbai, Maharashtra
Address for correspondence
Dr Dattatray Pawar
Medical Affairs Department, Alkem Laboratories Ltd, Alkem House, Senapati Bapat Marg, Lower Parel, Mumbai - 400 013, Maharashtra
E-mail: dattatray.pawar@alkem.com

used for the treatment of acute pain due to trauma and acute musculoskeletal disorders such as tendinitis, sprains, strains, soft-tissue injury and myalgia, low back pain (LBP), pain due to dental, orthopedic and other minor surgeries in adults.[2,3]

Liver damage is a rare but well-recognized adverse event associated with the entire NSAID drug class.[2] Studies have reported that about 15% patients taking NSAIDs experience at least transient serum aminotransferase elevations; however, a lower rate has been reported with nimesulide.[2] Only less than 1% patients report greater than threefold elevation in aminotransferase level with nimesulide therapy and in majority of the cases, elevated serum aminotransferase levels are transient, mild and asymptomatic, and may resolve even when the drug is used in continuum.[4]

The onset of symptoms is usually 1 to 4 months after commencing therapy.[5] Liver injury usually resolves 2 to 16 months after drug withdrawal.[5] Recent pharmaco-epidemiological studies concluded that the safety concerns with nimesulide are not higher compared with other NSAIDs, and the risk/benefit profile for hepatic side effects is comparable with other drugs in this class.[2]

Nimesulide is used in more than 50 countries, and is the most prescribed NSAID in Italy and Portugal, with Italy accounting for half the worldwide market.[6] Some studies have reported rare and unpredictable hepatic injury with nimesulide therapy.[2] However, in 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of systemic nimesulide-containing medicines outweigh their risks in the treatment of acute (short-term) pain, symptoms of painful osteoarthritis and primary dysmenorrhea when the dose of nimesulide was 100 mg twice a day and the duration of treatment was limited to a window of 15 consecutive days.[2] The Drugs Controller General of India (DCGI) approved nimesulide in 1995 for pain and inflammatory conditions.[7] In severe pain after extraction of impacted third molars or other dental procedure-associated pain, postoperative pain, the onset of therapeutic effect of nimesulide was faster (less than 15 minutes) it was stronger (according to patients' opinion) than ibuprofen. In another study, nimesulide was found to be more effective in relieving pain in osteoarthritis of the hip and knees, with faster onset of action and fewer side effects than diclofenac and celecoxib.[8] Nimesulide is readily available, and maximally inhibits the COX-2 enzyme at a high dose.

However, till date, to the best of our knowledge, there are no published studies using systematic evaluation methods to quantitatively assess the safety profile of nimesulide related to hepatotoxicity in peer reviewed journals especially in Indian population.

Thus, the present study was planned to evaluate the safety and efficacy of nimesulide/paracetamol fixed-dose combination in Indian adult patients with acute pain due to acute musculoskeletal disorders and trauma such as tendinitis, sprains, strains, soft-tissue injury and myalgia, LBP, pain due to dental, orthopedic and other minor surgeries.

MATERIALS AND METHODS

This SAFE (**S**UMO in **A**cute pain management: sa**F**ety and **E**fficacy) study was a prospective, open-label, observational, multicenter study conducted by 24 experienced physicians across India on 500 patients to evaluate the efficacy and safety of nimesulide/paracetamol (100 mg + 325 mg) fixed-dose combination. Independent Ethics Committee approval was taken and the study was conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the applicable Indian regulatory guidelines. An informed consent was obtained from all the patients prior to each patient enrollment after proper explanation of the study details, risks and benefits associated in their own regional language.

Data pertaining to all the required fields in order to fulfill the primary and secondary endpoints of the study were captured in a paper case record form (CRF). Data from the paper CRF were then transferred to an electronic-CRF (e-CRF) portal. This e-CRF portal is 21 CFR Part 11 & Health Insurance Portability and Accountability Act (HIPAA) compliant. Data entry, data query generation and resolution, source document verification and database lock were performed as per standard GCP guidelines.

Patients' demographics were recorded in the form of age, weight, heart rate, blood pressure and comorbidities. Indian patients aged 18 years or older with acute painful conditions such as tendinitis, myalgia, LBP, sprains, pulled muscle, soft-tissue injury and dental pain, dental procedure/surgery were enrolled in the study. Pregnant or lactating females, patients having hepatic, renal or cardiac diseases, and those with history of hypersensitivity to the drug were strictly excluded from the study. Eligible patients were prescribed a daily dose of nimesulide/paracetamol (100 mg + 325 mg) twice a day after meals for a duration of 3-14 days as per the physician's discretion.

The primary outcomes of the study included safety endpoints that were assessed, based on the altered liver enzyme levels; aspartate transaminase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), alanine transaminase (ALT)/serum glutamic-pyruvic transaminase (SGPT), serum bilirubin and alkaline phosphatase levels. The proportion of subjects with adverse effects (AEs) and severe adverse effects (SAEs) and the intensity of AEs and SAEs at baseline and at the end of treatment were also evaluated. The secondary outcomes included clinical efficacy endpoints assessed and observed, based on the numerical rating scale (NRS) and physician/patient global assessment scale (GAS) at baseline and at the end of treatment. The NRS scores were calculated on a 10-point rating scale, with scores ranging from 0 to 10, where 0: no pain; 1-3: mild pain; 4-6: moderate pain and 7-10: severe pain. The GAS scores were rated according to a 5-point rating scale where 1: complete relief of symptoms; 2: marked improvement of symptoms; 3: moderate improvement of symptoms; 4: slight improvement of symptoms and 5: no change in symptoms.

All qualitative parameters were summarized by frequency and percentage and quantitative variables by descriptive statistics such as mean and standard deviation (SD). The within group change p value was derived by paired *t*-test, and the between group change p value was derived by independent *t*-test. The mean changes within the groups and between the groups (p value) were compared by paired *t*-test and independent *t*-test, respectively. The changes across indications were compared by analysis of variance (ANOVA). A p value <0.05 was considered as statistical significance. The data were analyzed by statistical software R version 4.1.0 (R Core Team, 2021, Vienna, Austria).

RESULTS

A total of 513 patients were enrolled in the study of which 500 patients completed the study. The demographic analysis of 466 records showed the mean age of 40 years. The mean weight was 65.82 kg (n = 432). The baseline characteristics of the patients enrolled are shown in Table 1. The diagnosis was based as per the discretion of the treating clinician with major reported complaints such as myalgia, LBP, dental pain and other indications such as pulled muscle, soft-tissue injuries, sprains, tendinitis and traumatic pain. Few patients had comorbidities including hypertension, type 2 diabetes mellitus, gastric illness, liver disease and other illnesses.

Of all the patients, only 1 patient (history of diabetes, hypertension and gastric illness) reported periorbital swelling and pedal edema (1 in 500). Apart from this patient, none of the study participants reported any mild/SAEs at the end of treatment with nimesulide/paracetamol combination. The liver function tests (LFTs) were performed on all participants and the values before and after the treatment did not show any significant change in AST/SGOT, ALT/SGPT, serum bilirubin and alkaline phosphatase levels during the treatment period. The mean and SD of LFT parameters between baseline and endline by paired *t*-test and mean change with 95% confidence interval (CI) were also reported. Change was measured by baseline to endline, therefore negative change means increase. Analysis of LFTs during the treatment duration of ≤7 days vs. >7 days showed a slight increase in the AST/SGOT [-0.27 (95% CI -1.67 to 1.12) vs. -1.01 (95% CI -2.02 to -0.01); p = 0.398], ALT/SGPT [-0.81 (95% CI -2.18 to 0.56) vs. -2.32 (95% CI -3.88 to -0.76); p = 0.151], serum bilirubin [0 (95% CI -0.03 to 0.03) vs. -0.03 (95% CI -0.05 to -0.01); p = 0.063], and alkaline phosphatase levels [-2.01 (95% CI -9.18 to 5.16) vs. -1.86 (95% CI -6.41 to 2.69); p = 0.973], but did not exceed the normal range of the tested parameters (Table 2; Fig. 1 a-d).

Analysis of LFTs at the end of treatment showed no significant increase (mean change) in the AST/SGOT [-0.73 (95% CI -1.54 to 0.09); p = 0.081], ALT/SGPT [-1.73 (95% CI -2.82 to -0.64); p = 0.002], serum bilirubin [-0.02 (95% CI -0.04 to -0.001); p = 0.018] and alkaline

Table 1. Baseline Characteristics of Study Participants

Characteristic	
Age (years), mean	40.1
Weight (kg), mean	65.8
Gender (n = 500)	**No (%)**
Male	202 (40.4)
Female	298 (59.6)
Comorbidities (n = 84)	**No (%)**
Hypertension	37 (44.0)
Type 2 diabetes mellitus (T2DM)	33 (39.3)
Gastric illness	3 (3.6)
Liver disease	2 (2.4)
Others	9 (10.7)
Underlying painful condition (n = 463)	**No (%)**
Myalgia	149 (32.2)
Low back pain	108 (23.3)
Dental pain	80 (17.3)
Others (pulled muscle, soft-tissue injuries, sprains, tendinitis and traumatic pain)	126 (27.2)

Table 2. Analysis of LFT Parameters (During Treatment Duration)

Parameter	Group	Pre: Mean (SD)	Post: Mean (SD)	Within group change (95% CI)	Between group change (95% CI)
AST/SGOT	≤7 d	28.45 (12.39)	28.73 (14.84)	-0.27 (-1.67 to 1.12)	0.74 (-0.98 to 2.45)
	>7 d	28.34 (10.9)	29.35 (12.59)	-1.01 (-2.02 to -0.01)	P = 0.398
ALT/SGPT	≤7 d	30.2 (16.76)	31.01(18.93)	-0.81 (-2.18 to 0.56)	1.51 (-0.56 to 3.58)
	>7 d	28.92 (14)	31.25 (15.72)	-2.32 (-3.88 to -0.76)*	P = 0.151
Serum bilirubin	≤7 d	0.57 (0.28)	0.57 (0.27)	0 (-0.03 to 0.03)	0.03 (0 to 0.06)
	>7 d	0.62 (0.31)	0.65 (0.29)	-0.03 (-0.05 to -0.01)*	P = 0.063
Alkaline phosphatase	≤7 d	121.18 (66.92)	123.19 (80.55)	-2.01 (-9.18 to 5.16)	0.15 (-8.62 to 8.32)
	>7 d	128.06 (75.38)	129.92 (71.97)	-1.86 (-6.41 to 2.69)	P = 0.973

*Indicates statistical significance (p value $<$ 0.05).

LFT = Liver function test; SD = Standard deviation; CI = Confidence interval; AST = Aspartate transaminase; SGOT = Serum glutamic-oxaloacetic transaminase; ALT = Alanine transaminase; SGPT = Serum glutamic-pyruvic transaminase.

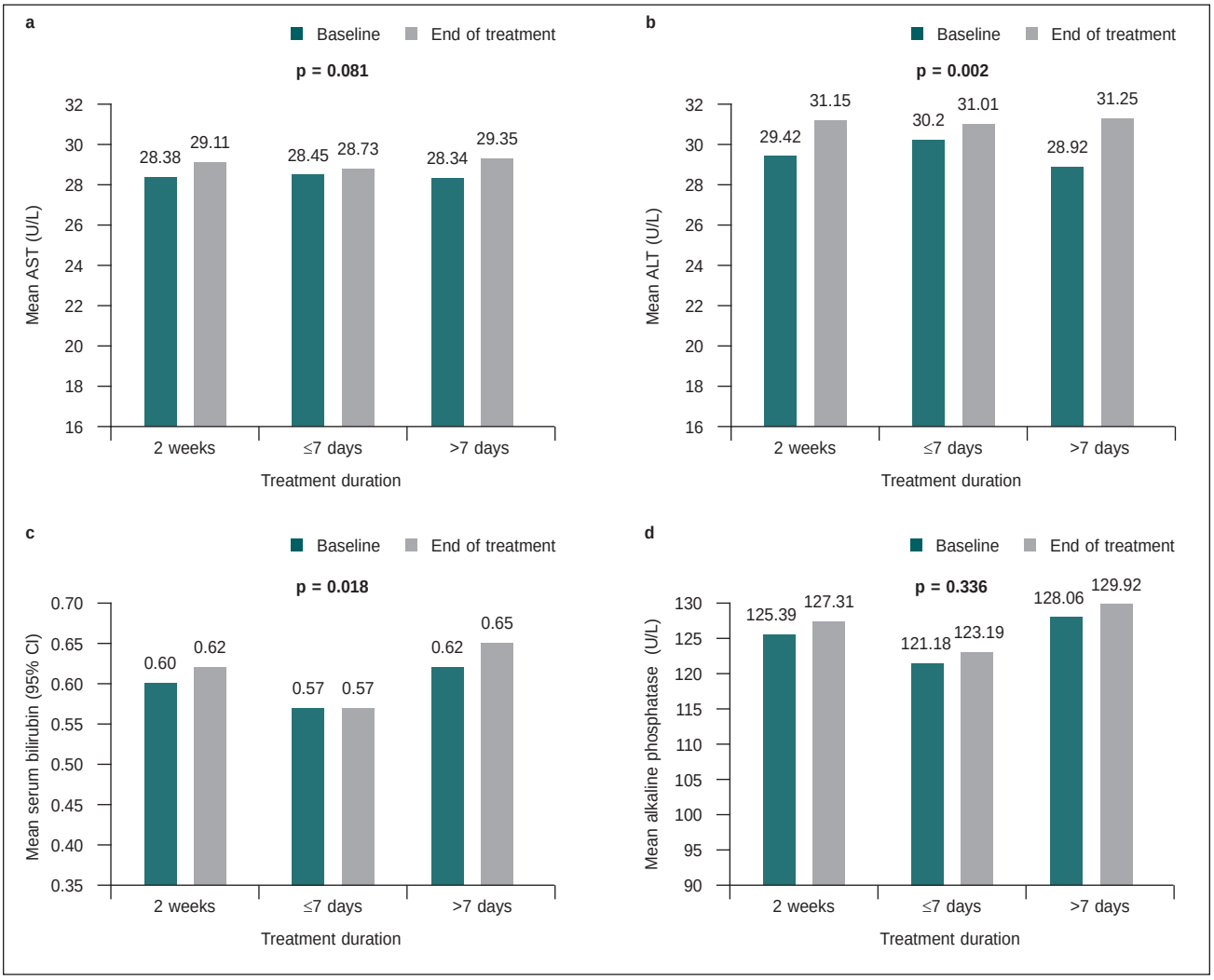

Figure 1. Mean comparison with 95% CI between baseline and end of treatmentfor all LFT parameters. **(a)** Mean comparison for treatment duration of AST, **(b)** Mean comparison for treatment duration of ALT, **(c)** Mean comparison for treatment duration of serum bilirubin and **(d)** Mean comparison for treatment duration of alkaline phosphatase.

Table 3. Analysis of LFT Parameters at the End of Treatment

Variables	Period	N	Mean (SD)	Mean change (95% CI)	P value
AST/SGOT	Baseline	500	28.38 (11.49)	-0.73 (-1.54 to 0.09)	0.081
	Endline	500	29.11 (13.5)		
ALT/SGPT	Baseline	500	29.42 (15.13)	-1.73 (-2.82 to -0.64)	0.002
	Endline	500	31.15 (17.02)		
Serum bilirubin	Baseline	500	0.6 (0.3)	-0.02 (-0.04 to -0.001)	0.018
	Endline	500	0.62 (0.28)		
Alkaline phosphatase	Baseline	500	125.39 (72.23)	-1.92 (-5.84 to 2)	0.336
	Endline	500	127.31 (75.41)		

Table 4. Analysis of NRS Scores for Intensity of Pain at Rest and Movement During Treatment

Variable	Group	Pre: Mean (SD)	Post: Mean (SD)	Within group change (95%CI)	Between group change (95%CI)	% Reduction
NRS at rest	≤7 d	4.88 (1.43)	1.54 (1.3)	3.35 (3.09 to 3.6)*	0.05 (-0.29 to 0.39)	68.44
	>7 d	4.81 (1.71)	1.52 (1.37)	3.29 (3.06 to 3.53)*	P = 0.769	68.39
NRS at movement	≤7 d	5.65 (1.54)	2 (1.23)	3.65 (3.39 to 3.91)*	0.1 (-0.46 to 0.25)	64.6
	>7 d	5.68 (1.76)	1.93 (1.35)	3.75 (3.5 to 4)*	p = 0.574	66.02

*P < 0.05

NRS = Numerical rating scale.

phosphatase levels [-1.92 (95% CI -5.84 to 2); p = 0.336]. Thus, all the LFTs were reported to be in the normal range of the tested parameters (Table 3; Fig. 1 a-d).

The secondary outcomes included analysis of NRS scores for the intensity of pain at rest and movement during treatment and at the end of the study. Analysis of NRS at rest during the treatment duration of ≤7 days showed that the mean change within the groups was 3.35 (95% CI 3.09 to 3.6); p < 0.05 and 3.29 (95% CI 3.06 to 3.53); p < 0.05 for treatment duration of >7 days (Table 4). Analysis of NRS at movement during the treatment duration of ≤7 days showed that the mean change within the groups was 3.65 (95% CI 3.39 to 3.91); p < 0.05 and for treatment duration of >7 days, it was 3.75 (95% CI 3.5 to 4); p < 0.05 (Table 4). The study showed that nimesulide/paracetamol combination demonstrated significant reduction in the pain intensity at rest [4.88 (1.43) vs. 1.54 (1.3); p < 0.05; (Fig. 2; Table 4)] in the first 7 days and [4.81 (1.71) vs. 1.52 (1.37); p < 0.05; (Fig. 2; Table 4)] for treatment duration of >7 days. A significant reduction in the pain intensity was also observed at movement during the initial 7 days [5.65 (1.54) vs. 2 (1.23); p < 0.05; (Fig. 3; Table 4)] and [5.68 (1.76) vs. 1.93 (1.35); p < 0.05; (Fig. 3; Table 4)] for treatment duration of >7 days.

