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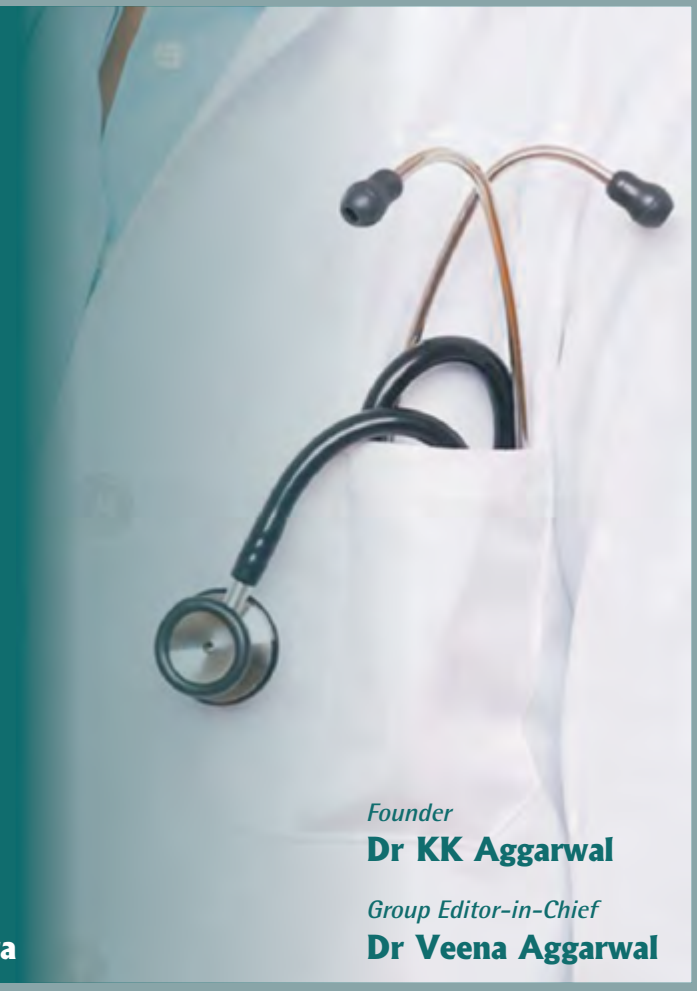

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Medicine Update

A NEW TREATMENT FOR BLADDER CANCER

The combination of enfortumab vedotin-ejfv and pembrolizumab has received FDA (Food and Drug Administration) approval for the treatment of locally advanced or metastatic cancer of the urinary bladder, irrespective of their eligibility for cisplatin-containing chemotherapy… (*Source: US FDA. Dec. 15, 2023*).

METFORMIN REDUCES RISK OF ARMD IN PATIENTS WITHOUT DIABETES

Use of metformin reduces the likelihood of developing age-related macular degeneration (AMD) by 17% in patients without diabetes. This association was independent of dose of metformin… (*Source: JAMA Ophthalmology. Nov. 30, 2023*).

SARS-COV-2 CAN BE DETECTED IN LUNGS FOR UP TO 2 YEARS POST-INFECTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus can persevere in the lungs for up to 2 years after the infection, according to a preclinical study conducted jointly by the Institut Pasteur and the Alternative Energies and Atomic Energy Commission published in the journal *Nature Immunology*. The amount of the virus that remained in the alveolar macrophages in the lungs was lower for the Omicron strain compared to the original strain of the virus. The persistence of the virus has been attributed to the failure of innate immunity… (*Source: Pasteur Institut. Dec. 5, 2023*).

HISTOLOGIC ACTIVITY INCREASES RISK OF SERIOUS INFECTIONS IN IBD PATIENTS

Presence of histologic inflammation in patients with inflammatory bowel disease (IBD) are at high risk of serious infections including opportunistic infections and sepsis compared to those who achieved histological remission. The risk persisted even after adjusting for medications… (*Source: Clin Gastroenterol Hepatol. Oct. 30, 2023*).

A STEROID-FREE TOPICAL FOAM TREATMENT FOR SEBORRHEIC DERMATITIS

A topical steroid-free foam treatment for seborrheic dermatitis has been accorded FDA approval. Roflumilast 0.3% is approved for use in individuals aged 9 years and older. It is to be applied once in a day… (*Source: Dermatology Times. Dec. 15, 2023*).

ACOG RECOMMENDS FLU VACCINE FOR PREGNANT WOMEN

In its Committee Statement, the American College of Obstetricians and Gynecologists (ACOG) has recommended all pregnant women should take the influenza vaccine during the influenza season. It further states that all obstetricians and gynecologists should recommend influenza vaccination and counsel them about the benefits of vaccination. Both influenza and COVID-19 should be considered in the differential diagnosis of pregnant women presenting with symptoms… (*Source: Obstet Gynecol. Nov. 28, 2023*).

PATIENTS WITH ADVANCED RENAL CELL CARCINOMA NOW HAVE ANOTHER TREATMENT OPTION

Belzutifan has been approved by the US FDA for patients with advanced renal cell carcinoma who have been treated with a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI). The dose is 120 mg once daily

orally until there are signs of progression of disease or intolerable adverse effects occur… (*Source: US FDA. Dec. 14, 2023*).

RECENT SURGE IN RESPIRATORY ILLNESS IN CHINA DUE TO SEASONAL INFECTIONS, SAYS CHINA: WHO

Chinese health authorities attribute the sharp increase in the number of cases of children with respiratory diseases including pneumonia in Northern China to known pathogens such as influenza, *Mycoplasma pneumoniae*, respiratory syncytial virus (RSV) and SARS-CoV-2 as well as the advent of winter, says the World Health Organization (WHO). The organization is "closely monitoring the situation and is in close contact with national authorities in China"… (*Source: WHO. Nov. 23, 2023*).

THE PROFID EHRA TRIAL ENROLLS ITS FIRST PATIENT

The first clinical trial to examine the benefits of defibrillator implantation along with drug treatment vis-a-vis medical treatment alone in post-myocardial infarction patients with symptomatic heart failure and left ventricular ejection fraction of ≤35% has started with enrollment of the first patient from Germany. Some of the outcomes to be examined in the trial include all-cause death and sudden cardiac death. The PROFID EHRA noninferiority trial will be conducted in 13 countries with around 3,505 patients. Results are expected in early 2027… (*Source: ESC. Nov. 21, 2023*).

AGA PUBLISHES UPDATED GUIDELINE FOR USE OF BIOMARKERS IN CROHN'S DISEASE

The American Gastroenterological Association (AGA) recommends use of serum C-reactive protein (CRP) and fecal calprotectin to monitor patients with asymptomatic or symptomatic Crohn's disease rather than relying on symptoms alone. It advocates a cut-off of <150 μg/g for fecal calprotectin and/or <5 mg/L for CRP to exclude active inflammation in patients with symptomatic and endoscopic remission, whereas patients with symptomatic but not endoscopic remission should undergo endoscopy to exclude active inflammation… (*Source: Gastroenterology. Dec. 2023*).

LEBRIKIZUMAB APPROVED IN EUROPE FOR MODERATE TO SEVERE ATOPIC DERMATITIS

Atopic dermatitis patients who have not responded to topical therapies can now be treated with lebrikizumab, a monoclonal antibody, which inhibits interleukin-13. It has been approved by the European Commission for the treatment of patients aged ≥12 years with moderate to severe atopic dermatitis… (*Source: Medscape. Nov. 20, 2023*).

UPPER GI ENDOSCOPY ENABLES DIAGNOSIS OF IRON DEFICIENCY ANEMIA ETIOLOGY IN CHILDREN

The use of upper gastrointestinal (GI) endoscopy enabled identification of the cause of iron deficiency anemia in ≥70% of children with severe unexplained iron deficiency anemia. Sixty-eight percent were found to have polyps, gastronodularity or erosions, while 12% had duodenitis or ulcers. Histopathology revealed gastritis in 72% and *Helicobacter pylori* in 50% of children… (*Source: HCPLive Oct. 23, 2023*).

A CATHETER LOCK SOLUTION FOR RENAL FAILURE PATIENTS ON CHRONIC HEMODIALYSIS

A catheter lock solution containing taurolidine and heparin has been approved by the US FDA to prevent catheter-related bloodstream infections in patients with renal failure on chronic hemodialysis via a central venous catheter. It is available in single dose 3 mL and 5 mL vials and is to be used only as a catheter lock solution. The product carries a warning about heparin-induced thrombocytopenia… (*Source: US FDA. Nov. 15, 2023*).

STUDY LINKS HIPPOCAMPAL ATROPHY TO COGNITIVE DECLINE

Decrease in the volume of the hippocampus is associated with cognitive impairment. The Harvard Aging Brain Study reported that the faster the atrophy of the hippocampus occurred, faster was the cognitive decline. These observations were independent of amyloid-beta (Aβ) and tau levels… (*Source: AAN. Nov. 15, 2023*).

THE FIRST HOME DIAGNOSTIC TEST FOR COMMON STIs

LetsGetChecked's Simple 2 Test has been accorded marketing approval as the first diagnostic test for 2 common sexually transmitted infections (STIs) Chlamydia and gonorrhea for patients aged ≥18 years. It is available over-the-counter and the sample can be collected at home… (*Source: US FDA. Nov. 15, 2023*).

■■■■

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Rx in Anaemia associated with

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- Menorrhagia
- Nutritional & Iron Deficiency
- Chronic Gastrointestinal Blood Loss
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My Work is for a King

ONE PHRASE, VARIED MEANINGS

"*My work is for a King*".

The motto of Dame Edith Brown, this phrase adorns the walls of Christian Medical College, Ludhiana, India, the institution that she founded over 125 years ago (Fig. 1).

What does this statement mean, and what does it convey to health professionals? The same sentence can mean different things, in an individual-specific and situation-specific manner. For one, it may mean submitting one's work as an offering to a higher authority on earth, e.g., a supervisor or boss. For another, it may suggest that every work is being done for a spiritual leader or 'guru'. Irrespective of the person and place involved, however, *"My work is for a King"* shares the concept of finding joy and satisfaction in one's profession and work.

MAY YOU NEVER SIT IDLE

A traditional Multani (Saraiki) blessing states: *"May you never sit idle"*.[1]

While this is meant as a blessing, a prayer for a "full and joyful" life, the person at the receiving end may have his or her own opinion about work. One may view work as drudgery, or as punishment. Overworked doctors and nurses, whether at junior, mid-career or senior level, will have a rational excuse to explain their viewpoint. However, such thought process has no benefit. In fact, thinking about work as an unwanted chore leads to negativity, and kickstarts a vicious cycle of self-pity and deprecation. These feelings may be magnified by the not-so-insignificant social demands of patients and the public.

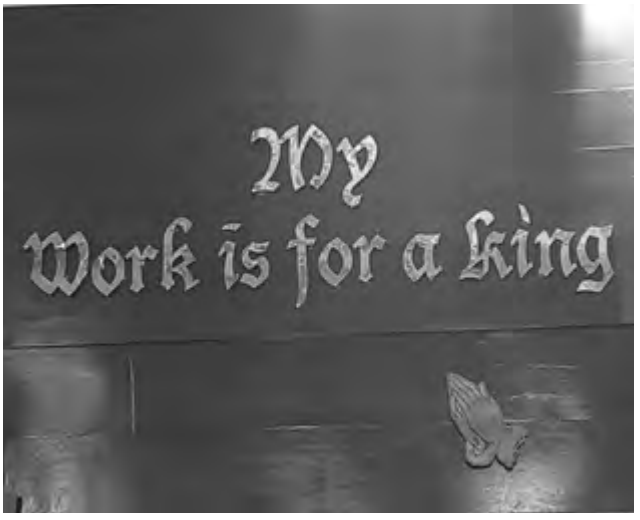

Figure 1.

Dame Edith Brown offers a way out of this self-defeatist quagmire. *"My work is for a King"* reminds us that whatever work we do should be viewed as a service or offering to a higher authority, to our Creator. God may be present in any form, and can appear disguised as a humble patient. If we accept this concept, suddenly our attitude towards work will change. Once we view God in every patient we encountered, we will begin treating him or her as such.

Now, every clinical, administrative, public health or academic challenge appears as an opportunity to serve our "King" or Creator. A challenging case, or a complex academic question, should be treated like an arduous pilgrimage or a difficult religious fast, and approached with expectant optimism. If one welcomes these opportunities with joy, a positive feedback mechanism or

virtuous cycle of satisfaction and happiness will automatically be set in motion.

UNIVERSAL PHILOSOPHY

The concept of working for a King holds relevance for each and every person on earth. Once we internalize this concept, our quality of work, as well as quality of life, automatically improve.

Dame Edith Brown's ideology was inspired by The Holy Bible. However, similar philosophy is followed by other spiritual scriptures as well.[2-4]

"*…it is not advisable to abandon a prescribed duty…*"

—*Bhagavad Gita 18:7*

"*…do perform your allotted duty; for action is superior to inaction.*"

—*Bhagavad Gita 3:8*

"*Man will not get anything unless he works hard.*"

—*Surah al-Najm, 53:39*

(One who works is the friend of Allah, and one who does not work is considered, by Allah, to be His enemy.)

"Verily, Allah loves that when anyone of you does something he does it perfectly."

—*Al Bukhari*

Rabindranath Tagore, the national poet of India, summed this eloquently:[5]

"*I slept and dreamt that life was joy. I awoke and saw that life was service. I acted and behold, service was joy.*"

ADMISSION

We, the authors, admit that we sometimes consider routine clinical work as nonsatisfying and nongratifying. We then remind ourselves of Dame Edith Brown's words and lo and behold, our work becomes joy.

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Characterization of Resolution of Incident Ovarian Cysts

Smaller ovarian cysts smaller than 3 cm resolve faster than cysts that are larger than 6 cm, suggests a study published in the journal *Obstetrics & Gynecology*.[1]

Over a 30-year period, 47,762 people were enrolled in the University of Kentucky Ovarian Cancer Screening Trial (UK-OCST), 2638 of whom had incident cysts. The objective of the study was to determine the surveillance intervals of these incident ovarian cysts. Various factors associated with the resolution of the cysts such as age, body mass index (BMI), use of hormone replacement therapy (HRT), cyst diameter, cyst structure, menopausal status and family history of ovarian cancer were also assessed.

Of the 2,638 women who had incident cysts, 1,667 (63.2%) had cyst resolution in 1.2 years, while the cysts persisted in 971 (34.8%) women. While the resolution rates of unilocular and septated cysts within a year were comparable (35.4% and 36.7%, respectively), the unilocular cysts had a shorter time to resolution (mean 1.89 years vs. 2.58 years, respectively). Cysts smaller than 3 cm, whether unilocular or septated, resolved more quickly than those larger than 6 cm. Younger age, premenopausal status (except for synchronous bilateral cysts) and family history of ovarian cancer were factors linked to percent resolution. Non-use of HRT and age ≥70 years were linked to a faster cyst resolution rate. Cyst resolution time was not correlated with BMI or family history.

This study highlights the different resolution times for ovarian cysts in relation to the age, cyst structure, cyst size and use of HRT. This will help guide clinicians to plan their line of management, whether to go in for surgery or continue monitoring the cyst.

Reference

1. Lasher A, et al. Variables associated with resolution and persistence of ovarian cysts. Obstet Gynecol. 2023 Oct. 12.

CONSENSUS STATEMENT

Consensus on Stroke Prevention in Atrial Fibrillation and Utilization of NOACs in the Real-World Setting in India

PONDE CK, SHAH VT, SHAH DHIREN, KHAN AZIZ, VERMA GAURAV, KOCHHAR ARUN, MAHONAN PP, DAVE TARUN, DWIVEDI SHAILENDRA, NARAYANA MURTHY, JOHN SATISH, ROUTRAY SN, HAZRA PK, BHADURY SPANDAN, KULADHIPATI INDRA, SHARMA AD, MAYABHATE MM, PAWAR DB

ABSTRACT

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia. Prevention of stroke and systemic thromboembolism remains the cornerstone of the management of AF. Even today, there are unresolved knowledge gaps in AF pathophysiology, screening and therapeutic strategies and stroke prevention. The modified DELPHI method was used to develop the best practice recommendations for the management of AF in a real-world setting with the participation of 500 cardiologists across India. The experts concurred that the decision to initiate antithrombotic treatment in patients with transient AF could be based on the duration of transient AF, the co-existence of the risk factor for stroke and echocardiographic abnormalities impact the decision. The decision to initiate anticoagulant therapy in device-detected atrial high-rate episodes (AHRE) can be decided based on the duration of AHRE, the burden of AHRE and the individual's risk of stroke and thromboembolism. The benefit of early anticoagulation should be balanced with the risk of intracerebral hemorrhage (ICH), especially in elderly patients and in severe strokes. Apixaban is the preferred drug in patients with concomitant ischemic heart disease (IHD), patients with a history of gastrointestinal (GI) bleeding, patients with underlying malignancy, elderly patients with AF, patients with comorbid diseases and patients with hepatic disease or renal disease. Apixaban was considered to be an affordable novel oral anticoagulant (NOAC) for Indian patients for primary and secondary stroke prophylaxis in AF patients.

Keywords: NOACs, stroke prevention, atrial fibrillation, apixaban, dabigatran

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia affecting 43 million people globally.[1] Its incidence and prevalence have increased over the last 20 years and will continue to increase over the next 30 years, especially in countries with a middle socio-demographic index.[1] The current European guidelines recommend a holistic AF Better Care (ABC) pathway, involving anticoagulation to avoid stroke, improved control of symptoms and approaches for the reduction of cardiovascular events.

Despite significant advances in its detection, mechanistic understanding and management, AF continues to have a major impact on the morbidity and mortality of millions of patients, partly because of unresolved knowledge gaps in its pathophysiology, screening and therapeutic strategies and stroke prevention. The development of actionable personalized approaches, which take into account patient-specific profiles will be essential to overcome the current challenges in AF management.[2]

Prevention of stroke and systemic thromboembolism remains the cornerstone for the management of AF.[3] Despite the strong association with stroke, there is no evidence that screening for AF in asymptomatic patients improves clinical outcomes. The clinical dilemma is identification of patients who should be screened for risk of stroke.[4] Similar dilemmas need to be identified and the best possible clinical approach to resolve these dilemmas needs to be developed.

