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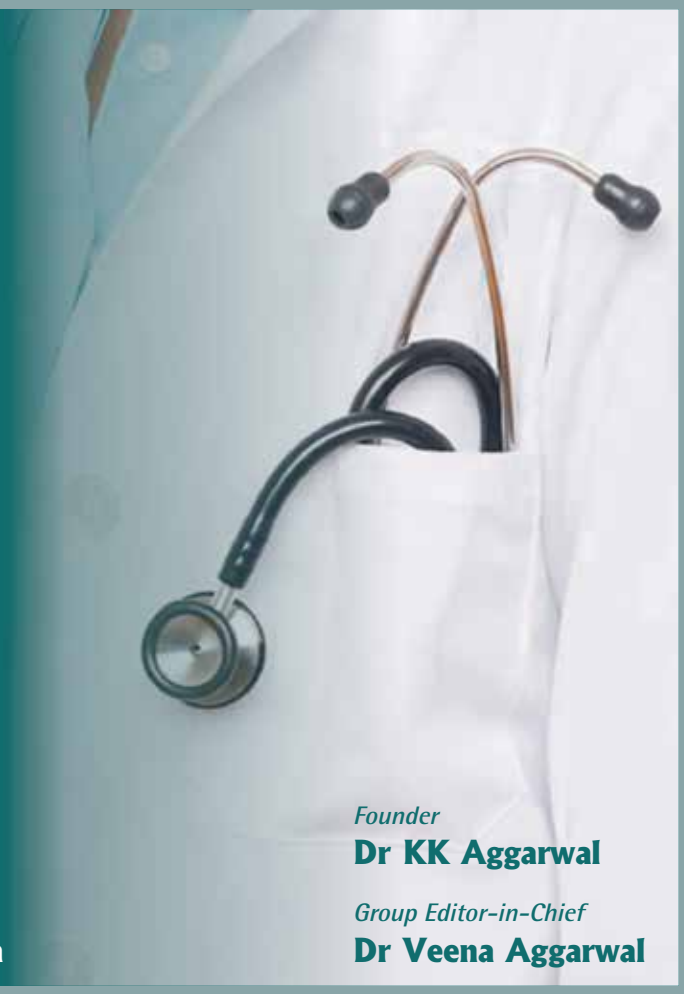

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Health Budget 2023: Highlights

The Union Finance Minister presented the last budget of the second term of the Modi government on 1st February, 2023. The Union Budget 2023-24 has a strong focus on health care and the environment, which we welcome at Heart Care Foundation of India. We welcome the increased focus on health care research, which will enable us to be better prepared to tackle all new and unknown illnesses that we may be threatened by in the future.

One Health was a concept that our founding president Dr KK Aggarwal strongly focused on and the provisions in the budget to help achieve net zero emissions by 2070 through the adoption of more energy-efficient ways of travel and fuel consumption will have a great impact on our overall physical well-being as well.

Promoting nursing education through the **setting up of 157 new nursing colleges** will help make quality care accessible to a larger population.

We hoped to see more focus on training centers on heart disease and cardiopulmonary resuscitation (CPR) in the budget given the drastic increase in the number of heart attacks among the younger population in India. Metabolic diseases deserve specific attention as well given the pandemic proportions of these diseases due to the high-stress and unhealthy lifestyle that the population at large is now leading. The government **campaign to promote millets** for their numerous health and environmental benefits will help check the metabolic disease such as diabetes in check to an extent. The Hyderabad-based Indian Institute of Millet Research (IIMR) will be supported as a centre of excellence to make India the "global hub" for millets.

Mental health has come to the fore with COVID-19 in mammoth proportions and deserved to be given more priority in the budget as well.

We hope that skill development initiatives and multi-disciplinary courses for medical devices would promote self-dependence or "atmanirbharta" in medical devices and equipments among other things.

Here are some key health-related highlights of the budget 2023.

- Launch of a **mission to eliminate sickle cell anemia by 2047** by creating awareness and universal screening of 7 crore people in 0 to 40 years age group in affected tribal areas.
- Select **ICMR labs will be available for research** by public and private medical college faculty and private sector R&D teams for encouraging collaborative research and innovation.
- Launch of a **new program to promote research and innovation in pharmaceuticals.**
- **Three centres of excellence of artificial intelligence (AI)** will be set up to in top educational institutions, leading industry players will partner in conducting interdisciplinary research, develop cutting edge applications and scalable problem solutions in the areas of health, agriculture and sustainable system.
- **30 skill India international centers** will be set up across various states. Pradhan Mantri Kaushal Vikas Yojana (PMKVY) 4.0 will be launched to skill lakhs of youth within the next 3 years. It will cover courses for Industry 4.0, COVID, AI, robotics, mechatronics, IoT and drones.

- **Dedicated multidisciplinary courses for medical devices** will be supported in existing institutions to ensure availability of skilled manpower for futuristic medical technologies, high-end manufacturing and research.
- Cigarettes have become expensive. A welcome step as India bears a high burden of tobacco-related diseases being the second largest consumer and producer of tobacco.
- The budget allocation for **Jal Jeevan Mission** has been substantially increased to Rs. 50,000 crore. Rs. 2.87 trillion has been announced for the launch of the Jal Jeeven Mission Urban. It aims at universal water supply in all 4,378 urban local bodies with 2.86 crore household tap connections as well as liquid waste management. The target of ongoing Har Ghar Jal mission is to supply water to all rural households by 2024.
- The budget has lot of initiatives for **green growth**, which should bode well for the environment and indirectly to health. Under the **National Green Hydrogen Mission** aiming to move towards a low-carbon intensity economy and reducing dependence on fossil fuel imports, India is targeting to reach an annual production of 5 MMT of green hydrogen by 2030. To promote circular economy, **500 new 'waste to wealth' plants** will be established under GOBARDhan (Galvanizing Organic Bio-Agro Resources Dhan) scheme.
- Substantial benefits have been announced for **personal income tax**. This will definitely reduce stress among the common people, especially the middle class. A new tax regime has been introduced. The number of slabs has been reduced to five. Under the new tax regime, the **tax rebate limit has been increased to 7 lakhs from the earlier 5 lakhs**. **Tax exemption limit has been increased to Rs. 3 lakh.**

The new tax rates

Total income (Rs.)	Rate (%)
Up to 0-3 lakh	Nil
From 3-6 lakh	5
From 6-9 lakh	10
From 9-12 lakh	15
From 12-15 lakh	20
Above 15 lakh	30

In 2022-23, the expenditure in health sector was 2.1% of the gross domestic product (GDP) as per the Economic Survey 2023. The National Health Policy 2017 has envisaged increasing the government's health expenditure to 2.5% of GDP by 2025. Reaching this target appears elusive.

■■■■

Nondiabetic Kidney Disease in Patients with Type 2 Diabetes

A study published in the *British Medical Journal* revealed that patients with type 2 diabetes develop kidney disease in 18.2% of cases due to other reasons. The study was conducted by a group of doctors from the state-run Institute of Post-Graduate Medical Education and Research (IPGMER). The study is titled, "Prevalence of nondiabetic kidney disease and the inability of clinical predictors to differentiate it from diabetic kidney disease: results from a prospectively performed renal biopsy." Dr Sujoy Ghosh, Professor of Endocrinology at IPGMER, stated that the true prevalence of diabetic kidney disease and nondiabetic kidney disease is unknown. He added that most of the published medical literature derives its data from a retrospective analysis of biopsy studies.

In the study, 6,247 patients from two departments, i.e., endocrinology and nephrology, were screened for type 2 diabetes. Only 869 patients fulfilled the inclusion criteria, out of whom only 818 were feasible for renal biopsy. Only 110 patients, however, agreed to a renal biopsy. The findings of the study showed that 73 patients (66.4%) had diabetic kidney disease. The study showed that only 20 patients (18.2%) had nondiabetic kidney disease, whereas 17 patients (15.4%) were found to have mixed kidney disease.

Hence, the researchers concluded that nondiabetic kidney disease and mixed kidney disease in type 2 diabetes mellitus with renal involvement are very common. They added that clinical decision-making in these cases is impaired by the traditionally used parameters. Additionally, the study highlighted the limitations of currently used indicators for differentiating between nondiabetic kidney disease and diabetic kidney disease. (*Source: https://timesofindia.indiatimes.com/education/news/study-finds-high-prevalence-of-non-diabetic-kidney-disease-in-patients-with-type-2-diabtetes-mellitus/articleshowprint/96686351.cms?val=3728*)

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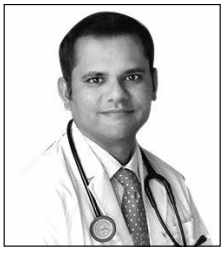

Dr Ameya Joshi
Dept. of Endocrinology, Bhaktivedanta Hospital, Mumbai, Maharashtra, India

Dr Bharti Kalra
Consultant, Dept. of Obstetrics and Gynecology, Bharti Hospital, Karnal, Haryana, India

Dr Navneet Agrawal
Dept. of Medicine, Diabetes Obesity and Thyroid Centre, Gwalior, Madhya Pradesh, India

The Spirit and Science: Is the Endocrine System the Essence of Existence?

ABSTRACT

In this reflective opinion piece, the authors offer a unique insight into the connection between spirituality and science. A reading of the Shrimad Bhagvad Gita, through the eyes of an endocrinologist, uncovers unexpected corollaries and correlations between spirituality or religion on one hand, and science or rationale, on the other.

Keywords: Endocrinology, holistic health, hormone, integrative care, person-centered care, spiritual health

The Shrimad Bhagvad Gita is a celestial song, which offers answers to the challenges faced by us in routine life.[1] While the Gita relates a conversation between Lord Krishna and Arjuna, it's content is relevant to virtually every aspect of human life. We have shared the inspiration we have derived from this holy book in earlier communications.[2,3]

INTROSPECTION

In this opinion piece, we explore some verses from the Gita. We invite our reader to assess them from a neutral viewpoint: do these statements represent 'the spirit', or do they describe the endocrine system and its hormones? Do they picturize both or one? Are both the same, or does one create another? We do not have answers to these rhetorical questions. Rather, we encourage our readers to expand their horizons of thought, develop insights into these interesting domains of "being", and translate them into action on the ground. This action, in the clinic, the ward, the intensive care unit and the public health arena, should strengthen person-centered health care,[4,5] integrating spiritual and emotional domains into our work.

INSIGHTS FROM THE GITA

"I shall speak to you at length about that which ought to be known, and knowing which one attains supreme Bliss…." (13:12)

[The importance of the subject]

"It has hands and feet on all sides, eyes, head and mouth in all directions, and ears all-round; for it stands pervading all in the universe."(13:13)

[The universality of endocrinology]

"Though perceiving all sense-objects, it is really speaking devoid of all senses. Nay, though unattached, it is the sustainer of all nonetheless; and though attribute less, it is the enjoyer of Gunas, the three modes of Prakriti." (13:14)

[The stimulation, secretion and strength of hormones]

"*It exists without and within all beings, and inanimate creation as well. And by reason of its subtlety, it is incomprehensible; it is close at hand and stands afar too*." (13:15)

[The vast spectrum: endocrine, paracrine, autocrine; hormones, pheromones]

"*Though integral like space in it is undivided aspect, it appears divided as it were in all animate and inanimate beings….*"(13:16)

[Holistic and reductionist approaches to endocrinology]

"*…That godhead is knowledge itself, worth knowing worth attaining through real wisdom, and is particularly abiding in the heart of all*." (13:17)

[The importance of education]

"*Thus the truth of the Kshetra and the knowledge, as well as of the object worth knowing has being briefly discussed….*" (13:18)

[An overview of the system]

"*Prakriti and Purusha, know both these as beginning….*" (13:19)

[The eternity of endocrinology]

"*The Spirit dwelling in this body, is really the same as the Supreme. He has been spoken of as the Witness, the true guide, the Sustainer of all, the Experiencer…, the Overlord, and the Absolute as well*." (13:22)

[Hormones work a witness, guide, sustainer, experience, overlord]

"*He who know the Purusha (Spirit) and Prakriti (Nature) together with the Gunas,….*" (13:23)

[The endocrinologist who understands mind, body and medicine; biopsychosocial health]

"*Some by meditation behold the supreme Spirit… with the help of their refined and sharp intellect; others realize it through the discipline of knowledge; and still others through the discipline of Action, i.e., Karmayoga*." (13:24)

[Person-centered learning]

"*…whatever being, moving or unmoving, is born, know it as emanated through the union of Kshetra (Matter) and the Kshetragya (Spirit)*." (13:26)

[Mind-body union]

"*He who sees that actions are performed in every way by nature Prakriti and the Self as the non-doer, he alone verily sees*." (13:29)

[Neurohormonal coordination of life]

"*…as one sun illumines this entire universe, so the one Atma (Spirit) illumines the whole Kshetra (Field)*." (13:33)

[The hypothalamus-the seat of the spirit]

INTENTION

Chapter 13 of the Shrimad Bhagavad Gita is entitled "The yoga of discrimination between the field and the knower of the field". As medical professionals, we are aware that we do not know the entirety of our field. This humility actually helps us work harder to seek knowledge, in an effort to help our patients.

As the Gita says, (18:63), it is up to the reader to interpret the wisdom contained in its pages. These verses from the Shrimad Bhagavad Gita can be understood in multiple ways. They remind us of the importance of endocrinology in human life, the relationship between hormones and spiritual health, and the centrality of endocrine homeostasis in ensuring holistic health.

Hope you enjoyed reading this.

We invite our readers to share their thoughts and opinions about this, and other aspects of health.

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REVIEW ARTICLE

Etiology of Chronic Kidney Disease in Nigeria and Management Challenges

SOTUBOSOTOMIWA O*, AWOBUSUYI OLUGBENGA JACOB†, SOURABH SHARMA‡

ABSTRACT

The prevalence of chronic kidney disease (CKD) is increasing globally and is one of the noncommunicable diseases associated with increase mortality globally in the last two decades. The prevalence of CKD in Nigeria, it is 1.6% to 12.4%. Ninety percent of end-stage renal disease (ESRD) patients are said to die within 3 months of commencing dialysis. Indices are even worse in resource poor countries like Nigeria where prevention and adequate intervention are usually hampered by funds. In regions like Nigeria, it will be cheaper to prevent CKD than treating its complications. Hence, it is important to identify the common etiologies of CKD in Nigeria and prevent or promptly address them before causing irreversible damage to the kidneys. The most common cause of CKD in Nigeria includes hypertension, glomerulonephritis and diabetes mellitus. Many of these etiologies are preventable/treatable and should be looked for as a major way to reduce the incidence of CKD in Nigeria. Challenges identified in Nigeria, propagating CKD include westernization, inadequate manpower, late presentation, diagnostic challenge and poorly equipped facilities. Interventions like encouraging healthy lifestyle, making available essential drugs, training of health personnel, subsidized cost of treatment, legislation and policies to curb drug abuse. Therefore, resource-poor settings should focus on creating more awareness and making legislations and/or policies focused on these preventable causes of CKD as this is more realistic and effective in these settings.

Keywords: Chronic kidney disease, Nigeria, Africa, end-stage renal disease, hypertension, diabetes mellitus

The prevalence of chronic kidney disease (CKD) is increasing globally and is one of the many noncommunicable diseases associated with increased mortality in the last two decades.[1] The prevalence of CKD in West Africa is 16%, and in Nigeria it is 1.6% to 12.4%.[2] Ninety percent of end-stage renal disease (ESRD) patients are said to die within 3 months of commencing dialysis.[3] Indices are even worse in resource-poor countries like Nigeria where prevention and adequate intervention are usually hampered by funds.[4,5] In a study by Ulasi et al, only 59% of all ESRD patients needing dialysis during the period of study were able to afford it, because most patients pay out of pocket.[4]

*Nephrology Unit
†Head of Nephrology Unit
Dept. of Medicine, Lagos State University Teaching Hospital, Lagos, Nigeria
‡Assistant Professor Nephrology, VMMC & Safdarjung Hospital, New Delhi, India
Address for correspondence
Dr Sourabh Sharma
Assistant Professor Nephrology
VMMC & Safdarjung Hospital, New Delhi, India
E-mail: drsourabh05@gmail.com

In regions like Nigeria, it will be cheaper to prevent CKD than treating its complications. Hence, it is important to identify the common etiologies of CKD in Nigeria and prevent or promptly address them before they cause irreversible damage to the kidneys.

ETIOLOGY OF CKD IN NIGERIA

Olanrewaju et al in his study showed that hypertension is the commonest cause of CKD[3] in Nigeria. Similar findings were found by Odubanjo et al indicating that hypertension and chronic glomerulonephritis are the most common causes of CKD in the region.[2] In another study, the common causes were chronic glomerulonephritis, hypertension, diabetes mellitus and obstructive nephropathy in the following percentages, 34.2%, 23.3%, 18.8% and 10.4%, respectively.[6] Below is the list of etiologies of CKD in Nigeria from different researchers:[2,3,6-8]

- Hypertension
- Chronic glomerulonephritis
- Diabetes mellitus
- Obstructive nephropathy
- Sickle cell nephropathy

- Autosomal dominant polycystic kidney disease
- Chronic interstitial nephritis
- HIV-associated nephropathy (HIVAN)
- Chronic pyelonephritis
- Chronic kidney disease of unknown origin (CKDu).

Many of the above etiologies are preventable/treatable and should be looked for as a major way to reduce the incidence of CKD in Nigeria.

Most studies agree that hypertension, chronic glomerulonephritis and diabetes mellitus are the most common causes of CKD in Nigeria,[2,3,6,8] which is not different from that of international studies.[9,10] Hence, majority of the interventions towards preventing CKD should be directed towards these.

A study conducted in the Northeast part of Nigeria by Sulaiman et al suggests that CKDu makes up to 20.5% of causes of CKD in the region; however, the environmental and cultural risk factors are yet to be investigated.[11]

The prevalence of sickle cell nephropathy is 3.33%,[12] according to a study by Akaba et al; however, Bukar et al found that the prevalence in the northern region of the country was as high as 38.9%, which increased with advancing age.[13] This is significant because Nigeria has the highest burden of sickle cell disease worldwide, affecting about 4 to 6 million people. About 3.5% of patients with sickle cell nephropathy are in ESRD requiring renal replacement therapy.[13] This is a great challenge because their outcome is lower in terms of morbidity and mortality when compared with the non-sickle cell transplant population.[13] Close and regular clinic visits for follow-up and interventions like hydroxyurea have been identified to slow down the progression of CKD in sickle cell nephropathy.

HIVAN is the most common form of kidney disease resulting directly from HIV infection.[14] Prevalence of kidney disease among HIV patients ranges between 22.9% and 51.8%, and is associated with significant morbidity and mortality.[15] The black race in particular has been found in several studies to be an important risk factor for the development of HIVAN.[14] Commercial sex workers and intravenous drug abusers have been identified as a major driver of HIV infection in Nigeria,[15,16] therefore it will be wise to put policies in place to curb this.

LIFESTYLE IN NIGERIA

The prevalence of hypertension and diabetes mellitus has been consistently on the increase, and is projected to rise further.[17,18] Major drivers of this alarming rise have been attributed to westernization and lifestyle, which include increasing age, increasing body mass index (BMI), physical inactivity, urban dwelling, unhealthy diet, stress, smoking and alcohol.[19,20]

Despite the various efforts and initiatives to prevent or manage hypertension, there are still some barriers limiting optimal outcomes. These barriers can exist at the level of patients, staff or health system and administration. Such barriers include a lack of funding, which affects basic day-to-day operation of health care facilities, scarcity of and difficult access to health care centers in a community, staff shortages in health care centers, shortage of drugs in clinics and dispensaries, limited availability of equipment and insufficient maintenance and insufficient patient health education and communication in clinics.[21]

Most doctors prescribe lifestyle modifications to treat hypertension rather than preventing hypertension; hence, opportunity for primary prevention is usually missed.[22]

CHALLENGES AND SOLUTION IN MANAGEMENT

Hypertension

Prevalence of hypertension in Nigeria ranges from 8% to 46.4%[23] but the percentage of people who take their medications is just 60% in a study conducted by Akpa et al in Port Harcourt.[24] This is similar to the nonadherence global figure of 43% to 65.5%.[25] Most people do not get regular health checks until they fall sick or develop complications related to long-standing hypertension; therefore, more awareness and health education of Nigerians to seek healthy health practices is needed.[26] Single-pill combined therapy has also been shown to improve adherence in hypertensive patients;[24,27] unfortunately they are more expensive in this region compared to single pill.[28,29] Pharmaceutical companies should make efforts to get these drugs produced locally to make it more affordable without reducing the quality.