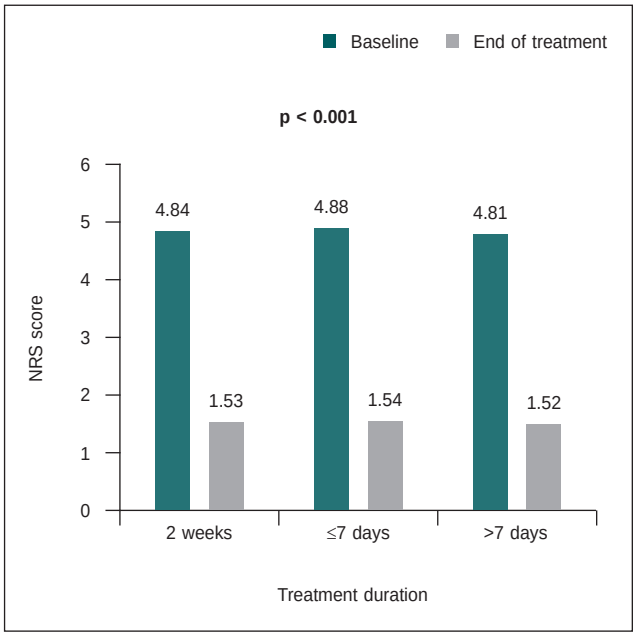

Figure 2. Mean comparison of NRS scores during treatment duration for pain intensity at rest.

NRS scores at baseline vs. at the end of treatment showed significant reduction in the pain intensity at rest (4.84 vs. 1.53; p < 0.001; Fig. 2; Table 5) and at movement (5.67 vs. 1.96; p < 0.001; Fig 3; Table 5), respectively.

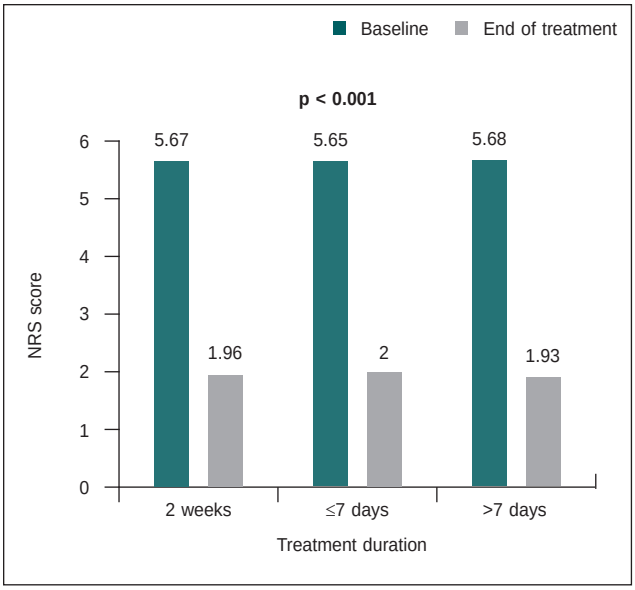

Figure 3. Mean comparison of NRS score during treatment duration for pain intensity at movement.

The reduction in NRS scores for the intensity of pain at rest, ≤7 days and >7 days were reported to be 68.44% and 68.39%; $p < 0.05$ (Table 4). At the end of treatment, the reduction in NRS scores for intensity of pain at rest was observed to be be 68.38%; $p < 0.001$, respectively (Table 5).

The reduction in NRS scores for the intensity of pain at movement, ≤7 days and >7 days were reported to be 64.60% and 66.02%; $p < 0.05$ (Table 4). At the end of treatment, the reduction in NRS scores for intensity of pain at movement was observed to be 65.43%; $p < 0.001$, respectively (Table 5).

The patient GAS within 7 days vs. >7 days was 1.85 vs. 1.94; $p = 0.19$ and the physician GAS was 1.80 vs. 1.97; $p = 0.022$, respectively (Table 6). The patient and physician GAS at ≤7 days, >7 days and at the end of the treatment showed marked improvement in symptoms in 96.6% patient GAS and 97.2% physician GAS (Table 7).

Table 5. Analysis of NRS Scores for Intensity of Pain at Rest and Movement at the End of Treatment

Variable	Period	N	Mean (SD)	Mean reduction (95% CI)	P value	% Reduction
NRS at rest	Baseline	500	4.84 (1.61)	3.31 (3.14 to 3.49)	<0.001	68.38
	Endline	500	1.53 (1.34)			
NRS at movement	Baseline	500	5.67 (1.67)	3.71 (3.53 to 3.89)	<0.001	65.43
	Endline	500	1.96 (1.3)			

Table 6. Comparison of GAS Patient and Physician in GAS

Parameter	Group	N	Mean	SD	P value
Patient global assessment	≤7 d	194	1.8505	0.7841	0.19
	>7 d	306	1.9477	0.8399	
Physician global assessment	≤7 d	194	1.8041	0.7637	0.022
	>7 d	306	1.9706	0.8273	

GAS = Global assessment scale.

Table 7. Patient and Physician GAS for Improvement in Symptoms

Parameters	Patient GAS (N = 500)		Physician GAS (N = 500)	
	Count	%	Count	%
1 = Complete relief of symptoms	175	35	172	34.4
2 = Marked improvement of symptoms	212	42.4	218	43.6
3 = Moderate improvement of symptoms	96	19.2	96	19.2
4 = Slight improvement of symptoms	17	3.4	13	2.6
5 = No change in symptoms	-	-	1	0.2

N = Number of study participants.

DISCUSSION

Nimesulide has been in clinical use for more than three decades and is still sustained owing to its effectiveness in controlling pain and inflammation as well as its favorable safety profile with regard to a reduced propensity to cause adverse gastrointestinal effects.[2,9] The gastrointestinal absorption of nimesulide is rapid and complete, and it gets rapidly distributed in the synovial fluid, where it persists for a longer duration than blood, thus explaining its effectiveness in pain control.[10] From the perspective of safety, the preferential activity of nimesulide on COX-2 attributes to a lower risk of upper gastrointestinal bleeding.[10] In patients with moderate renal impairment, the pharmacokinetic profiles of nimesulide are not altered.[2]

In the present multicenter, open-label study, nimesulide/paracetamol combination was well-tolerated and only 1 patient experienced AEs with the drug combination. Except this patient, none experienced any mild/serious AEs and continued the treatment as directed. The no/low incidence of AEs of nimesulide, may be attributed to the preferential COX-2 inhibition, thus a lower potential for gastrointestinal side effects.[2,4]

In the present study, the primary outcomes involved assessment of patients for changes in LFTs including ALT, AST, serum bilirubin and alkaline phosphatase levels when given nimesulide/paracetamol fixed-dose combination. Though a very mild increase in the liver aminotransferase levels were reported in the study patients, they were within the normal range of the tested parameters. Comparable inferences can be drawn from the results of a post-marketing surveillance study of patients prescribed nimesulide and assessed for LFTs which reported that ALT, AST and serum bilirubin values post-nimesulide treatment remained unaltered.[11]

In this study, the effectiveness of nimesulide/paracetamol combination was assessed and observed using NRS score over a short period of 3-14 days of treatment in relieving pain at rest and at movement, in patients suffering from painful conditions. A significant reduction in the degree of pain was observed based on the evaluation of the NRS scores, for the intensity of pain at rest on the 7th day of treatment, which was 1.54 points and at movement, reported as 2 points. These observations indicate the anti-inflammatory and analgesic effects of the studied combination by effectively restoring the functions in patients with painful conditions. The study findings were in accordance with a similar study conducted by Shikhkerimov et al on 54 patients to assess the efficacy and safety of nimesulide 200 mg/day in the treatment of acute LBP.[12] The analysis took into account assessment of the pain intensity at rest and at movement. Treatment with nimesulide resulted in pain relief and increased mobility in the lumbar spine on the 5th day of treatment indicating effectiveness to restore the previous functional status of patients with LBP.[12]

Marked improvement was observed in symptoms at the end of the treatment based on the GAS scores for patients reported as 96.6% and GAS scores of physicians was reported to be 97.2%, respectively. These results were comparable to a study conducted by Khan et al on 125 Indian patients with soft-tissue injuries and had been prescribed nimesulide for a period of 7 days.[13] The study demonstrated that the GAS was rated as "good" by both physicians (88.7%) as well as patients (83.9%).[13] The overall treatment compliance was very good leading to the conclusion that nimesulide is well-accepted by the patients and enhances the treatment adherence. [13]

All the participants in the present study completed the trial and only one reported AEs. Our study showed that the incidence of adverse events was low with the fixed-dose combination of nimesulide/paracetamol. The laboratory investigations of LFTs including SGOT, SGPT, serum bilirubin and alkaline phosphatase levels were done as suggested by the physicians. All patients underwent these tests and none of the patients reported any significant change in the tested parameters. These observations indicate that nimesulide/paracetamol combination demonstrates no potential role with respect to clinically significant increase in LFTs when used for a period of 3-14 days. Majority of the patients showed significant reduction in the pain intensity at rest and at movement, and an improvement in symptoms during the treatment period assessed using the NRS scores and the patient and physician GAS scores. Overall, our study showed that nimesulide/paracetamol combination was observed to be a safe and effective regimen with good tolerability profile in patients with acute pain conditions.

CONCLUSION

The SAFE study showed that the incidence of altered LFTs with nimesulide/paracetamol combination treatment was rare and at par with other conventional NSAIDs. Nimesulide/paracetamol combination given for acute painful conditions for a duration of 3 to 14 days, sporadically showed no clinically significant change in the liver enzymes elucidating the hepatic safety of this combination. Based on the LFT parameters, NRS and GAS scores, the nimesulide/paracetamol fixed-dose

combination was safe and clinically effective for use in acute pain conditions.

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Insignia Communications Pvt. Ltd. managed the overall execution of the study and also carried out the analysis and drafted the manuscript.

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Conflict of Interest

None

Informed Consent Statement

The work represented has been carried out in an ethical way. Informed consent was obtained from all the Investigators and study subjects who took part in the study.

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REVIEW ARTICLE

A Novel Diabetes Education Program to Improve Diabetes Knowledge, Awareness and Glycemic Control

RISHI SHUKLA[*,†], MANISHA GUPTA[*,†], DEEPAK YAGNIK[‡], NEHA AGARWAL[#], SANGEETA SHUKLA[£], BHASKER GANGULI[§], ANURAG BAJPAI[¥]

ABSTRACT

Diabetes self-management education (DSME), an integral part of diabetes management is delivered by trained educators in well-developed countries. Unfortunately, there is a dearth of an organized, concise and easy-to-deliver diabetes education module in India. The relationship between diabetes self-care and glycemic control has been studied extensively. The present review discusses an innovative diabetes self-education training module that can be easily reciprocated by others to benefit the larger population.

Keywords: Type 2 diabetes, diabetes self-management, patient education

Diabetes self-management education (DSME) is globally recognized as an integral part of diabetes management and, in most developed countries, is delivered by trained diabetes educators. Diabetes self-care includes a range of activities like self-monitoring of blood glucose, regular physical activity, balanced diet, adherence to medicine and foot care. The relationship between glycemic control and self-care has been documented extensively.[1-3] However, in India, it is still not considered as an integral part of diabetes management.

Khunti et al reported a Diabetes Education and Self-Management program for Ongoing, and Newly Diagnosed (DESMOND)[4] patients. This program involved 13 primary care centers in the United Kingdom and imparted diabetes education within 12 weeks of diagnosis. In this program, diabetes self-care led to dramatic improvements. Another meta-analysis of 31 studies showed that DSME reduced glycated hemoglobin (HbA1c) by 0.76% at immediate follow-up.[5] A study included in the meta-analysis demonstrated interventions delivered face-to-face to be better when compared with telecommunication.[6]

There are limited studies on DSME in the Indian context.[7] Diabetes awareness is limited in India. Almost 50% of the Indian population has undiagnosed diabetes.[8] A controlled study, including 100 patients, has recently been reported from North India. Patients were offered diabetes education and leaflet at baseline and, at first, follow-up. At the end of the study, there was a significant improvement in knowledge, attitude, practices and glycemic control.[8] The Prevention, Awareness, Counselling and Evaluation (PACE) project was done to increase awareness of diabetes in Chennai, Tamil Nadu.[9]

Shukla et al have evolved a DSME program whose impact has been assessed in 50 patients. The diabetes education course aims to empower participating individuals with skills and knowledge of diabetes education.[10] The present article describes the diabetes education course and the methods used in administering the program so that it can be reciprocated by others benefitting a larger population.

TARGET AUDIENCE

The diabetes education program is targeted to all individuals with type 2 diabetes mellitus (T2DM) along with those involved in care of these patients. The course

*Consultant and Head, Dept. of Endocrinology, Regency Health Care, Kanpur, Uttar Pradesh; Society for Prevention and Awareness of Diabetes (SPAD)
†Chief Consultant, Centre for Diabetes and Endocrine Disease, Kanpur, Uttar Pradesh
‡Consultant, Yagnik's Diabetes Center, Kanpur, Uttar Pradesh; SPAD
#Consultant Pediatric Endocrinologist and Diabetologist, Institute of Neurosciences, Kolkata, West Bengal
£Consultant and Head, Dept. of Ophthalmology, Regency Health Care, Kanpur, Uttar Pradesh
§Consultant Diabetologist, Member-SPAD
¥Consultant Endocrinologist, Regency Health Care, Kanpur, Uttar Pradesh
Address for correspondence
Dr Rishi Shukla
Chief Consultant, Centre for Diabetes and Endocrine Disease, Kanpur, Uttar Pradesh
E-mail: drrishishukla@gmail.com

is aimed to be used by the clinicians, diabetes educators and people living with diabetes.

Training Module

The total duration of the course is 75 minutes, and it can be imparted to the learners in a single session. The trainers received a training to implement the program, over a period of 2 months. The trainers can deliver the training to a group of people. Diabetic educators may also conduct the course either through physicians or directly. Many pharmaceutical companies can also conduct programs for the patients. With the online portal, patients may also assess the program directly and get empowered.

Educational Module

The key areas covered under the course include introduction to diabetes, diet and exercise, acute complications, chronic complications, screening investigations, self-monitoring of blood glucose, insulin delivery and sick day rules. Table 1 provides the framework of the course.

Introduction to diabetes

Diabetes is defined by either an impairment of insulin production or its inability to function eventually leading to raised blood sugar levels. There are three types of diabetes – Type 1 diabetes mellitus (T1DM), T2DM and gestational diabetes (GD). T1DM usually starts in childhood and requires insulin from the onset of disease. T2DM usually starts in adulthood after the age of 25 years; however, it has been observed in obese children especially with a family history of diabetes. GD is detected for the first-time during pregnancy and increases the chances of T2DM later in life.

The risk factors of diabetes comprise of family history of diabetes, obesity, sedentary lifestyle, hypertension, dyslipidemia, history of diabetes during pregnancy or prediabetes.

Diabetes can be identified by common symptoms including excessive thirst, frequent urination, weight loss and early fatigue. In a large number of cases, there are no warning symptoms, hence diabetes goes undetected.

Doctors may interpret your blood glucose and HbA1c level to diagnose prediabetes or diabetes (Table 2).

Diet and diabetes

Various myths are prevalent about diet in diabetes, despite of diet being a crucial part of diabetes management. The diet for diabetes needs to be a healthy diet. The three main components of the diet are carbohydrates, proteins, fats and minor components like vitamins, minerals and fibers.

- **Carbohydrates:** Carbohydrates are the primary source of energy in our body. Wheat and rice are the primary sources of carbohydrates, and it is also

Table 1. Description of the Educational Module on Type 2 Diabetes

Topic	Description
Introduction	Classification of diabetes, and how to identify diabetes risk.
Diet and diabetes	Understanding the immediate and long-term implications of balanced diet in managing diabetes.
Exercise	Importance of different forms of exercise in optimization of blood glucose levels and maintaining a healthy BMI.
Acute complications	Hypoglycemia and hyperglycemia, how to manage them and when to seek help
Chronic complications	Uncontrolled blood glucose and different chronic complications such as retinopathy, neuropathy, nephropathy, diabetic foot and cardiovascular diseases linked with it.
Screening and investigations needed	Investigations needed, their frequency and significance in screening complications related to diabetes.
Self-monitoring of blood glucose	The role of self-monitoring in effective management of blood glucose.
Insulin	Awareness about insulin use, allaying fears related to misconception about insulin.
Sick day rules	What to expect during sick days and what should be done.