The association between AF and stroke is firmly established, and anticoagulation reduces stroke risk in patients with AF.[5] However, the role of anticoagulation is still evolving and many questions about the appropriate use of novel oral anticoagulants (NOACs) for stroke prevention remain to be answered. In the absence of well-designed clinical trials to answer some of these questions, a consensus meeting of Indian cardiologists

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was convened. Data collection began in July 2022 with the first meeting of 12 key opinion leaders (KOLs) in Mumbai, Maharashtra. The second meeting was conducted at 48 locations across the country in August 2022 with 500 cardiologists.

METHODOLOGY

The modified DELPHI method was used to develop the best practice recommendations for the management of AF in a real-world setting. The DELPHI method has defined the methodology to develop consensus recommendations by enlisting the participation of experts from India. The methodology was conducted in two rounds.

In the first round, the questionnaire was framed by the core group after a literature review. The literature review was done using PubMed database. In Round 2, the questionnaire was administered to 500 cardiologists across India. Voting for answers to the questions was conducted and >70% of votes in favor of the answer were taken as a positive point to frame the consensus statement.

The consensus statements were framed and perused by experts and participants prior to the preparation of the manuscript for publication (Fig. 1).

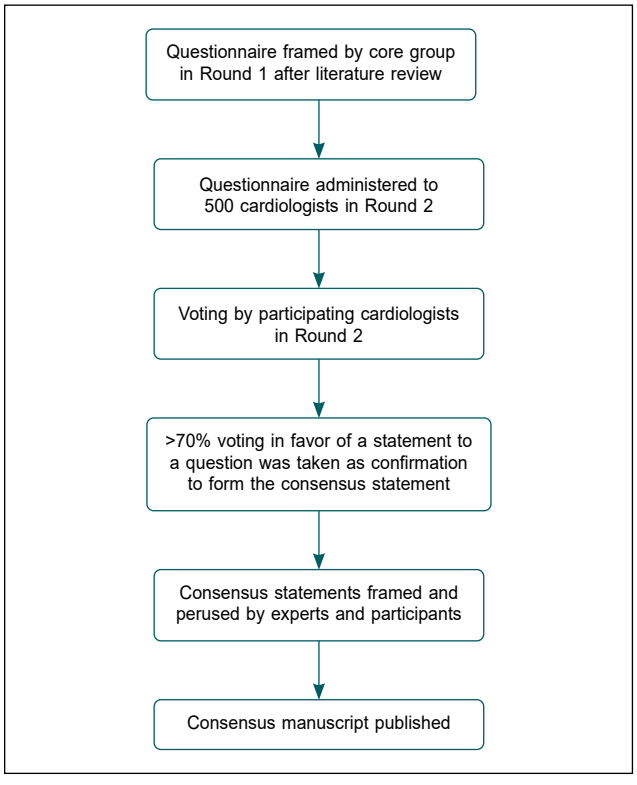

Figure 1. The DELPHI methodology followed for framing the consensus statements.

Which are the Populations Ideal for Screening of AF in a Real-World Setting?

Background

A wide range of risk factors have been identified for AF including coronary heart disease, hypertension (>140/90 mmHg), heart failure (HF) (with reserved and preserved ejection fraction), chronic obstructive pulmonary disease, left ventricular diastolic dysfunction, diabetes, hyperthyroidism, obesity, left atrial dilatation, left ventricular hypertrophy, obstructive sleep apnea (OSA) syndrome, atrial conduction delay/PR interval and chronic kidney disease.[6] The core group identified some of these risk factors as commonly seen in their patients in the real-world setting in India.

Patients with mitral stenosis often have AF due to pathogenic events such as left atrial enlargement because of constant pressure and volume overload.[7] Both HF and myocardial infarction (MI) are associated with an increased risk of AF and vice versa creating a feed-forward loop that increases mortality.[8] OSA is present in 21% to 74% of patients with AF. A structural remodeling as well as transient and acute apnea-associated transient atrial electrophysiological changes can occur as a result of long-term OSA.[9] The link between AF and ischemic stroke is strong. The subtype most commonly associated with AF is cardioembolic stroke, which is particularly severe and shows the highest rates of mortality and permanent disability.[10] AF increases the risk of stroke fivefolds.[11] About 25% to 30% of patients with an ischemic stroke and >80% of those with cardioembolic ischemic stroke have AF.[12] A Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus, Prior Stroke or TIA or Thromboembolism, Vascular Disease, Age, Sex Category (CHA_2DS_2-VASc) score ≥3 has been associated with about 3.2 stroke events per year.[11] Patients with coronary artery disease (CAD) and a dual or triple chamber implantable cardioverter-defibrillator (ICD) show a high incidence of device-detected AF.[13] The prevalence of AF increases exponentially with age. It is reported to be about 9.9% at age 70 to 79 and 23.5% at age 80 to 89.[14] Two-thirds of patients with AF are aged over 75 years.[15]

Recommendations from guidelines

The 2020 European Society of Cardiology (ESC) guidelines for AF recommend opportunistic screening for AF in hypertensive patients as well as in patients with OSA.[16]

Experts' polling responses

The analysis of the DELPHI voting is presented in Table 1.

Table 1. The DELPHI Voting Analysis

Criteria	Voting in favor (%)
Mitral stenosis	71
Echocardiogram with unexplained left atrial enlargement	89
Patients with ≥2 vascular risk factors (CHA_2DS_2-VASc score ≥3)	90
Patients with sleep apnea	83
Obese patients	76
Intracardiac device patients	76
Stroke patients (cryptogenic and ischemic)	90
All persons >75 years of age	84

Consensus statement 1

The populations ideal for screening of AF in a real-world setting include obese patients, intracardiac device patients, stroke patients (cryptogenic and ischemic), patients with mitral stenosis, unexplained left atrial enlargement on echocardiogram, sleep apnea, patients with ≥2 vascular risk factors (CHA_2DS_2-VASc score ≥3) and all persons >75 years of age.

What should be the Approach to Decide Whether Antithrombotic Therapy is Required for the Management of Transient AF?

Background

Currently, AF is usually diagnosed based on intermittent electrocardiogram (ECG) or external event monitors. But with this approach, one may miss the diagnosis of paroxysmal AF in an outpatient until complications such as systemic embolization ensue. Secondly, patients may be over-treated with oral anticoagulants (OACs), when in fact it may not be warranted, based on the AF burden and significant bleeding risk as defined by HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio [INR], Elderly [age ≥65 years], Drugs/Alcohol Concomitantly) score ≥3.

Often, a patient may not be in AF chronically, and the AF burden (the amount of time the patient is in AF out of the total monitored time) is not calculated. An AF burden of ≥1 hour daily is postulated to be associated with a higher risk of embolization. In patients with a history of AF who maintain normal sinus rhythm or in patients with low AF burden, long-term OACs may be more harmful than beneficial. This is especially true in the elderly population with high risk of bleeding.[17] Hence, it is critical to identify the clinical context and carefully consider the risk-benefit ratio of all approaches when making treatment decisions.[17]

The association between AF and stroke is well known, and the use of anticoagulants lowers the risk of stroke in patients with AF.[5]

Currently, data is awaited regarding the minimal amount of subclinical AF, which validates the use of anticoagulants for stroke prevention.[5]

Recommendations from guidelines

- Anatomical imaging provides the left atrium (LA) size, shape and fibrosis. The most accurate assessment of LA dilation is obtained by cardiac magnetic resonance (CMR) or computed tomography (CT). For routine assessment, two-dimensional (2D) or (preferably) three-dimensional (3D) transthoracic echocardiography is used. The 3D echocardiographic normal volume values are 15-42 mL/m^2 for men and 15-39 mL/m^2 for women.
- In patients with AF initially at low risk of stroke, the first reassessment of stroke risk should be made 4 to 6 months after the index evaluation.[18]
- In AF patients with stroke risk factors not taking OAC before ablation, it is recommended that pre-procedural management of stroke risk includes initiation of anticoagulation and preferably, therapeutic OAC for at least 3 weeks before ablation or alternatively, the use of transesophageal echocardiography (TEE) to exclude LA thrombus before ablation.[18]

Experts' polling responses

The experts concurred that the decision to initiate antithrombotic treatment in patients with transient AF could be based on the duration of transient AF; the co-existence of the risk factor for stroke and echocardiographic abnormalities also impact the decision (Table 2).

Table 2. Factors Affecting Antithrombotic Drug Initiation in Patients with Transient AF

Criteria	Voting in favor (%)
Duration of transient AF	80
Co-existence of the risk factor for stroke	93
Echocardiographic abnormalities	91

Consensus statement 2

The decision whether antithrombotic management of transient AF is indicated can be decided based on the duration of transient AF, the co-existence of the risk factor for stroke and echocardiographic abnormalities.

What are the Factors Affecting the Initiation of Anticoagulation Therapy in Patients with Device-detected AHRE?

Background

Cardiac implanted electronic devices (CIEDs) help in the detection of self-terminating atrial arrhythmias commonly, e.g., atrial high-rate episodes (AHREs), which are also termed subclinical atrial tachyarrhythmia or subclinical AF. The reported incidence of AHRE varies considerably from 10% to 70%.[19] Patients with device-detected AHREs are at an elevated risk of stroke and may have unmet anticoagulation needs.[20]AHRE episodes ≥5 minutes are associated with a higher risk of ischemic stroke. The absence of randomized trials to explore the place of anticoagulation therapy in patients with device-detected AHRE makes the management of these patients challenging studies. Currently, treatment with anticoagulants like NOACs must be individualized.[21] Based on current data, antithrombotic therapy can be advocated in patients without documented AF showing AHRE >24 hours and a CHA_2DS_2-VASc score ≥1.[22] The European Heart Rhythm Association (EHRA) recommends anticoagulation for patients with AHRE ≥5.5 hours per day and a CHA_2DS_2-VASc score of ≥2 (≥3 in females). Anticoagulation could be recommended for CHA_2DS_2-VASc scores of 1 (2 in females). In patients with several risk factors, anticoagulation should be considered even in cases with a shorter duration of AHRE.[23] In HF patients, device-detected atrial arrhythmias are associated with an increased incidence of thromboembolic events. A cut-off point of 3.8 hours over 24 hours has been observed to be associated with significant increase in the event rate. Anticoagulation initiation and the optimization of cardioprotective HF therapy could be useful in this patient population.[24]

Recommendations from guidelines

Structured characterization of AF, which includes clinical assessment of stroke risk, symptom status, burden of AF and evaluation of substrate, should be considered in all AF patients, to streamline the assessment of AF patients at different health care levels, inform treatment decision-making and facilitate optimal management of AF patients (IIa).[25]

Table 3. Application of Anticoagulation Therapy in Patients with Device-detected AHRE

Criteria	Voting in favor (%)
Duration of AHRE	86
The burden of AHRE	87
The individual's risk of stroke and thromboembolism	92

Experts' polling responses

The duration of AHRE and the burden of AHRE were the two factors that were voted for by the experts (Table 3).

Consensus statement 3

The decision to initiate anticoagulant therapy in patients with device-detected AHRE can be decided based on the duration of AHRE, the burden of AHRE, and the individual's risk of stroke and thromboembolism.

What is the Optimal Timing of Initiating Anticoagulation Therapy with NOACs in Elderly Patients with Valvular AF and Ischemic Stroke?

Background

The prevalence of AF increases with age, ranging from approximately 9% to 17% in adults aged 80 years.[26] Elderly patients have a challenging set of clinical issues such as a decline in renal function, altered body composition and a high risk of falling. The bleeding risk associated with warfarin in the elderly is a much-debated issue. The benefit-risk ratio must be considered when choosing the strategies for antithrombotic therapies in this population.[27] The elderly population, especially those ≥75 years, is often underrepresented in clinical trials. But, almost 40% of the trial population in large NOAC approval studies consists of the elderly.[28]

Primary and secondary prevention of stroke in elderly patients poses a challenge due to the escalation of both thrombotic and hemorrhagic risks with age. Hence, there is often a delay in the initiation of NOACs in the elderly population after an AF-related ischemic stroke, a stroke of the undetermined cause, after intracranial bleeding or in a high-risk bleeding situation associated with stroke in the real-world setting.[29]

With the advent of new NOACs such as apixaban, early anticoagulation in the elderly population has become a strategy for stroke prevention. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study included the

elderly population (39% aged 65-74 years, 18% aged 75-79 years and 13% aged ≥80 years).[26] Apixaban was associated with less major bleeding, less total bleeding and less intracranial hemorrhage regardless of age. The absolute benefits of apixaban were greater in the older population.[30] Data from phase III clinical trials on AF indicate that apixaban and edoxaban in elderly patients were associated with the highest reduction of extracranial bleeding events versus warfarin.[26] All patients ≥75 years of age are recommended to receive OAC with a Class Ia recommendation irrespective of the presence or absence of additional risk factors.[31,32]

Recommendations from guidelines

Though infarct size/stroke severity is used clinically to guide the timing of OAC initiation, the usefulness of such an approach in estimating the net benefit of early treatment may be limited. Strong evidence to comment on the optimal timing for (re)initiation of OAC after acute stroke is currently not available. From the cardiological perspective, OAC should be (re)initiated as soon as considered possible from the neurological perspective (in most cases within the first 2 weeks).

In AF patients, who presented with acute ischemic stroke despite taking OAC, optimization of OAC therapy is of key importance—if on vitamin K antagonist (VKA), optimize time in therapeutic range (TTR) (ideally >70%) or switch to a NOAC; if on NOAC, ensure appropriate dosing and good adherence to treatment. Inappropriate NOAC under-dosing using lower or reduced doses of specific NOACs has been associated with an increased risk of stroke/systemic embolism, hospitalization and deaths without appreciable reduction in major bleeding.[18]

Experts' polling responses

The experts opined that the benefit of early anticoagulation should be balanced with the risk of intracerebral hemorrhage (ICH), especially in elderly patients and in severe strokes. The age of the patients does affect the decision about the best time to initiate anticoagulant treatment; however, this criterion did not meet the predetermined cut-off value of >70% to merit inclusion in the consensus statement (Table 4).

Table 4. Factors Affecting Optimal Timing of Initiating Anticoagulation Therapy

Criteria	Voting in favor (%)
The benefit of early anticoagulation should be balanced with the risk of ICH, especially in elderly patients and in severe strokes.	94
The decision of timing will be affected by the patient's age.	69

Consensus statement 4

The benefit of early anticoagulation should be balanced with the risk of ICH, especially in elderly patients and in severe strokes.

Which Parameters Must be Considered When Choosing the Most Appropriate NOAC in Order of Significance?

Background

There are scant trials conducting a head-to-head comparison of different NOACs to ascertain the choice of a NOAC in diverse patient populations.[33] The factors affecting the choice of a NOAC include age, gender, comorbid conditions, bleeding risk, CHA_2DS_2-VASc and HAS-BLED scores, concomitant medications, hypertension, history of bleeding, alcohol abuse, renal function and hepatic function.[34]

A retrospective registry-based cohort study (n = >50,000 patients of AF) by Gundlund et al evaluated patients treated with a NOAC (dabigatran, rivaroxaban or apixaban) using the comprehensive Danish health databases. A subanalysis demonstrated that patients with a prior intracranial hemorrhage were more likely to be initiated on apixaban compared with a VKA (OR 1.42, 95% confidence interval [CI] 1.09-1.86). Further, patients who had previously suffered from gastrointestinal (GI) bleeding were less likely to be initiated on rivaroxaban compared with a VKA (OR 0.84, 95% CI 0.73-0.97). Patients treated with dabigatran were younger and had lower CHA_2DS_2-VASc and HAS-BLED scores, whereas patients treated with either rivaroxaban or apixaban were generally older than those initiated on VKAs. Additionally, patients initiated on apixaban had higher predicted risk scores than those initiated on VKAs.[31,35]

In elderly population, the higher risk of bleeding has to be considered when making the choice of NOAC. The Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial showed that in patients with AF (aged ≥75 years), a lower dabigatran dose (110 mg twice daily) was observed to be associated with major bleeding rates comparable to warfarin. A higher dose (150 mg twice daily), however, resulted in a higher risk of major bleeding. This prompted the recommendation to use only a lower dabigatran dose (110 mg twice daily) in patients older than 80 years.[36] The ARISTOTLE study included 39% of patients who were aged 65 to 74 years, 18% 75 to 79 years and 13% >80 years. In this study, apixaban treatment resulted in decreased major bleeding, total bleeding and intracranial hemorrhage than the comparator treatment, warfarin, regardless of age.[30]

Park et al conducted a cross-sectional analysis of NOAC-using patients with nonvalvular AF (NVAF) (n = 6,061 patients) who were aged ≥65 years on the index date. Patients aged ≥75 years and women were more likely to use apixaban relative to rivaroxaban. Patients with prior stroke/transient ischemic attack (TIA)/ thromboembolism had higher odds of using dabigatran and apixaban. Patients with renal disease had increased odds of using apixaban. These findings are consistent with the efficacy and safety profiles reported in pivotal trials and observational studies comparing individual NOACs.[37]

The factors influencing OAC prescription for AF are not well understood. Hence, the current DELPHI method was adopted to understand the factors affecting the choice of NOAC by Indian experts in the real-world setting based on their experience with different NOACs.

Recommendations from guidelines

- For bleeding risk assessment, a formally structured risk-score-based bleeding risk assessment is recommended to help identify nonmodifiable and address modifiable bleeding risk factors in all AF patients and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up. Bleeding risk scores should be considered in AF patients on OAC to identify modifiable risk factors for major bleeding.
- For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban or edoxaban, the performance of the ablation procedure without OAC interruption is recommended.[16]
- In patients on VKAs with low time in international normalized ratio (INR) therapeutic range (e.g., TTR <70%)
  - Switching to a NOAC but ensuring good adherence and persistence with therapy; or
  - Efforts to improve TTR (e.g., education/counseling and more frequent INR checks) (IIA) is recommended.[18]

Experts' polling responses

There was no clear consensus regarding the choice of NOAC in diverse patient profiles. But, age, risk of stroke, bleeding risk, comorbidities and renal and hepatic impairment were regarded as important factors to be considered when choosing a NOAC for the patient (Table 5).