Controlling hypertension is set to cut down cardiovascular mortality by 15%[30] and this, consequently is likely to impact on the incidence of CKD.[31,32]

Late Presentation

Opportunity for early diagnosis are missed because many patients with kidney disease present late to the hospital.[6] Many of the patients would have first visited quacks or tradomedical personnel who might have

prescribed herbs or cocktail of drugs that may have precipitated or worsened kidney impairment.[33] A study by Li et al showed that there is high patronage of the tradomedical personnel in Ibadan (largest city in West Africa), which can be addressed with both western education and adequate health education.[34]

Diagnostic Challenge

Renal biopsy is key in the diagnosis of many glomerulonephritides, which will also influence the line of management.[35,36] In a study conducted by Okani et al, it was discovered that there has been a decline in the request for renal biopsy by the nephrologists. This was attributed to the lack of trained health personnel, poor health insurance scheme and lack of facilities.[37] The cost of this procedure can be subsidized by the government to make it more affordable for the patients. Physicians should be supported by society and government in form of financial and career developing grants as performing large numbers of biopsies will help improve their skills and also give them an opportunity to train younger doctors.

Abuse of Analgesics

Abuse of nonsteroidal anti-inflammatory drugs (NSAIDs) is also very common especially among youths.[38] Prevalence of drug abuse in Nigeria is said to be as high as 22%,[38] which is similar to international prevalence of 24%.[39] This is possible because many drugs are sold over-the-counter without prescription.[40,41] This can be curbed by appropriate legislation and policies and enforcement of these policies to prevent over-the-counter prescriptions of these potentially nephrotoxic medications.[42]

Status of Dialysis Facilities

The number of dialysis centers in Nigeria increased from 27 in 2006 to 186 in 2021 while the dialysis population increased from 300 in 2000 to over 3,000 in 2018.[43,44] This shows that the number of dialysis centers in Nigeria compared to the number of patients requiring dialysis is grossly inadequate.

Public-private partnership (PPP) in hemodialysis delivery should be encouraged as this has been shown to increase the number and sustainability of hemodialysis centers in Nigeria.[45]

Manufacturers of drugs and equipment for health services related to treating kidney diseases and renal replacement therapy, should be encouraged to make them locally so as to make them more affordable as is done in some other countries.[46]

Status of Transplant Centers

Though kidney transplant is the preferred renal replacement therapy for patients with end-stage kidney disease, it is only accessible to a few due to the high costs and lack of infrastructure. About 90% of kidney transplant recipients had their transplants in India,[47,48] the few transplants done in Nigeria are more in the Private sector.[49] Funding is a major limitation to kidney transplant in Nigeria in addition to sourcing for donors.[49]

PPP can also be deployed here with more funds allocated to the health sector by the government. Bilateral relationship should be formed with high volume kidney transplant centers to help develop transplant centers in the country.

Paucity of Manpower

Nigeria currently has two major bodies awarding Nephrology fellowship to doctors. Nigeria has only 240 nephrologists, 697 registered dialysis nurses and 120 dialysis technologists/technicians, many of whom have left the country to seek better opportunities. This is grossly inadequate to cater to the large CKD population in the country. Policies and incentives, especially financial, can be put in place to encourage young doctors to choose Nephrology as a subspecialty. A healthy working environment should also be setup and encouraged.

CONCLUSION

Resource-poor settings should focus on creating more awareness and making legislations and/or policies focusing on these preventable causes of CKD as this is more realistic and effective in these settings.

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■■■■

Serum Uric Acid Levels and Risk of Gestational Diabetes

Increase in serum uric acid levels prior to 24 weeks of gestation has been linked to risk of gestational diabetes (GDM) in an observational study recently published in the *Journal of Clinical Endocrinology and Metabolism*.[1]

Researchers retrospectively analyzed data of pregnant women with singleton pregnancies from February 2018 to June 2022 to investigate the association between serum uric acid levels before 24 weeks of gestation and subsequent odds of GDM and other adverse pregnancy outcomes.

Out of the 24,023 women included in the study, 3,204 (13.34%) developed GDM between 24 and 28 weeks of gestation. A strong association was observed between uric acid levels and risk of GDM, the primary outcome of the study. The relative risk for GDM was 1.43 among women with uric acid levels ranging from 240 to 300 μmol/L. The relative risk increased to 1.82 with rise in serum uric acid levels >300 μmol/L. A similar association was observed between serum uric levels and the secondary outcomes of the study, which were GDM type A2 requiring medication for optimal glycemic control, preterm birth and GDM combined with pre-eclampsia.

These findings show that detection of elevated uric acid levels before 24 weeks of gestation is associated with risk of GDM. The study further suggests that "the best time to test for uric acid is before 18 weeks of gestation". Hence, monitoring of uric acid levels in early pregnancy may identify women at risk of GDM allowing early intervention.

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CLINICAL STUDY

Randomized Clinical Trial of an Ayurvedic Formulation, BV-7310 in Alcoholic Liver Disease

NARENDRA BHATT*, JASMIN JOHNSON*, SUNETRA CHASKAR*, DEEPA CHITRE†

ABSTRACT

Alcoholic liver disease (ALD) is caused by excessive intake of alcohol for many years. The incidence is as high as 25% in the United States, India and several other countries. The disease spectrum varies from fatty liver in initial stages, to hepatitis and finally cirrhosis. Untreated ALD can be fatal. Yet the options for prescription drugs are limited, and not easily available or affordable to the masses worldwide. BV-7310 contains herbal extracts of *Phyllanthus niruri, Tephrosia purpurea, Boerhavia diffusa* and *Andrographis paniculata.* The individual plants are known hepatoprotective agents in Ayurveda. The objective of this study was to investigate the safety and efficacy of BV-7310, a proprietary combination standardized formulation, in subjects with ALD. A multi-centric, double-blind, placebo-controlled, randomized study of 61 subjects was conducted for a period of 12 weeks. Subjects on BV-7310 showed improvement in clinical features of ALD as compared to placebo, including reduction and normalization of transaminases. BV-7310 also reduced bilirubin levels to normal, showing improvement in the detoxifying and excretory capabilities of the liver. No significant adverse events were seen in the treatment group. Based on the data shown, BV-7310 shows promise as a safe and effective hepatoprotective in patients of ALD.

Keywords: Hepatoprotective, alcoholic liver disease, Ayurveda, alcoholic steatohepatitis, fatty liver disease, Periban®

Alcohol, its abuse and health effects of the same have been known to mankind since millennia. Alcoholic liver disease (ALD) spans a clinical and histological spectrum.[1] At the earliest and most common stage, it causes fatty liver or steatosis characterized by infiltration of fat within the liver cells. The next stage is that of alcoholic hepatitis or inflammation and destruction of the liver cells. This progresses to fibrosis and cirrhosis, which is replacement of normal liver cells with nonliving scar tissue. Untreated, this can be a precursor for hepatocellular carcinoma.[2,3] Nearly all heavy drinkers develop fatty liver. However, according to data from clinical and autopsy studies, only 20% to 30% develop alcoholic hepatitis or cirrhosis.[4,5]

Quantitatively, the liver is the major organ involved in the metabolic disposal of ethanol. The cytosolic alcohol dehydrogenase, microsomal ethanol-oxidizing system and peroxisomal catalase metabolize ethanol to acetaldehyde, which is a reactive metabolite that can produce injury in a variety of ways.[6] Acetaldehyde is further metabolized to acetate by acetaldehyde dehydrogenase localized in the mitochondria and abundantly found in the liver. The rate of acetaldehyde formation is also highest in the liver. Hence, the liver is an early target for alcohol-induced injury. Nonoxidative pathways of ethanol metabolism include formation of ethyl esters of long-chain fatty acids, which also affect mitochondrial function.[7] Several risk factors including genetic predisposition and malnutrition contribute to the cascade of events leading to sequential dysfunction of hepatic cells. This is manifested by cell membrane damage, hypermetabolic state in the hepatocytes most prominent in the perivenular area of the hepatic lobule, oxidative injury, steatosis, triggering of immune responses, precipitation of cytoskeletal elements and production of collagen. The cytokines, thus released can also induce apoptosis in the liver cells. With this understanding of the pathogenesis of ALD and in view of the relentless progression of the disease, there is a need for clinical evaluation of potential candidates for hepatoprotection.[8]

There are limited options for prevention and treatment of alcoholic liver damage. Several agents like S-adenosyl methionine (Sam-E),[9] dietary epigallocatechin-3-gallate (EGCG) in green tea,[10,11] propylthiouracil,[12,13] colchicine[14] and silymarin[15,16] have been tested in the management of

*Bioved Pharmaceuticals Pvt. Ltd., Pune, Maharashtra, India
†Bioved Pharmaceuticals, Inc., San Jose, California, USA
Address for correspondence
Dr Deepa Chitre
Bioved Pharmaceuticals, Inc. 1929 O'Toole Way, San Jose, CA 95131, USA
E-mail:dchitre@bioved.com

ALD. Steroids, biologics,[17] N-acetylcysteine and pentoxifylline have also been targeted for liver disorders.[18,19] However, insignificant clinical and biochemical outcomes,[20] toxicity profiles and costs are limiting factors in the availability and use of these agents.[21,22] Overall, with the limitations of the tried agents, there is a definite need of effective and affordable therapies for prevention and management of ALDs. As conventional medicine pursues a more integrated approach to managing disease, select herbs that influence liver function are being revisited and evaluated for their overall health promoting effects.[23,24] In this respect, the herbal treasure chest of Ayurveda offers a host of new phytopharmaceutical products that can be used to manage a spectrum of liver-related imbalances.

According to Ayurveda, the liver (*yakrut*) along with the spleen (*pleeha*) is the origin of the blood channels. Liver diseases such as *kamala* (jaundice) and its types are explained in ancient Ayurvedic texts. Consumption of excessive alcohol and its effects are described as "*madatyaya*". Its clinical diagnosis is similar to modern day ALD, and the management is well described. Ayurveda is an officially recognized healthcare system in India and countries such as Hungary, Switzerland, Brazil, United Arab Emirates, Malaysia and Romania among others. Ayurvedic science recognizes that balancing liver function is pivotal to ensuring overall health. In dealing with problems of the liver, the primary goal within the system of Ayurveda is to enhance the liver detoxification processes, reverse the injury and help protect against further damage to the liver. Based on traditional use, herbs are selected and combined for their ability to promote "balance" within the body and to nourish the liver and related functions, including digestion and bile acid secretion. These herbs act on multiple biochemical pathways to nourish the body as a whole and support various organ systems especially the liver.[25,26] BV-7310 (Periban®) has been formulated and developed using this same theory. The individual plant components of BV-7310 are known hepatoprotective agents singly for use in alcoholic and other chemically damaged liver subjects.[27-30]

However, there are limited validation studies for these individual herbs or in combination with others. Recently, we have shown the hepatoprotective effect of BV-7310 in different cellular and animal models.[31] The objective of this study was to investigate this proprietary and standardized formulation, BV-7310 (Periban®), for its safety, efficacy and hepatoprotective activity, in subjects with ALD.

MATERIAL AND METHODS

Composition of BV-7310

Each capsule of BV-7310 contained 480 mg of extracts of *Phyllanthus niruri (Bhuiamla), Andrographis paniculata (Kalmegh),* root extracts of *Tephrosia purpurea (Sharapunkha)* and *Boerhavia diffusa (Punarnava).* The dry powders were mixed in a weight/weight ratio of *P. niruri : T. purpurea : B. diffusa : A. paniculata ::* 2.5 : 1.75 : 1.5 : 1, respectively. Each of the specialized extracts were prepared by a proprietary process, and standardized using various methods such as high-pressure liquid chromatography (HPLC), thin layer chromatography (TLC) and ultraviolet visible spectrophotometry.

The plant extracts used in the formulation have been authenticated and standardized to ensure reproducibility of results. The plant materials under study were identified, authenticated and deposited in a Government of India Herbarium; namely the Central Council for Research in Ayurvedic Sciences (CCRAS) based in Pune, Maharashtra, India. The herbarium voucher numbers are *A. paniculata* (4401), *B. diffusa* (4402), *T. purpurea* (4403) and *P. niruri* (4404). Each of the 4 plants has been checked and is an accepted name by The Plant List www.theplantlist.org Version 1.1 of September, 2013. All plant extracts used in this study came from commercial crops. The use of resources and work has also been approved by the National Biodiversity Authority of India.

This was followed by qualitative standardization by TLC and quantitative standardization by HPLC of different batches of the final formulation, and stringent stability tests so that the efficacy and safety of the finished product is reproducible. The study formulation was tested for absence of residual solvents, pesticides and heavy metals. In addition, rigorous *in vitro* and *in vivo* testing was conducted to ensure safety of the formulation prior to entering into human clinical trials (data under publication).

The placebo capsules were identical in look and color, and contained inert excipients only.

Study Design

A multi-centric, double-blind, placebo-controlled, randomized clinical trial of 61 subjects was conducted over a period of 12 weeks. The study was conducted in two large fully accredited teaching hospitals and research centers namely, Topiwala National Medical Center/BYL Nair Hospital, Mumbai and King Edward Memorial Hospital, Pune, both in India. This study was

approved by the Ethics Committees of both institutions, as well as the in-house Ethics Committee of Bioved Pharmaceuticals Pvt. Ltd., India, which comprised of leading scholars, scientists, judicials and physicians. The study was conducted under guidelines of Good Clinical Practices (GCP) and the Declaration of Helsinki, and in conformance with International Council for Harmonization (ICH) guidelines, 1996.

Subjects were screened in outpatient settings at both hospitals. Sixty-six male subjects aged 20 to 60 years, diagnosed with alcoholic hepatitis based on history of alcohol abuse (drinking >30 mL of alcohol per day for at least 5 years), presence of clinical features, biochemical evidence - specified by aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) more than 2 times of normal limits, increased serum gamma-glutamyl transferase (GGT), and absence of serological markers of hepatitis B (HbSAg) or hepatitis C (anti-HCV) were included in the study. A written informed consent was taken in all cases. Subjects with cirrhosis of liver or decompensated liver disease, any severe/known systemic disease, use of any other investigational drug within 4 weeks of trial, use of corticosteroids, silymarin, milk thistle or other therapies with hepatoprotective or immunomodulatory potential within 4 to 6 weeks of trial were excluded from the study.

All enrolled subjects received, in a randomized fashion, BV-7310 or placebo for 12 weeks. The treatment was administered in a double-blind manner as follows:

- Group 1 – BV-7310, 1 capsule 2 times per day after meals for 12 weeks.
- Group 2 – Placebo, 1 capsule 2 times per day after meals for 12 weeks.

Subjects were advised to stop alcohol but this was not mandatory. In case of subjects continuing alcohol consumption despite advice, details of alcohol consumption during the trial were recorded wherever possible. The serum enzymes and other liver function tests were tested at screening, and at the end of weeks 1, 2, 4, 8 and 12. Hepatoprotective activity of BV-7310 was assessed by comparison of change in serum enzymes between subjects on BV-7310 and placebo. Safety parameters were tested at screening, and at the end of weeks 4 and 12. Liver ultrasound was done at screening and at the end of week 12.

Statistical Analysis

Fisher exact test was used to determine significance between groups in all parameters including demographics, clinical findings, laboratory efficacy endpoints, ultrasound findings and safety. Chi-square analysis was used to compare the difference between subjects who abstained from alcohol and those who continued to consume alcohol during the duration of the study.

RESULTS

In total, 66 male subjects from Mumbai and Pune area in India were screened and qualified for the trial. Of these, 3 subjects dropped out from the study before completion of 4 weeks of medication. One subject died of encephalopathy immediately after the screening visit. All the above 4 subjects were on placebo treatment. One subject on BV-7310 died during the study – he had advanced portal hypertension, esophageal varices and hematemesis at enrollment. His death was determined due to advanced disease condition and not related to the study product. Among the 61 subjects who completed the study, 31 subjects were treated with BV-7310 and 30 on placebo.

Demographics

The average age of subjects was 44.8 ± 8.5 years in the treatment group taking BV-7310 and that of subjects in the placebo group was 42.9 ± 9.1 years. The age of subjects in both groups was thus comparable (p = 0.4). The body weights of subjects in both groups were also comparable with 60 ± 8 kg in the treatment group and 61 ± 14 kg in the placebo group (Table 1). The nature of alcohol consumption was noted in the subjects. The

Table 1. Demographic Characteristics at Baseline*

Characteristic (Unit)	BV-7310 (n = 31)	Placebo (n = 30)	P value
Age (in years)	44.8 ± 8.5	42.9 ± 9.1	P > 0.05
Body weight (in kg)	60 ± 8.0	61 ± 14	P > 0.05
Duration of consumption of alcohol (in years)	14.06 ± 7.6	13.6 ± 6.4	P > 0.05
Quantity of alcoholic drink (in mL)	238 ± 157	234 ± 153	P > 0.05

n = number of subjects in group.

*The values shown are based on available data.

most frequently used alcoholic drink of all subjects was "Country (hard) liquor" diluted with water. The Country liquor has up to 42.8% alcohol by volume. The average alcoholic drink consumption by subjects was 238 ± 157 mL per day in the subjects enrolled to take BV-7310 and 234 ± 153 mL per day in the subjects who took placebo. The subjects on BV-7310 had past history of consumption of alcohol for 14.06 years and those on placebo had consumed alcohol for 13.6 years. The quantity of alcoholic drink consumed (p = 0.9) and the duration of consumption (p = 0.8) were thus comparable in the two groups (Table 1).

Subjects were encouraged to abstain from alcohol during the course of the trial. However, a significant number of subjects continued to consume alcohol. Hence, analysis of confounding due to alcohol abstinence was carried out. Subjects treated with BV-7310 were analyzed for any difference in the liver function tests between those who continued to consume alcohol and those who supposedly stopped alcohol consumption during the study period.

This comparison was possible only with one of the two study sites where continued alcohol intake was recorded in 29 subjects. Data on continuing consumption of alcohol was not available with the other site. Six of 14 subjects on BV-7310 in that study site continued to take alcohol during the study. Ten of 15 subjects on placebo gave history of consumption of alcohol during the trial period. The difference in the two groups is however not statistically significant (Chi-square = 2.14). History of continuation of alcohol consumption could not be recorded in 32 subjects. All the subjects were reasonably compliant to the study methods. No history of concomitant medication could be elicited in any of the 61 subjects studied.

Efficacy Endpoints

The most common clinical features at screening were nausea, vomiting, loss of appetite, abdominal pain, dizziness and altered sensorium. Twenty-one subjects treated with BV-7310 were icteric at initiation of study compared to 20 subjects in the placebo group. Anorexia, nausea, vomiting and fatigue did not show significant difference in baseline values in the cases and the controls.

The improvement in these clinical findings over the duration of study was more prominent in the subjects on BV-7310 than in those on the placebo in terms of reduction in icterus, nausea, vomiting, fatigue and pain in abdomen (Table 2).

Table 2. Subjects with Improvement in Clinical Findings at the End of the Study

Parameter	BV-7310 (n = 31)	Placebo (n = 30)	P value
Icterus	11 (35%)	8 (27%)	P = 0.14
Anorexia	6 (19%)	8 (27%)	P = 0.20
Nausea, vomiting	4 (13%)	2 (6.7%)	P = 0.11
Fatigue	4 (13%)	3 (10%)	P = 0.01*
Pain in abdomen	2 (6.4%)	1 (3.3%)	P = 0.004*

n = number of subjects in specified group.