Table 2. Interpretation of Blood Glucose Levels

Interpretation	Fasting blood glucose (FPG)	Postprandial blood glucose (PPBG)	HbA1c (%)	Random blood glucose
Normal	70-90 mg/dL	100-139 mg/dL	<5.7	
Prediabetes	100-126 mg/dL	140-200 mg/dL	5.7-6.5	
Diabetes	>126 mg/dL	>200 mg/dL	>6.5	>199 mg/dL with symptoms

present in vegetables and fruits. Carbohydrates should form 50% to 55% of total caloric intake with low glycemic index foods. The use of low glycemic index food prevents rapid rise of blood glucose. *Potatoes and rice are not restricted in individuals with diabetes but should be consumed in moderate amounts. Sugar-free tablets are not harmful; they make food palatable without any nutritive value.*

- **Proteins:** Meat, egg, milk, dry fruits and pulses are rich sources of protein in the diet. Proteins are needed for building the muscles and bones. Daily protein requirement is 0.8-1.0 g/kg/day or 15-20% of total caloric intake. Patients with renal failure should consult doctors for their dietary requirements, as protein intake may be reduced in these patients.
- **Fats:** Fats are an essential component of food and is available from oils, meat, dry fruits, milk, etc. Fats act as reserve store of energy and is also utilized in forming several hormones and enzymes. Typical diet should contain 20-25% of fats. There are three main types of dietary fats including saturated, polyunsaturated and monosaturated. Equal proportion of all types of fats should be included in the diet. People with high cholesterol should reduce fat intake in their diet.
- **Fibers:** Fibers are essential component of diet, particularly in individuals with diabetes. It helps in delaying the absorption of carbohydrates, thus preventing a quick rise in blood sugar level. The recommended daily intake of fiber should be approximately 20-35 g.
- **Minerals and vitamins:** Minerals and vitamins are usually present in a normal healthy diet; hence, they are not required in the form of extra supplements unless there is a deficiency. All green vegetables and fruits are rich sources of vitamins and minerals. It is advised that vegetarian people on metformin should take vitamin B12 as a supplement.

Exercise and diabetes

Exercise constitutes an integral part of the lifestyle management of diabetes. People with diabetes should be provided adequate training by trained physiotherapists and physical trainer.

Precautions should be taken before exercise, if your blood glucose is too high (>250 mg/dL) or too low (<90 mg/dL), if you are pregnant, if you have any cardiac disease or if there are any signs of nephropathy or retinopathy. Doctor should be consulted in all such cases. It is recommended to wear good-fitting footwear and carry an ID card depicting diabetes (and other diseases) and phone numbers to be contacted in case of an emergency.

- **Aerobic exercises:** Simplest form of exercise, such as brisk walking, cycling, dancing and swimming. The recommendation is to do exercise at least 30 min/day, with a minimum of 5 days/week.
- **Anaerobic exercises:** Anaerobic exercises help in breaking down glucose for energy without using oxygen. Anaerobic exercises are of short duration with high intensity, to ensure energy is released within a short period, and oxygen demand surpasses the oxygen supply. Anaerobic exercises comprise of weight-bearing exercises like dumbbells, sprinting and push-ups. The recommendation is for doing anaerobic exercises 2 to 4 times a week and three sets for each muscle group.
- **Yoga and Pranayama:** Respiratory and postural exercises are recommended for 30 minutes every alternate day.

Acute complications

The two most critical acute complications of diabetes include hyperglycemia and hypoglycemia.

- **Hyperglycemia:** Many times, high blood sugars may go unnoticed. The symptoms include increased hunger and thirst, fatigue, dryness of mouth, lethargy, blurring of vision, itching in genitalia. To manage hyperglycemia, check blood glucose regularly, take proper diet, drink plenty of water and take medicines regularly. It is important to adhere to doctor's prescriptions.
- **Hypoglycemia:** Blood glucose level below 70 mg/dL is referred to as hypoglycemia. It commonly occurs due to a mismatch between food intake and insulin/oral medicine doses. The reasons for hypoglycemia include delay or skipping meals, unable to eat due to lack of appetite or illness, unplanned exercises or not measuring blood glucose regularly.

Chronic complications

Uncontrolled blood glucose affects almost all organs of the body. Table 3 describes the different chronic complications associated with T2DM.

Screening and investigations

Diabetes may affect almost all the organs, hence, patients with diabetes are recommended several investigations to screen for the optimal functioning of these organs. All the routine screening tests are intended to keep an

Table 3. Chronic Complications Associated with Type 2 Diabetes Mellitus

Complications	Organ involved	Causes	Manifestations	Screening & management	Risks involved
Retinopathy	Eye/Retina affects the blood vessels supplying the retina.	Occurs in case of unmanaged long-term diabetes, in association with nephropathy and hypertension.	Blurring of vision, frequent changes in glasses; however, most have no problems.	Once a year examination of retina (fundus examination) is recommended. It can be prevented by optimal blood glucose and blood pressure management.	Four times high chances of blindness in individuals with diabetes compared with the general population.
Neuropathy			Pain and burning in lower limbs, constipation, dyspepsia, recurrent diarrhea, impotence, etc.	It can be prevented by managing blood glucose levels.	
Nephropathy	Kidney		Symptoms seen at much later stages.	Urine albumin to creatinine ratio, urine-R & M, S creatinine should be conducted annually. Can be managed by good blood sugar and blood pressure control.	
Heart diseases	Heart	Smoking, high cholesterol, uncontrolled blood pressure and overweight	Breathlessness and/or chest pain on walking, excessive fatigue, increased perspiration, choking of the throat, jaw pain, etc.	Sometimes, symptoms are minimal, but with strong suspicion. It can be prevented by consuming low-fat diet, regular physical activity, optimal blood glucose level, and blood glucose control. Cholesterol-lowering medications are also prescribed as a protective measure.	
Cerebrovascular disease or palsy	Brain	Uncontrolled blood pressure and diabetes.	Slurring of speech, weakness in one or more limbs, or one-half of the body and altered consciousness.		
Diabetic foot disease	Foot		Any signs of blister or wound on foot (redness, swelling, too cold or warm feet), presence of corn or thickening of the skin.	Foot examination once a year, check shoes daily for any nail or deformity, keep clean and dry feet.	

eye on the complications associated with T2DM. The first screening includes "**ABC"** of diabetes; ***A*** for A1c (defined as average of last 3 months glucose and should be under 7.0%), ***B*** for blood pressure which should be measured at every follow-up visit and target should be under 130/85 mmHg and ***C*** for cholesterol. In addition, other tests include serum creatinine (kidney function test), liver function test, annual fundus examination and ECG (heart function).

It is important to know the standard levels of these parameters to stay informed about the disease (Table 4).

Self-monitoring of blood glucose

Self-monitoring of blood glucose (SMBG) has assumed great significance in the management of T2DM. It is advisable not to monitor the blood glucose by symptoms but by SMBG. SMBG provides immediate information about the blood glucose level and through constant

Table 4. Optimal Levels of Blood Glucose, Blood Pressure and Lipid Profile

Parameter	Standard values
Blood glucose	Fasting – 80-130 mg/dL
	Postprandial – <180 mg/dL
	A1c – <7%
Blood pressure	Systolic – <130 mmHg
	Diastolic – <85 mmHg
Lipid profile	Total cholesterol – <180 mg/dL
	Low-density lipid – <70 mg/dL
	High-density lipid – >40 mg/dL (male); >50 mg/dL (female)
	Triglycerides – <150 mg/dL
	ECG – once a year

monitoring reduces the risk of diabetes-associated complications.

Need for SMBG

SMBG enables an individual with diabetes to track the effect of food, medicine, exercise and various stressors such as psychological or physical based on the blood glucose level.

Requirement for SMBG

For SMBG, an individual requires glucometer, glucose strips, needles and a logbook if the glucometer does not have a phone-based application to automatically log in data.

How to do SMBG?

Before conducting a self-test, the following steps should be carried out: 1) Wash your hands with soap and water, dry them; 2) Remove a glucometer strip and insert it into the glucometer; 3) Prick your finger at the side from the pricker (using a new needle for every prick); 4) Pour a drop of blood on the strip; 5) Wait for the blood glucose value to be displayed on the glucometer and 6) If not automatic, manually enter the blood glucose value in the logbook.

Frequency of blood glucose monitoring

Type 2 diabetes patients should check blood glucose once a week, 2 to 4 times. Type 1 diabetes patients should monitor daily, 4 to 6 times.

Interpreting the glucometer readings

The normal readings of the blood glucose are: 1) Fasting blood sugar 80-130 mg/dL (after 6-8 hours of sleep); 2) Two hours after meals 180 mg/dL and 3) Anytime blood sugar or random blood sugar <180 mg/dL.

It is important to note that the glucometer values are different from the laboratory values as the laboratory values use capillary blood while the laboratory uses venous blood. The lab values may be reduced by 10% to 15%.

Insulin

Several misconceptions are prevalent about insulin such as the insulin injection is the last resort treatment, it is addictive and it may have a negatively adverse effect on all body organs. On the contrary, insulin is important in T1DM patients. Hence, there is a need to bust these myths. When the oral antidiabetic medication is unable to optimize the blood glucose level, the patients may require insulin. During an emergency such as an infection, heart attack or surgery, insulin is required, and the patient returns to their regular treatment after they recover. Insulin has no adverse effect on the body; in fact the use of insulin leads to an overall improvement of blood glucose, allowing for organ protection. It is very important to consult the doctor, discuss the use of insulin and trust them about how to use insulin correctly.

Sick Day Management

Several triggers such as fever, injury, heart attack, stroke or emotional turmoil may lead to an increase in blood glucose levels, while in some cases such as diarrhea and vomiting, blood glucose levels may reduce. People with diabetes have several misinformations about sick days and its effect on blood glucose level.

To manage diabetes during sick days, regular blood sugar monitoring is needed (6 times or more), continue diabetes medicines or insulin, do not stop long-acting insulin such as glargine insulin, depending upon pre-meal blood sugar values change the doses of short-acting insulin. Individuals with diabetes on tablets should adhere to meals or try to eat something, at frequent intervals. If the blood sugar is persistently high (over 300 mg/dL) - consult your doctor and may need transition to insulin treatment. Another common problem during sick day is dehydration, so ensure an adequate intake of low-calorie, low-glycemic index fluids. Along with dehydration, diabetes may also be marked with polyuria. It is important to measure urine ketones, if blood sugar level is >300 mg/dL. Medical assistance is immediately required in case of positive urine ketones, diarrhea and vomiting for more than 12 hours, fever >24 hours, sick looking, not sure about hypoglycemia or ketoacidosis, blood sugar is <90 mg/dL despite oral glucose solution administered twice and blood sugar >250 mg/dL in last 12 hours.

CONCLUSION

To the best of our knowledge, this is the first organized Diabetes Education Program in the country. The authors have attempted to cover all the relevant and useful aspects to deal with diabetes. The main challenge was to conceptualize and develop a comprehensive program. Going ahead, the PowerPoint version is under planning to be put up on the website (www.spadonline.com) for broader coverage. The authors have also planned in the future to use an edited recording in the training program.

The authors anticipate the course to have a vast potential in successfully training individuals with diabetes and diabetes educators. The program is intended to be available to everyone; hence, it is anticipated to be cost-effective and useful. The authors hope that this program will go a big way in bridging the gap in diabetes awareness and help people with T2DM.

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Author Contribution

RS, DY, SS and AB conceptualized and planned the study. RS, NA and MG did literature review and drafted the initial manuscript. RS, BG and AB critically reviewed the manuscript and would act as guarantor of the paper.

Conflict of Interest

The authors declare that there is no conflict of interest.

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REVIEW ARTICLE

Reappraising the Role of Eplerenone in the Management of Heart Failure

TINY NAIR*, NAKUL SINHA†, JAGDISH HIREMATH‡, PK HAZRA#, MK SHAH§

ABSTRACT

Background: In India, the prevalence of heart failure (HF) is increasing at 1.2/1,000 people according to a study in northern India, and the mortality rate at 1 year (INTERnational Congestive Heart Failure [INTER-CHF]) is 37%. Due to the diverse phenotypes of HF, nonadherence to guideline-directed medical therapy (GDMT), resistance to uptitration of medication and underuse of mineralocorticoid receptor antagonists (MRAs), such as eplerenone, a uniform management approach may not be feasible. This review is aimed at assessing the burden of HF, reasons for underutilization of MRAs in treatment, evaluating the evidence and reappraising the disease-modifying role of eplerenone in HF management. **Methods:** An electronic database search was performed to identify relevant literature. **Results:** The review details various studies that demonstrate the role of MRA eplerenone as a disease-modifying agent in patients with mild-to-moderate hypertension and those with acute myocardial infarction (MI) complicated by left ventricular dysfunction and HF. It also outlines different patient profiles for eplerenone use and ways to handle minor side-effects. **Conclusions:** Eplerenone shows a promising effect in selectively blocking aldosterone receptors to suppress fibrosis and reverse cardiac remodeling.

Keywords: Heart failure, eplerenone, disease-modifying agent, biomarkers

Heart failure (HF) has emerged as a major global health concern, with an estimated worldwide prevalence of more than 37.7 million and its burden is projected to rise by 25% by the year 2030.[1] In India, the burden of HF is equally concerning, with post-admission mortality of 20% to 30%.[2] Interestingly, Indian patients experience HF at a much younger age than those in the West and show a different male-to-female ratio as shown in Table 1. HF prognosis in Indian patients is worse than those in the West. The Trivandrum Heart Failure Registry (THFR) observed almost twice the mortality at 8.4% compared to the 4% observed by the Acute Decompensated Heart Failure National Registry (ADHERE) in the US. Also, the INTERnational Congestive Heart Failure (INTER-CHF) study reported higher 1-year mortality in India at 37%.[1]

In Indian patients, medication adherence ranges from 25% to 50%, which is coupled with low tolerance of guideline-based medication along with limited access to devices such as implantable cardioverter-defibrillators (ICD), cardiac resynchronization therapy (CRT) devices and left ventricular assist devices (LVAD).[2]

Of the therapeutic options, mineralocorticoid receptor antagonists (MRAs) are associated with improved outcomes in heart failure with reduced ejection

Table 1. Lower Mean Age and Male-Female Ratio for Indians Compared to the West[1]

Name of the study	Country	Mean age of HF in years	Male: female ratio
Acute Decompensated Heart Failure National Registry (ADHERE)	USA	72.4	~ 50:50
Trivandrum Heart Failure Registry (THFR)	India	61.2	69:31
Medanta Registry	India	58.9	83:17
INTERnational Congestive Heart Failure (INTER-CHF)	Indian subset	56	62:38

~ Approximately

*Head, Dept. of Cardiology and Chief Consultant, PRS Hospital, Trivandrum, Kerala
†Director, Interventional Cardiology, Medanta Heart Institute, Lucknow, Uttar Pradesh
‡Director, Cath Lab, Ruby Hall Clinic, Pune, Maharashtra
#Director, Interventional Cardiology, AMRI Hospital, Kolkata, West Bengal
§Invasive Cardiologist, Lilavati Hospital, Mumbai, Maharashtra
Address for correspondence
Dr Tiny Nair
PRS Hospital
NH 47, Killipalam, Trivandrum - 695 002, Kerala
E-mail: tinynair@gmail.com

fraction (HFrEF).[3] They are also given a class I, level of recommendation A by the 2016 European Society of Cardiology (ESC) guidelines for prevention of HF hospitalization and death in patients with HFrEF, who have persistent symptoms despite treatment with an angiotensin-converting enzyme (ACE) inhibitor and a β-blocker and have a left ventricular ejection fraction (LVEF) below 35%.[4] Despite this, MRAs remain underutilized.[3] There is considerable difference between optimal, evidence-based, guideline-recommended care and what is delivered in practice, which is referred to as "care gap".[5] Hence, this review is aimed at understanding the current scenario in the management of HF, assessing the reasons for underutilization of MRAs, particularly eplerenone and evaluating the evidence to possibly reappraise the role of eplerenone.

METHODS

To reach the above-mentioned objective, we performed a literature search using electronic databases such as PubMed/MEDLINE and identified articles that fulfilled the criteria for HF, MRAs, cardiovascular diseases (CVDs), eplerenone, spironolactone, underuse, efficacy, safety, prevalence, diagnosis and management from the year 2000 to 2020, published in scientific literature in English language, limited to clinical and human data. The reviewed articles included systematic reviews, meta-analysis, randomized-controlled trials, review articles and clinical practice guidelines.

RESULTS

Lesser-known Markers of Heart Failure

Of the various biomarkers available for HF diagnosis, B-type natriuretic peptide (BNP) and N-terminal (NT)-pro hormone BNP (NT-proBNP) are widely used in clinical practice. However, although the negative predictive value of BNP/NT-proBNP is very high (0.94-0.98), the positive predictive value is low (0.64-0.67), which makes them a good tool to rule out HF, but a poor tool to help establish the diagnosis. Newer biomarkers such as suppressor of tumorigenicity (ST2) and galectin-3 show promising role in HF diagnosis. Their usage in Indian setting is still lagging due to high cost and availability issues.[1]

MRA: An Underutilized Drug Class?