Table 5. Parameters to Consider When Choosing the NOAC

Parameters when choosing the most appropriate NOAC	Preference (%)					
	1st	2nd	3rd	4th	5th	6th
Age	34	12	14	15	13	11
Risk of stroke	31	23	11	13	14	7
Risk of bleeding	31	19	22	13	8	6
Comorbidities	16	15	14	23	25	6
Body weight	11	10	7	10	27	35
Renal and hepatic impairment	25	18	11	14	16	16

Consensus statement 5

Apixaban could be the preferred drug in patients with concomitant ischemic heart disease (IHD), patients with a history of GI bleeding and patients with underlying malignancy. Apixaban is the NOAC of choice in the elderly, patients at high risk of stroke, patients at high risk of bleeding, patients with comorbid diseases and patients with hepatic disease or renal disease. Apixaban can be considered to be an affordable NOAC in India.

Which Oral Anticoagulant should be Chosen for Stroke Prevention in AF?

Background

It is a difficult task to choose the best OAC for stroke prevention, as the treating physician must be vigilant that the drug being used provides a complete protection from future thromboembolic conditions, while at the same time does not pose a threat for bleeding disorders. As the search continues, it is all the more important to consider the comorbid conditions in the patients like hepatic and renal impairment, advancing age, the use of multiple drugs, pre-existing bleeding conditions, etc. before choosing the therapy. Thus, the best OAC drug for each patient has to be individualized as per the personal medical history and comorbidities.[38]

Recommendations from guidelines

All 4 pivotal clinical trials comparing individual direct oral anticoagulants (DOACs) like apixaban, dabigatran, edoxaban and rivaroxaban with warfarin showed superiority or noninferiority to warfarin for the prevention of stroke or systemic embolism in patients with AF except for moderate to severe mitral stenosis or

mechanical heart valve. GI bleeding risks were significantly higher in the dabigatran 150 mg twice daily, edoxaban 60 mg once daily and rivaroxaban groups compared with the warfarin group. However, the apixaban group did not significantly increase the risk of GI bleeding compared with the warfarin group. Similarly, edoxaban and dabigatran are contraindicated in patients with creatinine clearance (CrCl) <15 mL/hour or on dialysis, while apixaban and rivaroxaban can be used in such population. Hence, multiple factors need to be considered before choosing the most suitable OAC.[38]

Experts' polling responses

A poll was sought to seek the opinion of the cardiologists in the meetings about their preference for apixaban in diverse patient profiles. In patients at high risk of bleeding, patients with a previous history of GI bleed and patients with renal disease, apixaban was preferred by >80% of the respondents over the other NOACs. Their opinions were based on the evaluation of the efficacy and safety reports of apixaban and also on their experience with apixaban in a real-world setting in India (Table 6).

Table 6. Voting in Favor of Apixaban as 1st Choice

Patient conditions	Voting in favor of apixaban as 1st choice (%)
Patients with renal impairment	89
Patients with hepatic impairment	72
Elderly patients (Above 75 years)	79
Frail patients (Weight <60 kg)	79
Patients at high risk of bleeding	81
Patients with high CHA_2DS_2-VASc score	65
Patients with recurrent stroke	67
Patients with compliance issues on multiple medications	54
Patients with cost concern	51
Patients with concomitant IHD	58
Patients with a previous history of GI bleed	81
Patients with underlying malignancy	72

Consensus statement 6

Apixaban can be the preferred NOAC for primary and secondary stroke prophylaxis in Indian patients with AF, patients with history of GI bleed and underlying malignancy, the elderly and frail patients and those with hepatic or renal insufficiency and high risk of bleeding.

DISCUSSION

Atrial fibrillation is the most common chronic arrhythmia in clinical practice, which is associated with a well-known increased thromboembolic risk. It is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.[39] The prevalence of AF is currently increasing owing to the longevity of the population globally. AF is independently associated with increased morbidity and mortality, including ischemic stroke, dementia, cognitive dysfunction, HF, MI and all-cause mortality.[6]

Early identification of the patients at risk of stroke can help in the primary prevention of stroke. The 2020 ESC guidelines of AF recommend opportunistic screening for AF in hypertensive patients and opportunistic screening for AF in patients with OSA.[16] Oral anticoagulation represents the cornerstone of treatment to reduce the risk of cardioembolic stroke in patients with AF (Class of recommendation I, level of evidence A).[26]

The use of OACs is well-established in AF. Oral anticoagulant therapy reduces this risk by 62%.[40] NOACs are now recommended as the first drug of choice as an alternative or in preference to warfarin in the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) and the ESC guidelines for AF management, respectively. These drugs do not require INR monitoring or frequent dose adjustment and are associated with fewer food and drug interactions than VKAs.[32]

But, in the absence of head-to-head comparisons between different NOACs, making the choice of the NOAC most appropriate for the patient poses a clinical dilemma to the clinician. Several retrospective studies based on patient databases have brought forth the efficacy and safety of different NOACs in different patient populations. The current expert recommendations made using the DELPHI method can help in answering some of the clinical questions unanswered by current clinical trials.

The expert group supported the use of apixaban in elderly patients, patients with a high risk of bleeding, patients with comorbid disease and patients at high risk of stroke. These opinions corroborated the findings of the ARISTOTLE trial of apixaban, where apixaban demonstrated consistent benefits across NVAF patients with a wide range of stroke risks vs. warfarin ($CHAD_2DS_2$-VASc score 1, 2, ≥3 and HAS-BLED scores).[41] The benefits of apixaban vs. warfarin were consistent in

patients with AF regardless of age. Owing to the higher risk at an older age, the absolute benefits of apixaban were greater in the elderly.[30] Apixaban treatment reduced the rate of stroke, death and major bleeding, regardless of renal function. Patients with impaired renal function seemed to have the greatest reduction in major bleeding with apixaban.[42] Apixaban benefits were observed in patients with NVAF regardless of prior VKA treatment.[43] The effects of apixaban versus warfarin were consistent in patients with AF with and without previous stroke or TIA. Owing to the higher risk of these outcomes in patients with previous stroke or TIA, the absolute benefits of apixaban might be greater in this population.[42]

The rates of stroke/systemic embolism and major bleeding were numerically lower among the patients assigned to apixaban, irrespective of prior VKA use.[44] Apixaban demonstrated consistent benefits across NVAF patients with mild to moderate renal impairment versus warfarin.[43] The AUGUSTUS trial findings supported the use of apixaban and a P2Y12 inhibitor without aspirin for most patients with AF and acute coronary syndrome and/or percutaneous coronary intervention, irrespective of a patient's baseline bleeding and stroke risk.[45]

CONCLUSION

Atrial fibrillation is the most frequent cardiac arrhythmia. In AF, NOACs offer significant benefits for the prevention of stroke balanced by safety. Lower risks of death and bleeding with NOACs have been reported in meta-analyses of controlled trials. In elderly patients and in patients with a high risk of bleeding, apixaban is the preferred NOAC. In other populations, there are no distinct differences between the NOACs in terms of prevention of stroke.

Authorship

All named authors take the responsibility for the integrity of the work as a whole and have given their approval for this version to be published. The details published herein are intended for discrimination of educational, academic and/or research purposes and are not intended as a substitute for professional medical advice, diagnosis or treatment.

Compliance with Ethics Guidelines

This article has been developed as per the expert group consensus based on available literature and clinical experience. It does not contain any studies with human participants or animals performed by any of the authors.

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ORIGINAL RESEARCH

Study of Resilience in Female College Adolescents and Young Adults: Tough Times Don't Last, Tough People Do

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ABSTRACT

This study is part of a multicentric youth project conducted by Association of Adolescent and Child Care in India (AACCI). We examined resilience and its association with demographic variables like age, sibling status, academic course, engagement in extracurricular activities, perceived internet/social media usage and dependence, substance use and perception of control over one's life. We used a cross-sectional design with a sample of 17- to 21-year-old female college students from Delhi. We found that students who perceived control over their lives had high total scores on resilience measures. Students who used social media had higher total and relational resilience than those who did not use social media. Students who did not use social media had higher individual resilience. Those who did not see themselves as dependent on social media had higher total resilience and relational resilience. Those who did not see themselves as dependent on the internet had higher relational resilience. There were no significant relationships between resilience and the other demographic variables. Results from the current study shed light on factors contributing to resilience among adolescents. We can use these findings to develop training programs that promote adolescent well-being.

Keywords: Resilience, youth mental health, social media, social media dependence, internet dependence, perceived control

Resilience is a multidimensional construct that has been studied from varied perspectives. While some have described it as the ability to obtain good outcomes despite threats and adversity,[1] others see it as the ability to cope with stress, change, misfortune and adversity.[2,3] Ungar[4,5] described resilience from an ecological and culturally sensitive perspective – an individual's capacity to navigate their way to available resources that can sustain their well-being in case of exposure to adversity. He also emphasized on the individual and collective capacities to negotiate for resources of well-being to be provided in culturally meaningful ways.

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The purpose of this study is to better understand resilience among a sample of Indian adolescents. Recognizing factors associated with resilience can help us build better resources for youth in the form of intervention programs and tools. This can contribute to improved overall well-being. While it can be beneficial to study resilience across all life stages, the current study aims to look at it in the lives of young people for several reasons. Adolescence is a period of rapid change and complexity. Adolescents are particularly vulnerable to stress, due to the functional and structural brain changes that occur during this period.[6] Additionally, although most mental disorders are detected later in life, they begin during youth. Due to this, mental disorders add to the disease burden in young people.[7]

AIMS AND OBJECTIVES

In 2017, the Association of Adolescent and Child Care in India (AACCI) initiated the project on "*Building Resilience*" among school and college students in India. As part of this project, AACCI has been conducting multicentric studies on youth behavior using standardized psychometric tools to study: a) resilience and b) some components that help to

build resilience, such as self-esteem, self-regulation, emotional intelligence and social self-efficacy. Based on the findings from the surveys, AACCI continues to customize various intervention programs in addition to the Life Skill education workshops that are regularly conducted in various schools and colleges for the holistic wellness of children and adolescents.

The current study aimed to determine the scores of the Resilience Scale in 354 college girls from a women's college in Delhi and draw age-based comparisons (Group I: 17-19 years and Group II: 20-21 years) for the same. AACCI has published a study conducted with females studying in an engineering college in Pune[8] to explore the relationships between individual scale scores and sociodemographic variables, including age, sibling status and academic courses (Bachelor of Arts [BA], Bachelor of Commerce [BCom] and Bachelor of Science [BSc]), engagement in extracurricular activities, perceived internet and social usage and media dependence, substance use and perception of control over one's life.

METHODOLOGY

Sample Characteristics

Participants included 354 women (n = 354; age range: 17-22 years, M_{age} = 18.63 years, standard deviation [SD] = 1.06 years) pursuing BA, BCom or BSc from an all-women's college in North India.

Sample Selection

Participants were selected via convenience sampling. AACCI conducted an awareness program at this all-women's college in North India (pursuing BA, BCom or BSc courses) and requested students to participate in their survey. Participants filled out the online survey questionnaire under the supervision of their college professor and a team of student volunteers trained by AACCI.

Exclusion and Inclusion Criteria

There were no exclusion criteria, and all the students who volunteered to participate in the survey were included in the study.

Study Design

A cross-sectional study was conducted using convenience sampling.

Study Duration

The study spanned 3 months from July to September 2018.

Procedures

As part of its multicentric studies on youth behavior in India, AACCI designed and administered a survey questionnaire, which focused on collecting socio-demographic data in addition to the following five psychometric tools to gauge the participants' stratum of resilience, self-efficacy, emotional intelligence, self-regulation and self-esteem, respectively: 1) Child and Youth Resilience Measure-28 (CYRM-28[9,10]), 2) Social Self-efficacy Scale[11], 3) Schutte Emotional Intelligence Scale (SEIS[12,13]), 4) Adolescent Self-Regulation Inventory (ASRI[14]) and 5) Rosenberg's Self-Esteem Scale (RSES[15,16]).

Additionally, the form contained a questionnaire to gauge the participants' sociodemographic details. Participants first reported their age, sibling status (no sibling, one sibling and more than one sibling), and academic course (BA/BCom/BSc). The questionnaire explored their participation in inter-school/college competitions, especially athletic and sociocultural competitions. The questionnaire also explored their self-perceived internet and social media usage and dependence. Participants were asked to report if they consumed tobacco products or alcohol. Lastly, they were asked if they believed that they were in control of their life.

Additionally, AACCI has published individual papers for the aforementioned scales[17] exploring their distinct relationships with the demographic variables for the same cohort. The current paper discusses the analysis of the results of the CYRM-28.

Tools Used

The CYRM-28 is a self-report tool to measure resilience from a socioecological perspective. It is a popular tool that has been used by practitioners and researchers worldwide. It was developed as part of the International Resilience Project (IRP) at the Resilience Research Centre (RRC). It is suitable for individuals between 10 to 23 years of age. The scale includes 28 items to which individuals responded on a 5-point Likert scale ranging from 1 indicating "not at all" to 5 indicating "a lot". It has three subscales reflecting subcategories of resilience- individual, relational and contextual.

The scale has good psychometric properties. Confirmatory factor analysis provided strong support for the three-structure model. Internal reliability was found to be acceptable with Cronbach's α ranging from 0.65 to 0.91. It was also found to have good reliability and convergent validity when tested with a sample of Indian adolescents.[18]

Justification for Sociodemographic Variables Included in the Study

The primary aim of this study was to see the level of (scale) scores in the sample, to compare them with other studies and to determine age-related differences.

Age: Several studies using functional magnetic resonance imaging (MRI) and positive emission tomography (PET) scans have shown that brain development begins from behind and towards the front. The hypothalamic limbic system (which controls our emotions) matures first and the prefrontal cortex (which controls the hypothalamic limbic system and helps to make rational decisions with an ability to see the future consequences of one's actions) matures last–at around 25 years. Hence, it is expected that there may be age-based differences in brain development among adolescents (17-19 years) versus young adults (20-21 years) in the current sample.[19] Accordingly, the sample was divided into two groups and age-based differences in resilience were studied.

In our previous study,[8] we studied the aforementioned scale scores about participation in athletic and non-athletic intercollegiate competitions. It was found that females who participated in athletic and nonathletic intercollegiate competitions scored higher on social self-efficacy and self-regulation than nonparticipants. In addition, the current study also explored the relationship between the following demographic variables and individual scale scores.

Sibling status: AACCI also wanted to explore the relationship between sibling status (no siblings, one sibling and more than one sibling) on resilience. Siblings have been recognized as a source of support, strength and affection. Resilience can differ among individuals who have grown up among siblings, learned to share, talked about their feelings and supported one another. Adlerian studies on sibling rivalry have shown associations with unhealthy competitiveness, perceived parental rejection and poor self-image.[20] Accordingly, the current study aimed to explore differences in resilience among participants who had no siblings, one sibling or more than one sibling. We have not conducted an in-depth analysis of the gender and age of siblings, inter-sibling relationships, sibling rivalry, differential parenting, etc. as that was not the focus of our study.

Academic course: One's choice of academic pursuits often depends on their aptitude, interest and realities (familial pressure, finances, grades, etc.). Different streams have different entrance requirements, tap on various soft skills, demand different intensities of work, and require varying coping and regulatory strategies; the struggles for the same could impact the students' resilience.[21] Accordingly, the current study explored differences in resilience among participants pursuing BSc, BA and BCom.

Participation in intercollegiate nonathletic competitions: Participation in intercollegiate competitions is known to increase self-confidence and self-esteem and also enhance the ability to deal with stress, reduce performance anxiety and strengthen other soft skills.[22] Accordingly, the current study tried to see if there is a difference in resilience among participants who participated (vs. did not participate) in intercollegiate nonathletic competitions.

Participation in intercollegiate athletic competitions: Sports are known to enhance executive functions, teamwork, resilience and the capacity to deal with failures. Our previous study showed that the engineering college girls who participated in sports competitions scored higher on social self-efficacy and self-regulation than nonparticipants.[8] Accordingly, the current study tried to see if there is a difference in resilience among participants who participated (vs. did not participate) in intercollegiate athletic competitions.

Internet usage; social media usage; self-perceived dependence on the internet and self-perceived dependence on social media: During the global pandemic of COVID-19, the internet and social media were primary sources that fostered connectedness. This continued post-COVID and has led to issues like addiction, breach of privacy and disconnect from the real world. AACCI has previously studied the impact of internet addiction using Kimberly Young's internet addiction test (IAT).[17] As we had studied the psychometric scales in addition to sociodemographic questions in this study, we did not add the IAT scale to avoid fatigue among participants while filling out the questionnaire. Since they were all between the ages of 17 and 21 years and mature enough to report their self-perception, we inquired about their self-proclaimed dependence on the internet (yes vs. no) and on social media (yes vs. no) on resilience. This was preceded by an inquiry about whether they used the internet and social media (yes vs. no).

Consumption of alcohol and consumption of tobacco: Consumption of substances is a common occurrence in adolescence and young adulthood. Indulgence in substance use is often a result of curiosity and experimentation, peer pressure, or even an unhealthy coping mechanism during distressing situations.[23] The ability to say no and refrain from this indulgence

requires high self-esteem, emotional regulation and self-control. Hence, we explored the differences in the scores of participants who consumed (vs. did not consume) alcohol and (vs. did not consume) tobacco.

Self-perceived control over one's life: Several studies have established associations between perceived control over one's life (yes/no/may be), resilience and one's overall well-being. As stated previously, AACCI did not use this standardized scale to avoid fatigue among participants while filling out the questionnaire.

Permissions and Ethical considerations: Ethical clearance for this project was given by AACCI's Institutional Ethics Committee. Permission for conducting the current study was procured from the college's principal. Informed consent was obtained via the questionnaire. This was not a clinical trial, and the participants were not patients.

STATISTICAL ANALYSIS

The data were analyzed using the IBS SPSS version 28.0.0. T-tests were conducted to study the effects of age and engagement in extracurricular activities. Further, one-way ANOVAs were conducted to determine the effects of sibling status, academic course and self-perceived control over one's life. The statistical significance of the calculated coefficients was considered at $p < 0.05$.

RESULTS

We compared total scores on the CYRM-28 across two groups, Group I: 17-19 years (Late adolescence) and Group II: 20-21 years (Young adults). The majority of the late adolescence group had scores in the high range (79.22%), followed by the moderate range (75%) and lastly low range (33.33%). In the case of young adults, majority of the young adults had scores in the low range (66.67%), followed by the moderate range (25%) and lastly the low range (20.78%) (Table 1).