*Statistically significant.

Laboratory Findings

Liver function tests, especially AST and ALT were considered the primary efficacy endpoints. AST was greater than normal in all the subjects on BV-7310, at initiation of therapy and returned to normal in 8 of these 31 subjects. In the placebo group, 1 subject had normal AST at initiation of therapy and 4 had AST values in the normal range at the completion of trial. The mean reduction in AST was also analyzed. The improvement, i.e., reduction in the AST value by the end of study was significantly greater in the subjects on BV-7310 as compared to those receiving placebo (p = 0.04, Fisher exact test) (Table 3).

ALT was normal in 15 of 31 subjects on BV-7310 at initiation of therapy and in 27 subjects at end of treatment. In the placebo group, 17 subjects had normal values at initiation of therapy and 20 had ALT values in the normal range at the completion of trial. The number of subjects who achieved normal values of ALT at end of study is higher in subjects on BV-7310 than in those on placebo (p = 0.054, Fisher exact test). The differences at baseline were comparable. The number of subjects who showed improvement in the ALT values and return to normal range is 12/16 in the active group and 3/13 in the controls. This difference is highly significant (p = 0.01, Fisher exact test). The improvement, i.e., reduction in the ALT value was greater in the subjects on BV-7310 as compared to those on placebo (Table 3).

AST:ALT ratio was compared at initiation and at the end of the trial. Mean AST:ALT ratio at initiation of trial was 3.2 ± 1.2 in cases and 2.9 ± 1 in controls. The change in ratio at end of trial is however not statistically significant with a mean difference of 1.23 ± 0.93 in treatment group and 0.93 ± 0.96 in controls (p = 0.32). The mean serum GGT values were also analyzed. The baseline serum GGT values were comparable in

Table 3. Serologic Parameters in BV-7310 and Placebo-treated Groups

Serologic parameters	BV-7310 Mean ± SD (n = 31)		Placebo Mean ± SD (n = 30)		P value
	Initial	At end of treatment	Initial	At end of treatment	
ALT (U/L)	52.1 ± 31.8	38.8 ± 33.3	41.9 ± 18.3	34.9 ± 18.4	0.01*
AST (U/L)	144.1 ± 59.6	64.1 ± 40.0	113.8 ± 48.8	63.6 ± 36.7	0.04*
GGT (IU/L)	152 ± 121.0	79.3 ± 46.6	102.9 ± 74.2	62.7 ± 69.5	0.17
Bilirubin (mg/dL)	6.1 ± 7.2	2.8 ± 2.6	6.9 ± 8.7	3.5 ± 3.7	0.05*

n = number of subjects in specified group.

LFTs = Liver function tests; ALT = Alanine transaminase; AST = Aspartate transaminase; GGT = Gamma-glutamyl transferase.

Bilirubin values are expressed as mean ± SD.

*Statistically significant.

both groups. The improvement, i.e., reduction in the serum GGT value is greater in the subjects on BV-7310 (72.7 ± 117) as compared to placebo (40.3 ± 49.8); however, the difference is not statistically significant (p = 0.17) (Table 3).

Confounding Effect of Abstaining from Alcohol during the Trial

Subjects were encouraged to abstain from alcohol during the course of the trial. A significant number of subjects, however, continued to consume alcohol. Hence, analysis of confounding due to alcohol abstinence was carried out. The cases, i.e., the subjects on BV-7310 were analyzed for any difference in the liver function tests in the subjects who continued to consume alcohol during the course of treatment and those who supposedly stopped alcohol consumption in the study period. This comparison was possible only with one of the two centers (in 29 subjects) where continued consumption of alcohol was recorded. The difference in improvement in the efficacy criteria (AST, ALT and GGT) of subjects on BV-7310 (n = 14) is not significant in the two groups, i.e., those continuing and those who have discontinued alcohol in the study period (p > 0.05).

Other Laboratory Findings

Serum alkaline phosphatase (ALP) was not significantly affected by the course of BV-7310 therapy. Upon completion of therapy, serum ALP was increased in subjects on BV-7310 (as compared to initial values), the difference being 9.59 and decreased in subjects on placebo, the mean difference being 3.29. These changes are statistically insignificant (p = 0.1). Serum protein values increased in the subjects on BV-7310 by 1.37 ± 9.69. The values increased in the group on placebo by 0.77 ± 3.2. This finding is also statistically insignificant (p = 0.7) though showing a good trend for improving the liver functions to normal in subjects treated with BV-7310.

Serum bilirubin was within normal range in 8 subjects on BV-7310 at initiation of study, but was normal in 15 subjects by the end of study. In the placebo group, however, serum bilirubin was normal in 12 subjects at initiation of study and in 13 subjects by the end of study. Hence, a reduction in bilirubin to normal range was seen in 7/23 subjects with high baseline values on BV-7310 treatment and in only 1/18 subjects with high baseline values in subjects on placebo. Thus BV-7310 facilitated reduction in bilirubin values to normal values by the end of study (p = 0.05). The mean reduction in serum bilirubin is however comparable in both groups (Table 3). The INR (ratio of patient's prothrombin time with normal laboratory value) was $[1.5]^{ISI}$ ± 0.5 at screening in the cases and $[1.3]^{ISI}$ ± 0.5 at end of study. The values were $[1.5]^{ISI}$ ± 0.7 at screening in the controls and $[1.2]^{ISI}$ ± 0.3 at end of study. The results are comparable in the two groups.

The Maddrey's discriminant function, a fairly good indicator of prognosis in liver disease is derived from the prothrombin time and serum bilirubin. A score of >32 suggests poor prognosis and possible benefit from steroids. In this study, there were 12 patients in the active group with a score >32 at start and 7 at the end of the study. In the placebo group, there were 12 patients with a score >32 at start and 3 at end of study (p > 0.05) (data not shown). This suggests a better prognosis in subjects treated with BV-7310.

The mean corpuscular volume of erythrocytes did not show significant change in either group (p > 0.05). The mean reduction in blood glucose in the active treatment group was 18.7 and that in placebo or controls was 8.07; the difference was not statistically significant. This

parameter is not an indicator of activity under this study; however, it shows a general trend to normalize the liver metabolic functions with the study formulation and is a positive factor in this study.

Ultrasonography

Findings on ultrasonographic (USG) examination were recorded at initiation of therapy and at end of therapy in 28 of the 31 subjects on BV-7310 and in 26 of the 30 subjects on placebo. No subjects on BV-7310 showed any deterioration in USG findings over the course of study. Improvement and return to normal was seen in 13 subjects and no change in 15 subjects. In contrast, 5 of the 26 subjects on placebo had deterioration of USG findings at the last visit; improvement was seen in 3 subjects and no change in 18 subjects. The improvement in terms of size of liver, ascites and change in echo texture of the liver on USG examination was highly significant in the subjects on BV-7310 ($p < 0.05$) (Table 4).

Table 4. Number of Subjects with Improvement in Ultrasound Examination

Observation	Improvement	No change	Deterioration
Active (n = 28)	13	15	0
Placebo (n = 26)	3	18	5

n = number of subjects in specified group.

Safety

No adverse events or side effects of treatment were seen during the study duration in both groups. Two subjects, 1 in each group, died during the study, their deaths were determined to be unrelated to the study or product under study. Pulse, respiratory rate, blood pressure and body temperature remained reasonably constant during the course of therapy in both subjects on BV-7310 and placebo.

The hemoglobin, red blood cell (RBC) count, total and differential white blood cell (WBC) count, platelets, erythrocyte sedimentation rate (ESR), blood glucose, blood urea nitrogen (BUN), serum creatinine and urine routine and microscopic examinations did not show any significant changes over the course of treatment in either group (Table 5).

Global Impression

The investigator/s and the patient/s rated the mode of treatment at the end of study. Ten subjects on BV-7310 and 8 on placebo rated the treatment as excellent. The outcome of treatment was rated poor by 1 patient on placebo.

The treatment outcome was rated as excellent by the investigators in 14 subjects on BV-7310 against 4 subjects on placebo. The outcome was poorly rated in 4 subjects, all on placebo.

Table 5. Blood Safety Parameters in the Two Groups and Significance of Difference

Parameter	BV-7310 (n = 31)		Placebo (n = 30)		Significance of difference of means
	1st visit	Last visit	1st visit	Last visit	
Hemoglobin (g%)	11.9 ± 2.8	11.67 ± 2.38	11.7 ± 3.2	11.5 ± 2.6	P > 0.05
RBC count (per mm^3)	4.5 ± 0.6	4.59 ± 0.4	4.67 ± 0.6	4.5 ± 0.6	P > 0.05
WBC count (per mm^3)	8,920 ± 3,450	8,071± 2,388	9,080 ± 3,540	7,642 ± 1,528	P > 0.05
Neutrophils (%)	71.8% ± 13.5	66.48% ± 8.67	71.4% ± 10.4	68.2% ± 9.2	P > 0.05
Lymphocytes (%)	25.3% ± 12.6	32.28% ± 8.35	25.3% ± 9.5	29.5% ± 9.6	P > 0.05
ESR (Westergren method mm/hr)	13.9 ± 10.6	11.4 ± 7.85	15.6 ± 8.6	13.2 ± 9.2	P > 0.05
Fasting blood glucose (mg/dL)	110 ± 42.7	93.71 ± 19.48	102.5 ± 25.6	93.2 ± 14.9	P > 0.05
Blood urea and nitrogen (mg%)	20.3 ± 14.7	15.36 ± 7.29	21.1 ± 14.9	14.8 ± 8.6	P > 0.05
Serum creatinine (mg%)	0.86 ± 0.39	0.764 ± 0.287	0.8 ± 0.3	0.8 ± 0.2	P > 0.05
Platelet count (per mm^3)	290,313 ± 2,84,970	237,538 ± 9,40,448	214,530 ± 1,10,030	211,615 ± 75,390	P > 0.05

n = number of subjects in specified group.

WBC = White blood cell; RBC = Red blood cell; ESR = Erythrocyte sedimentation rate.

DISCUSSION

BV-7310, commercially named Periban®, is a proprietary mix of 4 specialized herbal extracts, namely *P. niruri (Bhuiamla), A. paniculata (Kalmegh),* root extracts of *T. purpurea (Sharapunkha)* and *B. diffusa (Punarnava)*. While the 4 extracts have been studied individually for therapeutic applications, this unique combination was studied in a randomized clinical trial for the first time. Only males were included in the study because both alcohol abuse and dependence rates are higher in men than in women. However, that trend is changing rapidly in both developed and developing nations of the world. Of concern is that women's risk for developing severe ALD increases with daily intake of 20 to 40 g of alcohol, while the threshold for men appears to be 60 to 80 g.[32] Four subjects, all on placebo, dropped out before completion of 4 weeks of study and were not considered for any analysis. Demographics and average alcohol consumption was well-matched in the two groups.

There was significant improvement in nausea, vomiting, icterus, pain in abdomen and fatigue in the subjects on BV-7310 than those on the placebo. The reduction in the ALT and AST values is significantly greater in the subjects on BV-7310 as compared to placebo. This reduction and normalization of the transaminases indicates a role of the product in reduction of hepatocellular inflammation and necrosis. The mean AST:ALT ratio at initiation of trial was greater than 2 in cases and controls, which was highly suggestive of ALD. The change in ratio at end of trial is not statistically significant and suggests that a study of longer duration may be warranted or that a higher dose of BV-7310 would prove to be more efficacious.

The GGT values at baseline were similarly increased in both subjects on BV-7310 and placebo at initiation of therapy. GGT being an inducible enzyme is elevated in all forms of fatty liver, making it a sensitive indicator, though not specific of liver disease. The improvement, i.e., reduction in the GGT value is greater in the subjects on BV-7310 as compared to placebo though not significant. GGT has a long half-life of 26 days, making its role limited in evaluation of liver disease. This could be a reason for not obtaining a statistically significant difference in improvement though seen to be improved in the subjects on BV-7310 versus those on placebo.

Serum ALP was not significantly affected by the course of therapy. It is a marker of obstructive liver disease and therefore not a marker of ALD. Serum protein values have shown marginal increase in the subjects on BV-7310 as compared to the group on placebo. Serum proteins are good markers of hepatic function in terms of synthesis. However, a rise in total proteins may be seen even in the presence of liver disease in case of an acute phase response, the reactants of which are synthesized in the liver.

Serum bilirubin was raised in 23 subjects on BV-7310, and in 18 subjects on placebo, at initiation of therapy. This was however not manifested as icterus in some subjects as the rise in bilirubin was <3 mg/dL in these instances. BV-7310 facilitated significant reduction in bilirubin values to normal values by the end of study. This indicates that BV-7310 helps restore the detoxification and excretory functions of liver which play a pivotal role in progression of ALD. There is improvement in the blood sugar levels in BV-7310 group versus placebo. Though not statistically significant, this signifies a causative effect in improvement in overall metabolism and liver function with BV-7310. Blood counts, other chemistry and prothrombin time did not show statistical significance between the two subject groups. Of note is that leukocytosis and thrombocytopenia are common in ALD. These occur secondary to direct alcohol toxicity or to hypersplenism found in portal hypertension. However, both the leukocyte counts and the platelet counts were within normal limits in the subjects for the entire duration of study. The formulation, BV-7310, therefore had no obvious toxic effects on long-term consumption (for a period of 12 weeks in this study).

Most common findings on USG were bright echo texture of liver suggestive of fatty liver, free fluid in abdomen suggestive of ascites and hepatomegaly. The improvement on USG examination of liver is highly significant in the subjects on BV-7310 indicating improvement in overall liver function and recovery from injury. Subjective measures in investigation of therapeutic agents best reflect the influence on disease from the patient's and investigator's perspective, because a subjective response most likely integrates best the clinical efficacy and safety. The investigator's global impression here showed very good correlation with the nature of study formulation in the wake of the study being a double-blind trial. Treatment outcome was rated excellent in 14 subjects on BV-7310 as against 4 subjects on placebo. Poor treatment outcome was not seen in any patient on BV-7310 but was seen in 4 subjects on placebo.

CONCLUSION

Alcohol use disorders (AUD) and ALD are prevalent worldwide and increasing over time.[33] During the pandemic, there has been a further acceleration of

AUD and ALD numbers.[34] BV-7310 (Periban®) showed some improvement in clinical features of ALD as compared to placebo and significantly helped in reduction and normalization of the transaminases. This indicates a role of the product in improvement and reversal of hepatocellular inflammation and necrosis. These changes are observed despite continuation of use of alcohol during the course of therapy. BV-7310 aids reduction of elevated serum bilirubin levels to normal, thus playing a role in improving the detoxifying and excretory capabilities of the liver and facilitates correction of fatty deposits in hepatocytes, ascites and hepatomegaly. BV-7310 is safe for uninterrupted use for a prolonged period in the prescribed dose.

There is consistent improvement in parameters of alcoholic hepatitis in subjects in active group, even though some of the efficacy criteria may not be statistically significant in this study. The authors believe that being the first study of its kind, with a new formulation, the subjects were under-dosed in this study; and doubling the dose may show statistically significant improvement in the remaining parameters as well. Alcoholic hepatitis mimics the changes in liver structure and function seen in other chemically-induced liver damage such as with prescription medicines, e.g., antituberculosis drugs, cancer chemotherapy and biologic response modifiers; and with recreational drug abuse. Based on this clinical study, it is anticipated that BV-7310 may have a meaningful efficacy in these conditions as well.

Hence, BV-7310 (Periban®) shows promise as a safe and effective oral hepatoprotective and therapeutic agent for use in subjects of ALD. Further studies are warranted for use of BV-7310 (Periban®) both in ALD as well as other liver conditions.

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CLINICAL STUDY

A Pilot Study to Evaluate the Effects of Cerebroprotein Hydrolysate on Neurological Outcomes and Hospital Stay in Patients Admitted for Ischemic and Hemorrhagic Stroke

M UWAIS ASHRAF*, NIKHAT PARVEEN†, M UZAIR ASHRAF‡, DIVYASHSISH BHARADWAJ†, DEVASHSISH BHARADWAJ#, AREEB ABBASI#

ABSTRACT

Introduction: Neurological stroke is the most common cause of disability and leaves nearly 65% of survivors with sensory, motor and coordinative disabilities. At present, there are no therapies to prevent long-term neurological deficits after stroke. Many neuroprotective drugs are being tested with the aim to ensure these effects. Preclinical studies have shown a modulatory effect of cerebroprotein hydrolysate on synaptic remodeling and facilitated synaptic transmission. **Material and methods:** This was a hospital-based, open-label pilot study conducted in a tertiary care hospital of North India. All patients admitted with a diagnosis of stroke both ischemic and hemorrhagic, were included in the study. Patients were randomized into two groups. The test group was given cerebroprotein hydrolysate, along with standard treatment for stroke, whereas the other group was kept on standard treatment for stroke as per the latest guidelines, without cerebroprotein. **Results:** A total of 50 patients of stroke, admitted in a tertiary care center were included in the study. The mean age of the patients was 65.7 ± 11.86 years. Twenty-six (52%) were males and 24 (48%) were females. Out of the total 50 patients, 23 (46%) had ischemic stroke and 27 (54%) had hemorrhagic stroke. Twenty (40%) had diabetes, 37 (74%) had hypertension, 8 (16%) were known cases of coronary artery disease, 28 (56%) had dyslipidemia, 22 (44%) were smokers, 7 (14%) had a history of ethanol consumption and 13 (26%) were obese. Mean Barthel score at admission was 21.2 ± 11.3 and mean Rankin score at admission was 3.6 ± 1.37. Mean Barthel score at end of treatment was 53.9 ± 28.72 and mean Rankin score at end of treatment was 2.6 ± 1.65. The mean duration of admission was 6.8 ± 3.57 days. **Conclusion:** The current study highlights the role of cerebroprotein hydrolysate in improving the neurological scores and reducing hospital stay among patients hospitalized with stroke.

Keywords: Barthel score, Rankin score, neuroprotective, neurological deficit

Neurological stroke remains the most common cause of disability and leaves nearly 65% of survivors with sensory, motor and coordinative disabilities.[1] At present, there are no therapies to prevent long-term neurological deficits after stroke. Pharmacological interventions in the acute management of stroke aim to restore blood flow to the ischemic tissue in order to minimize brain damage and future complications. Many neuroprotective drugs are being tested with the aim to ensure these effects. Cerebroprotein hydrolysate is a neuropeptide preparation that mimics the action of endogenous neurotrophic factors and protects the brain against the impact of stroke by supporting the cerebral reorganization process.[2] Preclinical studies have shown a modulatory effect of porcine brain tissue hydrolysate on synaptic remodeling and facilitated synaptic transmission.[3] It has also shown improvement in oligodendrogenesis and neurogenesis.[4] Thus, cerebroprotein hydrolysate has shown a beneficial effect on endogenous brain recovery processes in various model systems of stroke and traumatic brain injury.[5]

In previous studies with neuroprotective agents in stroke patients, there has been a mismatch between preclinical studies and clinical trials, probably due to a failure to

*Assistant Professor, Dept. of Medicine
†Intern
‡Research Scholar
#MBBS Student
JN Medical College, AMU, Aligarh, Uttar Pradesh
Address for correspondence
Dr M Uwais Ashraf
Assistant Professor
Dept. of Medicine, JN Medical College, AMU, Aligarh, Uttar Pradesh
E-mail: uwaisashraf@gmail.com

activate long-term brain repair processes.[6] Stroke causes neuronal damage within gray matter and axonal injury within white matter tracts.[7] Cerebroprotein hydrolysate is a mixture of low-molecular-weight neuropeptides derived from purified porcine brain tissue. The ability to penetrate biological membranes and pass through the blood-brain barrier makes cerebroprotein hydrolysate a strong candidate for clinical use in stroke patients. *In vivo*, cerebroprotein hydrolysate has been demonstrated to improve functional outcomes, promote neurogenesis, reduce neuroinflammation and inhibit free radical formation.[8,9]

MATERIAL AND METHODS

This was a hospital-based, open-label pilot study conducted in a tertiary care hospital of North India. Fifty patients admitted with a diagnosis of stroke were included in the study. Out of all the stroke patients, 23 suffered from ischemic stroke and 27 from hemorrhagic stroke. Patients were randomized into two groups. A total of 25 patients were randomly assigned to each group. The test group was given cerebroprotein hydrolysate, along with standard treatment for stroke, as per the existing guidelines for ischemic and hemorrhagic stroke, respectively; whereas the other group was kept on standard treatment for stroke, as per the latest guidelines but without cerebroprotein.