In a US based national sample, out of >12,000 hospitalized patients of HF, only one-third received MRA prescription at discharge, depicting the underutilization of MRAs. As per a survey done amongst health care professionals, 51% were unfamiliar with eplerenone and 6% did not know about spironolactone. Focus-group analysis identified 8 barriers to MRA use in 3 categories: patient-related barriers (concerns about polypharmacy and comorbidities, adverse effects, perceived patient nonadherence), provider-related barriers (unclear roles and responsibilities, coordination and transitions of care, lack of experience or familiarity with MRAs) and system-based barriers (system overload and provider time constraints, lack of systematic follow-up procedures).[6]

As per a study by Savarese et al from the Swedish HF Registry in patients with HFrEF (ejection fraction [EF] <40%), New York Heart Association (NYHA) class II-IV and HF duration ≥6 months, characteristics independently associated with MRA nonuse in descending order of magnitude were: lower creatinine clearance (<60 mL/min), absence of need for diuretics, no CRT/ICD, raised blood pressure (BP), no digoxin use, higher EF, outpatient setting, older age, lower income, ischemic heart disease, male sex, follow-up in primary as against specialty care, lower NYHA class and no diagnosis of hypertension. Their decreased usage was not related to elevated potassium but to impaired renal function, even at creatinine clearance range of 30-59.9 mL/min, where MRAs are not contraindicated. Moreover, the underuse is associated with nonspecialist care, milder HF and nonusage of other HF therapy.[3]

Further, in guideline-eligible patients with HFrEF, the relative underuse of MRAs has largely been accredited to the fear that it will cause hyperkalemia and/or renal insufficiency, particularly in patients having diabetes mellitus (DM) and/or chronic kidney disease (CKD). Contradictory to the perceived fear, observations from a subgroup study of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial showed that eplerenone reduces all-cause mortality and hospitalizations in patients with HFrEF including those with DM and/or CKD.[7]

Eplerenone: Reappraising the Role in HF Management

Eplerenone as a disease-modifying agent

Aldosterone is a key factor in hypertension, congestive heart failure (CHF), ventricular arrhythmias, myocardial hypertrophy, renal dysfunction and increased mortality. Evidence, thus suggests that selective aldosterone blockade can help in lowering the incidence of cardiovascular damage.[8] Also, HF activates the renin-angiotensin system (RAS), which leads to rise in

aldosterone and BP, and stimulates vasoconstriction, fibrosis and left ventricular hypertrophy (LVH). Therefore, most of the therapies work by blocking this pathway.[9]

Although most patients are treated with ACE inhibitors, angiotensin receptor blockers (ARBs) and β-blockers, trials have shown clinical superiority of three more drug classes, i.e., MRAs, sodium-glucose cotransporter 2 (SGLT2) inhibitors and angiotensin receptor-neprilysin inhibitors (ARNIs) compared to placebo in increasing the life expectancy in patients with HFrEF.[10]

Being a selective aldosterone blocker, eplerenone selectively targets aldosterone receptors and thus minimizes the risk of adverse hormonal effects. Additionally, it is better tolerated than spironolactone in patients with hypertension.[8] According to a meta-analysis by Li et al, there may be beneficial effects of MRA treatment on the reversal of cardiac remodeling and improvement of left ventricular function.[11]

Furthermore, in late stage of CHF, there is immunoregulation, which activates T-lymphocytes (Tregs) proliferation via the up-regulation of Kv1.3 potassium channel (regulating T-lymphocytes activation). This stimulates cardiac fibrosis by primarily secreting the fibrogenic cytokine transforming growth factor beta (TGF-β). Eplerenone's high affinity to Kv1.3 channel allows it to antagonize the Kv1.3 channels directly, thereby suppressing Tregs proliferation, which in turn can have an immunoregulatory role in CHF by preventing cardiac fibrosis.[12]

Evidence analysis

Numerous studies have illustrated the positive role of eplerenone in HF management.

- In Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone along with optimal medical therapy was shown to reduce mortality as compared to placebo. A reduction in both primary endpoint and secondary endpoint was observed with eplerenone – mortality among patients due to any cause (relative risk [RR] 0.85; 95% confidence interval [CI] 0.75-0.96; p = 0.008), death from cardiovascular causes or hospitalization (RR 0.87; 95% CI, 0.79-0.95; p = 0.02), death from any cause or any hospitalization (RR 0.92; 95% CI, 0.86-0.98; p = 0.02), and rate of sudden cardiac deaths (RR 0.79; 95% CI, 0.64-0.97; p = 0.03).[13]
- As per EMPHASIS-HF trial, mortality with placebo was higher than with eplerenone, i.e., 15.5% vs. 12.5%, respectively (hazard ratio [HR], 0.76; 95% CI 0.62-0.93; p = 0.008); percentage hospitalizations for any cause (HR = 0.77; 95% CI, 0.67-0.88; p <0.001) and for HF (HR = 0.58; 95% CI, 0.47-0.70; p <0.001) were lower with eplerenone compared to placebo.[14]

None of the deaths in the EPHESUS and EMPHASIS trials were due to hyperkalemia. Moreover, add-on eplerenone therapy has shown to reduce LVH in patients with resistant hypertension.[13,14]

- A cross-trial analysis evaluated the treatment effects of comprehensive disease-modifying pharmacological therapy (ARNI, β-blocker, MRA and SGLT2 inhibitor) versus conventional therapy (ACE inhibitor or ARB and β-blocker) in chronic HFrEF patients. The study made indirect comparisons of three vital trials: EMPHASIS-HF, Prospective Comparison of ARNI with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF), and Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF); the control group was of the EMPHASIS-HF trial (ACE inhibitor or ARB and β-blocker). The HR for primary endpoint of cardiovascular death or hospital admission for HF was (0.38 [95% CI 0.30-0.47]); HRs were also favorable for cardiovascular death alone (0.50 [95% CI 0.37-0.67]), hospital admission for HF alone (0.32 [0.24-0.43]) and for all-cause mortality (0.53 [0.40-0.70]).[10]

These results support the use of MRAs in high-risk subgroups, i.e., the population likely to have the most beneficial effect from disease-modifying therapies.

- In another study by Udelson et al, eplerenone showed greater reductions in markers of collagen turnover, i.e., amino-terminal propeptide of type I procollagen (PINP) and BNP (P values 0.01 and 0.04, respectively) compared to placebo in patients with mild-to-moderate HF symptoms and left ventricular systolic dysfunction (LVSD), as can be observed from Table 2.[15]
- In another multicenter, open-label, uncontrolled trial by Burgess et al in patients with mild-to-moderate essential hypertension, 74.4% patients in the intent-to-treat population achieved BP control during treatment with eplerenone of which 44.8% had received eplerenone monotherapy and 30.0% had received eplerenone plus another antihypertensive agent over a period of 14 months.[8]

Table 2. Changes in Markers of Collagen Turnover and BNP with Eplerenone Treatment from Baseline to 36 Weeks[15]

Markers	Baseline (Mean ± SE)		Δ Week 36 (Mean ± SE)		P* value
	Eplerenone	Placebo	Eplerenone	Placebo	
PIIINP (µg/L)	4.9 (0.16)	4.5 (0.15)	−0.5 (0.17)	−0.1 (0.18)	0.28
PINP (µg/L)	42.7 (2.31)	44.0 (1.66)	−6.7 (2.04)	−2.4 (1.46)	0.01
BNP (pg/mL)	248.3 (34.65)	197.5 (20.79)	−73.7 (31.55)	18.2 (25.40)	0.04

SE = Standard error; PIIINP = Amino-terminal propeptide of type III procollagen; PINP = Propeptide of type I procollagen; BNP = Brain natriuretic peptide.

*P value is associated with the change from baseline to Week 36 EDVi and the ANCOVA model with treatment group and baseline value as the only factors.

Efficacy of Eplerenone

For patients with CKD (eGFR <60 mL/min/1.73 m^2) and DM

- A decrease was observed in incident potassium >6.0 mmol/L, 8 (1.9) in eplerenone patients versus 25 (2.74) patients on placebo, p = 0.01.[16]
- There was no increase in serum potassium >6.0 mmol/L, 17 (3.8) in eplerenone versus 8 (2.1) on placebo, p = 0.16 in patients with DM; no more patients discontinued eplerenone due to hyperkalemia in diabetes compared to no-diabetes patients (interaction p = 0.12).[16]
- In CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) and DM patients, fewer of them in eplerenone group (16.1% and 15.1%, respectively) discontinued treatment due to an adverse event or any other reason as compared to higher percentage discontinuation (22.3% and 18.1%, respectively) in the placebo group.[16]

For patients with below median systolic BP (<123 mmHg)

- Incidence of potassium >5.5 mmol/L in patients with a systolic BP <123 mmHg in eplerenone group was higher than the placebo group; however, there was no increase in serum potassium >6.0 mmol/L.[16]
- Also, there was no increase in the incidence of serum potassium >5.5 nor >6.0 mmol/L in patients in the lowest quartile of baseline systolic BP (<110 mmHg) and in patients between lowest quartile and median (between 110 and 123 mmHg) in the eplerenone group.[16]

Side Effects: Are All MRAs the Same?

As far as class effect is concerned, both spironolactone and eplerenone have been shown to manifest common adverse events like hyperkalemia and gynecomastia. However, spironolactone, a nonselective MRA having structural similarities with progesterone, leads to side effects like loss of libido, menstrual irregularities and gynecomastia in addition to hyperkalemia. On the other hand, eplerenone, a second-generation MRA that binds selectively to the mineralocorticoid receptor with minimum binding to progesterone and androgen receptors causes fewer incidences of sexual adverse events.[17] From the EPHESUS trial; it was evident that deaths were not related to hyperkalemia unlike the normal perception. This emphasizes the need for proper dose titration of eplerenone. Risk of hyperkalemia could be reduced using Cockcroft-Gault formula to estimate creatinine clearance, excluding patients with moderate-to-severe renal insufficiency, treating mild renal insufficiency with loop diuretics, and adherence to 25 to 50 mg/day dosage of eplerenone.[13]

An analysis of the EPHESUS trial comparing spironolactone's and eplerenone's pharmacological properties showed an increase in level of glycated hemoglobin (HbA1c) by spironolactone, but no increase in HbA1c and cortisol with eplerenone. On one hand, spironolactone improves endothelial function in patients with HF, but it fails to do so in those with DM whereas eplerenone does. This indicates that eplerenone can be the MRA of choice in patients with DM and/or CKD.[18]

Managing Hyperkalemia Concerns

Various treatment options exist for managing severe hyperkalemia encountered during eplerenone use.

- Sodium polystyrene sulfonate (SPS) can be used in patients >50 years of age for long-term lowering of serum potassium levels.[19]
- Patiromer, a potassium binder is approved by the US Food and Drug Administration (FDA) for use in patients >50 years of age. As per a randomized, multicenter, open-label 52-week trial in patients having HF and CKD, type 2 diabetes and hypertension, patiromer decreased serum potassium mean level to ≤5.0 mEq/L and maintained this level for about a year.[19]

- Sodium zirconium cyclosilicate (ZS-9), a sodium-potassium cation exchanger is >125 times more selective for potassium than SPS *in vitro*. Efficacy of ZS-9 has been demonstrated in the Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) phase-III trial.[19]

Efficacy of Eplerenone Across Patient Populations in the Management of HF

Patients with mild symptoms of HF

Analysis of EMPHASIS-HF trial for first and repeat hospitalizations, with focus on HF hospitalizations showed that first hospitalizations were more in the placebo group as compared to eplerenone (277 vs. 186). Repeat HF hospitalizations (excluding the first) gave a rate ratio for the eplerenone group, of 0.52 (95% CI, 0.33-0.82; p = 0.004) in comparison with placebo. The analysis revealed that in systolic HF with only mild symptoms, hospital admission of patients due to worsening HF is common and repeat admission is frequent. Eplerenone not only reduces the risk of first admission, but also lowers the possibility of second and subsequent admissions.[20]

Patients with MI and mid-range ejection fraction

A large percentage of patients with a recent myocardial infarction (MI) have an EF of 40% or greater irrespective of the presence or absence of signs and symptoms of HF. An analysis of the EPHESUS trial to evaluate the characteristics, event-rates and the effect of eplerenone in patients with mid-range EF (EF between 40% and 50%), compared to those with EF <40%, showed reduction in hospitalization and mortality in patients with MI and mid-range EF with eplerenone equivalent to patients having EF <40%. These findings should be taken into consideration during therapeutic decisions.[21]

Patients with resistant hypertension and obstructive sleep apnea

In patients with obstructive sleep apnea and resistant hypertension, eplerenone when added to standard antihypertensive therapy showed significant reduction (p < 0.001) in the night-time BP parameters for the treatment group including improved night BP fall from 4.6% to 8.9%. Further, the number of nondipper patients decreased by 45.1%. A significant decrease in LVH and in the apnea-hypopnea index was also seen. The potential benefit of eplerenone in treatment of patients with resistant hypertension is evidently seen in this study.[22]

Post-STEMI in patients without history of HF

In a randomized, placebo-controlled, double-blind trial, Montalescot et al studied outcomes in ST-elevation myocardial infarction (STEMI) patients. Critical parameters such as re-hospitalization/extended initial hospital stay for HF; BNP > threshold (≥1 month post randomization); cardiovascular death, HF and arrhythmia (combined) were lesser in eplerenone group compared to placebo.[23]

Post-AMI in diabetic patients with CHF

In a post-hoc analysis on diabetic group of EPHESUS trial, with LVSD and signs of CHF following acute MI (AMI), use of eplerenone in a mean dose of 43 mg/day for 3 to 14 days following AMI led to reduced mortality from cardiovascular causes or hospitalization for cardiovascular events.[24]

Patients with bilateral idiopathic hyperaldosteronism

A parallel-group, Prospective, Randomized, Open-label, Blinded-Endpoint (PROBE) study by Karagiannis et al showed a rapid decrease in mean systolic BP with eplerenone from baseline to Week 8 to Week 12 to Week 16. Relative systolic BP decrease from baseline to Week 16 in eplerenone was 29.3 ± 2.7% versus 27.0 ± 3.6% with spironolactone (p < 0.05). However, baseline systolic BP decreased considerably in both groups by the end of the study (i.e., at Week 24) (29.5 ± 3.4% with spironolactone and 30.2 ± 3.4% with eplerenone, p = 0.559).[25]

Patients with chronic heart failure

Plasma adiponectin levels are shown to have negative correlation with insulin resistance, so they might predict cardiovascular events in chronic HF patients. HbA1c levels are reported to be an independent risk factor for mortality in diabetic and nondiabetic patients, and cortisol levels are an independent predictor of cardiac events in chronic HF patients. Randomization of 107 mild chronic HF patients receiving standard therapy to eplerenone (50 mg/d) or spironolactone (25 mg/d) showed that plasma adiponectin levels were significantly decreased (12.6 ± 1.4-11.2 ± 1.3 μg/mL, p < 0.0001) with spironolactone, whereas HbA1c and cortisol levels were significantly increased (5.61 ± 0.1-5.8 ± 0.1%, p < 0.0001, 11.3 ± 0.8-14.7 ± 1.3 μg/dL, p = 0.003, respectively). In contrast, in patients receiving eplerenone (n = 73), plasma levels of adiponectin, HbA1c and cortisol did not change. These findings indicated that the metabolic effect of eplerenone differed from that of spironolactone and that eplerenone had a superior metabolic effect, especially on HbA1c in chronic HF patients.[26]

CONCLUSION

Management of HF is challenging, and suboptimal use of guideline-directed medical therapy (GDMT) predisposes a patient to increased morbidity and mortality. MRAs, a cornerstone of HFrEF management, have been clinically underutilized in HF patients despite strong favorable evidence from randomized controlled trials. Amongst the MRAs, eplerenone has shown beneficial effects in suppressing post-AMI collagen turnover changes, thereby preventing cardiac remodeling and the deleterious effects of aldosterone in patients with HFrEF. Various trials have confirmed the efficacy, safety and tolerability of eplerenone as a disease-modifying agent. Eplerenone significantly reduces mortality, risk of hospitalization and improves the quality of life in HFrEF patients, which calls for the optimal use of MRAs, specifically eplerenone to improve patient outcomes in HF.

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■■■■

India's First-ever Thinnest Implant Surgery Accomplished

Dr Rajeev Kapila, the Cochlear Implant surgeon and his team at the Deep Hospital in Ludhiana successfully performed the thinnest Cochlear Implant Surgery on a boy aged 4 years who had complete deafness, making it the first surgery of its kind in India. The doctors used the thinnest implant platform in the world with 3 Tesla MRI compatible implants. The implants would be functional from next week enabling the boy to hear for the first time since birth.

The founder of Deep Hospital, Dr Baldeep Singh praised the team and said that parents should be more vigilant if the child doesn't respond to different noises normally and visit the doctor for an accurate diagnosis in case they see some deviation. Awareness about treatment options for hearing loss and early diagnosis could help the children receive treatment sooner and help to resolve their problems. (*Source: ETHealthWorld, June 10, 2022*)

Elevated CSF1 Levels Act as a Key Driver of Alcoholism Relapse

A recent discovery in Molecular Psychiatry revealed that the anxiety associated with withdrawal from excessive alcohol use that may contribute to relapse, may be driven in part by the release of an immune protein in the brain colony-stimulating factor 1 (CSF1), which could be a potential target of future treatments for alcohol use disorder (AUD).

The researchers discovered a group of neurons in the medial prefrontal cortex (mPFC) of mice that are sensitive to corticotropin-releasing factor (CRF) because they express a CRF receptor called CRF1, which is involved in mood and behavior changes after alcohol exposure and withdrawal.

The preliminary findings suggest that knocking off these CRF-sensitive neurons makes mice less nervous, implying that the neurons are normally involved in anxiety-like behaviors. Subsequently, the researchers discovered that in alcohol-dependent mice experiencing alcohol withdrawal, these CRF-sensitive mPFC neurons become less excitable or less likely to transmit messages to neighboring neurons when stimulated. Nearby mPFC neurons without CRF receptors, on the other hand, become more excitable. Further investigations showed that increased CSF1 levels in the mPFC played key role in exhibiting alcohol withdrawal signs and symptoms.