The scores on the CYRM-28 between the two groups of Late adolescence and Young adults were compared and no statistically significant differences were found between the two groups (Table 2).

Among all the variables assessed, there was a statistically significant relationship between total resilience scores (TRS) and social media usage, dependence on social media and perceived self-control. Participants who reported using social media (M = 112.668, SD = 13.820) had significantly higher mean TRS than participants who did not use social media (M = 105.409, SD = 19.107), t (352) = 2.324, p = 0.021. Participants who did not experience perceived dependence on social media (M = 113.280, SD = 13.375) had significantly higher mean TRS compared to the participants who perceived dependence on social media (M = 109.796, SD = 15.953), t (352) = 2.124, p = 0.034. Participants who perceived being in control of their life (M = 115.439, SD = 14.223) had a significantly higher mean TRS compared to participants who did not perceive control over their life (M = 111.875, SD = 13.386) or were unsure of their perception of control (M = 108.362, SD = 13.705), F (2,351) = 10.045, p = <0.001. There were no statistically significant effects of the remaining variables on TRS (Table 3).

Scores on the first subscale of the CYRM-28, which is individual resilience showed a statistically significant relationship with social media usage and perceived self-control. Participants who did not use social media (M = 43.482, SD = 6.424) had significantly higher mean individual resilience scores compared to the participants who used social media (M = 39.318, SD = 9.756),

Table 1. Range of Total CYRM-28 Scores

CYRM-28 (Range)	Age	
	Late adolescence (n = 275) (Group I: 17-19 yrs)	Young adults (n = 79) (Group II: 20-21 yrs)
Low (28-62)	33.33%	66.67%
Moderate (63-106)	75.00%	25.00%
High (107-140)	79.22%	20.78%

Table 2. Age-wise Distribution of CYRM-28 Scores (N = 354)

CYRM-28 (Range)	Age			
	Late adolescence (n = 275) (Group I: 17-19 yrs)		Young adults (n = 79) (Group II: 20-21 yrs)	
	n (%)	CYRM-28 (M ± SD)	n (%)	CYRM-28 (M ± SD)
Total CYRM-28 scores (28-140)	77.68%	112.618 ± 12.907	22.32%	110.822 ± 18.302
Individual subscale (11-55)	77.68%	43.225 ± 6.286	22.32%	43.215 ± 8.158
Relational subscale (6-30)	77.68%	29.494 ± 3.984	22.32%	28.696 ± 5.547
Contextual subscale (11-55)	77.68%	39.898 ± 5.375	22.32%	38.911 ± 6.596

Table 3. Effects of Demographic Variables on Mean Total Resilience Scores

Variable	Responses	Number (%)	Total resilience scores			
			Mean ± SD	t score/F score	df	P value
Age	Group I: 17-19 yrs	275 (77.68%)	112.618 ± 12.907	t = 0.985	352	0.325
	Group II: 20-21 yrs	79 (22.32%)	110.822 ± 18.302			
Sibling status	No sibling	19 (5.37%)	113.737 ± 14.413	F = 1.017	2,351	0.363
	One sibling	186 (52.54%)	113.069 ± 13.061			
	More than one sibling	149 (42.09%)	110.959 ± 15.653			
Academic course	BA	70	113.371 ± 14.620	F = 0.381	2,351	0.683
	BCom	43	111.046 ± 15.020			
	BSc	241	112.091 ± 14.082			
Do you participate in any inter-school/college sports competitions?	Yes	55 (15.54%)	111.846 ± 14.546	t = 0.338	352	0.735
	No	299 (84.46%)	112.327 ± 14.202			
Do you participate in any other inter-school/college competitions?	Yes	111 (31.36%)	113.693 ± 12.089	t = 1.316	352	0.189
	No	243 (68.64%)	111.543 ± 15.150			
Do you use the internet?	Yes	352 (99.44%)	112.2045 ± 14.188			
	No	2 (0.56%)	114.500 ± 36.062			
Do you believe that you are dependent on the internet?	Yes	222 (62.71%)	111.351 ± 14.709	t = 1.483	352	0.139
	No	132 (37.29%)	113.674 ± 13.454			
Do you use social media?	Yes	332 (93.79%)	112.668 ± 13.820	t = 2.324	352	0.021
	No	22 (6.21%)	105.409 ± 19.107			
Do you believe that you are dependent on social media?	Yes	108 (30.51%)	109.796 ± 15.953	t = 2.124	352	0.034
	No	246 (69.49%)	113.280 ± 13.375			
Do you consume any tobacco products?	Yes	3 (0.85%)	112.333 ± 13.203			
	No	351 (99.15%)	112.216 ± 14.305			
Do you consume alcohol?	Yes	10 (2.82%)	105.700 ± 13.132			
	No	344 (97.18%)	112.421 ± 14.287			
Do you believe that you are in control of your life?	Yes	173 (48.87%)	115.439 ± 14.223	F = 10.045	2,351	<0.001
	No	141 (39.83%)	111.875 ± 13.386			
	Not Sure	40 (11.30%)	108.362 ± 13.705			

*p < 0.05, **p < 0.01, ***p < 0.005

t (352) = 2.835, p = 0.005. Participants who perceived being in control of their life (M = 44.855, SD = 6.423) had a significantly higher mean individual resilience score compared to participants who did not perceive control over their life (M = 42.600, SD = 7.302) or were unsure of their perception of control (M = 41.397, SD = 6.490), F (2,351) = 11.021, p = <0.001. All remaining demographic variables demonstrated no statistically significant effects on the individual resilience scores (Table 4).

Scores on the second subscale of the CYRM-28, which is relational resilience showed a statistically significant relationship with social media usage, dependence on social media and the internet and perceived self-control. Participants who used social media (M = 29.455, SD = 4.256) had significantly higher mean relational resilience scores compared to the participants who did not use social media (M = 27.227, SD = 5.739), t (352) = 2.321, p = 0.021. Participants who did not experience perceived

Table 4. Effects of Demographic Variables on Mean Individual Resilience Scores

Variable	Responses	Number (%)	Individual resilience scores			
			Mean ± SD	t score/F score	df	P value
Age	Group I: 17-19 yrs	275 (77.68%)	43.225 ± 6.286	t = 0.012	352	0.990
	Group II: 20-21 yrs	79 (22.32%)	43.215 ± 8.158			
Sibling status	No sibling	19 (5.37%)	45.631 ± 7.754	F = 2.984	2,351	0.052
	One sibling	186 (52.54%)	43.688 ± 6.344			
	More than one sibling	149 (42.09%)	42.336 ± 6.987			
Academic course	BA	70	44.228 ± 7.009	F = 0.991	2,351	0.372
	BCom	43	43.163 ± 7.141			
	BSc	241	42.941 ± 6.582			
Do you participate in any inter-school/college sports competitions?	Yes	55 (15.54%)	43.127 ± 7.331	t = 0.115	352	0.909
	No	299 (84.46%)	43.240 ± 6.634			
Do you participate in any other inter-school/college competitions?	Yes	111 (31.36%)	43.918 ± 5.820	t = 1.315	352	0.189
	No	243 (68.64%)	42.905 ± 7.105			
Do you use the internet?	Yes	352 (99.44%)	43.224 ± 6.695			
	No	2 (0.56%)	43.000 ± 16.970			
Do you believe that you are dependent on the internet?	Yes	222 (62.71%)	43.054 ± 6.745	t = 0.612	352	0.541
	No	132 (37.29%)	43.508 ± 6.738			
Do you use social media?	Yes	332 (93.79%)	43.482 ± 6.424	t = 2.835	352	0.005
	No	22 (6.21%)	39.318 ± 9.756			
Do you believe that you are dependent on social media?	Yes	108 (30.51%)	42.750 ± 7.87	t = 0.875	352	0.382
	No	246 (69.49%)	43.431 ± 6.581			
Do you consume any tobacco products?	Yes	3 (0.85%)	46.000 ± 5.567			
	No	351 (99.15%)	43.199 ± 6.747			
Do you consume alcohol?	Yes	10 (2.82%)	43.200 ± 6.196			
	No	344 (97.18%)	43.224 ± 6.760			
Do you believe that you are in control of your life?	Yes	173 (48.87%)	44.855 ± 6.423	F = 11.021	2,351	<0.001
	No	141 (39.83%)	42.600 ± 7.302			
	Not Sure	40 (11.30%)	41.397 ± 6.490			

*p < 0.05, **p < 0.01, ***p < 0.005

dependence on social media (M = 29.784, SD = 4.139) had significantly higher mean relational resilience scores compared to the participants who perceived dependence on social media (M = 28.250, SD = 4.752), t (352) = 3.067, p = 0.002. Participants who did not perceive dependence on the internet (M = 30.106, SD = 3.913) had a significantly higher mean relational resilience score compared to participants who perceived dependent on the internet (M = 28.847, SD = 4.588), t (352) = 2.634, p = 0.09. Participants who perceived being in control of their life (M = 29.942, SD = 4.376) had a significantly higher mean relational resilience score compared to participants who did not perceive control over their life (M = 29.350, SD = 4.407) or were unsure of their perception of control (M = 28.539, SD = 4.387), F (2,351) = 4.046, p = 0.018. All remaining demographic variables demonstrated no statistically significant effects on the relational resilience scores (Table 5).

Table 5. Effects of Demographic Variables on Mean Relational Resilience Scores

Variable	Responses	Number (%)	Relational resilience scores			
			Mean ± SD	t score/F score	df	P value
Age	Group I: 17-19 yrs	275 (77.68%)	29.494 ± 3.984	t = 1.428	352	0.154
	Group II: 20-21 yrs	79 (22.32%)	28.696 ± 5.547			
Sibling status	No sibling	19 (5.37%)	28.789 ± 4.454	F = 0.264	2,351	0.768
	One sibling	186 (52.54%)	29.451 ± 3.938			
	More than one sibling	149 (42.09%)	29.215 ± 4.899			
Academic course	BA	70	29.300 ± 4.688	F = 0.369	2,351	0.692
	BCom	43	28.790 ± 4.793			
	BSc	241	29.415 ± 4.230			
Do you participate in any inter-school/college sports competitions?	Yes	55 (15.54%)	28.818 ± 4.409	t = 0.916	352	0.360
	No	299 (84.46%)	29.408 ± 4.382			
Do you participate in any other inter-school/college competitions?	Yes	111 (31.36%)	29.783 ± 3.862	t = 1.357	352	0.176
	No	243 (68.64%)	29.103 ± 4.597			
Do you use the internet?	Yes	352 (99.44%)	29.318 ± 4.375			
	No	2 (0.56%)	29.000 ± 8.485			
Do you believe that you are dependent on the internet?	Yes	222 (62.71%)	28.847 ± 4.588	t = 2.634	352	0.009
	No	132 (37.29%)	30.106 ± 3.913			
Do you use social media?	Yes	332 (93.79%)	29.455 ± 4.256	t = 2.321	352	0.021
	No	22 (6.21%)	27.227 ± 5.739			
Do you believe that you are dependent on social media?	Yes	108 (30.51%)	28.250 ± 4.752	t = 3.067	352	0.002
	No	246 (69.49%)	29.784 ± 4.139			
Do you consume any tobacco products?	Yes	3 (0.85%)	25.000 ± 3.605			
	No	351 (99.15%)	29.535 ± 4.378			
Do you consume alcohol?	Yes	10 (2.82%)	26.000 ± 3.944			
	No	344 (97.18%)	29.413 ± 4.365			
Do you believe that you are in control of your life?	Yes	173 (48.87%)	29.942 ± 4.376	F = 4.046	2,351	0.018
	No	141 (39.83%)	29.350 ± 4.407			
	Not Sure	40 (11.30%)	28.539 ± 4.387			

*p < 0.05, **p < 0.01, ***p < 0.005

Table 6. Effects of Demographic Variables on Mean Contextual Resilience Scores

Variable	Responses	Number (%)	Contextual resilience scores			
			Mean ± SD	t score/F score	df	P value
Age	Group I: 17-19 yrs	275 (77.68%)	39.898 ± 5.375	t = 0.009	352	0.174
	Group II: 20-21 yrs	79 (22.32%)	38.911 ± 6.596			
Sibling status	No sibling	19 (5.37%)	39.315 ± 4.819	F = 0.388	2,351	0.679
	One sibling	186 (52.54%)	39.931 ± 5.264			
	More than one sibling	149 (42.09%)	39.409 ± 6.260			

Table 6. Effects of Demographic Variables on Mean Contextual Resilience Scores

Variable	Responses	Number (%)	Contextual resilience scores			
			Mean ± SD	t score/F score	df	P value
Academic course	BA	70	39.843 ± 5.704	F = 0.269	2,351	0.765
	BCom	43	39.093 ± 5.991			
	BSc	241	39.734 ± 5.627			
Do you participate in any inter-school/college sports competitions?	Yes	55 (15.54%)	39.673 ± 5.913	t = 0.007	352	0.994
	No	299 (84.46%)	39.678 ± 5.641			
Do you participate in any other inter-school/college competitions?	Yes	111 (31.36%)	39.991 ± 4.977	t = 0.701	352	0.484
	No	243 (68.64%)	39.535 ± 5.971			
Do you use the internet?	Yes	352 (99.44%)	39.661 ± 5.659			
	No	2 (0.56%)	42.500 ± 7.500			
Do you believe that you are dependent on the internet?	Yes	222 (62.71%)	39.450 ± 5.744	t = 0.978	352	0.329
	No	132 (37.29%)	40.060 ± 5.558			
Do you use social media?	Yes	332 (93.79%)	39.732 ± 5.669	t = 0.694	352	0.488
	No	22 (6.21%)	38.863 ± 5.841			
Do you believe that you are dependent on social media?	Yes	108 (30.51%)	38.796 ± 6.224	t = 1.944	352	0.053
	No	246 (69.49%)	40.065 ± 5.385			
Do you consume any tobacco products?	Yes	3 (0.85%)	41.333 ± 9.291			
	No	351 (99.15%)	39.664 ± 5.654			
Do you consume alcohol?	Yes	10 (2.82%)	36.500 ± 5.083			
	No	344 (97.18%)	39.770 ± 5.672			
Do you believe that you are in control of your life?	Yes	173 (48.87%)	40.642 ± 5.715	F = 6.138	2,351	0.002
	No	141 (39.83%)	39.925 ± 5.667			
	Not Sure	40 (11.30%)	38.425 ± 5.422			

*p < 0.05, **p < 0.01, ***p < 0.005

Scores on the third subscale of the CYRM-28, which is contextual resilience showed a statistically significant relationship with perceived self-control. Participants who perceived being in control of their life (M = 40.642, SD = 5.715) had a significantly higher mean contextual resilience score compared to participants who did not perceive control over their life (M = 39.925, SD = 5.667) or were unsure of their perception of control (M = 38.425, SD = 5.422), F (2,351) = 6.138, p = 0.002. All remaining demographic variables demonstrated no statistically significant effects on the contextual resilience scores (Table 6).

DISCUSSION

Resilience is positively associated with several factors in youth like improved problem solving,[24] perceiving self as more efficient with academics, being able to cope with novelty in life,[25] using all thinking styles,[26] better life satisfaction[27] and higher self-esteem[28] among other things. When youth see themselves as being able to cope with stress, they are more likely to be able to deal with novelty in life, particularly in academic contexts.[25] Thus, building resilience can have several advantages for youth.

Researchers have also been interested in recognizing factors that can predict better resilience. These protective factors are characteristics of the individual and their environment that can reduce the likelihood of experiencing negative outcomes from adverse events.[28,29] Some of these factors include having an internal locus of control (LOC), lack of adversity in relationships with parents and guardians[30] and parenting quality.[31] Besides

this, environmental factors like safe neighborhoods and healthy school environments can also play an important role in building resilience.[32]

The current study examined scores on the CYRM-28 among a sample of female students based in India. Participants' scores on the full scale as well as three subscales were used for comparison as seen in Tables 3 to 6. There were significant relationships between participants' scores on the Resilience Scale and their scores on perceived control, social media usage, dependence on social media and dependence on the internet amongst all the demographic variables assessed.

Age-wise Differences in Resilience Scores

The current sample included students between the ages 17 to 21 years who were divided into two groups, late adolescents or Group I: 17-19 years (n = 275, 77.68%), and young adults or Group II: 20-21 years (n = 79, 22.32%). There was no statistically significant difference between the two groups in terms of their mean TRS {t (352) = 0.985, p = 0.325} as well as subscale scores (Tables 2 and 3). We can conclude that the two groups are comparable in terms of their maturity. Thus, resilience is likely to be stable across a person's lifespan.

Relationship Between Resilience and Perceived Control Over Life

There was a direct relationship between scores on the Resilience Scale and participants perceived control over their lives. Particularly, participants who perceived being in control of their lives had a significantly higher mean TRS compared to other participants who did not perceive control over their lives (M = 111.875, SD = 13.386) or were unsure of their perception of control (M = 108.362, SD = 13.705), F (2,351) = 10.045, p = <0.001. They also had significantly higher scores on all three domains of resilience including individual resilience {F (2,351) = 11.021, p = <0.001}, relational resilience {F (2,351) = 4.046, p = 0.018} and contextual resilience {F (2,351) = 6.138, p = 0.002} compared to individuals who did not perceive control over their lives or were unsure.

Perceived control refers to an individual's beliefs about their ability to influence their internal states as well as their external environment. Perceptions of control have been known to contribute to reduced distress and increased overall well-being.[33] Several research studies have shown that seeing a relationship between one's choices and outcomes helps people deal with stress, manage caregiver burden and have better overall health.[34] Similar findings have been obtained by other researchers who have examined aspects related to perceived control over life such as LOC. Edwards et al (2016) found that adolescents with an inner LOC had higher levels of resilience than those with an external LOC.[30] Our study supports these findings and emphasizes the role that perceived control plays in resilience.

Relationship Between Resilience and Social Media Usage

Social media has become the norm in today's day and age. We were interested in recognizing the proportion of adolescents who do not use social media and if that would have an impact on resilience. In our sample, the majority of the individuals used social media (n = 332, 93.79%). We found that participants who reported using social media (M = 112.668, SD = 13.820) had significantly higher mean TRS than participants who did not use social media (M =105.409, SD = 19.107), t (352) = −2.324, p = 0.021.