The baseline characteristics were recorded and the patients were followed from the day of admission to the day of discharge/death for changes in Rankin and Barthel scores. Improvement in the above-mentioned scores and the duration of stay were taken into account to compare the two groups. Data were analyzed using SPSS software. Continuous variables with normal distribution were expressed as mean ± standard deviation, and the differences were assessed with analysis of variance (ANOVA). Categorical variables were presented as absolute and relative frequencies, and the differences were assessed with Fisher's test. A 'p' value of <0.05 was considered statistically significant. Kendall's Tau correlation test, McNemar's test, Paired sample *t*-test and Wilcoxon signed-rank test were used to compare changes before and after therapies, wherever applicable. A regression model was generated to analyze the effect of cerebroprotein on duration of hospital stay.

RESULTS

A total of 50 patients of stroke, admitted in a tertiary care center were studied. Mean age of the patients was 65.7 ± 11.86 years. Twenty-six (52%) were males and 24 (48%) were females. Out of the total stroke patients, 23 (46%) had ischemic stroke and 27 (54%) had hemorrhagic stroke. Twenty (40%) had diabetes, 37 (74%) had hypertension, 8 (16%) were known cases of coronary artery disease, 28 (56%) had dyslipidemia, 22 (44%) were smokers, 7 (14%) had a history of ethanol consumption and 13 (26%) were obese. Mean Barthel score at admission was 21.2 ± 11.3 and mean Rankin score at admission was 3.6 ± 1.37. Mean Barthel score at end of treatment was 53.9 ± 28.72 and mean Rankin score at end of treatment was 2.6 ± 1.65. The mean duration of admission was 6.8 ± 3.57 days. Table 1 presents the baseline characteristics at admission.

Out of the total 50 patients, 25 (50%) were given daily cerebroprotein injections along with the standard management of stroke as per the guidelines and the remaining 25 (50%) were given only the standard management, without cerebroprotein injections. Barthel scores and Modified Rankin scores were assessed on admission and at discharge.

The differences between Barthel scores on admission and discharge were significant in the two groups with their respective p values (Table 2). The differences between Modified Rankin scores on admission and discharge were significant in the case group but not in control group with their respective p values (Table 2, Figs. 1 and 2).

The average duration of hospital stay in those given cerebroprotein was 4.8 ± 2.11 days; whereas, the average duration of stay in the control group was 7.8 ± 3.89 days ($p = 0.02$). Figure 3 shows the relationship of duration of hospital stay with cerebroprotein supplementation ascertained using regression plots.

Table 1. Baseline Characteristics of Cases and Controls

	Number (%)
Males	26 (52)
Ischemic stroke	23 (46)
Hemorrhagic stroke	27 (54)
Diabetes	20 (40)
Hypertension	37 (74)
CAD	8 (16)
Dyslipidemia	28 (56)
Smoking	22 (44)
Alcohol	7 (14)
Obesity	13 (26)

CAD = Coronary artery disease.

Table 2. Differences in Barthel Scores and Rankin Scores at Admission and Discharge in the Two Groups

Scores		Mean	SD	P value
Cases	Barthel score at admission	19.6000	24.78743	0.004
	Barthel score at discharge	65.4000	29.71812	
	Rankin score at admission	3.7600	1.20000	<0.001
	Rankin score at discharge	1.9200	1.63095	
Controls	Barthel score at admission	22.6667	16.90	0.04
	Barthel score at discharge	42.7083	23.49	
	Rankin score at admission	3.5000	1.56	0.26
	Rankin score at discharge	3.2917	1.428	

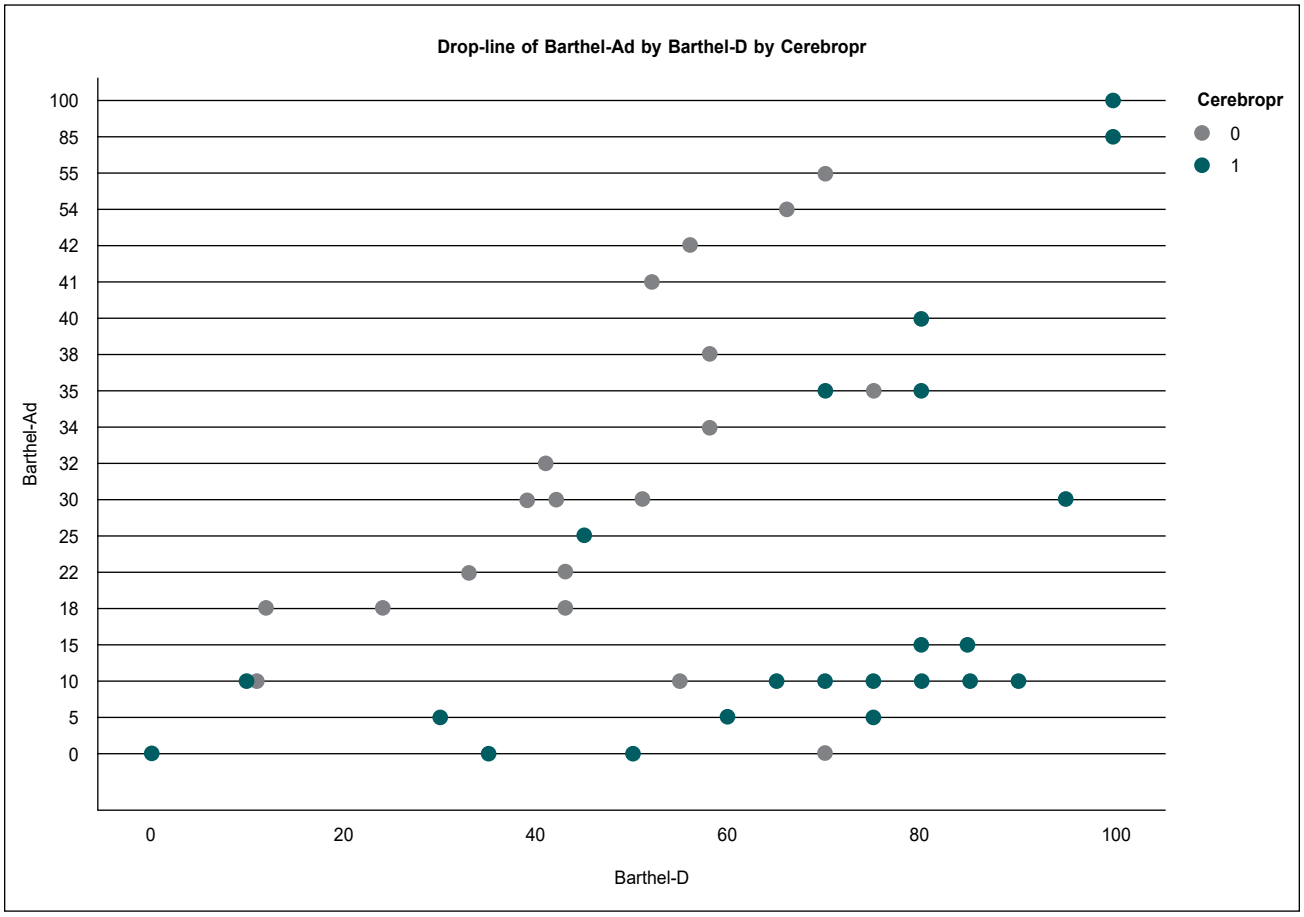

Figure 1. Comparison of changes in Barthel scores on admission and discharge between the two groups.

DISCUSSION

The present study was conducted on 50 stroke patients to compare the improvement in neurological functioning between two groups of patients.

The mean age of the patients in our study was 65.7 ± 11.86 years with 52% males and 48% females. Twenty patients had diabetes, 37 had hypertension, 8 had history of coronary artery disease, 28 had dyslipidemia, 22 were smokers, 7 had history of ethanol consumption and 13 were obese. This is in concert with previous studies on stroke patients. Charan et al have reported a mean age of 55 years in stroke patients.[8] In another study by Sridharan et al, the median age of stroke patients was 67 years.[10] A recent study conducted in Gujarat by Eapen et al also found that modifiable risk factors such as hypertension (40%), alcoholism (35%) and smoking (28%) are the commonest associations of stroke.[11]

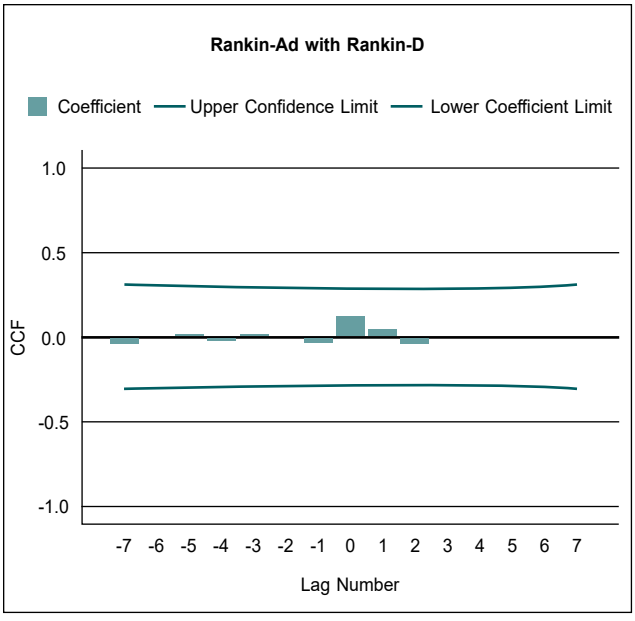

Figure 2. Comparison of changes in Rankin scores on admission and discharge between the two groups.

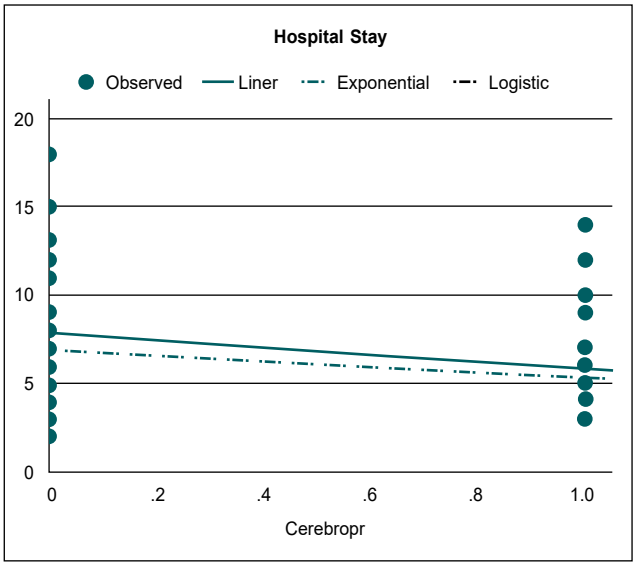

Figure 3. Regression analysis, showing the difference in duration of hospital stays between the two groups.

The efficacy of the treatment was assessed using standardized scales, which showed that the Barthel scores were significantly better ($p < 0.01$) in all items (personal hygiene, bathing, feeding, toilet, stair climbing, dressing, bowel control, bladder control, ambulation and chair/bed transfer) in the case group. Also, the Modified Rankin Scale showed more improvement ($p < 0.01$) in the case group, as compared to the control group.

The result of this study showed that in the case group, the mean Barthel score was 19.6000 (± 24.78) and Modified Rankin score was 3.7600 (± 1.2) at the time of admission and the mean Barthel score was 65.4 (± 29.71) and Modified Rankin score was 1.9200 (± 1.63) at the time of discharge. These results were consistent with a similar study conducted by Charan et al on 100 ischemic and hemorrhagic stroke patients, in which two out of four groups received cerebroprotein hydrolysate and in those two groups, Barthel Index score at baseline were 15 and 13 and at the end of 12 weeks were 88 and 84, Modified Rankin score at baseline were 4.64 and 4.80 and at the end of 12 weeks were 2.21 and 2.28, showing that patients receiving cerebroprotein hydrolysate had significant improvement in functional outcomes of patients.[8]

The differences in the mean Barthel score and mean Modified Rankin score on admission and discharge were significant ($p < 0.001$) in the two groups in our study. These results were consistent with the similar study conducted by Haffner et al.[12]

The average duration of hospital stay in the case group was 4.8 ± 2.11 days while in control group was 7.8 ± 3.89 with p value being 0.02, which was significant.

These results suggest that patients receiving cerebroprotein hydrolysate injections along with standard therapy show higher level of improvement in neurological functions as compared to those receiving only standard therapy. Cao et al in their study on mice assessed the long-term effect of cerebroprotein hydrolysate on gray and white matter integrity as well as axonal plasticity in late stage of ischemic stroke.[13] They observed an increase in the SMI/MBP ratio after distal middle cerebral artery occlusion (MAAO), which indicates the exacerbation of white matter injury encompassing both axons and myelin in mice; this injury was mitigated by cerebroprotein hydrolysate treatment and hence has role in improvement in sensorimotor functional outcomes in stroke patients.

Cerebroprotein hydrolysate further facilitated the *in situ* endogenous axonal regeneration and tract-tracing assessment of axons projecting from the contralesional motor cortex in animal models.[13] Similar studies conducted in the past have shown that cerebroprotein hydrolysate improves neurological functioning after stroke and plays a key role in post-stroke rehabilitation.[14] This may be due to the fact that cerebroprotein hydrolysate is porcine brain tissue derivative containing bioactive substances and free amino acids, which can simulate the effects of neurotropic factors such as brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNF) and nerve growth factor (NGF).[15]

Ren et al suggested in their study that cerebroprotein hydrolysate may exert a protective effect by mediating the MEK-ERK-CREB pathway, increasing BDNF expression, and thus improving neurological function and apoptosis in MCAO/reperfusion (MCAO/R) rats and concluded that cerebroprotein hydrolysate may regularly ameliorate the neural function, apoptosis and cerebral infarct volume in MCAO/R rats. It promotes multiple brain remodeling processes including angiogenesis, neurogenesis and axonal regeneration.[15]

In our study, significant improvement was observed in mean Barthel score in both groups but it was greater in the case group. Significant improvement was seen in modified Rankin score in the case group but no significant improvement was seen in control group. Therefore, we propose an approach combining cerebroprotein hydrolysate with standard therapy for treatment of stroke patients.

Cerebroprotein hydrolysate has not been reported to produce serious side effects. Few side effects like nausea, headache, vertigo, perspiration, confusion, irritability, fever, hallucinations, etc. have been reported. It is contraindicated in hypersensitivity, epilepsy and severe renal impairment. It should be used with caution in pregnant and lactating ladies as the safety profile is still not established.[16] Our study was limited by a small sample size. So, further studies with a larger sample size and studies on safety profile of cerebroprotein hydroysate are needed.

CONCLUSION

The current study highlights the role of cerebroprotein hydrolysate in improving the neurological scores and reducing hospital stay among patients admitted with stroke. To the best of our knowledge, this is the first study to take into account both ischemic and hemorrhagic strokesat the same time. The improvement in stroke assessment scores is a confirmation of the *in vivo* studies, highlighting the role of cerebroprotein in neuroregeneration after stroke.

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A Novel Solution To Prevent And Treat PROM / PPROM

Forisil

A proprietary blend of Amino acids and ingredients

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PREVENTS & SEALS RUPTURE FETAL MEMBRANES

Ensures Safe Environment For Amniotic Fluid & Fetus

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To Prevent PROM/PPROM In Patient With Previous History

Forisil 1 Capsule BID from 14th week of gestation till pregnancy ends

To Prevent PROM/PPROM In Patient Who Conceive With Difficulty

Forisil 1 Capsule BID, immediately after completion of first trimester

In Active treatment of PROM/PPROM

Day 1	When Patient Reports	Initiate 2 capsules stat
Day 1	Then After 3 hours	2 capsules
Day 1	Followed by	2 capsules every 8 hourly for 72 hours
Day 4	Then from 4th day	1 capsule BID for 15 days
Day 19	From 19th day	1 capsule OD till pregnancy ends

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CLINICAL STUDY

The Efficacy and Safety of a Combination of Amino Acids, Vitamins and Probiotics in PROM and PPROM

ANITA KANT

ABSTRACT

The prevalence and severity of prelabor rupture of the membranes (PROM)/preterm PROM (PPROM) are a worldwide public health concern. PROM is the result of a cascade of events involving matrix metalloproteinase (MMP)-9, tissue inhibitor of metalloproteinases 1 (TIMP1), cytokines and proapoptotic genes, which is initiated by several factors such as infection, genotoxic agents or some unknown etiology. In PROM, there is an increased expression and activation of MMP-2, MMP-3 and MMP-9 and a reduction of TIMP1. p53 and tumor necrosis factor (TNF)-α mediate the major apoptotic pathway of PROM. p53 can transactivate some MMP genes, resulting in the overexpression of MMPs. This leads to apoptosis. MMP-2 and MMP-9 degrades type-IV collagen, which is the major structural component of chorioamnion. Understanding the fundamental pathology at the molecular level, it appears necessary to adjust the biologically protective mechanism to prevent spontaneous preterm labor. Our findings show that the novel combination of arginine, ascorbic acid, folic acid, glutamine, glutathione, thiamine, lactic acid bacillus spores, vitamin E acetate and pyridoxine is safe and effectively prevents PROM and PPROM (97% patients) and prolongs pregnancy term.

Keywords: Amino acids, vitamins, Lactobacillus spp., PROM, PPROM

Prelabor rupture of membranes (PROM) is defined as the rupture of membranes before the onset of labor. When membrane rupture occurs before delivery and 37 weeks of gestation, it is referred to as preterm PROM (PPROM).[1] Rupture of membranes results from various factors that ultimately result in accelerated membrane weakening. The primary causes are increased local cytokines, untimely abnormal expression and activation of metalloproteinase (MMP)-9 that leads to an imbalance between MMPs and tissue inhibitors of metalloproteinases (TIMP), increased collagenase and protease activity. Factors activating MMP also activate the apoptotic pathway mediated by p53 and tumor necrosis factor (TNF). The protein p53 triggers apoptosis by regulating the expression of two genes, Bax and Bcl-2. p53 increases proapoptotic Bax gene expression and down-regulates the antiapoptotic Bcl-2 gene.[2] The synergy between MMPs activation and apoptotic change leads to rupture of the fetal membranes and low Lactobacillus spp.[3] Hence, termination of a series of cytokine activation followed by reduction of activated MMP with the introduction of specific amino acids, vitamins and Lactobacillus spp. spores may encourage resealing of the ruptured fetal membranes. The previous study suggests that supportive factors like glutathione, folic acid, glutamine, vitamin E, pyridoxine and L-arginine help in membrane resealing.[4] Hence, a prospective study was conducted among mothers diagnosed with PROM, PPROM, minor or high leakage, twin pregnancy or a history of PROM in the last pregnancy to establish the efficacy and safety of a novel combination of arginine, ascorbic acid, folic acid, glutamine, glutathione, thiamine, lactic acid bacillus spores, vitamin E acetate and pyridoxine.