As a result, scientists believe that targeting CSF1 would be a good strategy for AUD treatment, and tests on the preclinical models would be done for the same. (*Source: Hindustan Times, June 09, 2022*)

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CONTEMPORARY ARTICLE

Motivating Persons Living with Diabetes for Insulin/Injectable Therapy

SANJAY KALRA*, NAVNEET AGRAWAL†, ABHINAV GARG‡

ABSTRACT

Motivating patients to initiate or intensify insulin is a challenging aspect of diabetes practice. This paper reviews certain motivational strategies and methods used for insulin initiation/intensification. It places various domains of motivational interviewing in perspective, under a single umbrella, making it easier for practitioners to understand the art and science of insulin motivation.

Keywords: Diabetes, insulin therapy, patient-centered care, person-centered care, psychosocial aspects

A large proportion of patients with diabetes is poorly controlled, and suffers an unnecessary burden of poor glycemic control before their therapy is up-titrated or intensified.[1] While many reasons have been put forward for this clinical inertia, one of the major reasons is physician's inability (or their self-perceived inability) to motivate patients to initiate or intensify insulin therapy.[2]

The model we share in this article is being used with success at our centers. It is a simple and easily replicable method, which can be learnt by physicians and paramedical staff alike, and used in resource-limited or time-challenged settings as well as in optimal health care environments.

INSULIN MOTIVATION – 'WATER' APPROACH

The WATER approach[3] is a mnemonic coined for a method of motivational interviewing (MI) used at our centers. It is a checklist designed to remind the health care practitioner about the basics of MI, and to ensure good quality provider – patient bonding so that optimal therapeutic outcomes are achieved (Box 1).

Box 1. The WATER Approach

W – Welcome warmly	• Body language • The OPD encounter
A – Ask and assess	• Identifying and using cues ▪ Internal, external, laboratory • Hierarchy of questioning • The insulin encounter
T – Tell truthfully	• Mid-Sentence analysis • Verbal/Nonverbal cues • Analogy building
E – Explain with empathy	• Examples/Experience – sharing • Demonstration • Coping skills training
R – Reassure and return	• Agree upon the next visit/contact • End with positivity

W stands for 'Welcome warmly', which reminds the health care provider (HCP) to greet the patient, with genuine warmth, in a gender, age- and socio-culturally appropriate manner.

BODY LANGUAGE

The physician should make a conscious effort to learn the nuances of body or nonverbal language, make the patient feel at ease, diagnose his or her level of comfort, and plan further conversation or therapeutic intervention. A pleasant greeting is followed by a detailed history taking, reflected by A for Ask and Assess. The patient is asked for his or her perception

*Dept. of Endocrinology, Bharti Hospital, Karnal, India
†Dept. of Diabetology, Diabetes Obesity Thyroid Centre, Gwalior, India
‡Dept. of Medicine, Medicutis Clinic, Prashant Vihar, New Delhi, India
Address for correspondence
Dr Sanjay Kalra
President elect, South Asian Federation of Endocrine Societies (SAFES)
Past President, Endocrine Society of India (ESI)
Bharti Hospital & BRIDE, Karnal - 132 001
E-mail: brideknl@gmail.com

of diabetes. History is accompanied by an assessment of barriers to insulin therapy, cues[4] (such as concerns, symptoms, signs, laboratory reports and external influences), which may stimulate insulin use and felt needs of the patient.

HIERARCHY OF QUESTIONING

Using the correct order of questioning is of utmost importance in history taking, if one wants to motivate a major change in health-related behavior, e.g., insulin use. While conversing, one should slowly move from the patient's comfort zone to his or her non-comfort zone, from non-personal to personal, from familiar to unfamiliar. One should first identify and/or create a major felt need, and then position insulin as the treatment for that need, while focusing on its positive benefits.

A conversation where the doctor asks about sexual function or financial issues before talking of weight loss or asthenia will be not welcomed by most patients.

CUES

The motivation model utilizes 'internal' and 'external' cues, gleaned from an intensive history taking, and 'laboratory' cues, taken from investigation reports, for insulin motivation. Internal cues are signs and symptoms, which have a high index of perceived severity, or are a 'felt need' for the patient, such as a frozen shoulder, recurrent urogenital infection or weight loss. External cues may be motivation by 'social' or 'environmental' factors. An impending or developing renal failure due to diabetes, or a child learning about the complications of diabetes at school, may act as a factor for insulin acceptance. Laboratory results such as a high HbA1c or a high vibration perception threshold on biothesiometry can be utilized for insulin motivation.

MID-SENTENCE ANALYSIS

During the process of "asking and assessing", one can keep a close watch on the patient's verbal language or nonverbal cues, to assess the patient attitudes towards insulin. For example, one can start a sentence as "Guidelines tell us to begin insulin in you ……" and wait to see the patient's response. If he or she moves backwards or says "But I will never take insulin!" or makes a wry face, the sentence can be completed as "……. but let us try tablets for 2 weeks. Do you mind taking an expensive tablet with only 2 years history of experience?"

Box 2. The CARES Approach

- **C**onfident Competence
- **A**uthentic Accessibility
- **R**eciprocal Respect
- **E**xpressive Empathy
- **S**traightforward Simplicity

If on the other hand, the patient keeps a neutral stance and facies, one can complete the conversation as: "…, so let us begin twice daily insulin."

Such a mid-sentence analysis is an effective tool of reducing "counseling casualties" and getting resistant patients to gradually accept insulin or other appropriate therapy.

One should T (Tell the truth) to the patient after having assessed his needs. The truth or HCPs clinical opinion should be told in an appropriate manner, described as the five-pointed CARES approach (Box 2). These are the five attributes, which a diabetes care professional must possess.[5]

Telling the truth alone is not enough; one should Explain the situation with empathy. Explanation is accompanied by analogy building,[6] quotation of examples and use of demonstration devices. Cues gleaned during history are utilized to provide a starting point for patient engagement, and given back to patients, paraphrased as suggestions or solutions.

The last step is R (Reassure and Return). Reassurance is essential to ensure that the patient returns for follow-up.

The physician may not succeed in motivating the patient for insulin or injectable therapy during the first OPD encounter, but will at least shift him or her from the pre-contemplation to the contemplation phase (Prochaska's theory of knowledge).[7]

EXPERIENCE – SHARING WITH PEERS

Most oriental cultures encourage sharing of illness-related experiences with friends and community. Health is usually not reviewed as a private matter, unlike in western cultures. Depending upon social mores, one can use examples of successful insulin initiators in the community to encourage insulin initiation and intensification.

COPING SKILLS TRAINING

Reassurance is combined with coping skills training (CST), which helps the patient handle the stress of diabetes in a better manner.

Table 1. Coping Styles

Negative	• Blaming oneself, e.g., I have developed diabetes because of sins in my past life
	• Blaming others, e.g., my sister didn't take care of me so I developed high blood pressure
	• Extremely bad thoughts, e.g., I will die due to high glucose
	• Pervasive bad thoughts 24 x 7, e.g., Thinking only and only about diabetes throughout the day
Neutral	• Acceptance, e.g., I accept that diabetes and insulin are a part of my life
Positive	• Put in perspective, e.g., Let me count my blessings and strengths
	• Positive spin-off, e.g., Insulin will make me more disciplined in my life
	• Pleasant thoughts, e.g., May be I will make new friends at the next diabetes advocacy meeting
	• Plan for the future, e.g., Let me begin saving money to buy an insulin pump

Coping skills training is a method of improving the method(s) by which a person responds to a seemingly insurmountable challenge (for example, living with diabetes, controlling diabetes). Each and every person has both positive and negative coping skills. Our model of diabetes counseling focuses on diagnosing a particular patient's coping methods.

One should begin by Asking and assessing the individual's current coping styles. This gives an idea of the negative skills which have to be Eliminated, before positive coping mechanisms can be Introduced and Internalized. These changes have to be Observed on a Ongoing basis, so that one can continually Upgrade one's Understanding and health care-related behavior. This has been termed the AEIOU approach. Table 1 lists the common coping styles that can be identified and optimized.

REDUCING DISCOMFORT OF CHANGE

One should always strive to reduce the discomfort associated with change.[9] Simple steps such as building a rapport with the patients, abbreviating bad news, and expanding good news, making change appear as if it were a choice, handing overcharge to the patient, and breaking the change into small bits, help in reducing the discomfort associated with change of lifestyle or pharmaceutical modality.

CONCLUSION

This article tries to encapsulate, under one umbrella, the various facets of patient motivation for insulin or injectable therapy in people with diabetes. It should sensitize physicians and other diabetes care professionals to the science behind the art of insulin motivation, and help improve the quality of care provided to persons living with diabetes, by reducing clinical inertia as well as patient resistance related to insulin usage.

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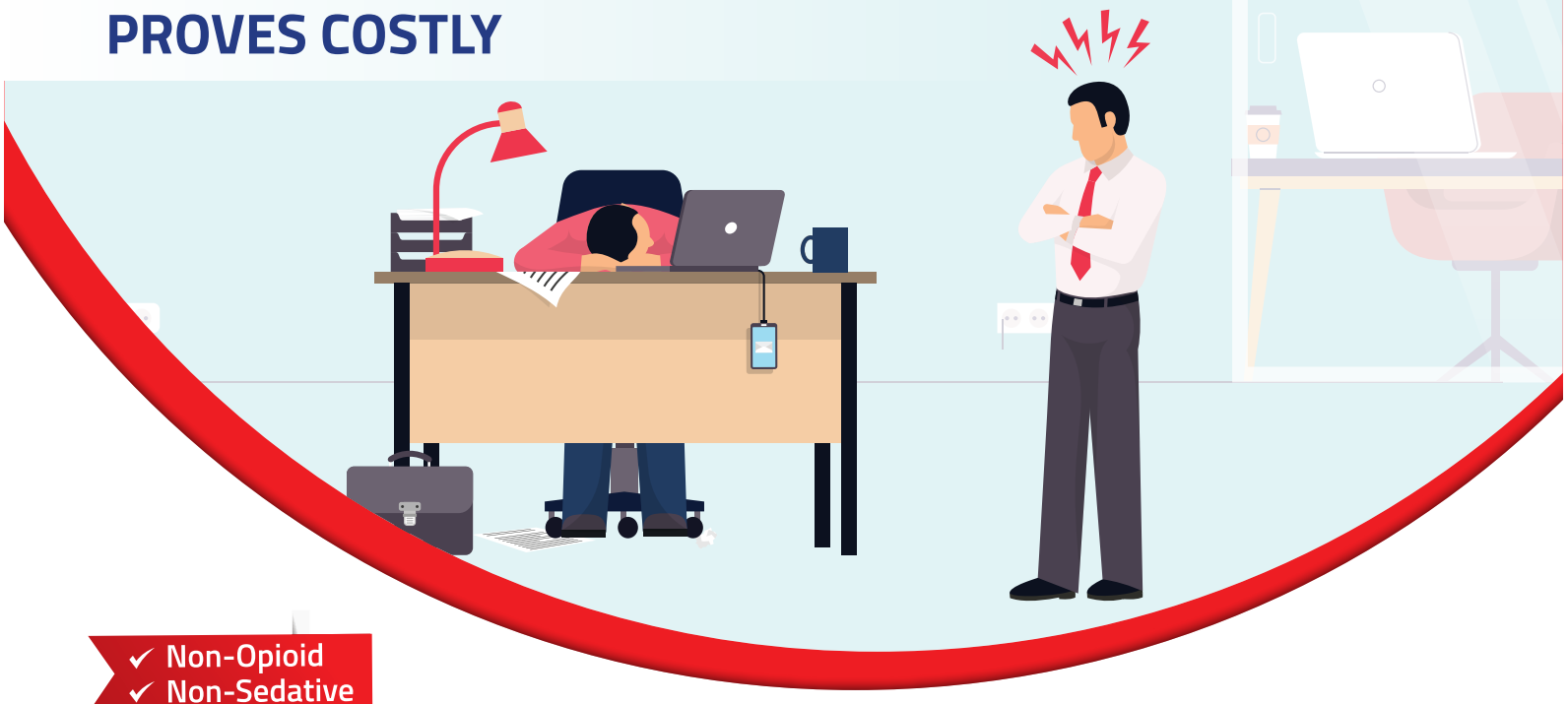

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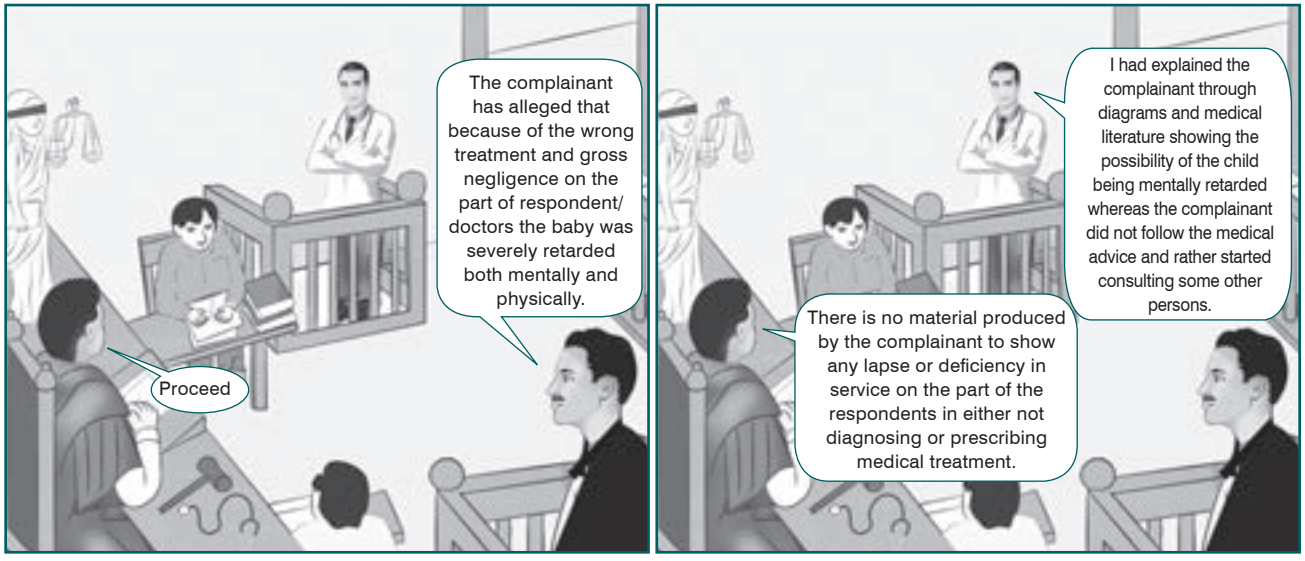

Lesson: In its order in the FIRST APPEAL NO. 490 of 2007 NCDRC stated that the appellant has not been able to prove through any credible evidence that there was medical negligence or deficiency on the part of the respondents or any action or omission on their part which resulted in or aggravated the congenital condition of the infant. On the other hand, there is credible evidence that right through the prenatal period and after the birth due medical attention and proper treatment was given by both respondents who are well qualified specialists in their fields. We agree with these findings and therefore, uphold the order of the State Commission. The first appeal is dismissed.

COURSE OF EVENTS

- This first appeal has been filed by the complainant before the State Commission and appellant herein, being aggrieved by the order of the State Consumer Disputes Redressal Commission, Delhi (hereinafter referred to as the 'State Commission') which has rejected his complaint of medical negligence against Respondents No. 1 and 2, respectively.
- In his complaint to State Commission, appellant had contended that his wife delivered a male child at Shubham Hospital, New Delhi and the delivery was handled by Respondent No. 1 who was a Gynecologist and thereafter by Respondent No. 2, a Pediatrician.
- The appellant had alleged that because of the wrong treatment and gross negligence on the part of respondent/doctors the baby was severely retarded both mentally and physically.
- The appellant had specifically stated that his wife who was suffering from fever in her 32-34 weeks of pregnancy had visited Respondent No. 1 who failed to conduct a basic test known as Torch test which would have clearly indicated the nature of the prenatal viral infection and whether it had infected the fetus. Instead the patient was given only paracetamol to check the fever.
- The baby was born after 36 weeks of gestation i.e. 4 weeks before the full gestation period with symptoms of the present disease but he was not given the required medical treatment at birth as a result of which, as per the certificate issued by the All India Institute of Medical Sciences (AIIMS) in 1996, he has cerebral palsy with spastic tendencies, mental retardation and 90% permanent physical impairment.
- The certificate from AIIMS specifically stated that the perinatal viral infection was the cause of this

condition. If due medical treatment had been given at birth instead of just tonics and vaccines by Respondent No. 2, appellant contended that the extent of disability would not have been so extensive.