Our findings suggest that social media use could be associated with better resilience among college students. While there has been a lot of research on the negative impact of social media, several researchers have tried to look at its potential benefits. Sigalit et al (2017) found positive correlations among nursing students use of social media and resilience.[35] Several studies have pointed out that social media plays an important role in building resilience in times of disaster.[36] Online networks may serve to build a sense of belonging, allow expression and provide resources that people need to deal with threats thus contributing to resilience.[37]

We also found that, among all the subscales, participants who used social media (M = 29.455, SD = 4.256) had significantly higher scores on the relational resilience subscale compared to the participants who did not use social media (M = 27.227, SD = 5.739), t (352) = 2.321, p = 0.021. This suggests that the nature of social media use could be linked to better relational resilience. Social media may serve as a tool to foster communities among people to maintain connections. Zhao (2021) found that college students who use social media mainly for 'social use' including interacting and communicating with others, rather than for 'entertainment use' which includes playing games, listening to music, etc., had higher subjective well-being.[38]

Participants who did not use social media (M = 43.482, SD = 6.424) had significantly higher mean individual resilience scores compared to the participants who used social media (M = 39.318, SD = 9.756), t (352) = −2.835, p = 0.005. Individual resilience as measured in our

study by the CYRM-28, reflects an individual's personal and social skills. It is possible that students who do not use social media may be able to avoid the potential risks of social media, and thus have better individual resources. For example, studies have shown that Facebook use leads to a decline in subjective well-being among a sample of young adults.[39] Adolescents with stronger emotional involvement with social media, tend to experience greater levels of anxiety and depression and suffer from low self-esteem.[40]

All these findings together reflect the diversity in students' usage of social media and its possible implications on their lives. These factors could be explored in greater detail in future studies.

Relationship Between Resilience and Perceived Dependence on Social Media

Due to the prevalence of social media in today's age, we were interested in examining individuals' relationships with social media. Our findings suggest that besides social media usage, there is also a need to look at each individual's perceptions of their own social media use.

When it came to perceived dependence on social media, we had two main findings. Firstly, participants who did not experience perceived dependence on social media (M = 113.280, SD = 13.375) had significantly higher mean TRS compared to the participants who perceived dependence on social media (M = 109.796, SD = 15.953), t (352) = 2.124, p = 0.034. It is possible that individuals with higher levels of resilience can cope better with the stressors in their lives, and do not rely on social media to cope with stress. Other researchers have reported an inverse relationship between psychological resilience and social media addiction. They also reported that scores on psychological resilience could predict social media addiction.[39]

Secondly, participants who did not experience perceived dependence on social media (M = 29.784, SD = 4.139) had significantly higher mean relational resilience scores compared to the participants who perceived dependence on social media (M = 28.250, SD = 4.752), t (352) = 3.067, p = 0.002. Relational resilience is associated with an individual's social support. Our findings suggest that people who are not dependent on social media may have good systems of social support in their lives, reflecting higher scores on relational resilience. Other research studies have shown that individuals with higher levels of perceived social support tend to have lower levels of social media addiction.[41]

Relationship Between Resilience and Dependence on the Internet

Internet has become an integral part of our daily lives and we intend to look at how it impacts adolescent's lives. Participants who did not perceive dependence on the internet (M = 30.106, SD = 3.913) had a significantly higher mean relational resilience score compared to participants who perceived dependence on the internet (M = 28.847, SD = 4.588), t (352) = 2.634, p = 0.09. Relational resilience, as measured by the CYRM-28, reflects the individual's social support and relationships with primary caregivers.[18,42]

Our findings suggest that dependency on the internet could have an association with adolescents' interpersonal relationships. Lack of social support or poor quality of interpersonal relations could be linked to increased dependency on the internet. Similar findings have been reported by other researchers. Adolescents who reported having poor social relationships were more vulnerable to engaging in problematic internet use patterns.[43,44]

Relationship Between Resilience and Sibling Status

The majority of the students in the sample had either one sibling (n = 186, 52.54%) or more than one sibling (n = 149, 42.09%). A small number of students reported having no siblings (n = 19, 22.32%). We found no significant relationship between sibling status and mean TRS {F (2,351) = 1.017, p = 0.363}.

Some studies have found a positive correlation between sibling relationships and resilience.[45] More than the number of siblings, it is the quality of sibling relationships that influences an individual's resilience.[46] However, examining this was beyond the scope of the current study.

Relationship Between Resilience and Academic Course

The majority of the students in the current sample were pursuing a BSc degree (n = 241) followed by BA (n = 70) and BCom (n = 43). The mean TRS of the three groups were as follows – BSc: (M = 112.091, SD = 14.082); BA (M = 113.371, SD = 14.620) and BCom (M = 111.046, SD = 15.020). There were no statistically significant relationships between academic courses and mean TRS {F (2,351) = 0.381, p = 0.683}.

Relationship Between Resilience and Participation in Competitions (Sports and Intercollege)

We did not find any association between students' participation in various intercollegiate competitions

(athletic and nonathletic) and their resilience. When asked about participation in sports competitions, the majority of the participants reported not participating (n = 299, 84.46%). Similarly, when asked about nonathletic competitions, students reported not participating (n = 243, 68.64%). There were no significant relationships between participation in sports competitions and resilience scores {t (352) = 0.338, p = 0.735} and participation in nonathletic competitions and resilience scores {t (352) = 1.316; p = 0.189}.

Relationship Between Resilience and Internet Usage

The majority of the participants reported using the internet (n = 352, 99.44%). Since the sample did not consist of many students who did not use the internet, further comparative analysis regarding resilience scores could not be conducted.

Unsurprisingly, the majority of the participants use the internet, since we live in the digital age. We have included internet usage as a separate variable to better understand patterns of engagement with the internet. Distinguishing between internet use and self-perceived internet dependence can shed light on factors that lead to or influence dependency. However, this is beyond the scope of the current research and can be explored further.

Relationship Between Resilience and Consumption of Tobacco and Alcohol

Most participants reported that they did not consume alcohol (n = 344, 97.18%) or tobacco products (n = 351, 99.15%). Since the sample did not consist of many students who did consume alcohol or tobacco, further comparative analysis regarding resilience scores could not be conducted.

It is important to consider that participants in the current study may have responded in a socially desirable manner due to the setting of the study and the stigma associated with substance use, particularly among women.

Implications for Health Care

Prevention is better than cure. In health care, it is more important to focus on preventive aspects for holistic health in the community, which includes both physical and mental health. The global COVID pandemic has made the world realize that those individuals who had resilience were able to cope with the adversities far better than those who were not resilient. Building resilience in the community requires a lot of sustained effort. Training to become resilient should begin in childhood and continue into adolescence and adulthood.

AACCI has been providing WHO life skill education for children and youth since its inception in 2007 (www.aacci.in and www.aaccitrainingprograms.com).

Limitations

The current study was cross-sectional and the sample was obtained through convenience sampling due to which generalizability of the results may be limited. Data for the study was obtained through self-report measures and thus could be subject to socially desirable responses or inaccuracies. Future studies may use objective sources of data as well as reports from other individuals like parents, teachers, etc. The current sample was selected from a single college and included only females. Other researchers may consider the same variables with a more diverse sample and a larger sample size.

Recommendations

Our results can be used to create training programs to build resilience among adolescents. It shows the need to create tools that reflect the multifaceted nature of resilience- and the need to strengthen skills at three levels- individual, relational and contextual. Besides building individual capacities, we also need systems that support individuals. There is also a need to find innovative methods to prevent social media dependence. We can equip adolescents to make better use of social media platforms by educating them about their potential risks and benefits.

CONCLUSION

Our study examined the relationship between resilience and factors that are important in an adolescent's life. Our findings show that resilience is not associated with age. However, it is associated with adolescents' perceptions of control over their lives, their usage of social media and dependence on social media and the internet.

Building resilience during adolescence can be crucial to their overall well-being. Understanding factors that influence resilience at this age can help us create the right tools to support adolescent mental health. This study also contributes to the growing understanding of the role of social media in the lives of adolescents. Our findings also suggest the need to educate adolescents to appropriately use the internet and social media. Training can be created such that adolescents know

how to use social media to their advantage and also make them aware of possible signs of misuse. Thus, this study can be beneficial for adolescents as well as individuals working with adolescents in various settings like schools, colleges, health care setups and community centers.

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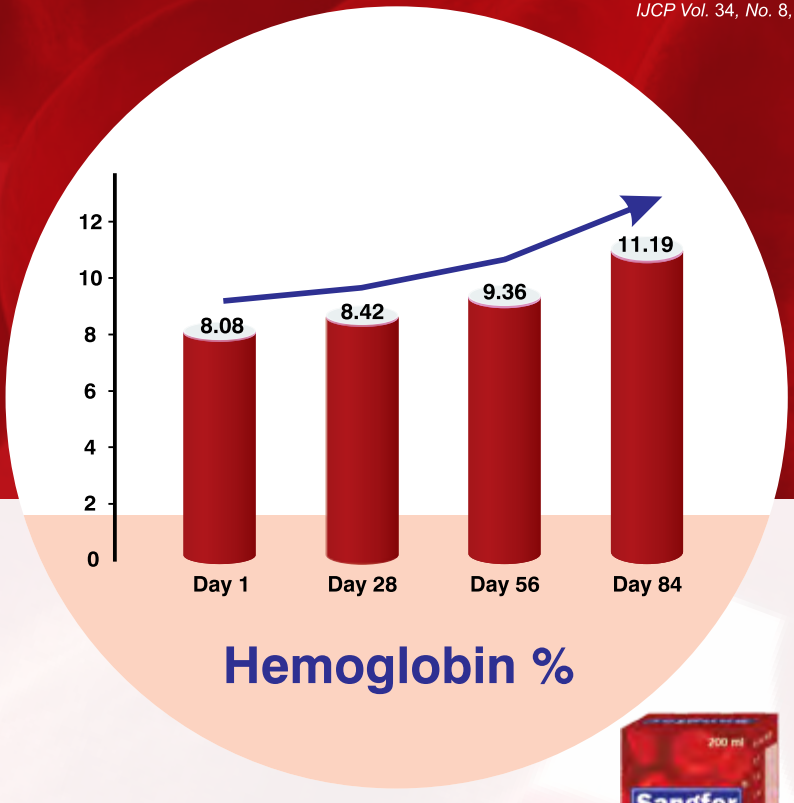

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CLINICAL STUDY

Clinical Evaluation of an Ayurvedic Preparation "Sangfer" for the Treatment of Anemia in Pregnant Women: An Open-labeled Clinical Study

SUSHMA KR*, BG VARUNI†

ABSTRACT

Background: Iron deficiency during pregnancy is one of the primary causes of anemia in infants and young children. It has a negative impact on maternal and fetal health throughout pregnancy with higher likelihood of adverse maternal and fetal outcomes. Maternal iron supplementation is a critical tool to address the global problem of iron deficiency and prevent its negative consequences. **Method:** An open-label non-comparative prospective clinical trial was carried out to evaluate the effectiveness of "Sangfer" liquid in 16 pregnant women with anemia. "Sangfer" is a polyherbal Ayurvedic proprietary medication containing elemental iron and zinc and four medicinal herbs viz. *Withania somnifera*, *Emblica officinalis*, *Asparagus racemosus* and *Pueraria tuberosa*. The aim of the study was to examine its efficacy and safety in treating anemia in pregnant women. The dose administered was 10 mL twice daily after food for 12 weeks (84 days). Patients were evaluated at screening (Visit 1 at Day 0), baseline (Visit 2 at Day 1) and during follow-ups (Visit 3 at Day 28, Visit 4 at Day 56 and Visit 5 at Day 84). **Results:** There was a significant increase in mean hemoglobin levels from 8.08% at Day 1 to 11.19% at the final visit at Day 84. The anemia sign and symptom scores also significantly reduced from Day 1 to different follow-up visits. The mean Physician Global Assessment (PGA) score was found to reduce from 1.0 at Day 1 to 0.0 at the final follow-up visit. **Conclusion:** "Sangfer" is highly effective for the treatment of anemia during pregnancy. No adverse effects including serious adverse effects were observed during the study period.

Keywords: Iron deficiency anemia, pregnancy, liquid, medicinal herbs, hemoglobin, anemia sign and symptom scores

Iron deficiency anemia (IDA) is very common, particularly in underdeveloped countries, and is now reaching a state of pandemic.[1] Iron deficiency during pregnancy is one of the primary causes of anemia in infants and young children.[2] Pregnancy increases iron demand, which increases the risk of anemia. It has a negative impact on maternal and fetal health throughout pregnancy, and has been associated with higher morbidity and fetal mortality.[3] Breathing difficulties, fainting, fatigue, palpitations and sleep problems are common among affected mothers.[4] They are also more likely to have perinatal infection, pre-eclampsia and bleeding. There are also concerns of postpartum cognitive decline and behavioral difficulties.[5,6] Anemia during pregnancy is also associated with poor perinatal outcomes such as preterm labor, intrauterine growth retardation, low birth weight, birth asphyxia and neonatal anemia.[7,8] Maternal iron supplementation is a critical tool to address the global problem of iron deficiency and prevent its negative consequences.[9] Since ancient times, numerous iron formulations have been empirically used in the treatment of anemia in Ayurveda.[10]

In this study, an Ayurvedic proprietary medication "Sangfer" containing elemental iron and zinc and four medicinal herbs *Withania somnifera, Emblica officinalis, Asparagus racemosus* and *Pueraria tuberosa* was investigated for its efficacy in the treatment of anemia in pregnant women.

Therefore, an open-label non-comparative prospective clinical trial was carried out to assess the effectiveness of "Sangfer" liquid in pregnant female participants with anemia.

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STUDY OBJECTIVES

Primary Objective

The primary objective of this study was to evaluate the efficacy of "Sangfer" liquid in anemia in pregnant women.

Secondary Objective

The secondary objective was to assess the tolerability of the supplement in study participants.

STUDY DESIGN

This study was an open-label, single-arm, non-comparative prospective clinical study to evaluate the efficacy and tolerability of "Sangfer" liquid in pregnant women suffering from anemia. The 84-day study duration consisted of five assessment points, including screening (Visit 1, Day 0), baseline (Visit 2, Day 1), two follow-ups (Visits 3 and 4, Days 28 and 56, respectively) and final visit (Visit 5, Day 84). After receiving informed consent, subjects were evaluated for eligibility based on inclusion and exclusion criteria.

After baseline assessment at Visit 2, "Sangfer" liquid was given to all eligible subjects. Subjects were instructed to take the liquid 10 mL twice daily after food for 84 days (12 weeks).

STUDY POPULATION

Pregnant women with anemia were recruited from the outpatient clinic. Potential subjects were identified by the site investigator or by designated physician based on the inclusion and exclusion criteria. A total of 16 subjects were recruited for this study.

Inclusion Criteria

Subjects who met all of the following criteria were included in the study:

- Pregnant women aged between 18 to 35 years.
- Subjects up to the 7th month of pregnancy with a clinical diagnosis and laboratory confirmation of anemia, but with hemoglobin level not <8 g/dL.
- Subjects with hemoglobin level ≤10 g/dL and peripheral blood imaging showed microcytic, normocytic and hypochromic red blood cells.
- Subjects who were able to understand the risks/benefits of the protocol.
- Subjects who gave their written informed consent and agreed to come for regular follow-up.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

- Participants with hemoglobin level ≤8 g/dL.
- Participants with a history of anemia due to any bleeding condition such as bleeding hemorrhoids, menorrhagia (cyclical vaginal bleeding excessive in quantity or duration), gastric ulcers, etc.
- Individuals with bleeding disorders such as coagulation defects, thalassemia, etc.
- Presence of any other comorbid disease such as renal failure, coronary disease, hypertension, tuberculosis, diabetes mellitus, etc.
- Subjects with history of thyroid dysfunction.
- History of psychiatric disorder that could affect subjects' ability to give written informed consent.
- Subjects with a history of stroke, myocardial infarction, coronary artery disease, heart failure, angina, life-threatening arrhythmia in the past 6 months.
- Subjects with uncontrolled diabetes (fasting blood sugar >140 mg/dL) and high blood pressure >130/90 mmHg.
- Subject with acquired immunodeficiency syndrome (AIDS) or history of any other sexually transmitted diseases (STDs).
- Subjects with high alcohol consumption (>2 standard drinks per day), smokers and recreational drug use (such as cocaine, methamphetamine, marijuana, etc.)/nicotine/caffeine dependence.
- Subjects who had participated in a clinical study in the last 30 days prior to entering this study.

STUDY PRODUCT DETAILS

The study product "Sangfer" is a proprietary Ayurvedic oral liquid for the treatment of anemia in pregnant women. "Sangfer" liquid contains medicinal plants (*W. somnifera, E. officinalis, A. racemosus* and *P. tuberosa*) used in Ayurvedic medicines.

CONCOMITANT THERAPY

No concomitant medication was allowed during the study. However, if participants reported any clinical symptoms during the study, the study physician prescribed the appropriate medication, which was documented.

STUDY ENDPOINTS

Primary Endpoint

- The primary endpoint included the mean change in hemoglobin level from baseline to the end of the study.

Secondary Endpoints

The secondary endpoints were included:

- Mean change in the global assessment on overall improvement by the investigator and by the patient from baseline to the end of the study.
- Change in subjective scores in the improvement of weakness (*Daurbalya*), fatigue (*Shrama*), breathlessness (*Shwasa*), pallor – skin, face, sclera, nails (*Pandu Varna Twak*, etc.) from baseline to the end of the study.
- Mean changes in vital sign parameters from baseline to end of study.
- Frequency and severity of the occurrence of adverse events during the treatment period.
- Proportion of subjects who discontinued study treatment due to adverse events.

STUDY ASSESSMENTS

Visit 1 (Screening): Screening events were performed at Visit 1 (Day 0). Potential subjects were identified and written informed consent was obtained from all participants. Eligible subjects meeting the entry criteria were enrolled in the study. All subjects were assessed for physical examinations, vital signs, demographic data, medical histories, including concomitant medications.

Visit 2 (Baseline): Baseline data was evaluated at Visit 2 (Day 1). During this visit, all subjects underwent physical examination, vital signs, concomitant medications, blood test for hemoglobin level, anemia sign and symptoms (weakness, fatigue, breathlessness and pallor) scores and Physician Global Assessment (PGA) score.