METHODS

The study was a real-world prospective, questionnaire-based study to assess the efficacy and safety of the novel combination and the occurrence of adverse events in mothers diagnosed with PROM, PPROM, minor or high

Chairman and Head, Dept. of Obstetrics and Gynecology, Asian Institute of Medical Sciences, Faridabad, Haryana
Address for correspondence
Dr Anita Kant
Chairman and Head, Dept. of Obstetrics and Gynecology, Asian Institute of Medical Sciences, Faridabad, Haryana
E-mail: dranitakant@yahoo.com

leakage, twin pregnancy or a history of PROM in the last pregnancy. The data was collected anonymously. Formal written consent was obtained from the study participants after they were informed about the study, the usage of the medication for their condition, and the potential adverse effects. The responses were analyzed using a simple percentage calculation.

RESULTS

The study included 210 expecting mothers aged 21 to 41 years diagnosed with PROM, PPROM, minor or high leakage, twin pregnancy or a history of PROM in the last pregnancy. Most patients were diagnosed with PROM, minor leakage or at risk of PROM due to medical history (Fig. 1). Patients were treated as the doctor recommended. Most study participants

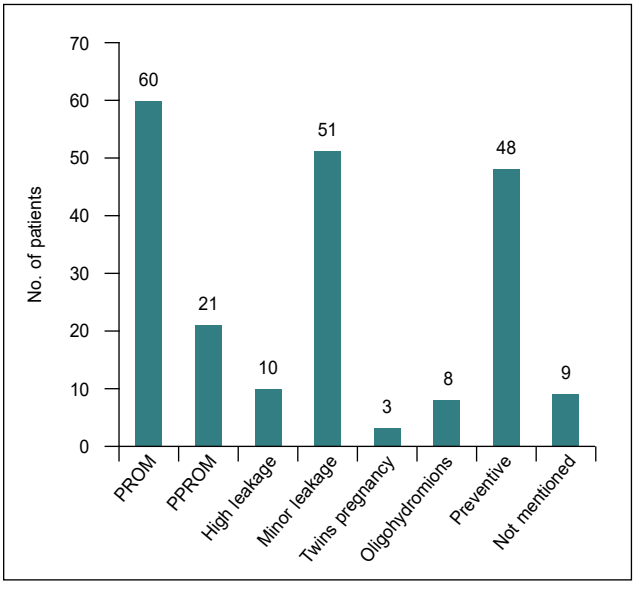

Figure 1. Diagnosis of participating patients.

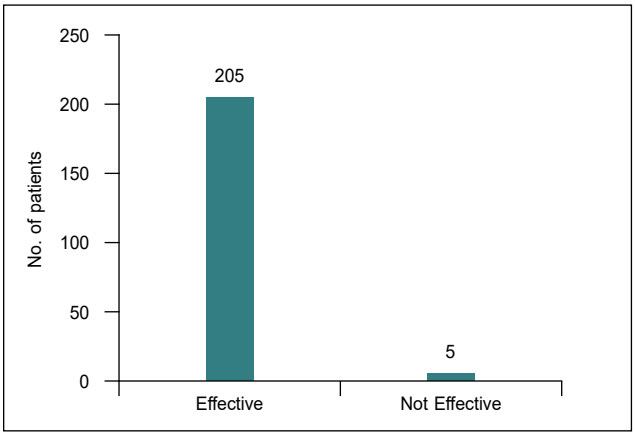

Figure 2. Effect of intervention of the novel combination in preventing and sealing ruptured fetal membranes.

(97%) found it effective in preventing leakage of amniotic fluid from ruptured fetal membranes and in prolonging the gestational age (Fig. 2). According to our survey, it was well tolerated by most patients. Only 3 subjects had adverse effects, although the prevention of leakage was effective. Clinicians found the novel combination of amino acids, vitamins and probiotics to be an excellent remedy for sealing the rupture of fetal membranes in PROM, PPROM and in the prevention of the same.

DISCUSSION

PROM/PPROM continues to be a global health challenge. Assisted by innate immunity, amnion epithelial cells appear vital in healing ruptured fetal membranes. Chorion is a multilayered cytotrophoblastic layer with collagen-rich connective tissue, and amnion comprises a single epithelial layer. The elasticity of membranes depends on chorion, and tensile strength depends on amnion. Increased levels of MMP, p53 and neutrophil elastase contribute to apoptosis. Increased apoptosis resulting in the breakdown of amniochorion has been reported in PROM.[5]

PROM is the result of a cascade of events involving MMP-9, TIMP1, cytokines and proapoptotic genes, which is initiated by several factors such as infection, genotoxic agents or some unknown etiology. In PROM, there is an increased expression and activation of MMP-2 and MMP-9 and a reduction of TIMP1. The imbalance between MMPs and TIMP1 results in extracellular matrix (ECM) degradation. The major apoptotic pathway of PROM is mediated by p53 and TNF-α. p53 can transactivate some MMP genes, resulting in the overexpression of MMPs. p53 triggers apoptosis by down-regulating Bcl-2 (antiapoptotic gene) and overexpressing the apoptotic BAX gene. This leads to apoptosis. p53 also induces MMP-2 expression. MMP-2 degrades type-IV collagen, which is the major structural component of chorioamnion.[6-8]

Arginine inhibits the Bax-induced cell apoptosis by reducing the amount of Bax mRNA expression. Hence, enhances cell proliferation and reduces apoptosis in human endometrial cells.[9] This is important for the prevention and healing of ruptured fetal membranes.

Amino acids are also important for the management of secondary infections. For example, arginine deficiency has been linked to an increased risk of secondary infections in sepsis.[10] Glutamine is an essential precursor for the synthesis of not only protein but also other molecules of enormous biological importance. Glutamine

improves TIMP1 protein production, thereby reducing the activity of MMP-2, MMP-9 and helping in the prevention and treatment of PROM. Hence, fetal and placental development depends on the abundance of glutamine.[10,11] Additionally, pregnant women with high levels of Lactobacillus show a relatively low risk of preterm birth.[3] The capacity of Lactobacilli to adhere and compete for adhesion sites in the vaginal epithelium and the capacity to produce antimicrobial compounds (hydrogen peroxide, lactic acid, bacteriocin-like substances) are important in the impairment of colonization by pathogens. It reduces infection and restores vaginal pH. Lactic acid can also inhibit the production of metalloprotease.[12] Dam et al and Gangwal et al studied the effect of a combination of arginine, glycine, cysteine, glutamate and vitamins along with Lactobacillus spores in PROM. Amino acids combinations were proved to have a definite role in PROM as it helps in the prolongation of gestational age by 3.21 ± 6.16 weeks and 3.87 ± 6.00 weeks (24-30 weeks), respectively.[4,5]

Poor folate status in mothers has also been linked to an increased risk of premature birth.[13] Direct activation of proMMP-2, MMP-9 by homocysteine is one of the established mechanisms involved in ECM deterioration.[14] It has been shown to induce apoptosis in endothelial cells. Folic acid supplementation can lower homocysteine levels and therefore may decrease the risk of apoptosis in endothelial cells.[15] This helps in the prevention and healing of ruptured fetal membranes.

Vitamins C is another important ingredient that modulates collagen metabolism and improves strength through increased helix formation. Vitamin C markedly stimulates collagen synthesis without affecting the synthesis of other proteins.[16]

Recent studies proved that vitamin C administration to women with a previous history of PPROM is efficient and safe in preventing such events in the current pregnancy. Another study proved that pretreatment with vitamins C and E prevent this damage in the amniotic epithelial layer.[17] Thiamine inhibits intracellular p53 activity. It also reduces the production of TNF-α and interleukin-6.[18,19]

Glutathione is an antioxidant that protects against fetal membrane damage and provides strength to the fetal membrane. Along with pyridoxine, it plays an important role in attenuating protective placental inflammatory and oxidative stress.[20] Glutathione prevents preterm parturition and fetal death by targeting macrophage-induced reactive oxygen species production in the myometrium.[21]

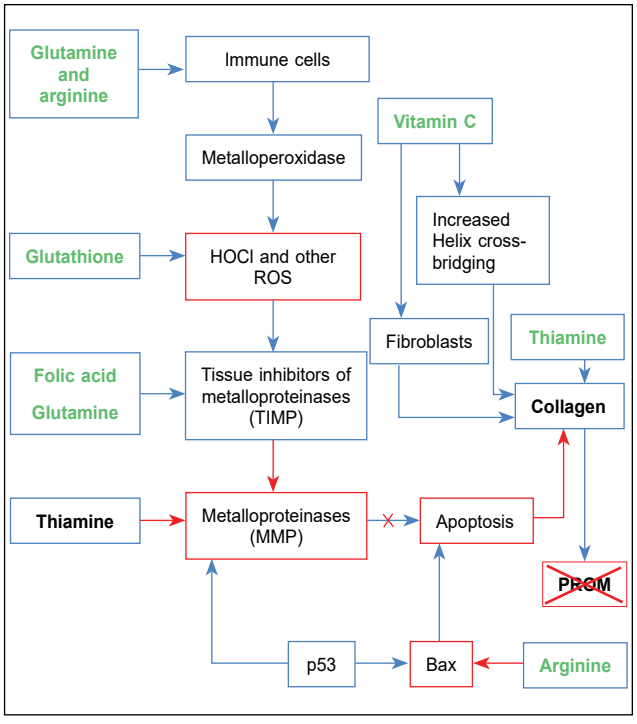

Figure 3. Role of the combination of amino acids and vitamins in PROM and PPROM.

HOCl = Hypochlorous acid; ROS = Reactive oxygen species.

The probable mechanism of action of the ingredients in membrane sealing has been depicted in Figure 3.

In our study, most participants had complained of PROM or minor leakage or a history of PROM in the previous pregnancy. Supplementation of the combination of arginine, ascorbic acid, folic acid, glutamine, glutathione, thiamine, lactic acid bacillus spores, vitamin E acetate, and pyridoxine helped in treating and preventing these conditions through membrane sealing and prolonging the term. Hence, supplementing the combination of these protective factors significantly increases beneficial effects in preventing and treating PROM/PPROM.

CONCLUSION

Based on our research, we propose that a novel combination of arginine, ascorbic acid, folic acid, glutamine, glutathione, thiamine, lactic acid bacillus spores, vitamin E acetate and pyridoxine is able to stop the leaking of amniotic fluid thereby can help prevent preterm labor in pregnancies.

It helps in the prolongation of gestational age. It is an oral medication, so it is simple to provide to the patient and hold up the promise of a healthy and safe pregnancy.

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CASE REPORT

A Lady with a Broken Heart

DEVENDRA SINGH BISHT*, KAMAL KISHORE†, MOHIT JAIDKA‡

ABSTRACT

Broken-heart syndrome (BHS) is an acute reversible myocardial injury of left or right ventricular myocardium in the absence of coronary occlusion. We, herein, discuss a case of a postmenopausal female presenting with angina equivalent with surface electrocardiogram (ECG) and echocardiography consistent for acute coronary syndrome. The patient was subsequently diagnosed and treated as BHS.

Keywords: Acute coronary syndrome, reversible cardiomyopathy, acute heart failure

Broken-heart syndrome (BHS) is an acute reversible condition of left or right ventricular myocardium usually preceded by a stressful trigger.[1] It was first described in Japan in 1990 and is also recognized by other names like stress-induced cardiomyopathy, Takotsubo (octopus pot) cardiomyopathy and apical ballooning syndrome. The prevalence is currently estimated at 1% to 2% of patients with suspected acute coronary syndrome.[2] BHS predominantly involves postmenopausal females and is commonly associated with emotional or physical stress.[3] Stress cardiomyopathy represents a form of neurocardiogenic myocardial stunning for which the exact pathophysiologic mechanism is unknown. But leading hypothesis suggests catecholamine excess and sympathetic nervous system hyperactivity resulting in regional microvascular dysfunction accompanied by cellular calcium overload in susceptible individuals.[4-8] Several diagnostic criteria have been proposed with the most commonly used one being the Mayo Clinic 2004 diagnostic criteria[3,9] that were modified in 2008. The revised criteria include:

- Transient hypokinesis, akinesis or dyskinesis of the left ventricular mid-segments with or without apical involvement; the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present.
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
- New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin levels.
- Absence of pheochromocytoma or myocarditis.

BHS is a self-limiting condition, usually with rapid resolution of symptoms and left ventricular dysfunction.[3] Therapy is largely supportive and tailored based on patient's presentation. Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers can be considered for treatment. Care should be taken to avoid QTc prolonging medications for their predisposition to malignant ventricular arrhythmia. Long-term prognosis is generally good but in-hospital mortality has been reported due to cardiogenic shock, left ventricular mechanical complications, malignant ventricular arrhythmia and systemic thromboembolism. Recurrences are common to the tune of 2% to 4% per year and up to 20% at 10 years, even after recovery of left ventricular functions.[3]

CASE REPORT

A 75-year-old diabetic female presented to the emergency department with complaints of acute onset shortness of breath and chest heaviness. She did not complain of any other abdominal or chest symptoms. Other than emotional frailty owing to social loneliness, her personal and family history were unremarkable. She was living with normal coronaries evaluated 4-year back for chest pain with ST-segment elevation on electrocardiogram (ECG). Follow-up ECG (Fig. 1A) and transthoracic echocardiography (TTE) over last few years were unremarkable. On general physical examination, patient was seen to be anxious. The heart

*Consultant Cardiologist, Mukat Hospital and Heart Institute, Chandigarh, India
†Consultant Cardiologist, Rama Superspeciality Hospital, Karnal, Haryana, India
‡Associate Consultant Cardiologist, Mukat Hospital and Heart Institute, Chandigarh, India
Address for correspondence
Dr Devendra Singh Bisht
Consultant Cardiologist, Mukat Hospital and Heart Institute, Chandigarh, India
E-mail: bisht2416@gmail.com

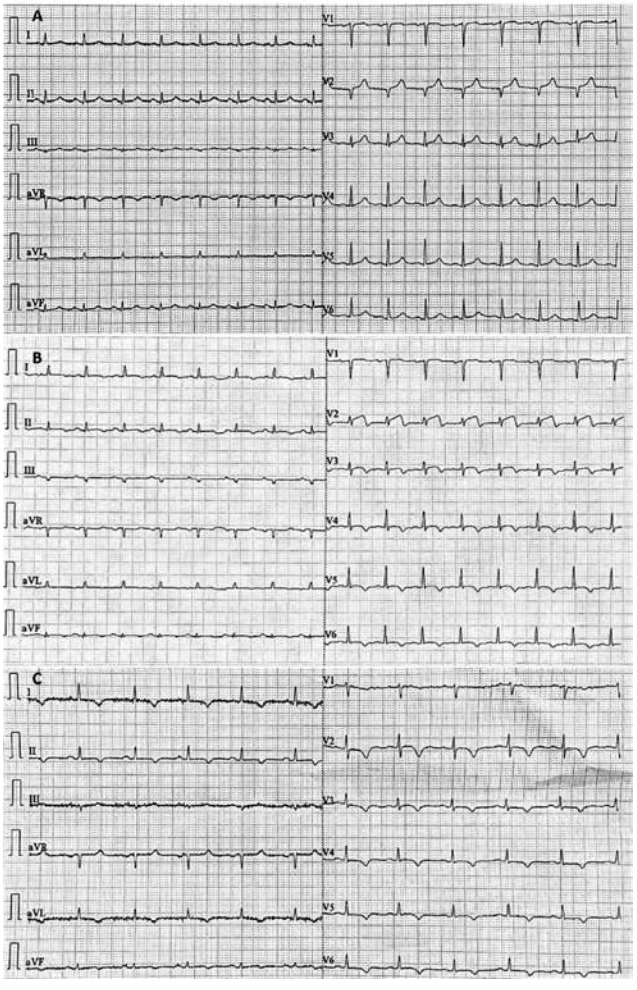

Figure 1. Serial ECGs demonstrating dynamic ST-T changes from before event (**A**); during event (**B**) and in 4 weeks follow-up period (**C**).

rhythm was regular with a rate of 108 beats/min; the blood pressure was 130/80 mmHg and respiration was thoraco-abdominal with a rate of 24 breaths/min. Findings from review of the systems, other than as reported above were normal. A 12-lead surface ECG showed sinus tachycardia and ST-segment coving with T-wave inversion in precordial and limb leads (Fig. 1B). Qualitative cardiac troponin T was negative and routine biochemical analysis including complete blood count, renal and liver function tests were unremarkable. TTE revealed severe left ventricular systolic dysfunction (ejection fraction about 35% by Simpson) with marked regional wall motion abnormalities in the mid anterior, mid-septal, mid inferior and apical segments of the left ventricle (Fig. 2A and 2B). The patient was immediately shifted to the catheterization laboratory, where coronary angiography was done. Angiography revealed normal coronary arteries with mild plaquing of major epicardial vessels (Fig. 3).

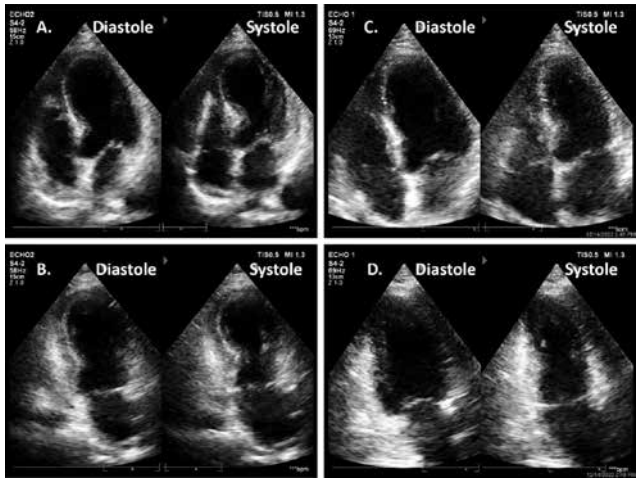

Figure 2. Echocardiogram in apical 4 chamber and apical 2 chamber views during acute event (**A & B**) showing apical akinesis and basal hyperkinesis leading to characteristic appearance of apical ballooning or Japanese Takotsubo (octopus pot) in systolic frame. Follow-up echocardiogram in same views after 4 weeks of follow-up (**C & D**) showing normalization of wall motion abnormalities.

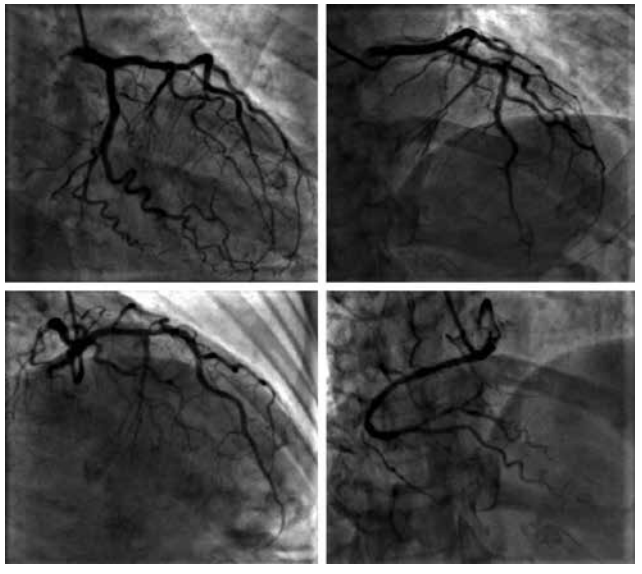

Figure 3. Coronary angiogram demonstrating normal epicardial coronary arteries.

The patient was treated with beta-blockers, ACE inhibitors, dual antiplatelets, statins, diuretics and antidepressants. She was discharged in a stable condition after 3 days without any complications. She was re-evaluated after 4 weeks. At the follow-up visit, all her symptoms had disappeared. ECG showed repolarization abnormalities in the form of T-wave inversion consistent for previous event (Fig. 1C). Echocardiography showed normalization of the left ventricular systolic function (ejection fraction about 60% by Simpson) with no residual wall motion abnormality (Fig. 2C and 2D).