- Appellant, therefore, approached the State Commission on ground of medical negligence and requested that respondents be directed to pay him Rs. 15 lakhs as compensation for mental agony and to enable him to provide the necessary treatment for his child.
- Respondents filed a written rejoinder denying that there was any medical negligence in the care and treatment of the appellant's wife and infant.
- The appellant's wife approached Respondent No. 1 for prenatal treatment for the first time in December, 1991 and she was accordingly advised necessary tests including ultrasound and no abnormalities were detected.
- In her 32-34 weeks of pregnancy the appellant's wife had fever and was prescribed Crocin to control the fever and no other drug.
- Growth retardation of the baby was noted at 34-35 weeks and the appellant's wife was advised bed rest.
- The appellant's wife was brought to the hospital in the 36th week in advanced labor and delivery took place within 1 hour with the umbilical cord wound thrice around the baby's neck and he had passed meconium because of which there was difficulty in spontaneous initiation of breathing at birth but the baby was successfully resuscitated within 2 minutes with normal APGAR count. Since, the baby was small for date, he was kept in a thermoneutral environment under an oxygen hood and prescribed prophylactic antibiotics and also medication for the mild jaundice which is common in newborns.
- The baby was discharged on 24.06.1992 in a suitable condition.
- On 03.07.1992, the baby was brought to the hospital with complaints of vomiting, lethargy and disinterest in suckling and Respondent No. 2 after examining him advised hospitalization which was not accepted by the appellant who thus acted against medical advice.
- On 01.08.1992 during another visit, spastic tendencies were visible and Respondent No. 2 explained the medical condition as also the prognosis to the parents and advised them to bring the baby for follow-up visit within 7 days but the baby was brought only after 21 days in poor medical condition. Amoxicillin for 10 days was prescribed but the parents discontinued the antibiotics after 3 days. Thereafter, the parents never brought the child to the respondent and probably got him treated elsewhere. There was thus no medical negligence in the treatment of either the mother or the baby and it was the appellant and his wife who repeatedly failed to follow medical advice.
- It was also contended that the first appeal was time barred as it was filed beyond the statutory period of 2 year from the date on which the cause of action had arisen.

ORDER OF THE STATE COMMISSION

- The State Commission after hearing both parties and on the basis of evidence filed before it concluded that no case of medical negligence was made out. The relevant part of the order of the State Commission is reproduced:

Here is a case where the child was born at 36 weeks gestation on 16-06-1992. The last when the complainant contacted the OP was till 15, September, 1992. The child subsequently has been diagnosed as suffering from cerebral palsy in 1996, which is indication of mental retardation. The complainant was advised hospitalization of the child but he declined. Medical treatment prescribed was not followed. There is no cure for cerebral palsy. Torch test is prescribed only if the mother is suffering from such fever in the first 12 weeks of pregnancy and not 34 weeks of pregnancy. Giving PCM (Paracetamol) to a mother who is in 34 week of pregnancy is absolutely safe and by no means can cause any kind of infection or abnormality to the child. The mental retardation of the child cannot be projected in the ultrasound examination. Merely because the child was born underweight is known as SFD (Small for Date).

The OP contended that the doctor had explained the complainant through diagrams and medical literature showing the possibility of the child being mentally retarded whereas the complainant did not follow the medical advice and rather started consulting some other persons. There is no material produced by the complainant to show any lapse or deficiency in service on the part of the OPs in either not diagnosing or prescribing medical treatment as is apparent from the aforesaid contentions. …..…….. The child was born with umbilical cord surrounding its neck. Though

we have all the sympathy for the complainant but the aforesaid facts do not make out a case of medical negligence or any deficiency in service on the part of the OP Hospital or doctors and they cannot be held liable for any lapse or negligence during or after delivery of the child. The complaint is dismissed being devoid of substance."

ALLEGATIONS OF COMPLAINANT

Appellant who was present in-person and Counsel for Respondents made oral submissions.

- Appellant reiterated that if proper tests including the Torch test had been conducted, the type of viral infection from which both the mother and the fetus had been obviously infected would have been detected and the mother could have been given proper medication instead of only crocin and the baby could have been given the medical attention required in such cases at birth instead of only antibiotics and tonics.
- The certificate from AIIMS clearly indicated that the condition of the child, who unfortunately is no more, was because of the perinatal viral infection. If proper medication had indeed been given immediately in all possibility the retardation would have been checked at birth instead of increasing over the years.
- Appellant apprehended that there was every possibility that the mother was given certain medications which were contraindicated though on a specific query from us, he could not state what other medicines were given.

REJOINDER OF RESPONDENTS

- Counsel for respondents on the other hand stated that both respondents are well qualified doctors with specializations in Gynecology and Pediatrics, respectively.
- Respondent No. 1 took due care during the pregnancy and right in the beginning various tests including ultrasound were conducted which could have revealed some growth problem but not spastic tendency or cerebral palsy because spastic tendencies cannot be diagnosed in a fetus.
- The fever which occurred in the 32-34 weeks of the pregnancy in the mother cannot cause fetal malformation which can occur if the mother contracts an infection in the first trimester, i.e., 12 weeks of the pregnancy.
- Since an ultrasound had confirmed that the fetus was small for date, as per medical practice, respondent planned to induce labor but before this could be done, the appellant's wife herself delivered 1 month prematurely with only 1 hour of labor pains.
- On birth, the infant was in respiratory distress because the umbilical cord was bound thrice round his neck and he had passed and swallowed meconium in the womb. He was immediately resuscitated, stabilized and put in intensive care and prescribed antibiotics and treated with other medication for mild jaundice and discharged thereafter in a stable and satisfactory condition.
- It was the appellant and his wife who failed to heed correct medical advice during subsequent follow-up visits by not agreeing to hospitalization of the baby and also not giving antibiotics for the prescribed period.

OBSERVATIONS OF NCDRC

We have heard the appellant and the Counsel for respondent and have carefully gone through the evidence on record.

- We note from the record that as observed by the State Commission due care was taken in the prenatal care of the appellant's wife by Respondent No. 1 and necessary tests were conducted.
- Appellant's contention that there was negligence in not conducting the Torch test when the appellant's wife contracted fever between 32-34 weeks of pregnancy is not borne out by the medical literature on the subject according to which a Torch test is prescribed within first 12 weeks of pregnancy in case the mother is suffering from fever because this is the period when fetal malformation can occur due to certain infections (Reference: American Pregnancy Association and MCRCK, manual on high-risk pregnancy risk factors).
- Admittedly, the appellant's wife suffered from fever only a few weeks before the delivery and she was given paracetamol which is not contraindicated.
- While it is a fact that the child was born with cerebral palsy and related problems, as per the medical literature, this could not have been detected in the womb or caused because of any medication or wrong treatment when the appellant's wife had fever just prior to her delivery.
- Since the fetus was small for date, due care was taken and a few days after the birth when covert

symptoms of cerebral palsy disease became apparent, appellant and his wife were immediately advised about the problem and also given a prognosis.

OPINION OF NCDRC

Appellant has not been able to prove through any credible evidence that there was medical negligence or deficiency on the part of the respondents or any action or omission on their part which resulted in or aggravated the congenital condition of the infant. On the other hand, there is credible evidence that right through the prenatal period and after the birth due medical attention and proper treatment was given by both Respondents who are well qualified specialists in their fields. Further, the certificate from AIIMS on which the appellant has relied was given some years later and only a question mark was put regarding the cause of the cerebral palsy being the prenatal viral fever from which the appellant's wife suffered and it was not a definite opinion on the same.

ORDER OF NCDRC

The State Commission has carefully considered all these aspects and has given a well-reasoned order concluding that the appellant has not been able to prove that this was a case of medical negligence or that there was any deficiency in service on the part of the respondents. We agree with these findings and therefore, uphold the order of the State Commission. The first appeal is dismissed with no order as to costs.

REFERENCE

1. Case no. 490 of 2007; Order date 13.09.2012.

■■■■

Research Reveals that Mixture of Chemical Pollutants was Associated to Falling Sperm Quality

Research, published in the journal *Environment International,* revealed that a number of chemical contaminants found in people's bodies were linked to poor sperm quality. The study found that chemicals including bisphenols and dioxins were present at considerably higher concentrations in males and that these chemicals interacted with hormones, resulting in low sperm quality.

The maximum danger was caused by bisphenol A (BPA), which is prevalent in milk and canned food and leaches from the packing linings, followed by dioxins, paracetamol and phthalates. The researchers measured nine substances in urine samples from over 100 Danish men aged 18 to 30 years old, including bisphenol, phthalates and paracetamol. When compared to acceptable levels of exposure, it was found that these men had been exposed to the dangerous combination of the chemicals which was 100 times more than the average acceptable limits.

Other pollutants, such as per- and polyfluoroalkyl substances (PFASs) compounds, air pollution, increased body weight, sedentary lifestyle and smoking, may also have an impact on sperm quality, but they were not included in this study.

Experts believe that low sperm counts are caused by environmental factors and that this has an impact on early pregnancy. However, they also claimed that a high-fat, processed diet was both dangerous in itself, as well as the original source of the chemicals and that it was the combination of these chemicals that was causing men's sperm counts to drop and affect their health. (*Source: The Guardian, 10 June 2022)*

HCFI Dr KK Aggarwal Research Fund

HCFI Round Table Environment Expert Zoom Meeting on "World Environment Day – Only One Earth: Benefits of Native Trees and Medicinal Plants"

June 5, 2022 (Sunday, 12 noon - 1 pm)

- This year marks the golden jubilee of the first World Environment Day held in Stockholm in 1972. The theme for this year is "Only One Earth" with the focus on "Living Sustainably in Harmony with Nature". This was also the theme in 1972.
- The Oslo Protocol, Helsinki Protocol and Montreal Protocol have proved that man-made challenges can be addressed. There has been consistent effort to protect biodiversity and climate change concerns.
- A Supreme Court-appointed Committee has submitted in a report that a tree's monetary worth is its age multiplied by ₹ 74,500.
- Out of this, the cost of oxygen alone is ₹ 45,000, followed by cost of bio-fertilizers, which are worth ₹ 20,000.
- A fully grown tree in lifespan of 60 years could be valued at about ₹ 50 lakhs.
- A heritage tree with a lifespan of well over 100 years could be valued at more than ₹ 1 crore.
- Native trees are already adapted to the environment and so do not need extra water or nutrients.
- They provide food, medicinal benefits and shade. They also contribute to nutrient recycling, absorbing nutrients from intensive agriculture, improve air quality and are vital for stabilizing soils, reducing sedimentation moderating erosion. They provide greater indigenous biodiversity, meaning greater resilience and a bigger range of functions within our ecosystem.
- Peepal, Bargad, Ber, Arjun Jamun, Neem, Mango, Bel are few examples of native species, which can combat pollution.
- There is a Triple Planetary Emergency that of climate change, Nature and biodiversity loss and pollution and waste.
- Biodiversity loss is an offshoot of the unsustainable path of development and is an emergency for everyone across the globe.
- An immense quantity of nano-/microplastics is in circulation in water, which is consumed by us and in turn affect health and out of pocket expenditure. This is an immediate challenge that needs to be addressed.
- Climate change is also overall related to the concept of well-being. Delhi recently experienced a temperature of nearly 50°C for the first time.
- Due to the high temperatures, a huge amount of water is needed to irrigate food crops, which is a challenge to the farmers. Crop failures also occur.
- A medicinal plant is any plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes or which are precursors for the synthesis of useful drugs.
- Medicinal plants are integral to human society for curing diseases as well as well-being well before the modern system of medicine came into existence. Because of overexploitation, much of it is getting drained from our natural system. Indigenous and tribal communities are very closely linked to medicinal plants.
- Studies have been carried out globally to verify their efficacy and some of the findings have led to the production of plant-based medicines.
- Shift from overexploitation to sustainable resource development is required.
- Arjun, Ashwagandha, Giloy, Neem, Aloe vera, Tulsi, Patharchatta, Punarnava, Brahmi, Shatavar, Shankhapushpi are few examples of medicinal plants, which have been extensively studied for their health benefits. All of us should try to grow some medicinal plants in our homes and/or plant some trees.
- The Skand Purana speaks of planting eight trees – Bodhi tree, Neem, Banyan tree, Tamarind tree, Kaith, Bilva, Indian gooseberry and Mango.
- The group of five trees – Peepal, Bel, Banyan, Amla and Ashok trees – is called Panchvati. These have immense medicinal benefits.
- We have started to become disconnected with our ancient culture with globalization. It is time to rediscover our ancient traditions. We have to restore our local indigenous, native tree and plant communities.

- Just tree planting is not the answer; tree community plantation is the answer as our aim is restoration of the ecosystem.
- Keeping green areas in cities is very essential. The quality of green cover is very important.
- The Green Delhi campaign started in 2017 and today Delhi has 23% of its geographical area under green cover.
- The Corona pandemic has taught us the challenge of managing real resources. We have suffered from the absence of open and green spaces during the pandemic.
- Many viruses are hiding in nature and many are dormant. With climate change and melting of the permafrost, new viruses may come up.
- There is a possibility of viruses jumping from forests to human areas and vice versa due to climate change.
- All plants, animals and humans should live in coexistence in a mutually beneficial manner.
- The pollination deficit is currently 25%; this has led to reduction in potential crops.
- These challenges are going to be very severe in cities than in the rural areas.
- Conflicts can lead to food crisis.
- We have to be resilient and be nonconflicting with nature.
- The rate of consumption of resources is 1.5 times the earth's resources. A huge amount of waste, particularly plastic waste, is also generated, which existing systems cannot handle.
- The dimension of forest health, which is quite prevalent in countries like South Korea must be promoted.
- Indigenous trees can withstand climate change and so should be encouraged throughout the country. They have more potential than imported species.
- Natural resources should be used appropriately without wasting any so that they are available and in good condition for the next generations to come.
- As scientists, we also have a social responsibility to see how research can help the society, especially the underprivileged.
- Biodiversity is essential for sustainable development.
- The chances of infectious diseases increase with extinction of biodiversity.
- The Aichi biodiversity targets should be implemented.
- Industry of Pharma plants can be developed.

Participants: Dr Anil Kumar, Mr Vivek Kumar, Mr Rajesh S, Mr Neeraj Tyagi, Mr Pradeep Khandelwal, Dr SK Tyagi, Dr Sanjeev Agrawal, Mr Mukul Chand, Mr BC Sabat, Mr RN Jindal, Dr S Sharma

Minutes of an International Weekly Meeting held by HCFI Dr KK Aggarwal Research Fund

Topic: Role of Radiology in COVID-19 Management. The Challenges Faced, the Solutions Offered and What We Learnt!!

Speaker: Dr Abhishek Bansal, *Consultant, Dept. of Radiology & Interventional Oncology, Rajiv Gandhi Cancer Institute & Research Centre, New Delhi*

June 4, 2022 (Saturday, 9.30-11)

- On 31st December, 2019, COVID-19 was reported to WHO China office. On 30th January, 2020, a public health emergency was declared and on the same day, India reported its first case of COVID-19 in Kerala. On 11th March, 2020, WHO declared the outbreak as a pandemic.
- Angiotensin-converting enzyme 2 (ACE2) is a functional reservoir for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). ACE2 is highly expressed in pulmonary epithelial cells.
- The global outbreak disrupted the steady world of health care and a vast proportion of health care resources were dedicated to the pandemic.
- The main challenge was the diversity of the virus. We didn't know how to manage these patients.
- The guidelines kept on changing. Many existing drugs were tried including plasma therapy. There is conflicting data about plasma therapy. It was realized that collaboration of multi-specialty clinical teams improves patient outcomes.
- Compared to the previous viral pandemics, for the first time, radiology was taking an active interest in diagnosing and also in managing these patients.
- There was a tsunami of COVID-19 publications even in Radiology journals.
- There was a huge demand for chest CT scans as aid to diagnosis of COVID-19 as there was a long waiting time for (reverse transcription-polymerase chain reaction [RT-PCR]).
- A human challenge vaccine trial was going on to look for a reliable vaccine. Then came the news about COVID dogs – medical sniffer dogs who could detect the infection. The UK government sanctioned 5,00,000 pounds on this.

- There was a sudden huge workload on radiology services as the number of chest CT scans in a day rose sharply.
- Lot of awareness had to be created to reduce the panic. There was a simultaneous impact on the economy.
- There was limited manpower and resources in the radiology departments. The scanners had to be sanitized after each scan.
- At Rajiv Gandhi Cancer Institute (RGCI), there was overall a 61.7% decline in workload between April 2019 and April 2020. A drastic drop was seen in mammography (89% drop) and interventional radiology (27% drop).
- It was then scary not just for the patients, but for the families of health care staff as well. Even now the pandemic is not over. Cases keep on coming and going but cases now do not have a serious presentation as seen previously.
- The total number of cases is around 4.32 crore and total deaths are 5.25 lakhs.
- Vaccination changed the course of the pandemic. 64.5% of population in India is fully vaccinated. Globally, 60.7% is fully vaccinated.
- Chest X-ray was the first imaging modality and was useful in serial monitoring of the patients. In acute infection, unilateral/bilateral basal consolidation with hazy opacification was seen on chest X-ray.
- CT scan has been the workhorse. COVID has highlighted the importance of CT amongst radiologists and also among the general physicians and the public. It changed how COVID was managed by informing the early features as well as the worse prognostic features so that these patients could be managed early.
- The typical CT findings in COVID-19 are peripherally distributed multifocal ground-glass opacities (GGOs) with lower lobe predilection. Increasing numbers, extent and density of GGOs on CT indicate disease progression. Thin-slice chest CT plays a vital role.
- Ultrasonography (USG) was useful for bedside evaluation of pleural effusion. Magnetic resonance imaging (MRI) was less useful and more time-consuming.
- It was difficult to manage cancer patients especially the hematological malignancy patients. Timely diagnosis and timely intervention are crucial to managing such patients.
- The Fleischner Society guideline says that look for pre-test probability. If there is moderate to high pre-test probability and there are risk factors for progression, then imaging is indicated. If there is worsening of respiratory symptoms, then again imaging is indicated. But CT scan is not a substitute for RT-PCR.
- In long COVID cases, the patches are seen to persist on CT scan. Fibrotic strands, some interstitial thickening and some nodules are also seen.
- Omicron cases usually did not undergo a CT scan, but those patients who had severe symptoms had a CT scan done and GGOs were still present.
- CT findings have always positively correlated with clinical findings.
- If D-dimers are very high and there is a high risk of pulmonary embolism (PE), then not just high-resolution computed tomography (HRCT) but a contrast CT is advised to look for PE.
- In a patient with moderate-to-severe symptoms, a CT scan would tell about the severity of the disease and serve to guide the treatment.
- COVID changed how the radiology department functioned. COVID screening clinics were outside the hospital; COVID test was necessary before interventional radiology; the entire CT room was sanitized after each CT scan. All precautions were taken such as staff wearing PPE kits. The timings were staggered; there were two teams on alternate days, minimal handling of the patient and working from home. Now, there is lot of gap between reporting stations.
- Physical academic meetings were a complete 'no'. Social distancing introduced us to the world of webinars. This was something new to us, but is here to stay. It brought people across the globe much closer to each other than before.
- India had a mobile app (Arogya Setu) for Bluetooth and GPS tracking.
- The pandemic has taught us that we have to be ready for the next variant/peak/pandemic. COVID-19 cannot be taken lightly yet.
- Along with lab upgradation, radiology infrastructure also needs to be upgraded. Most hospitals now have their own CT scanners and have integrated radiology as part of their routine clinical work. The existing upgraded radiological infrastructure has to be maintained.