Visit 3 (Follow-up): All participants underwent a medical assessment during Visit 3. At this visit, all subjects were assessed for the physical examination, vital signs, concomitant medications, adverse events, blood test for hemoglobin level, IDA sign and symptoms scores and PGA score.

Visit 4 (Follow-up): All participants underwent a medical assessment during this visit (Day 56). They underwent physical examination and were assessed for vital signs, concomitant medications, adverse events, blood test for hemoglobin level, IDA sign and symptoms scores and PGA score.

Visit 5 (End of the Study): All participants underwent a medical assessment during this visit (Day 84). At this visit, physical examination and assessment of vital signs, concomitant medications, adverse events, blood test for hemoglobin level, IDA sign and symptoms scores and PGA score were done.

STATISTICAL PLANS

Data were abstracted and presented as number, percentage, mean and standard deviation (SD). All efficacy and safety variables were summarized using descriptive statistics. Data comparison between baseline and follow-up visits was performed using paired *t*-test or one-way analysis of variance (ANOVA), as appropriate, and data were expressed as mean, SD, 95% confidence interval (CI) and p-value. A p value of 0.05 was considered statistically significant. Statistical analysis was done using statistical software SPSS 10.0.

RESULTS

Data Sets Analyzed

A total of 18 female subjects were screened for eligibility; 16 subjects enrolled in the study and 2 subjects were screening failures. All subjects were given the test product "Sangfer" liquid and instructed to take 10 mL liquid twice daily after meal for 84 days. All 16 subjects completed the study, and hence, the data of 16 subjects was analyzed for this study.

Demographic Data

The mean age of the participants was 23.94 ± 2.93 years. The maximum age enrolled was 31 years, and the minimum age enrolled was 20 years. The mean weight of the participants was 47.75 ± 2.89 kg.

Efficacy Assessment

Assessment of hemoglobin level

Hemoglobin levels were evaluated at Day 1 (V2) through Days 28 (V3), 56 (V4) and 84 (V5) (Table 1). Results showed a significant increase in the mean hemoglobin levels from Day 0 to different follow-up visits. Mean changes in hemoglobin levels on Days 56 and 84 were found to be statistically significant ($p < 0.0001$) compared to Day 1 (Table 2 and Fig. 1).

Table 1. Mean Hemoglobin Level at Different Visits

Parameters	Visit (V)	Mean (n = 16)	SD
Hemoglobin (g/dL)	Baseline (V2, Day 1)	8.08	0.39
	Follow-up (V3, Day 28)	8.42	0.39
	Follow-up (V4, Day 56)	9.36	0.55
	Final visit (V5, Day 84)	11.19	0.67

Table 2. Comparison of Mean Change in Hemoglobin Level from Day 0 to Different Follow-up Visits

Parameters	Visit (V)	Mean score (mean ± SD)	Change from V1 (mean ± SD)	95% CI of Diff.	P value
Hemoglobin (g/dL)	V2	8.08 ± 0.39	-	-	<0.0001
	V3	8.42 ± 0.39	0.34 ± 0.20	−0.8414 to 0.1539	
	V4	9.36 ± 0.55	1.29 ± 0.51***	−1.785 to −0.7898	
	V5	11.19 ± 0.67	3.11 ± 0.66***	−3.610 to −2.615	

Mean hemoglobin at Day 1 (V2) was compared with Days 28 (V3), 56 (V4) and 84 (V5) by one-way ANOVA test. Comparison: V2 vs. V3, V4 and V5. Level of significance ***p < 0.0001.

*P < 0.05, **P < 0.01, ***P < 0.001.

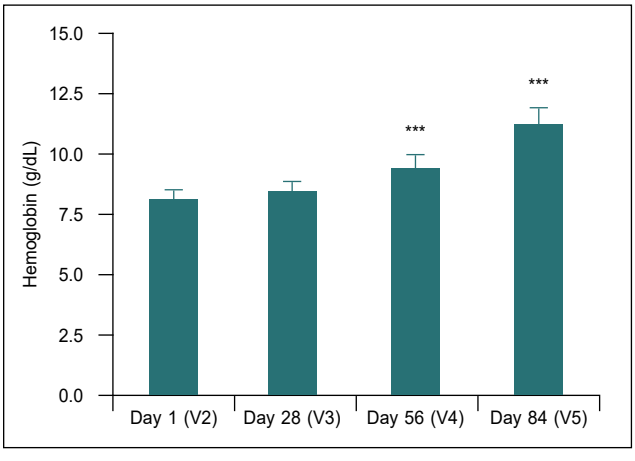

Figure 1. Comparison of mean change in hemoglobin level from Day 1 (V2) to different follow-up visits (n = 16).

Mean of hemoglobin at V2 was compared with Visits V3, V4 and V5 using one-way ANOVA. Comparison: V2 vs. V3, V4 and V5. Significance level ***p < 0.0001.

*P < 0.05, **P < 0.01, ***P < 0.001.

Assessment for anemia signs and symptoms

Anemia sign and symptom scores were assessed at Days 1 (V2), 28 (V3), 56 (V4) and 84 (V5) (Table 3). Results showed a significant reduction in anemia sign and symptom scores from Day 1 (V2) to different follow-up visits. Mean changes in all anemia sign and symptom scores (except weakness score at Day 28) were found to be statistically significant ($p < 0.0001$) from Day 28 (V3) onwards compared to Day 1 (V2) (Table 4). Reduction in weakness score was found to be statistically significant ($p < 0.0001$) from Day 56 (V4) onwards.

Table 3. Means of Anemia Sign and Symptom Scores at Different Visits

Parameters	Visit (V)	Mean (n = 16)	SD
Weakness	V2 (Day 1)	1.0	0.00
	V3 (Day 28)	0.73	0.46
	V4 (Day 56)	0.19	0.40
	V5 (Day 84)	0.0	0.0
Fatigue	V2 (Day 1)	1.0	0.0
	V3 (Day 28)	0.56	0.51
	V4 (Day 56)	0.0	0.0
	V5 (Day 84)	0.0	0.0
Breathlessness	V2 (Day 1)	1.0	0.0
	V3 (Day 28)	0.50	0.52
	V4 (Day 56)	0.0	0.0
	V5 (Day 84)	0.0	0.0
Pallor	V2 (Day 1)	1.0	0.0
	V3 (Day 28)	0.38	0.50
	V4 (Day 56)	0.0	0.0
	V5 (Day 84)	0.0	0.0

Assessment of PGA

Assessment of PGA score was assessed at all assessment points (Table 5). Results showed that the PGA score was significantly ($p < 0.001$) reduced at Days 28, 56 and 84 compared to Day 1 (Table 6 and Fig. 2).

Safety Assessment

Assessment of general health symptoms

During the study period, the general appearance, eyes, ears, nose, throat, abdomen, heart and chest of all subjects were examined to look for any treatment-related abnormalities. No abnormalities were observed at any study visit.

Assessment of vital signs

Vital sign parameters of all subjects, including heart rate, systolic and diastolic blood pressure, were measured at

Table 4. Comparison of Mean Change in Anemia Symptom Scores from Baseline to Different Follow-up Visits (n = 16)

Parameters	Visit (V)	Mean score (mean ± SD)	Change from V1 (mean ± SD)	95% CI of Diff.
Weakness	V2	1.0 ± 0.0	-	-
	V3	0.73 ± 0.46	0.31 ± 0.48	−0.029 to 0.563
	V4	0.19 ± 0.40	0.81 ± 0.40***	0.521 to 1.104
	V5	0.0 ± 0.0	1.0 ± 0.0***	0.709 to 1.291
Fatigue	V2	1.0 ± 0.0	-	-
	V3	0.56 ± 0.51	0.44 ± 0.51***	0.190 to 0.685
	V4	0.0 ± 0.0	1.0 ± 0.0***	0.753 to 1.247
	V5	0.0 ± 0.0	1.0 ± 0.0***	0.753 to 1.247
Breathlessness	V2	1.0 ± 0.0	-	-
	V3	0.5 ± 0.52	0.50 ± 0.52***	0.251 to 0.749
	V4	0.0 ± 0.0	1.0 ± 0.0***	0.751 to 1.249
	V5	0.0 ± 0.0	1.0 ± 0.0***	0.751 to 1.249
Pallor	V2	1.0 ± 0.0	-	-
	V3	0.38 ± 0.50	0.63 ± 0.50***	0.384 to 0.866
	V4	0.0 ± 0.0	1.0 ± 0.0***	0.759 to 1.241
	V5	0.0 ± 0.0	1.0 ± 0.0***	0.759 to 1.241

IDA sign and symptom scores at baseline (V2) were compared with follow-up visits (V3, V4 and V5) using one-way ANOVA. Comparison: V2 vs. V3, V4 and V5. Significance level ***p < 0.001.

*P < 0.05, **P < 0.01, ***P < 0.001.

Table 5. Means of PGA Scores at Different Visits

Assessment	Visit (V)	Mean (n = 16)	SD
PGA score	V2	1.0	0.0
	V3	0.31	0.48
	V4	0.0	0.0
	V5	0.0	0.0

Table 6. Comparison of Mean Change in PGA Score from Baseline to Different Follow-up Visits (n = 16)

Assessment	Visit (V)	Mean score (mean ± SD)	Change from V1 (mean ± SD)	95% CI of Diff.
PGA score	V2	1.0 ± 0.0	-	-
	V3	0.31 ± 0.48	0.69±0.48***	0.457 to 0.918
	V4	0.0 ± 0.0	1.0 ± 0.0***	0.769 to 1.231
	V5	0.0 ± 0.0	1.0 ± 0.0***	0.769 to 1.231

PGA score at Day 1 (V2) were compared with follow-up visits (V3, V4 and V5) using one-way ANOVA. Comparison: V2 vs. V3, V4 and V5. Significance level ***p < 0.001.

*P < 0.05, **P < 0.01, ***P < 0.001.

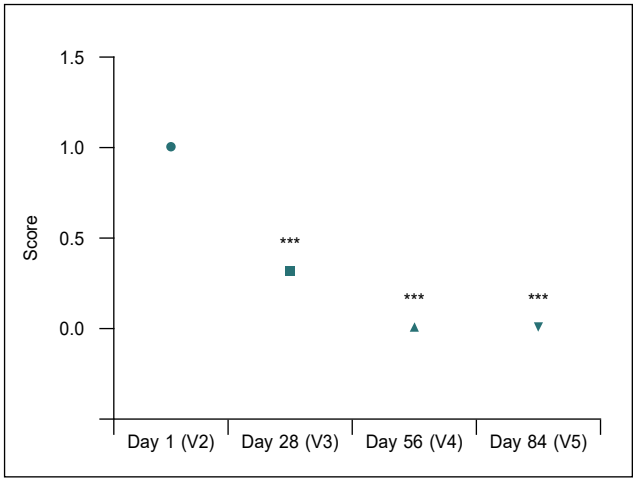

Figure 2. Comparison of mean change in PGA score from Day 1 (V2) to different follow-up visits (n= 16).

PGA score at V2 were compared with follow-up visits (V3, V4 and V5) using one-way ANOVA. Comparison: V2 vs. V3, V4 and V5. Significance level ***p < 0.001.

*P < 0.05, **P < 0.01, ***P < 0.001.

all assessment points (Table 7). The baseline (Day 1, V2) vital signs data were compared to the Days 28 (V3), 56 (V4) and 84 (V5). There was no significant difference in vital sign parameters between Day 1 and Day 84;

Table 7. Mean Vital Signs at Different Visits

Parameters	Visits	Range (Min. – Max.)	Mean (n = 16)	SD
Heart rate (bpm)	V2	72-86	81.56	3.52
	V3	72-82	79.25	2.52
	V4	80-82	80.75	1.0
	V5	78-82	80.38	1.09
SBP (mm/Hg)	V2	100-120	110.63	4.43
	V3	110-120	112.50	4.47
	V4	100-120	110.0	5.16
	V5	110-120	115.63	5.12
DBP (mm/Hg)	V2	70-80	72.50	4.47
	V3	70-80	74.38	5.12
	V4	70-80	76.25	5.0
	V5	70-80	73.75	5.0

Table 8. Comparison of Mean Change in Vital Signs from Baseline to Different Follow-up Visits

Parameters	Visit (V)	Mean ± SD (n = 16)	Change from V1 (mean ± SD)	95% CI of Diff.
Heart rate (bpm)	V2	81.56 ± 3.52	-	-
	V3	79.25 ± 2.52	−2.31 ± 4.35*	0.107 to 4.518
	V4	80.75 ± 1.0	−0.81 ± 3.75	−1.393 to 3.018
	V5	80.38 ± 1.09	−1.19 ± 3.78	−1.018 to 3.393
SBP (mm/Hg)	V2	110.63 ± 4.43	-	-
	V3	112.50 ± 4.47	1.88 ± 6.55	−6.514 to 2.764
	V4	110.0 ± 5.16	−0.63 ± 6.80	−4.014 to 5.264
	V5	115.63 ± 5.12	5.0 ± 6.32*	−9.639 to −0.361
DBP (mm/Hg)	V2	72.50 ± 4.47	-	-
	V3	74.38 ± 5.12	1.88 ± 7.5	−6.607 to 2.857
	V4	76.25 ± 5.0	3.75 ± 8.06	−8.482 to 0.982
	V5	73.75 ± 5.0	1.25 ± 7.19	−5.982 to 3.482

Vital signs data at Day 1 (V2) were compared to Days 28 (V3), 56 (V4) and 84 (V5) using the one-way ANOVA test. Comparison: V2 vs. V3, V4 and V5. Significance level *p < 0.05.

*P < 0.05, **P < 0.01, ***P < 0.001.

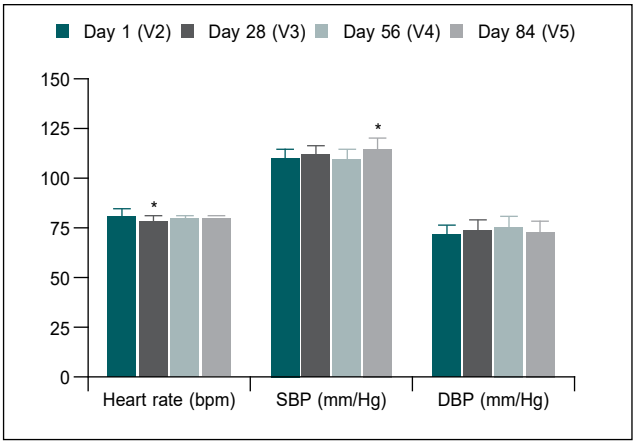

Figure 3. Comparison of mean change in vital signs from Day 1 (V2) to different follow-up visits.

Vital signs data at Day 1 (V2) were compared to Days 28 (V3), 56 (V4) and 84 (V5) using the one-way ANOVA test. Comparison: V2 vs. V3, V4 and V5. Significance level *p < 0.05.

*P < 0.05, **P < 0.01, ***P < 0.001.

all values were within the normal range (Table 8 and Fig. 3).

Adverse events

No adverse effects including serious adverse effects were observed during the study period.

DISCUSSION

W. somnifera or Ashwagandha is esteemed for its medicinal properties. It is commonly referred to as the "Indian Ginseng" due to its remarkable rejuvenating effects.[11] *W. somnifera* has been classified as a Rasayana (rejuvenation) in Ayurveda.[12] It is known to enhance vitality, energy, endurance and stamina, foster longevity and fortify the immune system, all without stimulating the body's reserves.[11] Studies have shown various properties of *W. somnifera* including antioxidant, anxiolytic, adaptogen, memory enhancing, antiparkinsonian, antivenom, sedative, diuretic, anti-inflammatory, antitumor and antistress properties.[13]

A study was conducted in anemic Albino Wistar rats to examine its antianemic activity. Following administration of the root extract of the herb, there was rapid and progressive recovery of the study animals due to the augmentation of erythropoiesis and defense against hemolysis caused by oxidative stress. The improvement in the hematological indices has been attributed to the iron content of the root extract. Iron plays a vital role in hemoglobin synthesis. These findings provide empirical support for the use of *W. somnifera* root extract in the treatment of anemia.[14] The oral administration of a concentrated root extract of Ashwagandha at a high

dosage was found to be associated with an elevation in maximal oxygen consumption (VO_2 max) thereby improving cardiorespiratory endurance and enhancing quality of life in healthy athletic adults. Additionally, it was observed that Ashwagandha root extract positively influenced the red blood cell (RBC) count and hemoglobin levels. The increase in RBC count allows for improved oxygen transportation directly to the muscles during exercise, thus enhancing the athletes' aerobic capacity. Overall, these findings propose a plausible mechanism for the ergogenic effect of Ashwagandha root extract.[11,15]

E. officinalis, also known as Amla or Indian gooseberry, is a rich source of vitamin C. It is often used as a Rasayana in Ayurveda for the management of IDA (*Pandu*).[16] The other major phytoconstituents of *E. officinalis* include polyphenols (gallic acid, ellagic acid), tannins and flavonoids (rutin and quercetin).[17] It has antioxidant, immunomodulatory, antipyretic, analgesic, cytoprotective, memory-enhancing, antitussive, gastroprotective, purgative and spasmolytic properties.[18,19]

Phytates in food inhibit the absorption of dietary non-heme iron, whereas vitamin C enhances bioavailability of iron.[16,20] The ascorbic acid enhances reduction of ferric iron to ferrous form leading to increase in iron absorption. It also prevents the inhibitory effect of phytates on iron absorption.[21] The effect of the aqueous extract of fruit of *E. officinalis* on various hematological parameters was evaluated in Wistar albino rats. Following administration of the extract in doses of 250 mg/kg and 500 mg/kg body weight, a significant increase in packed cell volume, hemoglobin concentration, RBC, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV) and platelet count was observed compared to controls. The white blood cell (WBC) count also showed a marked increase at all doses administered. Other important findings of the study were reduction in total cholesterol and triglycerides.[20,22]

A study was conducted in a tertiary care teaching hospital, to assess the impact of amloki on RBC, WBC and platelet count. A total of 43 pregnant women aged 18 to 36 years, between the 13th and 20th weeks of gestation and diagnosed with IDA were selected for this study. The participants were divided into two groups: Group A, which received oral iron and amloki supplementation, and Group B, which received only iron supplementation, for a period of 45 days. A significant increase ($p < 0.05$) in RBC count was observed in both groups following iron intervention. Furthermore, the iron + amloki supplemented group demonstrated a significantly higher increase in RBC count compared to the group receiving only iron supplementation. This study also observed an increase in WBC count in the iron + amloki supplemented group and a decrease in platelet count in both groups, although these changes were not statistically significant. The study concluded that combination of oral iron and *E. officinalis* (amloki) supplementation leads to an increased blood RBC count in pregnant women with IDA.[20]

A. racemosus or Shatavari is known as the "Queen of herbs" and is considered a health tonic and used as a rejuvenator. It improves longevity, vigor, mental function and boosts immunity. *A. racemosus* has antioxidant, anti-inflammatory, antiseptic and antimicrobial properties.[23] It also has potent adaptogenic activity, which reduces stress and protects against infection and illness.[24]

A study was conducted with the chloroform:methanol (2:1) extract of *A. racemosus* in rats with experimentally induced anemia and thrombocytopenia. The doses used in the study were 250, 500 and 750 mg/kg given orally for a duration of 10 days. Oral administration of 750 mg/kg of the root extract resulted in substantial increase in the number of RBC and hemoglobin, while the MCH and total leukocyte count decreased. The bleeding and clotting time was also reduced in comparison to the heparin group. This study demonstrated that the root extract of *A. racemosus* possesses noteworthy antianemic and antithrombocytopenic properties.[25]

Traditionally, *P. tuberosa* is a restorative tonic and is used for its antiaging and health-promotive activities.[26] It is an energizer, vital energy booster and immune booster.[27] The tubers and leaves are rich in phytoconstituents for example, puerarin, daidzein, genistein, quercetin, irisolidone, biochanin A, biochanin B, isoorientin and mangiferin, through which it exerts its beneficial activities mainly anti-inflammatory, antioxidant, anti-stress, nootropic, hypolipidemic, cardioprotective, among others.[28] The anti-inflammatory effect of extracts derived from *P. tuberosa* have also been attributed to the enhanced activity of the antioxidant enzymes present in RBCs, which act as the second-line of defense against oxidative stress. Glutathione is the first-line of defense against the damaging effects of oxidative stress. It effectively counteracts the harmful free radicals (FRs) directly and also in collaboration with other antioxidants like vitamins E and C.[29]

CONCLUSION

The results of the present clinical study demonstrated that "Sangfer" is highly effective for the treatment of

anemia during pregnancy, as evidenced by the significant increase in the blood hemoglobin level, anemia sign and symptoms and PGA scores. Furthermore, during the 84-day treatment period, no significant changes in vital signs were observed. There were no treatment-related side effects reported by any of the study participants.