DISCUSSION

Our patient was an elderly postmenopausal female, diagnosed with stress-induced cardiomyopathy or BHS after fulfilling Mayo Clinic diagnostic criteria. Retrospectively, her previous coronary event 4 years back, was likely the same event precipitated by extreme stress that went undiagnosed. As compared to acute coronary syndrome patients, the cardiac enzymes of BHS typically demonstrate mild elevation and return to baseline faster. Our patient did not have raised cardiac troponin despite marked ECG changes and significant wall abnormality in TTE.

Her cardiac functions normalized after both the events. BHS is a self-limiting condition, usually with rapid resolution of symptoms and ventricular dysfunction. The precise mechanism that cause this neurocardiogenic myocardial stunning are unknown but it has been postulated that catecholamine and hormones play important role in the pathogenesis; hence, it is also namedas Takotsubo endocrinopathy.[10]

CONCLUSION

BHS is an acute reversible cardiac disorder with a transient left or right ventricular wall motion abnormality. We should keep a high index of suspicion in postmenopausal women who present with acute coronary syndrome like symptoms after an intense emotional stress. The in-hospital mortality rate seems to be low, and there is a low risk for recurrence.

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BRIEF COMMUNICATION

Health Technology Use in Noncommunicable Disorders: Challenges and Opportunities in India

NITIN KAPOOR*, SUNEET KUMAR VERMA†, SUNIL KOTA‡

ABSTRACT

Health care in India is undergoing a rapid change from its historical focus on acute disease management to a focus more on chronic and continuous care-based model for noncommunicable disorders. Health technology could be a game changer as it has a potential to optimize costs and effectively manage such operations. IT solutions are likely to become an integral part of process management, patient care and the hospital management information system in future. This brief communication describes the key enablers and limitations of using health technology in chronic diseases in developing countries like India.

Keywords: Health care, IT solutions, game changer, continuous care-based model, digital health, smart technology

Technology is now embedded in many facets of daily life for large numbers of people across the world, and despite the fact that populations as a whole are increasingly tech-literate, the health sector has been hesitant in its approach to new technologies and inefficient in implementation of those with a strong evidence base. Health technologies can be powerful tools in supporting, expanding and enhancing all domains of health, including but not limited to: health care services, health surveillance, health education, research, prevention and patient treatment and management.[1]

In addition, the convergence of health care with upcoming technologies like cloud computing and wireless technologies will improve accessibility and meeting the challenge of skilled manpower shortage.[2] Several projects in India and other developing countries are already underway to assimilate health technology with existing health infrastructure.[3]

A recent study in rural India has shown that use of technology in the form of a mobile phone-based, nurse-facilitated clinical decision support system in primary care could improve the blood pressure and blood glucose control and has large potential to scale-up in resource-poor settings.

eHealth is defined by the World Health Organization (WHO) as use of information and communication technologies (ICT) for health, and includes the field of mHealth, which relates specifically to the medical or public health practices that are supported by mobile phones and other wireless devices. When member states of the WHO committed to work towards universal health coverage (UHC) in 2005, eHealth was made a priority in recognition of its "pivotal role" in achieving this aim and indeed WHO's Report on the third global survey on eHealth, published in 2016, asserts that "It has become increasingly clear that UHC cannot be achieved without the support of eHealth."[4]

ENABLERS AND KEY STAKE HOLDERS OF HEALTH TECHNOLOGY

The key attributes for developing a sustainable and scalable model for health technology include to first define the problem with careful consideration of appropriate future integration into relevant health policies (Fig. 1). This should be followed by an appropriate identification of the technology users and the setting in which it has to be applied. And last but not the least, to use a highly iterative technology design and development process that incorporates the perspective of the user and also addresses scalability right from its inception.[5] There are diverse benefits of utilizing health technology in the evaluation and management of chronic conditions. However, there

*Dept. of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, Tamil Nadu, India; Non Communicable Disease & Implementation Science Unit, Baker Heart and Diabetes Institute, Melbourne, Australia
†Sparsh Clinic, Peer Muchhalla, Zirakpur, India
‡Diabetes and Endocare Clinic, Berhampur, Odisha, India
Address for correspondence
Dr Nitin Kapoor
Professor of Endocrinology, Dept. of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore (TN) - 632004, India
E-mail: nitin.endocrine@gmail.com

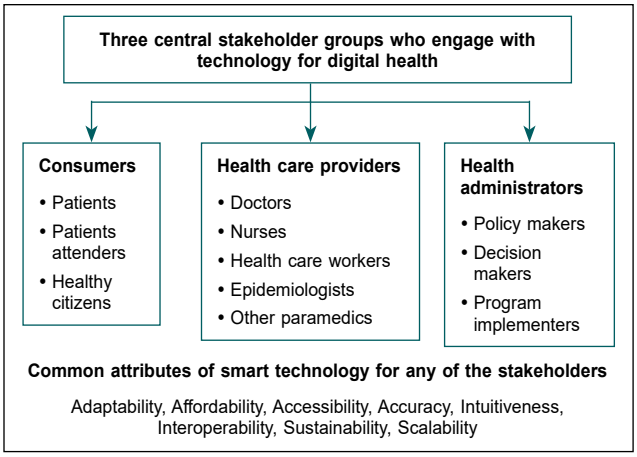

Figure 1. The key attributes for developing a successful program for health technology Obstacles for use of health technology in India.

are challenges that need to be addressed to ensure widespread and maximal utilization of technologies in health care delivery. A major concern raised by experts on these programs is ensuring availability of high-quality care to most individuals utilizing these support systems. In addition, the high cost that may be incurred in the development and dissemination of these technologies provides a challenge to health care institutions. More so in developing countries like India concerns regarding health literacy and poor electricity supply in remote areas were also raised in the forum.[6] Also, given the vast cultural and ethnic differences within the same country, it is important to tailor the use of technology to specific populations and settings.

CONCLUSION

The use of digital technologies to support the achievement of health objectives has been a 'hot topic' in public health for well over a decade. In that period, there have been rapid advances in computing and mobile technologies, matched by ever increasing access to these technologies and expansion of wireless and mobile networks. Although issues of equity cannot be ignored in cases where interventions require access to personal devices, other technologies have the potential to improve the equitable provision of health services to individuals and communities who are otherwise outside the existing health care services.

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India Launches the World's First Intranasal COVID Vaccine on its Republic Day

iNCOVACC, the world's first intranasal COVID vaccine was officially launched on 26th January by the Union Health Minister. The vaccine will be first available for administration in private hospitals. The cost in the private sector is Rs. 800 and Rs. 325 in the government hospitals.

The vaccine is approved for both primary vaccination (two doses) and heterologous booster dose for adults. iNCOVACC has been developed by Bharat Biotech, in collaboration with the Biotechnology Industry Research Assistance Council (BIRAC), under the Department of Biotechnology, Ministry of Science and Technology… (*Source: PTI, Jan. 26, 2023*)

In Dysmenorrhoea

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Mefenamic Acid 250 mg. + Dicyclomine HCl 10 mg. **Tablets**

For **Women**

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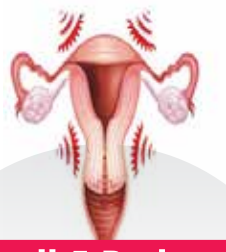

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- **Histamine** ✔ (Dicyclomine)
- **Bradykinin** ✔ (Mefenamic acid, Dicyclomine)

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Ref: 1. Rao KA, et.al. IJCP. 2022; 32: NLRP-3: NOD-like Receptor Protein 3
IL-1β: Interleukin 1 beta *Antispasmodic-Analgesic IMS November 2022

BLUE CROSS

CLINICAL PRACTICE GUIDELINE

Unraveling Prostaglandin and NLRP3 Inflammasome-mediated Pathways of Primary Dysmenorrhea and the Role of Mefenamic Acid and Its Combinations

A CONSENSUS STATEMENT

ANITA KANT, JAYAM KANNAN, SUNITA CHANDRA, CHANDRAVATI, BHARTI KALRA, HELEN MARY, PRABHU KASTURE*, BHARATI RAJSHEKHAR, ANSHU JINDAL, AMUTHAMBIGAI, SACHIN DALAL, REEMA JAIN, SUJATA KULKARNI, SUREKHA VINAY, UMMAMAHESHWAR SINDUR, PRAGYA OJHA, RENU CHAKRAVARTY, HARINI, ARCHANA MAYEKAR, JAYANTA KUMAR GUPTA, RUCHIKA GARG, TUSHAR PALVE, NITHYA VAIDYA, NUPUR CHANDAN, SONAM KUMARI, VAISHALI CHAUDHARY

ABSTRACT

Painful menstrual cramps during or around the time of the monthly cycle are known as dysmenorrhea. The estimated global prevalence in women of reproductive age ranges from 45% to 95%. It has a significant negative impact on regular activities and productivity at work. However, despite the severe consequences on quality of life, primary dysmenorrhea (PD) is underdiagnosed. Dysmenorrhea has complex pathogenesis. It involves the release of prostaglandins and activation of the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome and also includes the involvement of other mediators such as bradykinin, histamine and acetylcholine. Even though nonsteroidal anti-inflammatory drugs (NSAIDs) remain the most common type of pain medication, the question of which one should be the most preferred is still open to debate. The current review examines the existing evidence for the pathogenesis of PD and makes evidence based and clinical experience based recommendations for the use of mefenamic acid and its combination in the treatment of dysmenorrhea. Mefenamic acid alleviates PD by inhibiting endometrial prostaglandin formation, restoring normal uterine activity, and reducing the inflammatory response by inhibiting the NLRP3 inflammasome and reducing the release of cytokines such as interleukin (IL)-1β. It is also known to have bradykinin antagonist activity. Dicyclomine has a dual action of blocking the muscarinic action of acetylcholine in postganglionic parasympathetic effect or regions and acting directly on uterine smooth muscle by blocking bradykinin and histamine receptors to relieve spasms. According to the experts, mefenamic acid and dicyclomine act synergistically by acting on the different pathways of dysmenorrhea by blocking multifactorial agents attributed to the cause of dysmenorrhea. Hence, the combination of mefenamic acid and dicyclomine should be the preferred treatment option for dysmenorrhea.

Keywords: Dysmenorrhea, spasmolytic, mefenamic acid, dicyclomine

Dysmenorrhea is described as spasms in the lower abdomen that spreads to the thighs or lower spine, with mild to severe intensity pain occurring during the menstrual cycle. The pain is also associated with other symptoms such as vomiting, headache, back pain, diarrhea and fatigue.[1]

Estimated at a global prevalence of 45% to 95% in women of reproductive age,[2] studies from India have reported that dysmenorrhea prevalence ranges from 50% to 87.8%.[3]

In the United States, an estimated $2 billion is lost every year due to missed work and productivity.[4] The condition leaves a considerable impact on the quality of life, daily activity, work-related productivity and academic performance.[5] However, despite the significant effects on quality of life, not only is the prevalence of primary dysmenorrhea (PD) underestimated, but additionally, most women do not frequently seek

*Deputy Director-Medical Services and Pharmacovigilance, Blue Cross Laboratoires Pvt Ltd., Mumbai, Maharashtra
Address for correspondence
Dr Prabhu Kasture
Deputy Director-Medical Services and Pharmacovigilance, Blue Cross Laboratoires Pvt Ltd., Peninsula Corporate Park, Peninsula Chambers,
GK Marg, Lower Parel, Mumbai - 400 013, Maharashtra
E-mail: prabhu.k@bluecrosslabs.com

medical treatment as the common perception associated with dysmenorrheic pain is that 'it comes as a part of menstruation'.[6]

Despite being a common and recurrent problem, dysmenorrhea remains undiagnosed, unattended or inadequately treated due to multiple factors attributable to the several myths and misunderstandings prevailing in society as low awareness of this particular issue, poor health-seeking behavior accepting this pain as normal, leading to the assumption that treatment is neither required nor available. Even in the clinics, this problem is not proactively inquired about, and there are no uniform standards regarding pharmacotherapy in treating dysmenorrhea.

Menstruation is known to be a self-inflammatory process bringing about the sloughing of the endometrium functional lining at the end of the routine fertility cycles. In the absence of conception, the endometrium undergoes significant changes, including the release of hormones and decidualization of cells that play a key role in local inflammation within the endometrium leading up to PD. While the role of prostaglandin is established in triggering the symptoms of PD, the role of inflammation has a strong effect on the pathological process of PD.[7] The complex pathophysiology of dysmenorrhea having multifactorial components needs to be addressed while choosing treatment options. Though nonsteroidal anti-inflammatory drugs (NSAIDs) remain the mainstay in the management of pain, the question of which one should be the most preferred continues to baffle clinicians. The role of spasmolytic cannot be ignored in addressing the complex pathophysiology of dysmenorrhea. It has to be chosen wisely based upon its multiple actions on the various attributable factors and synergize with the preferred NSAID to act comprehensively on all the pathophysiological factors of dysmenorrhea. Through the expert group deliberations, we have aimed to develop a consensus about the use of mefenamic acid and its combination with dicyclomine in dysmenorrhea in the light of its additional and unique mode of action on these various pathogenetic pathways of dysmenorrhea.

MATERIAL AND METHODS

The present review examines the existing evidence on the pathogenesis of PD and presents evidence based and clinical experience based recommendations on the use of mefenamic acid and mefenamic acid + dicyclomine in the treatment of dysmenorrhea.

To generate the highest possible evidence base for the use of mefenamic acid and dicyclomine in dysmenorrhea, a comprehensive review of the literature was conducted on PubMed, Cochrane database and Google Scholar. Existing guidelines, meta-analysis, systematic reviews, randomized controlled trials (RCTs), non-RCT studies and experimental studies relating to the use of mefenamic acid, dicyclomine and the pathogenesis of dysmenorrhea were searched, scanned, selected and reviewed. Only articles in English and dysmenorrhea, experimental, clinical studies or reviews on mefenamic acid and dicyclomine were included. Articles in other foreign languages or those focusing on the treatment of secondary dysmenorrhea or surgery in PD were excluded from the selection. Recommendations for the treatment of dysmenorrhea are based on the available evidence and preliminary discussions among expert groups.

A panel of 25 gynecologists from across the country was created at the initiation of the study. Evidence synthesized was documented and shared with all the members of the expert panel at least a week before the meeting, which formed the evidence base for the discussions. The discussion undertook in two separate meetings conducted on April 9, 2022 and April 23, 2022, via virtual meeting. The recommendations and deliberations of the members were recorded for further analysis, refinement and inclusion in the consensus.

The recommendation formulated by the expert panel has been included in this article. If there was little or no evidence, the panel relied on logical empiricism and consensus to generate recommendations about the rational use of mefenamic acid or its combination with dicyclomine in the treatment of dysmenorrhea.

The Impact of Dysmenorrhea

Dysmenorrhea often has a debilitating effect on a woman's life, which becomes more concerning owing to its recurring nature. A study showed that almost 50% of the participants experienced a disruption of their daily activities, studying abilities and working productivity. Apart from absenteeism, the loss in annual productivity due to presenteeism was reported to be 7 times more than the annual productivity due to absenteeism. Further, the anticipation of severe dysmenorrhea in the upcoming month is another cause of mental stress and unproductivity in women.[5]

Despite being one of the most common recurring gynecological problems, most experts agreed that there is a lack of general awareness about dysmenorrhea, due to which most of the time it remains an underdiagnosed and undertreated condition. The problem frequently remains medically unaddressed as women and young girls do not get accurate and sufficient information, attempts at

self-management, undervaluing the condition, and a feeling of embarrassment in talking about the problem.[5]

Most of the experts were of the view that there is an urgent need to enhance awareness about the condition highlighting the reasons to adolescent girls and women as to why they should seek treatment for dysmenorrhea. Several experts believed dysmenorrhea should be included as the extension topic of menstruation.

The Pathways Involved in Primary Dysmenorrhea

It is a well-established fact that dysmenorrhea is an intricate meshwork of various pathogenetic mechanisms, including behavioral and psychological factors. It is an inflammatory event driven by prostaglandin, nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome and several other chemokines and pro-inflammatory cytokines.

Prostaglandins in Dysmenorrhea

Menstruation is a self-driven inflammatory process, where the release of prostaglandins is cited to be the trigger for causing PD.[5]

Prostaglandins are key mediators of underlying inflammation and essential for increasing abnormal uterine activity during menstruation. It is evident from the literature that women with PD have higher levels (2-7 times) of prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2). PGF2α in dysmenorrhea brings about vasoconstriction of the uterine wall and contraction of the myometrium, while PGE2 causes inflammation and contraction of the myometrium, reduced blood flow leading to uterine ischemia.[7,8]

NLRP3 Inflammasome

The NLRP3 inflammasome components immunolocalize to decidualized endometrial stromal cells right before menstruation.[9]

Activation of NLRP3 inflammasome helps activate the caspase-1, which in turn cleaves the pro-interleukin-1β and pro-interleukin-18 to active IL-1β and IL-18. Thus, before menstruation, the release of these pro-inflammatory cytokines along with leukocyte influx up-regulates the inflammatory response during menstruation, and their levels are reported to be present in high quantities in women with dysmenorrhea.[1]

Hence, curbing the activation and expression of NLRP3 inflammasome becomes an important approach to tackling dysmenorrhea.[10] PGE2, including its receptors, also regulates the production of inflammatory cytokines such as IL-1β, IL-6 and monocyte chemotactic protein-1, inducing a vicious cycle.[5]

Others Mediators in Dysmenorrhea

Histamine, bradykinin and acetylcholine are considered to be the significant factors for causing dysmenorrhea by increasing uterine contractility, which leads to ischemia and pain. Additionally, bradykinin increases the release of prostaglandins and also hypersensitizes the pain fibers.[5]

Mefenamic Acid

Mode of action

Mefenamic acid relieves dysmenorrhea via its multiple modes of action. It has a dual action of inhibiting prostaglandin synthesis and blocking the E-type prostanoid receptors. Mefenamic acid possesses the ability to inhibit pre-existing prostaglandin, which is the reason behind its faster onset of action.[5]

Mefenamic acid acts as an effective and selective inhibitor of the NLRP3 inflammasome. It blocks the channels viz. volume-regulated anion channel (VRAC) and transient receptor potential melastatin 2 channel (TRPM2), thereby reducing the cellular chloride efflux and calcium influx, respectively, which in turn blocks the activation of NLRP3 inflammasome. Since the secretion of the pro-inflammatory cytokine IL-1β is mediated by the activation of NLRP3, its inhibition by mefenamic acid attenuates the levels of IL-1β and alleviates inflammation. Mefenamic acid is a bradykinin antagonist, thus possessing an extended pathway of pain relief. It can inhibit the raised uterine contractility triggered by prostaglandin-endoperoxide analogs.[5]

Besides reduction in pain, it also reduces menstrual blood loss by improving platelet aggregation and degranulation through increased vasoconstriction.

Safety and efficacy

Mefenamic acid exhibited a superior efficacy when compared with other NSAIDs like ibuprofen, naproxen, indomethacin and paracetamol.[5,11]

It is usually well-tolerated, but common side effects may include headache, dizziness, nausea, diarrhea, abdominal discomfort, heartburn and hypersensitivity reactions.[5]

Mefenamic acid combination with dicyclomine

Mefenamic acid relieves PD by inhibiting endometrial prostaglandin formation, restoring normal uterine activity, and reducing inflammatory response by inhibiting the NLRP3 inflammasome and decreasing the release of cytokines such as IL-1β.[5] It is also known to possess bradykinin antagonism action.[7]

Expert's Comments

All the experts unanimously recommended the use of an NSAID that may have a direct analgesic effect via inhibition of prostaglandin synthesis and reduction of blood volume of the menstrual flow. Mefenamic acid is preferred by all of them due to superior clinical efficacy as observed during their clinical practice and additionally reducing the blood volume loss due to the excess menstrual flow.