- Radiological services play an important role in the multidisciplinary management of COVID-19 or other pandemics that may strike the human race. There have to be adequate training opportunities and telemedicine is going to stay at least for follow-ups.
- The way forward is to continue with the vaccination drive to cover the whole world and invest in health care suitably. Adequately sized hospitals should have full-fledged radiology departments. COVID appropriate behavior should stay with us.
- Chest imaging should be used cautiously. It is not indicated in suspected COVID-19 and mild clinical features unless patients are at risk for disease progression. Imaging is indicated in COVID-19 and worsening symptoms.
- In resource-constrained environment, imaging is indicated for medical triage of patients with suspected COVID-19 who present with moderate-severe clinical features.
- Rural areas have poor penetration of health care facilities as well as diagnostic radiological facilities. Without radiology it becomes difficult to diagnose and prognosticate these patients.
- Radiologists were also treating these patients, not directly, but indirectly by managing conditions that arose because of it such as pleural fluid aspiration, pericardiocentesis, management of PE, catheter thrombolysis, embolization, inferior vena cava (IVC) filter placements, etc. Percutaneous jejunostomy under LA was another procedure done during the peak when surgeons/anesthetists were not available and oxygen was in short supply.
- The biggest problem during the Delta peak was a dedicated oxygen supply. All elective surgeries were postponed. Radiology was playing a supportive role in the management of these patients.
- Modern day CT scanners are so optimally built that the radiation is very trivial.
- In a chest CT scan, the radiation dose varies from 2 to 3 milliSievert (mSv); in contrast CT scan, it is 10 mSv. In HRCT, the dose is 3 mSv. This is the average amount of radiation that a person receives from the cosmic world in a single year, though this varies in a range depending on geographical location. With this dose, side effects are not anticipated but the impact will be known only in few years. Follow-up is important.
- The risk has to be weighed against the benefits. But there should be no unnecessary CT scans.
- Radiologists work on the principle of ALARA, i.e., as low as reasonably achievable.
- In a shift from the earlier "no threshold theory" where any amount of radiation was harmful, a new developing "threshold theory" is being debated, which suggests that small radiation doses (≤50 mSv) are not harmful.

Participants – Member, National Medical Associations: Dr Yeh Woei Chong, Singapore, Chair CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong, Treasurer-CMAAO; Dr Marthanda Pillai, India-Member World Medical Council, Advisor-CMAAO; Dr Ravi Naidu, Malaysia; Dr Akhtar Hussain, South Africa; Dr Qaiser Sajjad, Pakistan; Dr Mvuyisi Mzukwa, South Africa; Dr Md Jamal Uddin Chowdhury, Bangladesh

Invitees: Dr Russell D'Souza, Australia UNESCO Chair in Bioethics; Dr Monica Vasudev, USA; Dr Abhishek Bansal; Dr Arvind Chaturvedi; Dr Anil Bansal; Dr Varun Sehrawat; Dr PK Tiwari; Dr PC Pahwa; Dr Yeo Khoon Hui; Dr Carol Lim; Dr EC Ng; Dr Rajiv Gupta; Dr Brij Bajaj; Dr Rajesh G Parthsarthi

Moderator: Mr Saurabh Aggarwal

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AIOC 2022: 80th Annual Conference of All India Ophthalmological Society

DO'S AND DONT'S: POSTERIOR POLAR CATARACT

Dr TP Lahane, Mumbai

Daljit Singh's classification

- Type 1: Opacity associated with posterior subcapsular cataract.
- Type 2: Opacity with ringed appearance like an onion.
- Type 3: Opacity with dense white spots at the edge often associated with thin or absent posterior capsule.
- Type 4: Combination of the above 3 types with nuclear sclerosis.

Do's

- Visual acuity and refraction
- Undilated and dilated fundus evaluation
- A Scan ultrasonography
- B Scan ultrasonography
- Anterior segment optical coherence tomography (ASOCT)
- ASOCT is a beneficial tool to assess the status of the posterior capsule preoperatively
- Intraoperative ASOCT
- Modified posterior optical coherence tomography
- Pujari et al defined conical sign with +20 dioptre and modified posterior coherence tomography (m-OCT)

Tips

- Patient counseling
- Adaptation in operative technique
- Posterior segment instrument stand-by

THE HARD CATARACT: A CHALLENGE

Dr Hemlata Gupta, New Delhi

- Thorough preoperative evaluation.
- Protect endothelium. Plan beforehand, and keep backup ready.
- Avoid wound burn-check inflow/outflow if any clogging.
- Viscoelastic may be injected behind nuclear fragments, to serve as a protective cushion over the posterior capsule. Reduce phaco parameters when dealing with last fragments.
- PCR: Management depends upon the stage of the surgical procedure at which posterior capsular tear is detected.
- POSTOP: Keep a check on inflammation and intraocular pressure.

MANAGEMENT OF POSTERIOR POLAR CATARACT – NEWER CONCEPTS

Dr JS Titiyal, New Delhi

The technique of femtosecond laser-assisted cataract surgery with a hybrid pattern of cylinder and chop is safe and effective in managing cases of posterior polar cataract, specifically for high grades of nuclear sclerosis. In the technique, a hybrid pattern of three cylinders (2, 4 and 6 mm) and three chops (6 mm in length) was used for nucleotomy. Block by block emulsification of the pre-chopped nucleus was done from the center outward, with the remaining outer rings acting as a protective cushion. Manual hydrodissection and hydrodelineation were avoided. In the postoperative uncorrected Snellen visual acuity was 20/25 or greater in all cases.

A CENTURY GONE IN VAIN – A CONSECUTIVE SERIES OF 100 BALL-RELATED EYE INJURIES!

Dr Rohit Agrawal, Kolkata

Worldwide, there are roughly 1.6 million people blinded by ocular trauma every year and about 2.3 million individuals have bilateral low vision due to these eye injuries. Retinal detachments have been reported in up to 9% of contusion injuries, can present many years post-trauma, and require a long-term follow-up. Sports with a high risk of eye injury include cricket, hockey, racket sports, handball, baseball, basketball, football, soccer and volleyball. Cricket is one of the most popular games in the Indian subcontinent and injuries are

reported both in professional and recreational matches. Blunt forces cause peripheral volume displacement with increased wedge pressure that causes damage to the area of least resistance along with the lens, iris root and trabecular meshwork. Lens subluxation, retinal dialysis, optic nerve avulsion and vitreous hemorrhage are more severe complications. The brow offers protection when the line of approach is horizontal, but when the ball approaches the eye laterally or inferiorly injuries are bound to happen. There are very few studies that have explored the vision-threatening complications, need for surgical intervention and final visual outcome after treatment for ball-related ocular trauma.

This is a descriptive report of 100 consecutive patients who presented to us with ball-related eye injuries; and describes the demography, ocular findings and medical interventions. The drawbacks of this study are that the mechanism of injury could not be determined in all cases and the lack of long-term follow-up to determine sequelae. While medical and/or surgical intervention can restore vision in most, more emphasis is needed for the preventive aspects. Most eye (and face) injuries can be prevented, or the effects of such injuries can be minimized by using protective eyewear like polycarbonate frames and lenses and helmets with face protection. The face mask may consist of metal wire, coated wire or a transparent polycarbonate shield. Education and awareness can go a long way in reducing the number and severity of injuries and prevent a lifetime of ocular morbidity.

SUBLUXATED IOL'S: HOW TO FIXATE THEM STRAIGHT?

Dr Keiki Mehta, Mumbai

Very often an implanted intraocular lens (IOL), moves out of position due to two major reasons: Inadequate capsule support due to a tear; Inadequate zonular support with sectoral dehiscence. If sutured, break in the sutures suspending. If the capsule is intact but the shift has occurred due to inadequate zonular support, the best technique to stabilize the IOL bag complex is a transcapsular suture.

CFS – HOW WE MADE IT!

Prof (Dr) Mahipal S Sachdev, New Delhi

A man without education is like a building without a foundation.

The CFS vision, 1996

- The need: super-specialty niche.
- The opportunity: no player in the corporate sector in North India.
- Foresight: Build an institution for the future, move beyond cataract clinics to a world-class comprehensive eye care setup.
- Clinical excellence + know - how of "business" of ophthalmology.
- Clear ideology: Institution above self, excellence above quick profit, first movers in technology.

Research and development

- In house institutional ethics committee.
- Three ongoing major international trials.
- Five national level multicentric trials are approved and underway.
- Training in research methodology and analysis.
- Mandatory podium presentation for all fellows.

You should stand for a culture of excellence!

LOOKING BEYOND OPHTHALMOLOGY: HOW DID THEY DO IT?

Dr Debashish Bhattacharya, Kolkata

Our vision and mission

- To ensure world-class eye care to patients of all segments of our society.
- Provide compassionate care through our faculty, residents, nurses, optometrists and other staff.
- Strive to provide services using the latest technology available in the world.
- Train specialist and super-specialist ophthalmologists in the largest postgraduate and residency training program in the world. To be the center of excellence in ophthalmic innovation and research.
- Make the national eye bank the nodal center for providing services and training personnel from all over India.
- Develop community eye care services for greater outreach to the people of our country.

We are meeting this vision at Dr. RP Centre for Ophthalmic Sciences through patient care, research and teaching. We have a unique concept of ocular subspecialties:

- Vitreo-retina and uvea
- Cornea and ocular surface
- Glaucoma
- Community ophthalmology
- Ocular biochemistry
- Ocular microbiology

- Ocular pathology
- Ocular pharmacology
- Ophthalmic anesthesia
- Ophthalmic radiology
- Low vision services
- Lens
- Refractive
- Strabismus and neuro-ophthalmology
- Oculoplasty and oncology services
- Cataract.

Research is a major part of the mandate at RP Centre.

RP Centre remains a leader in ophthalmic research in India with the largest number of articles published and presence of dedicated research departments in paramedical, ocular pharmacology, biochemistry, pathology and microbiology.

SMALL PUPIL – LARGE NUCLEUS

Dr Ragini Parekh, Mumbai

Managing strategy:

- Strong mydriatic 10% phenyl epinephrine and 2% cyclopentolate. Intracameral adrenaline
- Viscomydriasis - high-density visco
- Irish hooks
- Pupil ring expander - morcher
- Sphincterotomy
- Capsular tension ring (CTR) in case of zonular weakness in pseudoexfoliation syndrome (PXS).

Important points: Adequate use of viscoelastic is important for endothelial protection. The availability of effective intracameral mydriatic and anesthetic agents reduces the need for topical preparations. Plan and preparation can make the smallest of pupil surgery easy.

THERAPEUTIC KERATOPLASTY IN MICROBIAL KERATITIS

Dr JS Titiyal, New Delhi

- Therapeutic keratoplasty has a definitive role in the management of progressive microbial keratitis refractory to medical therapy.
- TPK offers a microbiological cure rate of up to 100% in bacterial keratitis, recurrence of infection remains a concern following fungal infections and Acanthamoeba keratitis.
- Appropriate timing of surgery is critical for success.
- In addition to adept intraoperative skills, intensive postoperative treatment and meticulous follow-up are pivotal to ensuring the success of a therapeutic graft.

ACANTHAMOEBA KERATITIS

Dr Rajesh Sinha, New Delhi

Acanthamoeba keratitis forms <1% of all infectious keratitis. The risk factors include CL users (85%), homemade saline, contaminated or swimming pool water, trauma, vegetable matter or orthokeratology.

Examination

- Epithelial irregularities: punctuate, linear, pseudo-dendritiform, haze 25-50%.
- Denotes early disease.
- Slow progression.
- Periods of remission: days to months.
- Absence of corneal neovascularization.
- Scleritis: (11-42%) – Deep scleral vascular engorgement, scleral nodules; resolution may lead to ectasia.

Combination therapy

- Biguanide: Chlorhexidine (0.02%) or polyhexamethylene biguanide (PHMB) (0.02%).
- Diamidine: Propamidine (0.1%) or hexamidine (0.1%) – 1-hourly for 48 hours round the clock; Hourly drops during daytime for 72 hours; After 5 days: 2-hourly by day for 3 to 4 weeks; Tailored thereafter, generally for 6 months.
- If drug toxicity occurs, withdraw for 3 to 5 days, continue PHMB.
- If inadequate response: Bacterial or herpes infection.

Supportive therapy

- Cycloplegic
- Antiglaucoma
- Lubricants in resolving keratitis with large epithelial defect.
- Pain relief: NSAIDs, opioids, lignocaine patch.

Newer treatments-phototherapeutic keratectomy:

- Effective when lesions are limited to about one-third.
- Beneficial option in medication-resistant.
- Direct removal of resistant amoebic cysts and better visual recovery without irregular astigmatism.

News and Views

NTAGI Recommends to Reduction of the COVID Booster Dose Gap to 6 Months

A reduction of 3 months in the waiting time in administering the precautionary doses of the coronavirus disease 2019 (COVID-19) vaccine after the second dose was suggested by the National Technical Advisory Group Immunization (NTAGI), India. The Standing Technical Sub-Committee (STSC) of NTAGI recommended decreasing the time gap from 9 to 6 months on June 16, while the final decision is awaited from the Health Ministry.

The government advisory panel denied recommendations for mix-matching COVID-19 vaccines as they found differences found in the results of the study performed at the Christian Medical College (CMC) in Vellore.

The panel agreed to give the third dose to renal transplant patients before the cautionary dose. They analyzed and reviewed the data on the Covaxin and Corbevax vaccines for children aged 6 to 12, which were approved for emergency use in April.

They also showed concern about the spread of monkeypox and discussed the need for vaccination to prevent the same. Currently, anyone above the age of 18 who has completed 9 months after receiving the second dose is eligible for the precautionary dose. Last month, the Union government permitted citizens and students traveling abroad to obtain the vaccine before the 9-month waiting time mandated by the destination country's standards. (*Source: ETHealthWorld, June 17, 2022*)

Altered Neurologic Symptoms Observed in Long COVID

Altered neurologic symptoms were observed in patients with long COVID and it persisted for a minimum of 6 months. Fifty-six COVID-19 positive people were included in a study conducted from October 2020 to October 2021 and monitored at the beginning of the study and 6 months later.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection caused neurologic symptoms were seen in all with multiple sclerosis in 16 patients. Fatigue was seen in 89.3% of participants while 80.4% complained of headaches, with lack of concentration, memory loss and sleeplessness being the other common complaints.

Among 27 patients, 68.8% complained of memory loss and 61.5% suffered from bad concentration after 6 months. A third of the individuals reported complete symptom alleviation after 6 months. Despite, an improvement in the average score on the Montreal Cognitive Assessment (MoCA), a low score was reported in 26.3% of participants. Delayed recall, language and interest were the most impaired regions of cognition from which the patients were suffering.

Uncoordinated movements and cognitive problems (PASC-TAC) were observed in 4 long-term COVID patients who had no antecedent neurologic disease and had normal imaging. These people recovered slowly, and several symptoms required medication and supportive care after the 6-month point. Six of the individuals, including two people with a history of neurologic disease, had cranial nerve impairment.

In the NeuCOVID study, the symptoms will be tracked annually for up to 10 years to figure out what mechanism was causing such a disorder and what kind of medical support these people needed. The results were published in the *Annals of Clinical and Translational Neurology.* (*Source: MedPage Today June 16, 2022*)

Immunosuppressive Drugs may not be Needed in Post-transplantation Patients

The New England Journal of Medicine disclosed that 3 children who recently received kidneys from their haploidentical parents may never need immuno-suppressive medicines.

The 3 children received their kidneys, as well as reduced-intensity conditioning and T-cell–depleted and CD19 B-cell–depleted hematopoietic bone marrow. The required medications including anti-thymocyte globulin (7.5 mg/kg), fludarabine (1 mg/kg/day for 4 days) and cyclophosphamide (1,200 mg/m^2), then total-body irradiation (200 cGy) and rituximab (200 mg/m^2) were administered to the patients to prepare for the HSCT (hematopoietic stem-cell transplantation).

The transplantation was done once donor myeloid and lymphoid chimerism following HSCT had been confirmed (at 5, 5.5 and 10 months for the individual patients). The patients were given intraoperative methylprednisolone and postoperative low-dose oral prednisone and tacro-limus in order to decrease reperfusion inflammation.

Doses of these drugs were tapered down by Day 30 and no further immunosuppression was required to be given.

The patients showed no clinical evidence of rejection. At 22 to 34 months after transplantation, renal function is normal. Two patients responded to further immunizations with a protective response, and the third was awaiting titer data at the time of publishing.