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CASE REPORT

Scrub Typhus with Acute Bilateral Cerebellar Ataxia: A Rare Presentation

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ABSTRACT

Scrub typhus, also known as Bush typhus, is a zoonotic infectious disease predominantly affecting rural and semi urban areas. It is caused by the bacterium *Orientia tsutsugamushi*. Scrub typhus is predominantly seen in monsoon and post-monsoon seasons. It a vector-borne disease and has a varying clinical presentation ranging from mild acute febrile illness to life-threatening multiorgan dysfunction. Neurological manifestations can occur in the form of meningitis, meningoencephalitis, polyneuritis cranialis, intracerebral hemorrhage; rarely, it can cause cerebellar dysfunction. Herein, we report a case of acute bilateral cerebellar ataxia, one of the rare neurological complications of scrub typhus.

Keywords: Bush typhus, zoonotic, Rickettsia, neurological complications

Scrub typhus is a common zoonotic disease, which is endemic in the Asia-Pacific region. Cases are usually on the rise during monsoon and post-monsoon season. It is caused by an intracellular Gram-negative organism *Orientia tsutsugamushi* (formerly called *Rickettsia tsutsugamushi*), belonging to the Rickettsiaceae family.[1] Scrub typhus is a vector-borne disease, which is transmitted to humans via an arthropod vector of the Trombiculidae family. Mite can serve as both vector and reservoir. Scrub typhus can affect people of all the ages and is a serious public health problem in countries with high prevalence. Although this disease is seen worldwide, it is endemic to a part of world known as the "tsutsugamushi triangle", which extends from northern Japan and eastern Russia in the north to northern Australia in the south and to Pakistan and Afghanistan in the west.[2-4]

The incubation period of scrub typhus is 6 to 21 days. The onset is characterized by fever, myalgia, headache, cough and gastrointestinal symptoms like nausea and vomiting. A classical case may have black eschar at the site of chigger bite and it can be present at any body part. But this is seen only in very few cases. Patient may develop regional or generalized lymphadenopathy with enlarged and tender lymph nodes. If untreated, patient may develop complications like acute respiratory distress syndrome (ARDS) with lung infiltrates, renal failure, pancreatitis, thrombocytopenia with bleeding manifestations, myocarditis and pan-digital gangrene. The clinical presentation therefore may vary from a mild disease to severe multiorgan dysfunction with high case fatality rates.

Common neurological complications of scrub typhus include state of altered sensorium, aseptic meningitis, seizure, meningoencephalitis. But some rare manifestations include pan-digital gangrene,[4] cerebrovascular accident (CVA),[5] acute disseminated encephalomyelitis (ADEM), cerebellar dysfunction, multiple cranial nerve palsies[6,7] and disseminated intravascular coagulation (DIC). Acute cerebellar ataxia is a rare complication of scrub typhus, which was seen in our patient.

CASE REPORT

A 21-year-old married, housewife female was admitted to Female Medicine Ward of RNT Medical College, Udaipur, Rajasthan with complaints of high-grade fever with chills for 15 days, nausea/vomiting for 12 days, altered sensorium and headache for 2 days. There was no history of seizure/dyspnea. She had been treated with

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antimalarials, antibiotics, antipyretics and intravenous fluids but the symptoms did not subside and instead she developed complications for which she was brought to our hospital. At the time of admission, patient was in a state of altered sensorium, irritable and not oriented to time, place and person. Her vital signs were pulse 120/min, respiratory rate 22/min, oxygen saturation (SpO_2) was 97% at room air and temperature was 102°F (axilla). Her general physical examination revealed mild pallor. No eschar, icterus, lymphadenopathy, petechiae/purpura were seen. Detailed central nervous system (CNS) examination could not be possible because patient was in altered mental state (Glasgow Coma Scale [GCS] = E2V2M5) and irritable but there were no signs of meningeal irritation; pupils were bilaterally symmetrical and reactive to light and the plantar response was bilaterally mute. Other systemic examination (respiratory/cardiovascular/gastrointestinal) showed no abnormality. So, a clinical diagnosis of acute febrile illness, i.e., cerebral malaria, scrub meningoencephalitis, meningitis and viral encephalitis was made.

Comprehensive laboratory investigations were performed. The complete blood count (CBC) showed hemoglobin - 11 g/dL, total leukocyte count (TLC) - 9,200/cu mm, platelet count - 2.35 lakhs/cu mm. The liver and kidney function tests (LFT/KFT), chest X-ray, ECG, noncontrast CT (NCCT) scan of the head were unremarkable. Viral markers for hepatitis B and C viruses and human immunodeficiency virus (HIV) were also negative. Examination of cerebrospinal fluid (CSF) showed total protein - 184 mg/dL, total cells - 178/cu mm (90% - lymphocytes, 10% other mononuclear cells).

This patient was further subjected to specific tests relevant to acute febrile illness like CSF-adenosine deaminase (ADA) and CSF cartridge-based nucleic acid amplification test (CB-NAAT) for *Mycobacterium tuberculosis* along with CSF polymerase chain reaction (PCR) neuro-panel (for human adenovirus, enterovirus, parechovirus, HSV-1 and 2, parvovirus B19, Epstein-Barr virus, varicella-zoster virus, cytomegalovirus, herpes virus 6 and 7), which were negative. Dengue virus NS1 antigen, Dengue IgM (by ELISA), malaria parasite quantitative buffy coat (MP-QBC), serum ELISA test for chikungunya, Rubella, Japanese encephalitis viruses were also negative. Scrub typhus IgM (by ELISA) came positive. Ultrasonography of whole abdomen revealed altered echo texture of liver.

A diagnosis of scrub meningoencephalitis was made and patient was put on injection doxycycline 100 mg IV twice-daily and injection chloramphenicol 1 g IV thrice-daily along with symptomatic treatment with hydration, antipyretics and supportive care. Magnetic resonance imaging (MRI) brain (contrast-enhanced) was planned, which revealed T2/FLAIR hyperintensity in bilateral cerebellum without diffusion restriction on DWI (suggestive of cerebellitis) (Fig. 1). The patient subsequently become afebrile 3 to 4 days after treatment and started following commands. During her recovery phase, examination of the nervous system revealed dysarthric, staccato and scanning speech, head titubation, bilateral upper and lower limb in coordination in form of abnormal finger-nose and heel-shin-knee test, abnormal rapid alternating movements, wide based gait with cerebellar ataxia, truncal ataxia, nystagmus and tremors of both hands. Cranial nerve/motor/sensory examinations were within normal limits. During hospital stay, the patient was shifted to oral doxycycline and chloramphenicol. She was discharged

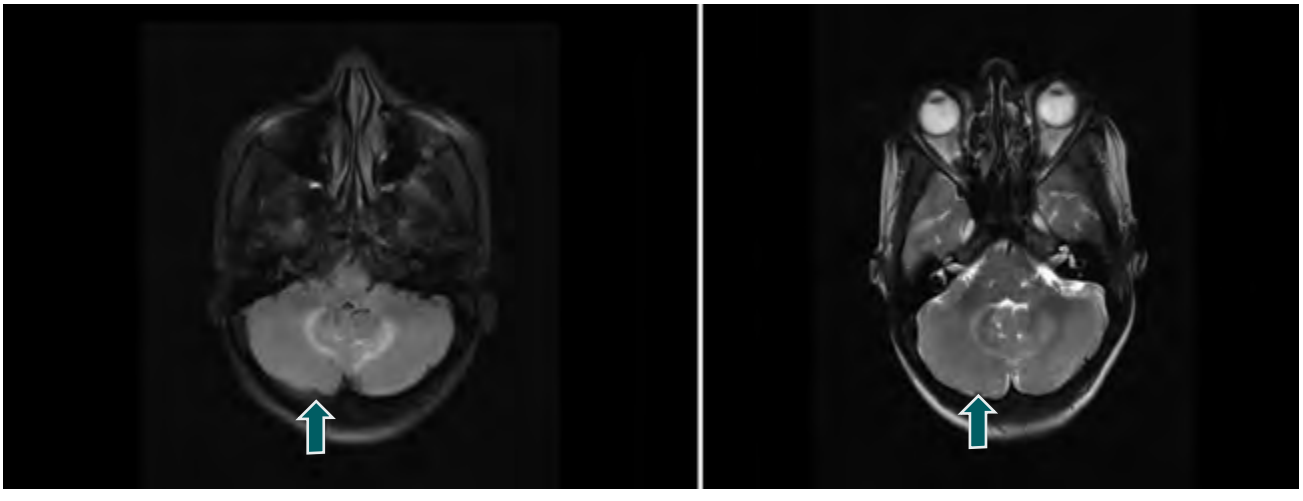

Figure 1. Contrast-enhanced MRI brain showing bilateral cerebellar hyperintensities (*arrows*) on T2 FLAIR (*left*) and T2 images (*right*) suggestive of bilateral cerebellitis.

on doxycycline and chloramphenicol for 14 days and instructed to visit Medicine OPD for follow-up.

DISCUSSION

Scrub typhus is a zoonotic disease, which has re-emerged in various part of India in last few years including southern Rajasthan. It shows seasonal variation; hence cases are predominantly seen during monsoon and post-monsoon season (i.e., July to November). It is transmitted by the bite of the chigger larvae of trombiculid mite. Man is an accidental host. Infection rates are higher in people living in rural areas with habit of open defecation, bare foot walking, people engaged in farming.[8]

The clinical manifestation can vary from mild acute febrile illness to severe illness mainly in untreated cases, which can even progress to various neurological complications and multiorgan dysfunction. The common neurological complications are aseptic meningitis, meningoencephalitis, and rare ones include cerebellitis, cerebral hemorrhage, ADEM, myelitis, cerebral infarction. As in our case report, the patient presents with isolated cerebellitis.

Previously Gupta et al[7] and Mahajan et al[8] have also reported isolated cerebellitis as a complication of scrub typhus. The likely pathophysiology is microangiopathy leading to focal or disseminated vasculitis or perivasculitis.[9-11]

Acute cerebellitis is a state of acute cerebellar dysfunction in which patient presents with incoordination, imbalance, gait instability, speech abnormality. Possible etiologies are viral and post viral infections, as part of disseminated meningoencephalitis, infarction or hemorrhage within cerebellar hemisphere, drugs and toxin (phenytoin, carbamazepine, lithium), inherited cerebellar ataxia like spinocerebellar ataxia (SCA), tumors. Scrub typhus rarely can cause bilateral cerebellitis as in our case. Other possible causes for acute cerebellitis should be ruled out. MRI may or may not be normal.[7,12]

Our case showed T2/FLAIR hyperintensity involving bilateral cerebellum. Scrub typhus response to doxycycline treatment is dramatic. Our patient too improved within 3 to 4 days of starting treatment for scrub typhus. Thus, early diagnosis and treatment is crucial to reduce complication rate and also case fatality rates. The patient may have a favorable outcome with no or minimal neurological deficit.

CONCLUSION

Scrub typhus is a growing or emerging disease in various parts of world and the Indian subcontinent. Case fatality rates in untreated cases are 7% but it can be as high as 30%. It can be missed because of the various atypical presentations; hence, high index of suspicion is required with knowledge of various common and uncommon complications. Early diagnosis and prompt treatment definitely results in better outcome. The purpose of this case report was to increase awareness about this rare presentation of scrub typhus.

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BRIEF COMMUNICATION

Innovative Urinals with Proteinuria Detection: A Potential Screening Tool for Diabetic Kidney Disease

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ABSTRACT

Chronic kidney disease (CKD) poses a considerable health challenge, particularly in populations with high-risk factors such as diabetes and hypertension. This article proposes a novel and cost-effective approach to address this concern by integrating proteinuria detection technology into urinals. We suggest the installation of these innovative 'smart' urinals in homes of individuals with diabetes, offering a convenient and proactive means of monitoring kidney health. Furthermore, the deployment of such 'smart' urinals in public places could serve as accessible screening facilities, enabling early detection of CKD in a broader population. The potential cost-benefit ratio of this approach is highlighted, emphasizing the long-term economic benefits associated with early intervention. We argue that the proposed technology has the potential to revolutionize CKD screening, providing a valuable tool for individuals at risk and contributing to the global effort to mitigate the impact of CKD on public health. Further research and pilot programs are warranted to explore the feasibility and effectiveness of this innovative screening strategy.

Keywords: Chronic kidney disease, diabetes mellitus, diabetic nephropathy, urinalysis, screening tool, public health, continuous home monitoring

Chronic kidney disease (CKD) poses a significant global health challenge, with diabetic kidney disease (DKD) being a prominent contributor.[1] Early detection and intervention are crucial in managing CKD,[2] especially in high-risk populations such as individuals with diabetes.[2] In this commentary, we propose the integration of proteinuria detection technology into urinals as a novel and cost-effective approach for screening DKD, both in home and public settings.

RATIONALE

Proteinuria is an early indicator of kidney dysfunction and a common marker for DKD.[3] Current screening methods often involve laboratory tests that may not be readily accessible or convenient for routine monitoring. The implementation of urinals equipped with proteinuria detection technology could serve as an unobtrusive and efficient means of early DKD detection.

In 2020, Park et al[4] created mountable toilet systems with readily deployable hardware and software, allowing for the collection and analysis of data related to human health. This advanced 'smart' toilet, equipped with intelligent technology, assesses urine by employing a colorimetric assay that derives red-green-blue values from images of urinalysis strips. Additionally, it utilizes computer vision as a uroflowmeter to compute urine flow rate and volume, and categorizes stool based on the Bristol Stool Form Scale.[4] Figure 1 depicts the potential abilities of proteinuria detecting 'smart' urinals.

HOME INSTALLATION

For individuals with diabetes, especially those with risk factors for CKD, having proteinuria-detecting 'smart' urinals at home could offer a proactive approach to monitor kidney health. This home-based screening tool would empower individuals to take charge of their health by enabling regular, noninvasive monitoring and

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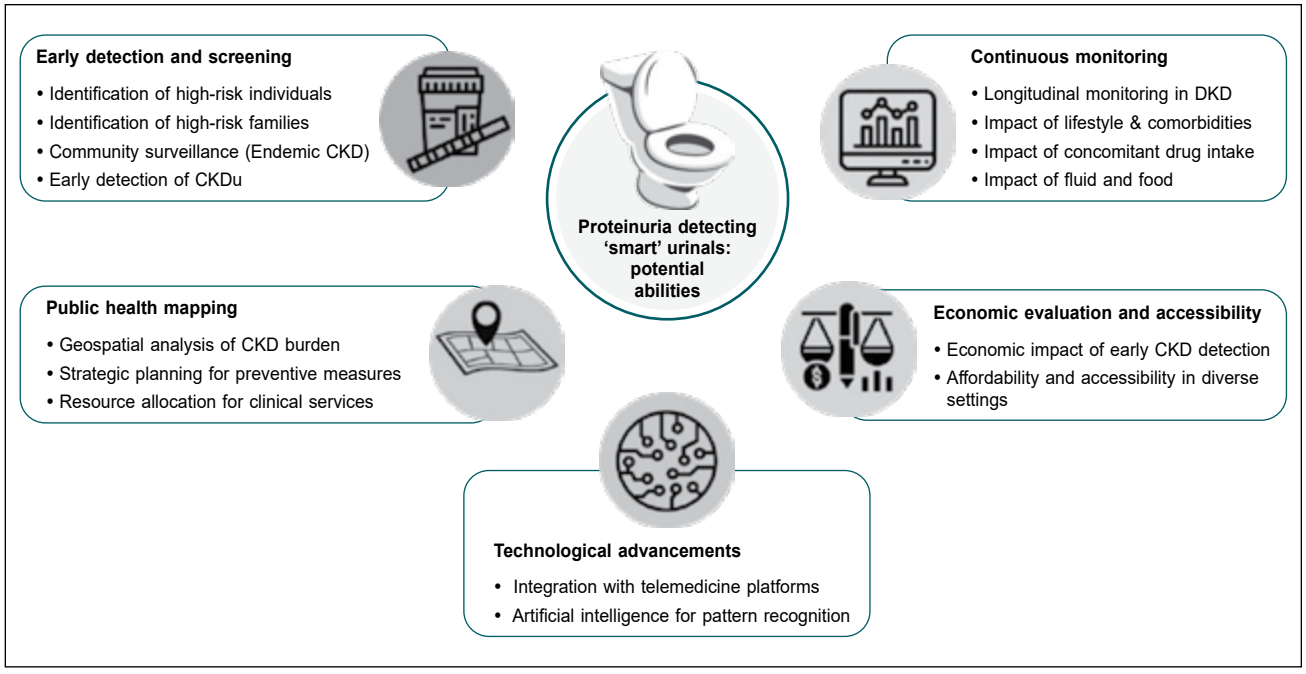

Figure 1. Potential abilities of proteinuria detecting 'smart' urinals.

facilitating early intervention in case of abnormal results. Nonetheless, this technology can also be helpful in screening the relatives who are at higher risk of developing DKD.[5]

PUBLIC HEALTH IMPACT

Installing such urinals in public places could have a substantial impact on the early detection of CKD in the broader population. Public facilities would serve as accessible screening points, allowing individuals without prior knowledge of their CKD risk to discover potential kidney issues. Early detection may lead to timely medical intervention, reducing the overall burden of CKD and associated health care costs.[3] This is especially important for communities where CKD is endemic, i.e., endemic CKD or CKDu (CKD of unknown etiology).[6]

COST-BENEFIT RATIO

Considering the high financial burden associated with CKD treatment, the proposed proteinuria-detecting urinals offer a potentially low-cost solution for early screening and intervention. The initial investment in installing this technology could be outweighed by the long-term savings resulting from reduced CKD-related health care expenses.