Further, the experts opined that as inflammation underpins dysmenorrhea, hence treatment approaches to target underlying inflammatory process dysmenorrhea will be useful in ameliorating or reducing menstrual pain and other associated inflammatory symptoms. The rather unexplored role of NLRP3 inflammasome activation in causing dysmenorrhea symptoms piqued the interest of the experts and they were of the view that a drug that can inhibit the activation of NLRP3 inflammasome in uterine tissues and the inflammatory processes involved in dysmenorrhea will be an important asset to the armamentarium of dysmenorrhea treatment.

The novel information on NLRP3 inflammation and its role in dysmenorrhea and the inhibitory action of mefenamic acid are a value addition and should be correlated clinically.

Considering the multiple mechanisms and pathways involved in causing dysmenorrhea, experts also suggested using synergistic combination of drugs that can effectively act on different pathways thereby effectively mitigating the symptoms associated with dysmenorrhea.

Dicyclomine has a dual action of blocking the muscarinic action of acetylcholine in postganglionic parasympathetic effector regions and acts directly on the uterine smooth muscles by blocking the bradykinin and histamine receptors to offer relief from spasmolytic pain.[5]

One of the studies found that the combination of mefenamic acid and dicyclomine was well-tolerated and more effective than dicyclomine alone in moderate to severe cases of dysmenorrhea.[5]

Studies have demonstrated that mefenamic acid and dicyclomine show synergistic activity (Fig. 1) in patients with dysmenorrhea. The combination is not only highly effective in treating spasmodic dysmenorrhea but also well-tolerated.

Most experts said that they have used mefenamic acid alone or in combination with dicyclomine, which is

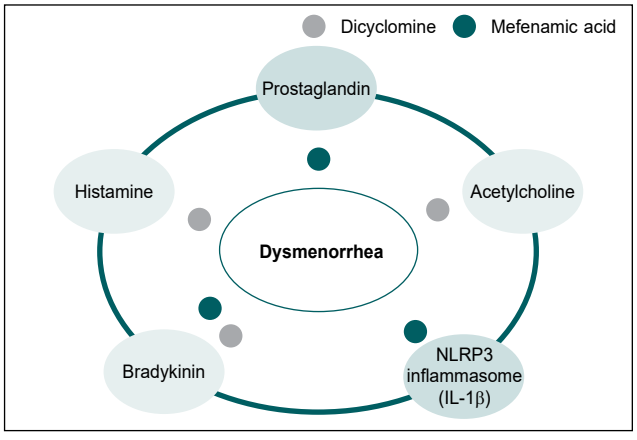

Figure 1. Synergistic action of dicyclomine and mefenamic acid on the various pathways of dysmenorrhea.

Expert's Comments

We know that women with PD experience four different uterine contraction-related issues that are increased uterine resting tone, enhanced active pressure, increased number of contractions and dysrhythmic uterine activity.

So, a combined NSAID + antispasmodic, such as mefenamic acid + dicyclomine will be beneficial in treatment of dysmenorrhea.

Mefenamic acid and dicyclomine exerts synergism by acting on the various pathways of dysmenorrhea thereby blocking the multifactorial agents as attributable to the causation of dysmenorrhea and should be the preferred choice of treatment in dysmenorrhea.

While discussing other combinations with mefenamic acid including drotaverine and camylofin, the experts were of the view that these drugs did not lead to any statistically significant pain relief when compared with the combination of dicyclomine and mefenamic acid.

In view of the experts, paracetamol and/or its combination were not preferred by them due to its weak analgesic and no anti-inflammatory action. Moreover, the dosage for analgesia would be higher up to 1 g per dose, which may then be associated with more adverse effects especially hepatic injury.

effective in alleviating the symptoms of dysmenorrhea. All the experts echoed similar recommendations and clinical practice experiences with mefenamic or mefenamic acid with dicyclomine to be the first choice of treatment depending upon the individual patient's symptoms. They had experienced positive results/outcomes with the use of the mefenamic acid and dicyclomine combination, and none of them ever

required or felt the need to use any other alternative for treating pain and other associated symptoms of dysmenorrhea.

RECOMMENDATIONS

- Women need to be in the optimum physiological and psychological conditions, and hence it becomes very important for women to address the menstrual burden and provide effective treatment. Measures such as providing educational literature, posters, and digital platforms with necessary information should be adopted and used by all gynecologists/clinicians to raise awareness about dysmenorrhea. To promote awareness about dysmenorrhea, school based and community-based initiatives can be undertaken by gynecologists/clinicians supported by NGOs, CSR functionaries of corporates, other professional bodies and community service groups. It is important to raise awareness amongst all the community members and health care professionals alike.
- The pathophysiology of dysmenorrhea is complex and multifactorial. Several pathogenetic and inflammatory mechanisms are at work in causing pain and other symptoms of PD. Prostaglandin release triggers the PD, and recent evidence has also implicated the NLRP3 activation leading to an increase in the release of pro-inflammatory cytokines playing a primary role in the underlying pathogenesis of dysmenorrhea. Apart from prostaglandins, other mediators, including bradykinin, histamine, acetylcholine, etc., also play an important role in causing PD.

  In patients with dysmenorrhea, paracetamol is not effective because of its weak analgesic and no anti-inflammatory actions. It has dose-dependent analgesic action on the prostaglandins, and since multiple factors are attributed to dysmenorrheic pain, it doesn't give complete relief.
- High dose paracetamol (1000 mg) has analgesic action for adults with mild to moderate acute pain, but 500 mg is sub-therapeutic for this action. It does not have any NLRP3 inhibitory action and, therefore, may not be suitable to alleviate the complex inflammatory process of dysmenorrhea. Thus, 500 mg dosage is an underdose and has no action on the complex pathophysiology of dysmenorrhea.
- The additional NLRP3 inflammasome inhibitory action of mefenamic acid gives an edge and makes it an ideal choice in the treatment of dysmenorrhea marked with dysregulated NLRP3 inflammasome.
- Mefenamic acid is recommended as the first-choice drug in the treatment of dysmenorrhea. It can be given in a dosage of 500 mg twice or thrice a day, based on the patient's requirement. It also provides the additional advantage of reducing the bleeding in associated cases of menorrhagia.
- In the case of adolescent patients, 250 mg thrice daily or 25 mg/kg/day of mefenamic acid in three divided doses is the recommended dosage.
- In case of inadequate pain relief, as may occur in moderate to severe cases, the combination of dicyclomine + mefenamic acid is recommended.
- The suggested dosage of the combination for adolescent and adult patients is 250/10 mg and 500 mg/20 mg, respectively. Adolescents with a weight of ≥60 kg can be administered the adult dosage.

Key Highlights

- Lack of awareness about dysmenorrhea and unmet need for social and emotional support; raises the need for spreading awareness amongst the community and health care professionals.
- Dysmenorrhea has a complex pathogenesis, involving release of prostaglandins, activation of NLRP3 inflammasome, and involvement of other mediators-bradykinin, histamine and acetylcholine.
- NSAIDs remain the mainstay in the management of dysmenorrhea and mefenamic acid is the most preferred choice.
- An ideal treatment would act on the different pathways causing dysmenorrheic pain and other associated symptoms.
- The combination of mefenamic acid and dicyclomine is the most preferred fixed-dose drug combinations (FDCs) because of its actions on the various pathways of dysmenorrhea and its synergism.
- Paracetamol is not effective as it has a weak analgesic effect and no anti-inflammatory actions.

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Disclosure

The authors report no conflicts of interest in this work.

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Contributors List	
Anita Kant	Dept. of Obstetrics and Gynecology, Asian Institute of Medical Sciences, Faridabad, Haryana
Jayam Kannan	Dept. of Obstetrics and Gynecology, Garbba Rakshambigai Fertility Centre, Chennai, Tamil Nadu
Sunita Chandra	Dept. of Obstetrics and Gynecology, Rajendra Nagar Hospital & IVF Center and Morpheus Lucknow Fertility Center, Lucknow, Uttar Pradesh
Chandravati	Dept. of Obstetrics and Gynecology, Krishna Medical Centre, Lucknow, Uttar Pradesh
Bharti Kalra	Dept. of Obstetrics and Gynecology, Bharti Hospital, Karnal, Haryana
Helen Mary	Dept. of Obstetrics and Gynecology, St. John's Medical College Hospital, Bengaluru, Karnataka
Prabhu Kasture	Deputy Director-Medical Services and Pharmacovigilance, Blue Cross Laboratoires Pvt Ltd., Mumbai, Maharashtra
Bharati Rajshekhar	Dept. of Obstetrics and Gynecology, Vaatsalya Hospital, Hassan, Karnataka
Anshu Jindal	Dept. of Obstetrics and Gynecology, IVF Specialist, Jindal Hospital and Fertility Center, Meerut, Uttar Pradesh
Amuthambigai	Dept. of Obstetrics and Gynecology, Uma Hospital, Tindivanam, Tamil Nadu
Sachin Dalal	Dept. of Obstetrics and Gynecology, IVF Specialist, Madhu Hospital and Embrion IVF & Fortis Hospital, Mumbai, Maharashtra
Reema Jain	Dept. of Obstetrics and Gynecology, Laparoscopic Surgeon and Infertility Specialist, Vaishnavi Nursing Home, Gurugram, Haryana
Sujata Kulkarni	Dept. of Obstetrics and Gynecology, Seeta Nursing Home, Nashik, Maharashtra
Surekha Vinay	Dept. of Obstetrics and Gynecology, Infertility Specialist and Laproscopic Surgeon, Gipson Clinic, Kurnool, Andhra Pradesh
Ummamaheshwar Sindur	Dept. of Obstetrics and Gynecology, Laparoscopic Surgeon, Sindur Hospital, Vijayapura, Karnataka
Pragya Ojha	Dept. of Obstetrics and Gynecology, VAMA - Centre for Women Health, Varanasi, Uttar Pradesh
Renu Chakravarty	Dept. of Obstetrics and Gynecology, Chakravarty Nursing Home, Panchkula, Haryana
Harini	Dept. of Obstetrics and Gynecology, Chikkaballapur Institute of Medical Sciences, Karnataka
Archana Mayekar	Dept. of Obstetrics and Gynecology, VN Desai Municipal General Hospital, Mumbai, Maharashtra
Jayanta Kumar Gupta	Dept. of Obstetrics and Gynecology, Apollo Multispecialty Hospitals, Kolkata, West Bengal
Ruchika Garg	Dept. of Obstetrics and Gynecology, Garg Clinic, Lucknow, Uttar Pradesh
Tushar Palve	Dept. of Obstetrics and Gynecology, Cama and Albless Hospital, Mumbai, Maharashtra
Nithya Vaidya	Dept. of Obstetrics and Gynecology, Yashada Nursing Home and Lifewave Hospital, Mumbai, Maharashtra
Nupur Chandan	Dept. of Obstetrics and Gynecology, Surya Clinic, Dhanbad, Jharkhand
Sonam Kumari	Infertility Consultant, Aveta Test Tube Baby Centre, Jharkhand
Vaishali Chaudhary	Dept. of Obstetrics and Gynecology, Siddhivinayak Hospital, Jalgaon, Maharashtra

The Patient was not Getting Cured. Can this be Termed as Medical Negligence?

No doctor can give 100% guarantee about the treatment or surgery. The only assurance which a doctor can give or can be understood to have given by implication is that he is possessed of the requisite skill in that branch of profession which he is practicing and while undertaking the performance of the task entrusted to him he would be exercising his skill with reasonable competence.

The Hon'ble Apex Court in various judgments, has duly held that no guarantee is given by any doctor or surgeon that the patient would be cured.

1. In the matter titled as **"P. B. Desai versus State of Maharashtra, AIR 2014 SC 795**, the Hon'ble Apex Court has held that:

   "It is not necessary for us to divulge this theoretical approach to the doctor-patient relationship, as that may be based on model foundation. Fact remains that when a physician agrees to attend a patient, there is an unwritten contract between the two. The patient entrusts himself to the doctor and that doctor agrees to do his best, at all times, for the patient. Such doctor-patient contract is almost always an implied contract, except when written informed consent is obtained. While a doctor cannot be forced to treat any person, he/she has certain responsibilities for those whom he/she accepts as patients. Some of these responsibilities may be recapitulated, in brief:

   a. to continue to treat, except under certain circumstances when doctor can abandon his patient;

   b. to take reasonable care of his patient;

   c. to exhibit reasonable skill: The degree of skill a doctor undertakes is the average degree of skill possessed by his professional brethren of the same standing as himself. The best form of treatment may differ when different choices are available. There is an implied contract between the doctor and patient where the patient is told, in effect, "Medicine is not an exact science. I shall use my experience and best judgment and you take the risk that I may be wrong. I guarantee nothing."

   d. Not to undertake any procedure beyond his control: This depends on his qualifications, special training and experience. The doctor must always ensure that he is reasonably skilled before undertaking any special procedure/treating a complicated case.

   e. Professional secrets: A doctor is under a moral and legal obligation not to divulge the information/knowledge which he comes to learn in confidence from his patient and such a communication is privileged communication."

2. In the matter **Malay Kumar Ganguly vs. Sukumar Mukherjee & Ors. AIR 2010 SC 1162, the Hon'ble Supreme Court of India** has held that:

   "INDIVIDUAL LIABILITY OF THE DOCTORS There cannot be, however, by any doubt or dispute that for establishing medical negligence or deficiency in service, the courts would determine the following:

   i. No guarantee is given by any doctor or surgeon that the patient would be cured.

   ii. The doctor, however, must undertake a fair, reasonable and competent degree of skill, which may not be the highest skill.

   iii. Adoption of one of the modes of treatment, if there are many, and treating the patient with due care and caution would not constitute any negligence.

   iv. Failure to act in accordance with the standard, reasonable, competent medical means at the time would not constitute a negligence. However, a medical practitioner must exercise the reasonable degree of care and skill and knowledge which he possesses. Failure to use due skill in diagnosis with the result that wrong treatment is given would be negligence.

   v. In a complicated case, the Court would be slow in contributing negligence on the part of the doctor, if he is performing his duties to be best of his ability. Bearing in mind the aforementioned principles, the individual liability of the doctors and hospital must be judged."

3. In the landmark judgment of **Jacob Mathew Petitioner v. State of Punjab & Anr. 2005 (3) CPR 70 (SC) the Hon'ble Supreme Court** has held that:

   "Para 28: No sensible professional would intentionally commit an act or omission which would result in loss or

injury to the patient as the professional reputation of the person is at stake. A single failure may cost him dear in his career. Even in civil jurisdiction, the rule of res ipsa loquitur is not of universal application and has to be applied with extreme care and caution to the cases of professional negligence and in particular that of the doctors. Else it would be counterproductive.

Simply because a patient has not favorably responded to a treatment given by a physician or a surgery has failed, the doctor cannot be held liable per se by applying the doctrine of res ipsa loquitur."

4. In the matter titled as **"Martin F. D'Souza versus Mohd. Ishfaq, 2009 (3) SCC 1" the Hon'ble Supreme Court** has held that:

   "*Para 124: It must be remembered that sometimes despite their best efforts the treatment of a doctor fails. For instance, sometimes despite the best effort of a surgeon, the patient dies. That does not mean that the doctor or the surgeon must be held to be guilty of medical negligence, unless there is some strong evidence to suggest that he is.*"

5. In the matter titled as **"Lok Nayak Hospital versus Prema, RFA No. 56/2006" the Hon'ble High Court of Delhi vide judgment dated 06.08.2018** has held that:

   "*8. Firstly, it is to be noted that the only allegation of negligence alleged by the respondent/plaintiff against the appellant/defendant is that the tubectomy/ sterilization operation failed.* ***Since medically there is never a 100% chance of success in sterilization operations, the mere fact that the operation was not successful, that by itself cannot be a reason to hold the appellant/defendant and its doctors guilty of negligence****. This aspect is no longer res integra and is so held by a Division Bench of this Court in the case of Smt. Madhubala Vs. Govt. of NCT of Delhi, 118 (2005) DLT 515 (DB).*"

■■■■

Hearing Loss and Dementia

Older adults with moderate to severe hearing loss are at risk of developing dementia, according to a study published online January 10 in the *Journal of the American Medical Association*.[1,2] Persons using hearing aids had lower risk of dementia.

In this study, Huang et al from the Cochlear Center for Hearing and Public Health at Johns Hopkins Bloomberg School of Public Health investigated the association of hearing loss and use of hearing aids with dementia among 2,413 participants selected from the ongoing National Health and Aging Trends Study (NHATS) database. The study subjects were aged ≥60 years and nearly half were older than 80 years. Information was collected from the participants via interviews and at-home testing using a portable audiometer. One third of the subjects (33.4%) had normal hearing, 36.7% had mild hearing loss, while nearly 30% had moderate to severe loss. Participants with moderate to severe hearing loss were more likely to be older, male and less educated.

The overall prevalence of dementia in the study was 10.2%. Data analysis showed a clear link between dementia and hearing loss, which increased as the severity of hearing impairment increased. Among persons with no hearing impairment, the prevalence of dementia was 6.1%. Among patients with mild hearing loss, the prevalence was ~9%. But among those with moderate to severe hearing loss, the prevalence was 16.5%. Compared to those with normal hearing, 853 participants with moderate to severe hearing loss had 61% higher risk of developing dementia with prevalence ratio 1.61. However in this group, the use of hearing aids reduced dementia risk by 32% (prevalence ratio 0.68).

These findings call for public health policy makers to improve access to screening for hearing impairment and also availability of hearing aids.

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HCFI Dr KK Aggarwal Research Fund

HCFI Round Table Environment Expert Zoom Meeting on "Challenges in Municipal Waste Management: Technological Interventions"

January 8, 2023 (Sunday 12 noon – 1 pm)

- The gap between waste generation and its scientific disposal is increasing leading to land, air and water pollution.
- Municipal solid waste (MSW) was not a problem in the past in India. It is a recent problem and is man-made.
- It is one of the most neglected subject in municipalities.
- The Technological Development Board under the Ministry of Science and Technology has initiated a program on waste management technologies, which is aligned with Swachh Bharat Mission Urban 2.0 aiming towards garbage-free cities.
- The program encompasses a variety of interventions in waste generation prevention, characterization and monitoring, treatment, handling reuse and ultimately residual disposal of solid wastes in a scientific manner.
- Lot of research is going on in this subject. The time has come for smart solid waste management. The routine practices are no longer sufficient for proper waste management.
- Waste to energy generation is the most innovative method in waste management. Smart bins, robotic recyclers, robotic trash cans are some other innovations in waste technology.
- MSW management starts from households with segregation of waste at source followed by collection, transport to the right place for processing, resource recovery and finally disposal.
- The biggest challenge in MSW management is waste segregation. Interventions and technologies are needed so that the right kind of waste in the right quantity reaches the right place were resource recovery takes place and least goes to disposal.
- In biomedical waste management, source segregation is a big help. Biomedical waste is segregated into contagious waste, less contagious waste and highly contagious waste, which goes into bar-coded different colored bags. Each bar code is monitored as to where the waste should move from collection point to the processing point. The technology of bar coding the type of waste is helping to collect the waste.
- Almost 70% of waste is getting collected. We should monitor GPS driven tracking of waste. There is an improvement in collection but more needs to be done.
- A technology which can be useful here is putting a barcode or weighing scale in the transport vehicle itself. This is important to understand which type of waste should go where.
- Dry waste goes to MRF (materials recovery facility) plants or to waste to energy plant/refuse-derived fuel (RDF) and finally the disposal of inerts in the landfills.
- In MRF plants, the dry waste can either go through optics or through weight density (densification) or through characterization of types of waste. While doing this, the entire system should be under a manifest system.
- The estimated waste should be audited by independent committees and validated through regulatory bodies like municipal corporations, pollution control boards, public works department (PWD).
- Technology can be adopted in the manifest system.
- The masterplan has to include planning for the place for waste management – processing or disposal facility, waste to energy plant, leachate treatment plant, biomethanation, etc.
- The MSW waste Rules have to be read in a holistic manner and technology has to be brought in.
- Waste is wealth only if it is properly managed. Intangible benefits of proper waste management are in terms of air pollution, ground water.
- No legacy waste should go in dumpsite. Only inert waste should go in dumpsites.
- Despite technological interventions, the net result is very disappointing. The output is not proportional to the investment done by the government and private sector. Small solutions are not sustainable.
- The problem should be analyzed. Reasons for failure should be discussed.