The researchers noticed that 1 year after kidney transplantation, peripheral blood mononuclear cells demonstrated functional tolerance to stimulator cells generated from their donor parent, and, thus, potentially unable to cause graft rejection even in the absence of immune suppression. However, in the presence of stimulator cells obtained from their nondonor parent or a healthy, unrelated control, their immune cells reacted normally and flourished. They further stressed the need for more studies to be conducted to evaluate if comparable results can be reached in allograft recipients who had a healthy pre-transplantation T-cell immunity and hematopoiesis. (*Source: MedPage Today June 15, 2022*)

Covaxin Safe for 2 to 18 Years Children, Shows Pune Trial

Covaxin developed by Bharat Biotech in collaboration with the Indian Council of Medical Research and National Institute of Virology has proven to be safe well-tolerated and highly immunogenic in pediatric subjects in phase II/III study.

In the study, no serious adverse events (AE) were reported out of the total 374 AE reported among the majority. These AE such as pain in the injection site, etc. were the mildest symptoms and resolved within 1 day. Dr Pragya D Yadav, stated that the inclusion of younger age groups in vaccination drives would help in breaking the infection chain and diminish the outbreak. She also added that the vaccine showed a superior response among the pediatric group in comparison to adults. However, supplementary surveillance studies are under process to identify and eliminate "rarer adverse events".

Dr Krishna Ella, Chairman and MD, Bharat Biotech, stated that the trial has established Covaxin as a universal vaccination that is safe and effective for adults and children in both dosage forms, i.e., primary immunization dose and the booster dose. Meanwhile, Dr Rajiv Jaydevan, Co-chairperson of, the Indian Medical Association's National Task Force, stated that the vaccine is capable of generating neutralizing antibodies to protect against infection. *(Source: https://timesofindia.indiatimes.com/city/pune/pune-trial-results-show-covaxin-safe-for-2-18-years-age-group/articleshow/92291222.cms*)

First COVID-19 Shot for Infants, Preschoolers Authorized

Recently, the Food and Drug Administration (FDA) authorized the first COVID-19 shots for infants and preschoolers, following the advisory panel's unanimous recommendation for shots from Moderna and Pfizer. However, there is one step left in the process, i.e., the CDC's guidelines on how to use the vaccines. CDC's independent advisors have begun debating for making suitable recommendations between the two-dose Moderna vaccinations versus the three-dose Pfizer vaccination regimen.

The FDA reports show that the little children developed virus-fighting antibodies with both vaccines. Although, both the vaccine studies showed side effects, including fever and fatigue, which were resolved in a short period; the Moderna vaccine showed an efficacy of 40% to 50% in comparison to Pfizer in the studies.

President Joe Biden, stated that the FDA approval is a huge relief for parents and families across America. For weeks, the Biden administration has been working on rolling out vaccinations for little kids with states, tribes, community health centers and pharmacies by pre-ordering millions of doses. Dr Peter Marx, FDA's vaccine Chief, stated that "both the vaccines have been approved with science and safety at the forefront of our minds." (*Source: https://health.economictimes.indiatimes.com/news/industry/fda-authorizes-1st-covid-19-shots-for-infants-preschoolers/92291696*)

Study: Omicron Carries Half the Risk of Long COVID as Delta

A recent study published in *The Lancet* showed that the Omicron variant poses half the risk of long COVID in comparison to the Delta variant. The chances of developing long COVID were found to be 4.5% from the Omicron variant in comparison to 10.8% from the Delta variant. Dr Claire Steves, King's College, London, stated that the reduced risk is good news, especially when Omicron is highly contagious. She also added that if the risk of developing long COVID symptoms were the same as the Delta variant or higher, the number of people with long COVID would have exploded.

Dr Steves and her colleagues have compared and tracked the patient symptoms for more than 56,000 people in the UK, who got Omicron infection between December 2021 to March 2022 with 41000+ people in the UK who tested positive for Delta variant between June 2021 to December 2021. On the other hand, the research team warned that the lower risk does not

mean people should not worry about long COVID as the study did not address the reason behind a lower risk of long COVID associated with Omicron variant infection. Dr David Putrino, New York, stated that though the study highlights an important disease pattern, the likelihood of contracting COVID that can progress to severe chronic illness is around 5%, which is a significant figure. (*Source: https://www.medscape.com/viewarticle/975841*)

National Exit Test to be Implemented in 2023

The National Exit Test (NeXT), a common qualifying examination, for Final year MBBS students, and simultaneously licentiate exam, will be introduced in 2023 by the Indian Government. The proposal to create a common examination came into being on 25th September 2020 through the National Medical Commission Act, 2019.

The NeXT will be a common qualifying exam that will grant permission to practice medicine in India and will serve as the criteria for merit-based allocation of post-graduate seats in broad specialties. Further, the exam will bridge the gap between students from foreign institutions willing to practice medicine in India.

A senior Central government official stated that if NeXT is introduced in the education system, then, it will do away with the need to conduct NEET PG. The official also stated that the commission plans to implement a mock test before implementing the final exam to test the procedures and remove the anxiety among medical students. (*Source: https://www.livemint.com/news/india/centre-likely-to-implement-national-exit-test-for-medical-students-in-2023-all-you-need-to-know-11655475822067.html*)

Repeated Exposure to Hurricanes can have Adverse Psychological Symptoms

A study published in *JAMA Network*, has associated the psychological outcomes with recurring natural disasters, especially with escalated threats of climate change. The researchers proposed that repeated exposure to hurricanes whether direct, indirect or media-based is associated with adverse mental health problems. Dr Dana Rose Garfin, Professor, UCI, stated that with extreme climate change, climate-related natural disasters will increase in frequency and severity in the next few years. She added that the study showed that people are not likely to habituate or get used to the disasters causing a negative impact on their mental health.

Professor Garfin and her team found that repeated exposure to the threat of catastrophic hurricanes was linked with symptoms of post-traumatic stress, depression, anxiety, fear and worry. These symptoms were further associated with greater social and work-life impairment including difficulty in interacting with others, performing work tasks and other daily activities. The team came to this conclusion after assessing Florida residents for any mental health changes who survived hurricane Irma in September 2017 and hurricane Michael in October 2018.

Dr Dana stated that some amount of distress is common after an extremely stressful event. However, a climate-related disaster can prolong the healing process due to repeated threat exposure. Anxiety is an adaptive response to disaster and can be reduced by motivating people to take protective action and be prepared for the next event. (*Source: https://www.hindustantimes.com/lifestyle/health/repeated-exposure-to-hurricanes-linked-to-adverse-psychological-symptoms-101655525809689.html*)

Liver Cancer Risks Reduced by Coffee and Tea Consumption

Study form China found that coffee and tea drinking were associated with a reduced danger, of hepatocellular carcinoma (HCC) and protected the liver, while more alcohol consumption increased the risk.

Over 2,00,000 people took part in the survey, which were divided into different categories such as ever/never drinker (n = 1,65,084), alcohol intake (n = 58,610), coffee consumption (n = 1,52,634), tea consumption (n = 152,653), milk consumption (n = 1,52,965) and yoghurt consumption (n = 1,52,097). Alcohol intake (odds ratio [OR], 1.57; 95% CI, 1.32-1.86; $p < 0.001$) and ever/never consumers of alcohol (OR, 1.11; 95% CI, 1.05-1.18; $p < 0.001$) were both positively linked with HCC risk. Lower risk of HCC was observed among coffee consumers (OR 0.69, 95% CI 0.53-0.90, $p = 0.007$), green or traditional tea consumers (OR 0.11, 95% CI 0.05-0.26) and milk and yoghurt consumers (OR 0.18, 95% CI 0.09-0.34 for both; $p < 0.001$ for both).

Previous studies showed that coffee had a protective effect against liver fibrosis. Coffee has been shown to protect against liver fibrosis in previous research. The current study found that dietary habits had a direct impact on HCC, emphasizing the necessity of maintaining healthy eating habits in the prevention of HCC. The study was published in *Hepatology Communications*. (*Source: MedPage Today June 10, 2022*)

■■■■

Soul does not Leave the Body Immediately after the Death

According to Prashna Upanishad, at the time of death, the Prana Vayu (life force and respiration) merges with Udana Vayu (brainstem reflexes) and leaves the body. But this does not happen immediately after clinical death, which is defined as stoppage of heart and respiration. Medically, the term used for clinically dead patients is sudden cardiac arrest.

As per modern medicine, in cardiac arrest, the brain does not die for the next 10 minutes and during this period, if the heart can be revived, life can be brought back.

The revival of patient during this period can be remembered by the "Formula of 10": Within 10 minutes of the stoppage of heart (cardiac arrest), if effective chest compressions are given for the next 10 minutes with a speed of 100 per minute (10 × 10), 80% of the cardiac arrest victims can be revived.

This period can be much longer in hypothermia state. If the temperature of the body is low, the soul does not leave the body till the temperature is brought back to normal. Today, this property of soul is also used as therapeutic measure where patients who cannot be revived in the first 10 minutes of clinical death are put in a freezing chamber and artificial hypothermia is produced and these patients can then be transported to an advance cardiac center where even after 24 hours, resuscitation measures can be applied after re-warming the body. Many people have been revived even after 24 hours of cardiac arrest with such a technology.

There are instances in literature where a newborn with hypothermia was declared dead but revived in the cremation ground when the environment heat brought the body temperature to normal and the pressure of the wood worked like cardiac massage.

This aspect of "life after death" is a contribution of the modern science to the Vedic science. Though in Vedic literature, it was a well-known phenomenon as Savitri brought life back into Satyavan even after his clinical death.

Take home message is that one should not declare a patient dead in the first 10 minutes; give cardiac massage and try reviving him with chest compression cardiopulmonary resuscitation (CPR).

■■■■

European Union's Health Agency Ruled Out that mRNA COVID-19 Vaccinations Caused Menstrual Irregularities

Recently, the European Union's Health Agency ruled out that mRNA COVID-19 vaccinations caused menstrual irregularities. Instances of irregularities in the menstrual cycle were reported post vaccinations with either Moderna or Pfizer-BioNTech vaccines.

Menstrual abnormalities can be caused by a variety of factors, including underlying medical diseases, stress and exhaustion. According to health officials, several cases of menstrual irregularities have been reported among COVID-19-infected females.

At the same time, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency is consistently assessing and analyzing the different cases of heavy menstrual bleeding documented which were associated with the two vaccines. Heavy periods are defined as bleeding of increased volume and/or duration that interferes with one's quality of life.

A potential concern triggered among experts, as a study from Norway revealed an increase in menstrual irregularities after receiving either of the two vaccines. The PRAC announced on June 10 that it had evaluated all available data on the potential danger but had asked vaccine manufacturers to provide an updated cumulative evaluation of instances. (*Source: ETHealthWorld, June 11, 2022*)

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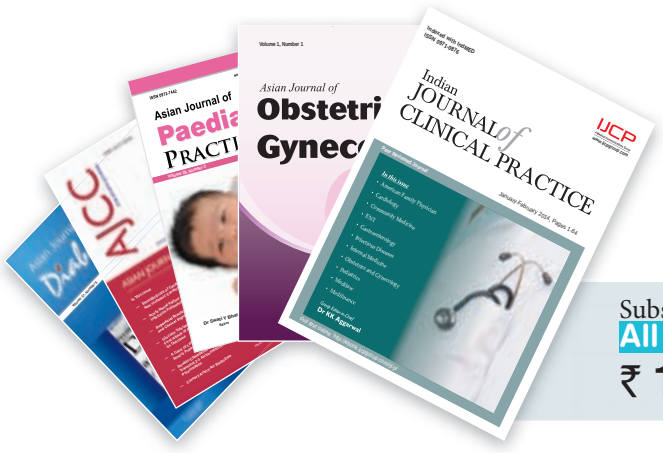

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Lighter Side of Medicine

INSPIRATIONAL STORY

THE TALKING BIRD

A fellow lived alone and went to a pet store to buy a parrot. He thought the bird might keep him company in his lonely hours. However, the very next day, he went back to complain that the bird didn't talk.

The store owner asked if he had a mirror in its cage, and the man replied that he didn't. The store owner said that parrots love mirrors. When he will see his reflection in the mirror, he'll start talking. So, he sold him a birdcage mirror.

The bird owner came back the next day to complain that the parrot still hadn't said a word. "That's peculiar", said the pet expert. He suggested that the bird owner should have a swing as birds really love little swings, and a happy parrot is a talkative parrot. So, the man bought a swing and installed it in the cage.

However, he was back the next day with the same complaint. The salesman asked whether he has a ladder in the cage. He suggested that once he has a ladder, he'll probably start talking. So, the man bought a ladder.

The man went back at the pet store the next day. The owner knew something was wrong and immediately asked, "Didn't your parrot like the ladder?" The bird owner said, "The parrot died".

"I'm so sorry", the store owner said. "Did he say anything?"

Well, yes. He finally talked just before he died. In a weak little voice, he asked me, "Don't they sell any bird seed at that pet store?"

Some of us mistakenly believe that happiness lies in lining our cages with toys, gadgets, and other expensive stuff. Excessive consumption has become the hallmark of our life. Whoever has the most toys wins seems to be the rule. But is it actually so?

The spiritual hunger in the human heart that can't be satisfied by seeing one's own image reflected back in vanity mirrors, playing with our grown-up toys or climbing the corporate ladder. Our hearts yearn for real nourishment. The love of family and friends, relationships over the pursuit of more things, personal integrity, a secure connection to God are the things that feed the soul.

HUMOR

DREAM OF A NECKLACE

After she woke up, a woman told her husband, "I just dreamed that you gave me a pearl necklace for our anniversary. What do you think it means?"

"You'll know tonight", he said.

That evening, the man came home with a small package and gave it to his wife.

Delighted, she opened it to find a book entitled "The Meaning of Dreams."

THINK ABOUT ME

Think big, Think smart,

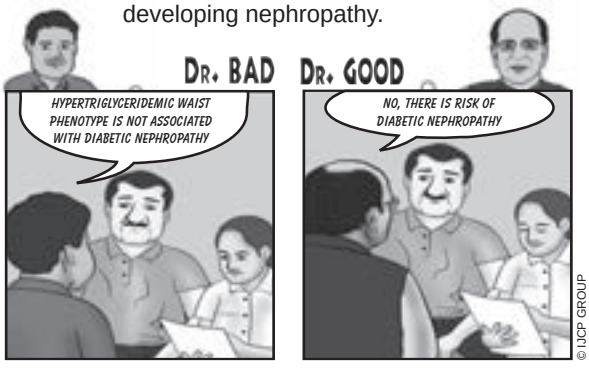
Think positive, Think beautiful,

Think great, I know this is too much for you, so here is a shortcut.

Just think about ME…

Dr. Good and Dr. Bad

SITUATION: A man with type 2 diabetes who had hypertriglyceridemic waist phenotype marked by serum triglyceride concentrations as 195 mg/dL and waist circumference as 94 cm was informed to be at risk of developing nephropathy.



LESSON: A cross-sectional study has shown a significant link between hypertriglyceridemic waist phenotype and early diabetic nephropathy in individuals with type 2 diabetes.

Cardiorenal Med. 2017;7(4):295-300.

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

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

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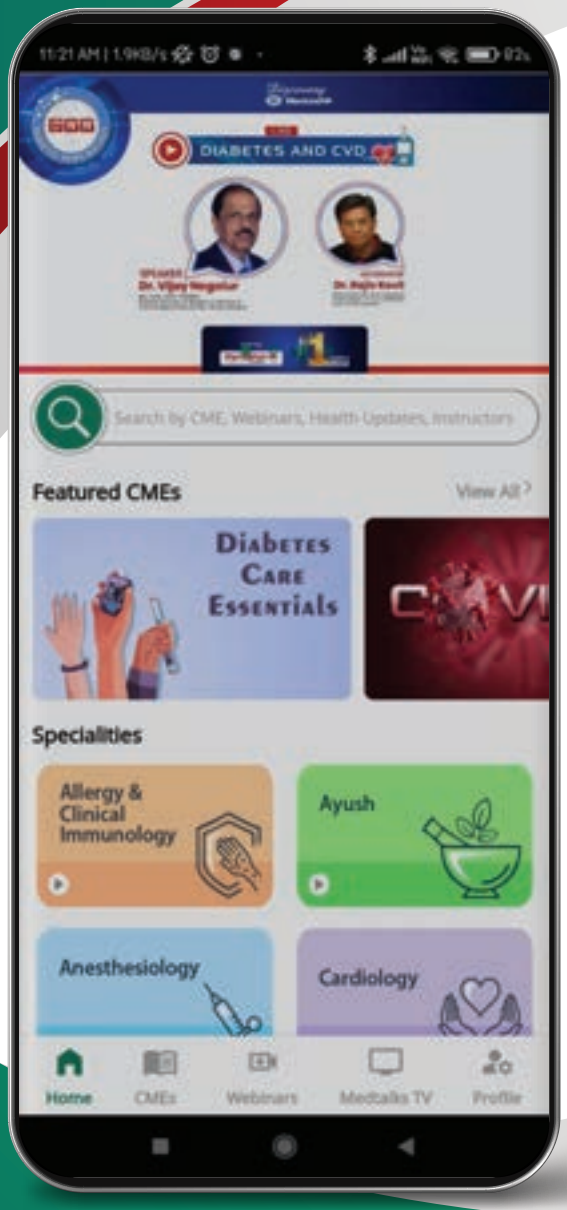

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