- In India, waste is mostly managed by the unorganized sector. However, the unorganized sector has become skilled with experience. They should be incorporated in the organized sector. They should not be condemned; instead their expertise should be utilized.
- Segregation at source is not being done in many homes. Waste from home is thrown out on the roads. The problem is due to the indifference of the home owners.
- There are technologies and mechanisms by which this can be managed but commitment from all stakeholders is essential to manage MSW.
- Attitude, training and awareness are missing. Waste is just being collected and dumped at the dumpsite. Awareness has to be tackled like a revolution.
- Waste can be better managed in a decentralized way.
- We should focus more on composting and biomethanation. Biodegradable waste can be either converted to compost which can be reused by the local horticulture department. Biomethanation produces some kind of biogas, which can be reused for heating or cooking purpose.
- Decentralization should be CBE (community-based enterprise) system.
- The Indian Pollution Control Association has a robust system of collection and using plastic waste to make bags, containers, etc.
- Individuals have to be sensitized about this and the learnings have to be practically implemented. Academic discussions no longer serve the purpose. The help of NGOs, religious trusts can be taken to get the message across to the people. School children should also be involved.
- Segregation and the idea of using what is obtained after processing should penetrate as deep as possible.
- Plastic waste should not go to waste to energy plants because of emission of furans.
- Recycling can have environmental and ecological benefits if it is done sustainably.
- A political will is necessary.
- All wastes can be handled at one place provided there is enough space for segregation and treatment.
- Solid waste should be considered a single subject, as there may not be experts at the municipal levels who can handle all types of waste separately.
- Use of incineration technology should be avoided as much as possible.
- A link with industries that can use the collected material should be established.
- MSW should be called household solid waste. This term is already being used in some countries.
- It is easier to implement waste collection system in housing societies.

Participants: Mr Paritosh Tyagi, Dr Dipankar Saha, Dr Ravindra Palakurthy, Mr Pradeep Khandelwal, Mr Sanjiv Kumar, Mr Neeraj Tyagi, Mr Lovekesh Chandra, Dr Anil Kumar, Dr S Sharma

Coronavirus Updates

BA.5.2 and BF.7 causing the surge in cases in China

The surge in cases in China is mainly due to the BA.5.2 and BF.7 sublineages of the Omicron variant causing 97.5% of all local infections, according to the World Health Organization (WHO). More than 2,000 genome sequencing have been performed by the Chinese Center for Disease Control and Prevention (CDC)… (*Source: Reuters, Jan. 4, 2023*)

Japan imposes strict border control measures for Chinese travelers

Strict border control measures for inbound travelers from China will be implemented from 1st January in view of the sharp increase in the number of people who test positive on arrival at airports. All travelers from China are required to submit a negative COVID test within 72 hours of the day of departure. Airlines have been asked to restrict the number of flights from China… (*Source: Medscape, Jan. 5, 2023*)

Negative COVID test mandatory for travelers from China coming into the US

Travelers from China, Hong Kong and Macau coming into the United States are required to furnish a negative COVID-19 test or documentation of recovery within 2 days of their departure from these countries. This is regardless of their vaccination status… (*Source: CDC, Dec. 28, 2022*)

XBB.1.5 causing surge in cases, says WHO

The XBB.1.5 Omicron sublineage may be causing the rise in number of cases, according to the WHO following a technical meeting recently. However, it also notes that since more than 80% of the sequences were from the US, this might not be an accurate assessment… (*Source: Reuters, Jan. 12, 2023*)

With inputs from Dr Monica Vasudev

Diabetes India 2022: 12th World Congress of DiabetesIndia

CONNECTED BLOOD GLUCOSE MONITORING FROM EVIDENCE TO CLINICAL PRACTICE

Dr Banshi Saboo, Ahmedabad

- Blood glucose monitoring is a cornerstone for the management of diabetes and helps health care providers:
  - To assess glycemic control
  - Adjust therapy accordingly
  - Help patients modify their lifestyle accordingly.
- Structured monitoring, pattern analysis and specific actions based on pattern providers better control of both hyperglycemia and hypoglycemia.
- Patients and physicians connecting blood glucose monitors ease the burden such as logbook maintenance, data sharing, evaluating blood glucose readings and remote monitoring.

PIONEERING THE NEW REVOLUTION IN THE MANAGEMENT OF T2DM WITH ORAL SEMAGLUTIDE

Dr Anil Bhansali, Chandigarh

- Oral semaglutide demonstrated significantly greater glycosylated hemoglobin (HbA1c) and weight reductions versus sitagliptin, empagliflozin and liraglutide.
- Oral semaglutide is superior compared to empagliflozin and sitagliptin in controlling HbA1c, while noninferior to liraglutide.
- Oral semaglutide has superior weight reduction properties compared to sitagliptin, linagliptin and empagliflozin.
- Cardiovascular safety: Confirmed for oral semaglutide in PIONEER 6, showing a 21% nonsignificant reduction in major adverse cardiovascular events in favor of oral semaglutide compared with placebo.
- Overall safety: Oral semaglutide was well-tolerated with a safety profile consistent with the glucagon-like peptide-1 receptor agonist (GLP-1RA) class. The most common adverse event was mild to moderate nausea.
- Efficacy was established when given early in therapy, late in therapy and regardless of renal or hepatic impairment.

2022 UPDATE IN DIABETES

Dr AK Das, Puducherry

- Remarkable advances were observed in recent years in the management of patients with type 2 diabetes mellitus (T2DM) or type 1 diabetes mellitus (T1DM).
- Regarding T2DM, changes in treatment paradigms were observed, moving from a glucocentric approach to a multi-risk strategy and, finally, in people at high-risk, to specific cardiorenal protection using new antidiabetic agents.
- Regarding T1DM, progress combined new insulin analogs with better pharmacokinetics, continuous and flash glucose monitoring, and improved insulin delivery systems with smart insulin pens and insulin pumps connected to a glucose monitoring device, allowing better glucose control with less hypoglycemia.
- Because of an increasing variety of therapeutic approaches, an individualized patient-centered strategy is recommended, ideally with the collaboration of a multidisciplinary team.
- Artificial intelligence, digitization and telemedicine will play an increasing role in the management of T1DM and T2DM, in a near future.

GLIPTIN, GLIFLOZIN, SYNERGY

Dr Vinod Mittal, New Delhi

- Robust/rapid HbA1c reduction – no added hypoglycemia.
- Weight loss – fat.
- Decrease in SBP…Uric acid.
- Cardiorenal protection.
- Less GTI.
- Cost, convenience, compliance.

■■■■

News and Views

Do Eyeglasses Protect Against COVID-19?

Wearing eyeglasses may protect against respiratory viruses, suggests a study of nearly 4,000 participants published in *JAMA Network Open*.[1] However, the study was inconclusive with regard to protection against spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

In this study, researchers enrolled 1,852 adults to investigate the efficacy of wearing eyeglasses as a barrier to SARS-CoV-2 and other respiratory viruses in public places for 2 weeks; the control group included 1,865 individuals. Two-thirds (~66%) of the study group was female. Persons who did not regularly wear eyeglasses, currently had no COVID symptoms and had not been COVID-positive in the preceding 6 weeks were included in this randomized controlled trial conducted from February 2 to April 24, 2022.

Sixty-eight (3.7%) subjects who wore assigned eyeglasses to be worn in public places had a positive result for COVID-19, which was the primary outcome of the study, compared to 65 (3.5%) in the control group with absolute risk difference of 0.2%. Nearly 10% of participants in the intervention group tested positive for SARS-CoV-2 based on self-report versus 11.5% in the control group. The incidence of respiratory symptoms was 30.8% among the glasses-wearing group compared to 34.1% of those who did not wear glasses (absolute risk difference, -3.3%). In this trial, conducted when Omicron was the dominant variant, the incidence of COVID-positive cases was comparable between the two groups. However, the incidence of respiratory infections was lower among those who wore eyeglasses. Although eye glasses or other types of glasses such as sunglasses were not conclusively proven to protect against COVID-19, wearing glasses can be considered as part of preventive measures because "it is simple, low cost and has few negative consequences". They may provide a partial barrier to the infection.

Reference

1. Fretheim A, et al. Effect of wearing glasses on risk of infection with SARS-CoV-2 in the community: a randomized clinical trial. JAMA Netw Open. 2022;5(12):e2244495.

Walk for a Healthy Heart

Walking 10k steps daily may seem an intimidating goal for many. Don't be disheartened, if you are not able to achieve this. A recent study published in the journal *Circulation* says that the beneficial effects of walking on heart health progressively increased even with small increases in the number of steps per day in older adults. Daily step count ranging between 6,000 and 9,000 lowered the risk of cardiac events by up to 50% among older adults compared to those who walked just 2,000 steps in a day.[1]

A meta-analysis of 8 studies involving 20,152 adults was conducted to examine the association of daily step counts and cardiovascular events - fatal and nonfatal coronary heart disease, stroke, heart failure – by age group (younger and older adults) and the amount of physical activity. The mean age of participants was 63.2 years; 52% were women. Based on the physical activity, the participants were categorized into four quartiles, quartile 1 being the least and quartile 4 being the group with the maximum activity. The hazard ratios (HR) were generated using restricted cubic spline models.

The older adults walked less with a median number of 4,323 steps per day, whereas the younger adults walked more with 6,911 steps per day. During a mean follow-up period of 6.2 years, 1,523 cardiovascular events (12.4 per 1,000 person-years) occurred. The association of daily steps and the first cardiovascular event, which was the primary outcome of the study, differed considerably between the older (≥60 years of age) and younger adults (<60 years of age).

The risk of a cardiac event was the least among older adults in quartile 4 (median steps 9,259) with HR of 0.51. For those in quartile 3 (median steps 5,520, the HR was 0.62; for quartile 2 (median steps 3,823), the HR was 0.80 compared with those in quartile 1 with the lowest step count (median steps 1,811). In the spline model, a significant curvilinear association was noted for older adults demonstrating the link between more steps and decreased risk of cardiovascular disease (CVD) in this age group. Among the younger participants, the HR for risk of CVD among quartile 2 was 0.79, 0.90 for quartile 3 and 0.95 for quartile 4 compared with the lowest quartile. These results were nonsignificant versus the lowest quartile. In the spline model, no significant association was noted between steps per day and CVD events for them.

No association was noted between the pace of steps and cardiovascular risk.

The key takeaway from this meta-analysis is the inverse relationship between the number of daily steps and risk of CVD among older adults. The risk progressively declined as the daily step count increased. Walking 6,000 to 9,000 steps per day reduced CVD risk by as much as 50% compared to those who walked 2,000 steps per day. However, no such association was observed for younger adults. This can be attributed to the shorter follow-up duration, which was insufficient to measure the incidence of heart disease in the younger adults. This, note the authors, is a limitation of their study.

These findings have significant clinical implications for older adults in particular. One, that it is important to be physically active and two, that gradually increasing the number of steps in a day reduces their risk of acute cardiac events. Physical activity also helps preserve their cognitive skills.

There is no age bar for exercise. Walking is the simplest and most inexpensive form of exercise. Physicians should set attainable goals for all their patients, not just the older adults, who walk less than 10,000 steps in a day and encourage them to be more active for optimum cardiovascular health.

Reference

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Booster Shot can Cut Down Omicron Transmission in Closed Settings

According to a study published in the journal *Nature Medicine*, booster shots helped limit the transmission of Omicron variants during the first wave. The study conducted by researchers from the University of California showed that the likelihood of viral transmission fell by 11% for each additional dose.

In the study, the researchers analyzed data collected from the California Department of Corrections and Rehabilitation (CDCR). The collected data showed that in the duration of 5 months, 22,334 inmates contracted SARS-CoV-2 Omicron infections, and 31 inmates were hospitalized. The researchers observed that the vaccinated residents were 28% less likely to transmit the COVID infection in comparison to 38% of the unvaccinated residents.

The study, however, found that the likelihood of transmission increased by 6% every 5 weeks since the last vaccine shot. Also, inmates with hybrid immunity acquired from both infection and vaccination were 40% less likely to transmit the virus. (*Source: https://www.daijiworld.com/news/newsDisplay?newsID=1035962*)

Study Reveals that Common, Serious Gut Disorders are Often Misdiagnosed

According to a study published in the journal *Neurogastroenterology & Motility*, rumination is frequently misdiagnosed as other gastrointestinal conditions, resulting in a delay in proper treatment. In this study, the researchers from the Massachusetts General Hospital (MGH) have described this syndrome, how to distinguish it from other conditions, and how to treat it.

The lead author of the study explained that rumination is a behavioral syndrome where patients regurgitate food into their mouths while eating and sitting upright. The research team categorized this syndrome as a disorder of gut-brain interaction (DGBI). They explained that in most cases, doctors think that regurgitations develop as a habit involving an uncomfortable, mounting sensation or inner tension caused by contraction of the abdominal walls after eating. As a result, the symptoms are often misunderstood as functional dyspepsia (stomach pain or indigestion) or gastroparesis.

In this study, the researchers screened 242 patients who were referred to specialists for gastric symptoms pointing toward rumination, such as dyspepsia and gastroparesis. The findings of the study showed that 31 patients (12.8%) checked all the boxes for rumination syndrome, which was determined using a gastric symptom scoring system.

Additionally, they found that patients with rumination were more likely to also experience heartburn, particularly daytime symptoms. Also, more than 48% of the patients reported psychosocial impairment associated with the symptoms of the syndrome. (*Source: https://theprint.in/health/study-reveals-common-serious-gut-disorder-is-often-misdiagnosed/1295548/*)

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Lighter Side of Medicine

INSPIRATIONAL STORY

JUST LISTEN...

I suspect that the most basic and powerful way to connect to another person is to listen. Just listen. Perhaps the most important thing we ever give each other is our attention. And especially if it's given from the heart. When people are talking, there's no need to do anything but receive them. Just take them in. Listen to what they're saying. Care about it. Most times caring about it is even more important than understanding it. Most of us don't value ourselves or our love enough to know this. It has taken me a long time to believe in the power of simple saying, "I'm so sorry," when someone is in pain. And meaning it.

One of my patients told me that when she tried to tell her story people often interrupted to tell her that they once had something just like that happen to them. Subtly her pain became a story about themselves. Eventually, she stopped talking to most people. It was just too lonely. We connect through listening. When we interrupt what someone is saying to let them know that we understand, we move the focus of attention to ourselves. When we listen, they know we care. Many people with cancer can talk about the relief of having someone just listen.

I have even learned to respond to someone crying by just listening. In the old days I used to reach for the tissues, until I realized that passing a person a tissue may be just another way to shut them down, to take them out of their experience of sadness and grief. Now I just listen. When they have cried all they need to cry, they find me there with them.

This simple thing has not been that easy to learn. It certainly went against everything I had been taught since I was very young. I thought people listened only because they were too timid to speak or did not know the answer. A loving silence often has far more power to heal and to connect than the most well intentioned words.

HUMOR

AT NINETY-NINE

When a grandmother was in her late eighties, she decided to move to Israel. As part of the preparations, she went to see her doctor and get all her charts. The doctor asked her how she was doing, so she gave him a litany of complaints - this hurts, that's stiff, I'm tired and slower, etc.

He responded with, "Mrs. Siegel, you have to expect things to start deteriorating. After all, who wants to live to 100?"

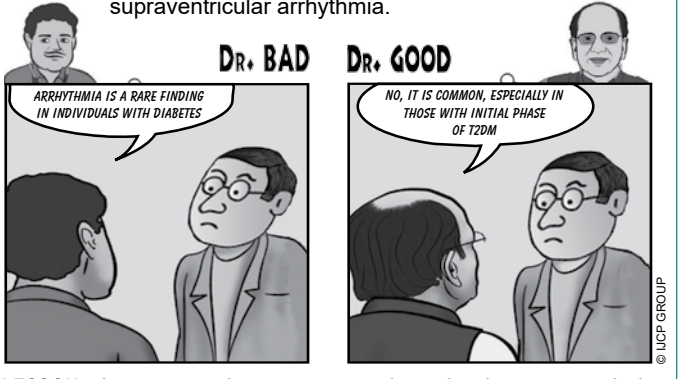
The grandmother looked him straight in the eye and replied, "Anyone who's 99."

HOPE YOU SAID HELLO TO THEM

Wife comes home late at night and quietly opens the door to her bedroom. From under the blanket she sees four legs instead of two. She reaches for a baseball bat and starts hitting the blanket as hard as she can. Once she's done, she goes to the kitchen to have a drink. As she enters, she sees her husband there, reading a magazine. "Hi Darling", he says, "Your parents have come to visit us, so I let them stay in our bedroom. Hope you said Hello to them."

Dr. Good and Dr. Bad

SITUATION: A 49-year-old male with recently diagnosed T2DM had supraventricular arrhythmia.



LESSON: A retrospective case-control study demonstrated the signs of morphological restructuring of the right chambers of the heart and a high prevalence of supraventricular arrhythmias in the early stages of T2DM. In addition, it was reported that the incidence of some kinds of supraventricular arrhythmias and the occurrence of tachycardia in type 2 diabetics could be majorly attributed to the restructuring of these chambers, which may, in turn, be caused by the peculiarities of the cardiac innervation, with the higher density of choline and adrenergic plexuses in the right chambers.

Diabetes Metab Syndr. 2017;11 Suppl 2:S567-76.

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- The introduction should state why the study was carried out and what were its specific aims/objectives.

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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.

Articles in Books

Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

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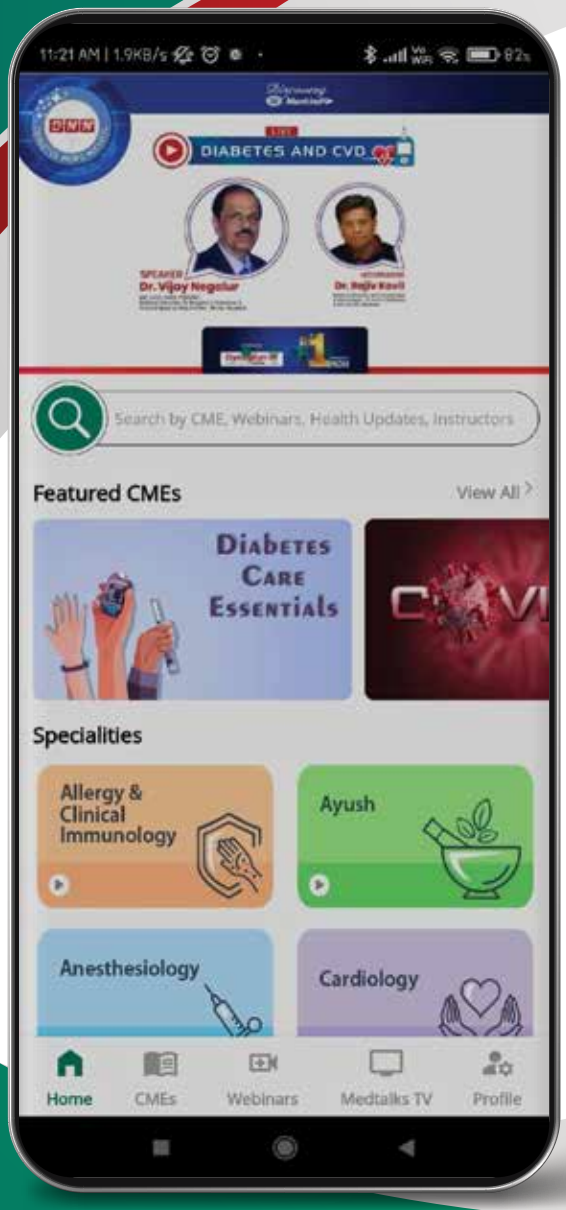

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