CONCLUSION

In conclusion, the integration of proteinuria detection technology into urinals represents an innovative and accessible approach to screen for DKD. This proactive method has the potential to revolutionize early detection strategies, particularly for individuals with diabetes who face an elevated risk of CKD.

The implementation of such urinals at both home and public locations could contribute significantly to the global effort to mitigate the impact of CKD on public health. Further research and pilot programs are warranted to explore the feasibility and effectiveness of this novel screening approach.

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Childhood Atopic Dermatitis and Risk of Nonatopic Comorbid Conditions

Children and adolescents with atopic dermatitis (AD) are at high risk of developing multiple nonallergic comorbid conditions, in addition to allergic conditions, as per the findings of a study published in the *Journal of The European Academy of Dermatology & Venereology*.[1,2]

This retrospective observational cohort study utilized data of patients, aged ≤18 years, with confirmed AD from primary and specialist care registers in Sweden between 2007 and 2017 to assess their risk of developing various comorbid conditions, both allergic and nonallergic. Type 1 diabetes (T1D), endocrine and metabolic disorders, skeletal disorders, ocular disorders, infections, neurological disorders, psychiatric disorders, immunological and inflammatory disorders and malignancies were among the conditions assessed. Out of the 1,65,145 patients included in the study, 1,26,681 had mild to moderate AD, mean age 5.13 years at the time of enrollment, and 38,464 had severe AD, mean age, 6.33 years. They were matched 1:1 with an equal number of participants without AD selected randomly from the general population as controls. The study group was followed up till December 2018.

Compared to the control group, patients with AD were at a greater risk of developing comorbid conditions for all the categories of disease conditions evaluated, with the exception of T1D and skeletal disorders. Results showed that 36.6% of AD patients had developed at least one comorbid condition during the follow-up versus 28.5% in the control group. The most common comorbid conditions were hypersensitivity and allergic disorders, which occurred in 18.5% of patients in the AD group versus 10% of patients in the control group. The next most commonly occurring comorbid conditions were infections (18.35% vs. 5.29%) followed by skeletal disorders (13.2% vs. 9.65%).

Patients with AD were at least thrice more likely to develop hypersensitivity and allergic disorders versus control group with HR of 3.87. The risk for immunological and inflammatory disorders as well as malignancies was more than doubled with HRs of 2.36 and 2.53, respectively.

Additionally, patients with AD were at a higher risk of developing several comorbid conditions. Of these, 27.1% of the AD patients and 19.7% of non-AD group developed more than two comorbidities. Active AD (vs. in remission) was associated with higher risk of comorbidity onset. As the severity of AD increased, the probability of developing a comorbidity increased.

AD constitutes a significant clinical burden in the affected children. This study shows that the risk of developing multiple comorbid conditions in addition to the atopic march is significantly increased in children with AD. The atopic march starts with AD and progresses to IgE-mediated food allergy, asthma and allergic rhinitis. Additionally, these findings demonstrated a positive correlation between the escalating severity of AD and the higher chances of the onset of comorbidity. AD is being recognized as a multiorgan disease. This study further adds to the growing evidence regarding this. Hence, it should be viewed as a systemic disease. Children with AD should be evaluated for other disease conditions and managed accordingly.

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News and Views

Combination Therapy in At-Risk Type 2 Diabetes Patients: The Way Forward?

New research published in the journal *Circulation* suggests that use of combination of sodium-glucose transporter-2 (SGLT2) inhibitor and glucagon-like peptide-1 receptor agonists (GLP-1RA), nonsteroidal mineralocorticoid receptor antagonist (MRA) drugs in patients with type 2 diabetes and kidney disease is beneficial in terms of reduced cardiovascular and renal events and mortality.[1]

This study utilized data from 12 trials (two of SGLT2 inhibitors [CANVAS and CREDENCE], 8 of GLP-1 rheumatoid arthritis trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL, Harmony Outcomes, REWIND, PIONEER 6 and AMPLITUDE-O) and two of nonsteroidal MRA [FIDELIO-DKD and FIGARO-DKD]) with the aim to compare the effects of combination therapy versus conventional care on cardiovascular, renal and mortality outcomes in patients with type 2 diabetes and urinary albumin:creatinine ratio of ≥30 mg/g. The absolute reduction in risk was estimated by applying calculated combination treatment effects to patients receiving standard care in the CANVAS and CREDENCE trials.

Results showed that compared to patients receiving standard care, those treated with the SGLT2 inhibitors + GLP-1RA + nonsteroidal MRA combination were at a lower risk of experiencing a major adverse cardiovascular events (MACE) such as nonfatal myocardial infarction, nonfatal stroke or cardiovascular death, the primary study outcome. The hazard ratio (HR) for MACE was 0.65 in this patient group. The heart rate for hospitalization for heart failure was 0.42 in the combination therapy group; the HR was 0.64 for cardiovascular death and 0.67 for all-cause mortality. The absolute risk reduced significantly by 4.4% amounting to a number-needed-to-treat of 23. The absolute risk reduction for hospitalization due to heart failure was 3.4%, 4.4% for chronic kidney disease (CKD) progression, 2.4% for cardiovascular death and 3.1% for all-cause mortality. In 50-year-old patients, initiation of this combination treatment led to an estimated event-free survival of 21.1 years versus 17.9 years for conventional care representing a gain of 3.2 years with respect to MACE-free survival.

Improvement in survival with no hospitalization due to heart failure was also seen with a gain of 3.2 years. A gain of 5.5 years was noted for CKD progression, 2.2 years for cardiovascular-related mortality and 2.4 years for death due to any cause. Even when assuming only 50% additive effects of combination therapy, there were still clinically relevant gains in event-free survival. These gains were observed for MACE (2.4 years), CKD progression (4.5 years) and all-cause death (1.8 years).

SGLT2 inhibitors, GLP-1RAs and nonsteroidal MRAs like finerenone are viewed as breakthrough therapies for patients with type 2 diabetes. They are now increasingly being used to treat these patients, not only due to their antihyperglycemic effects but also because of their proven cardiorenal protective effects. The authors also note that several major international guidelines like the American Diabetes Association and the European Association for the Study of Diabetes (ADA-EASD), Kidney Disease: Improving Global Outcomes (KDIGO) and National Institute of Health and Care Excellence (NICE) recommend "a multi-medicine strategy, tailored to individuals' residual cardiorenal risk".

This study highlights the potential clinical benefits of combining these 3 classes of drugs in improving overall survival as well as cardiac and renal outcomes in patients with type 2 diabetes and at least moderately increased albuminuria. These findings support the combined use of SGLT2 inhibitor, GLP-1RA and nonsteroidal MRA in high-risk patients with type 2 diabetes to prevent cardiorenal events and premature mortality including the need for educating patients about the associated cardiorenal risk for "shared decision-making by patients and clinicians".

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PRISm: A COPD Risk Factor

New research suggests that persons with preserved ratio impaired spirometry (PRISm) and respiratory symptoms are at risk of progressing to chronic obstructive pulmonary disease (COPD).[1] A total of 9,789 participants were enrolled for the Nagahama study; they were followed-up after 5 years. All the study subjects underwent spirometry and were given questionnaires to gather information about respiratory symptoms such as prolonged cough,

sputum and dyspnea including comorbid conditions. The aim of the study was to examine PRISm in relation to respiratory symptoms through a large-scale, longitudinal general population investigation. The aim of the study was to examine PRISm in relation to respiratory symptoms through this large-scale, longitudinal general population investigation. The aim of the study was to examine PRISm in relation to respiratory symptoms through this large-scale, longitudinal investigation involving the general population.

Findings published in the *Annals of the American Thoracic Society* reveal that 438 of the 9,760 patients who were examined overall had PRISm, which was independently correlated with dyspnea. Around 53% of them reported respiratory symptoms. Seventy-three percent of the subjects with respiratory symptoms continued to have the symptoms, while 39% of the subjects with PRISm without symptoms at baseline, developed respiratory symptoms within 5 years. PRISm was also found to be a risk factor for the development of airflow limitation among the people with respiratory symptoms but without airflow limitation at baseline, even after controlling for smoking history and comorbidities.

PRISm is characterized by a forced expiratory volume in 1 second (FEV1) of <80% predicted and a FEV1/forced vital capacity (FVC) ratio of ≥0.70. While the condition is "transient" in most individuals, some are at risk of progressive impairment in pulmonary function.[2] This study shows that over half of the participants with PRISm had respiratory symptoms and dyspnea was a prominent feature of PRISm. Around three-fourth of them had persistent respiratory symptoms over the 5 years of this study. Given the finding that PRISm itself is an independent risk factor for the development of COPD among subjects with respiratory symptoms, the clinical course of individuals with symptomatic PRISm should be carefully monitored since PRISm has been described as a "precursor" of COPD.[2]

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Diagnosing Diabetes: Impact of Type of Anemia on HbA1c Levels

Persons with iron deficiency anemia (IDA) without a history of diabetes have high glycosylated hemoglobin (HbA1c) levels, according to a study published in the journal *BMC Endocrine Disorders*.[1] Furthermore, correcting the anemia results in normalized HbA1c levels.

This study retrospectively reviewed medical records of 324 patients, including a control group and those with either B12-related megaloblastic anemia, sickle cell anemia, IDA or beta-thalassemia trait with a mean age of 46.62 years. Majority of the participants with anemia were female. Adults in good health who had normal hemoglobin and HbA1c levels and had no known diabetes or anemia made up the control group. Individuals who self-reported diabetes/prediabetes or had raised fasting, random blood sugar or 2 hours postprandial blood glucose or anemia due to any other cause were not included in the study group. This study was conducted at a tertiary university hospital in Saudi Arabia with the objective to analyze the effect of the four anemia types on HbA1c levels from 2016 to 2022. Less than half (40.2%) were being treated for anemia.

Out of the 324 study participants, 103 had IDA, 67 had megaloblastic anemia, 33 had sickle cell anemia and 17 had the beta-thalassemia trait. The control group included 104 subjects.

Compared to the control group, which had a mean HbA1c value of 5.32%, patients with sickle cell anemia had a mean HbA1c of 5.83% and IDA patients with HbA1c of 5.75%. Patients with beta-thalassemia trait and megaloblastic anemia had lower mean HbA1c levels at 5.45% and 5.38% and were similar to that of the control group. Following treatment, HbA1c significantly dropped from 5.75% to 5.44% in IDA patients. In sickle cell anemia patients, those with lower hemoglobin levels had a significantly higher red-cell distribution width (RDW), which correlated with higher HbA1c levels.

The ADA in its 2023 Standards of Care in Diabetes recommends the use of HbA1c for diagnostic screening of diabetes and to monitor glycemic control. HbA1c value ≥6.5% is the cut-off for making a diagnosis of diabetes.[2]

This study highlights the influence of specific types of anemia on HbA1c levels. Patients with sickle cell disease and iron deficiency anemia without diabetes had significant high HbA1c levels, while there was no discernible change among patients with megaloblastic anemia and beta-thalassemia trait. The HbA1c level returned to normal in IDA patients after their anemia was treated. In sickle cell anemia patients, hemoglobin and HbA1c levels were inversely related, whereas high RDW was positively correlated with high HbA1c levels.

The falsely elevated HbA1c levels in both sickle cell anemia and IDA can result in misdiagnosis of diabetes

leading to unnecessary treatment and associated distress that can well be avoided. Clinicians should exercise great caution when relying on HbA1c alone to diagnose diabetes in patients with IDA and sickle cell disease. The authors therefore "recommend correcting the anemia in patients with IDA before using HbA1c for diagnostic purposes".

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Intrapartum Antibiotic Prophylaxis and Perinatal Infectious Morbidity

The risk of clinical chorioamnionitis and peripartum infectious morbidity is reduced by nearly half in women who were positive for Group B Streptococcus and received intrapartum antibiotic prophylaxis, according to a study published in the December 2023 issue of the *American Journal of Obstetrics and Gynecology*.[1]

This study was designed as an exploratory secondary analysis of a randomized trial. A total of 491 women undergoing induction at term at a tertiary care center were included in the study. Group B Streptococci Detection Method using a carrot broth-enriched subculture was used (Hardy Diagnostics, Santa Maria, CA). These women had been screened for Group B Streptococcus in the third trimester and were administered intrapartum antibiotic prophylaxis. The maternal (chorioamnionitis, peripartum infectious morbidity) and neonatal (admission to neonatal intensive care unit [NICU]) outcomes were noted between the Group B Streptococcus positive patients who received intrapartum antibiotic prophylaxis and Group B Streptococcus unknown prophylaxis-naïve patients. Peripartum infectious morbidity, postpartum endometritis and wound infection were among the secondary outcomes of the study.

Group B Streptococcus status was identified in 466 of the 491 women recruited for the study. Of these, 174 (37.3%) were Group B Streptococcus positive women who received intrapartum antibiotic prophylaxis and 292 (62.7%) were Group B Streptococcus negative women who did not receive intrapartum antibiotic prophylaxis.

Seventy-eight percent of the study subjects were non-Hispanic Black. Approximately 60% were nulliparous. Other demographic, clinical, induction and labor variables did not differ across the groups. Women who were Group B Streptococcus positive had a lower risk of peripartum infectious morbidity at 8.1% compared to the Group B Streptococcus negative women (15.8%). The odds ratio (OR) was 0.47. The clinical chorioamnionitis rate was also lower in the Group B Streptococcus positive women (8.1%) versus those who were Group B Streptococcus negative (14.7%) with OR of 0.51. Children born to women with Group B Streptococcus positive status were less likely to require intensive care in the NICU; 3.4% versus 15.1%, respectively.

Group B Streptococcus is a known risk factor for clinical chorioamnionitis. This study demonstrates the positive impact of intrapartum antibiotic prophylaxis for Group B Streptococcus positive patients undergoing labor induction at term in reducing the risk of intrapartum and peripartum infections as well as neonatal outcomes.

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Groundbreaking "First in Human" Gene-Editing Treatment of Hypercholesterolemia: Advent of a New Era in Therapeutic Medicine?

A single dose of a CRISPR-based gene-editing therapy resulted in substantial reductions in low-density lipoprotein cholesterol (LDL-C) and proprotein convertase subtilisin kexin-9 (PCSK9) levels in patients with heterozygous familial hypercholesterolemia (HeFH) and atherosclerotic cardiovascular disease (ASCVD), according to the results of the phase Ib HEART-1 trial, which were presented at the 2023 Scientific Sessions of the American Heart Association (AHA) held in Philadelphia, Pennsylvania from November 11-13, 2023.[1-3]

Ten patients, which included 8 men and 2 women, mean age 54 years, from the UK or New Zealand were included in this ongoing, first-in-human trial. All the 10 participants had HeFH with an average LDL-C of 201 mg/dL even though almost all were receiving maximum tolerated doses of statins at the time of their enrollment in the study. But none of the participants was taking PCSK9 inhibitors. Most of them had significant ASCVD and had already undergone a coronary revascularization procedure. Approximately 50% of the subjects reported having suffered a myocardial infarction at least once. Each patient was administered VERVE-101 as a single intravenous infusion; the first group of 3 patients received a low dose of 0.1 mg/kg,

while the other three groups received increasing dosages to a maximum of 0.6 mg/kg.

The 3 patients who received the 2 highest doses of VERVE-101 (0.45 mg/kg and 0.6 mg) had the greatest reductions in LDL-C and PCSK9 protein levels. Reductions in LDL-C of 39% and 48% were seen in the 2 patients receiving the 0.45 mg/kg dose, while the 1 patient receiving 0.6 mg/kg dose had a 55% decrease in LDL-C. The blood PCSK9 protein levels were reduced by 47% and 59% in the 2 patients in the 0.45 mg/kg dose group, and by 84% in the single patient in the 0.6 mg/kg group. At 6 months, LDL-C declined in the only patient administered 0.6 mg/kg dose, with follow-up continuing. The majority of the adverse events to date were minor and not linked to the medication. Serious adverse cardiovascular events in the form of a myocardial infarction, an arrhythmia and a cardiac arrest occurred in 2 patients with underlying advanced coronary artery disease. The change in LDL has been stable for up to 6 months thus far, with follow-up still ongoing, according to the authors. "All safety events were reviewed with the independent data safety monitoring board, who recommended continuation of trial enrollment with no protocol changes required", they noted.

VERVE-101 is an experimental therapy, which permanently inactivates the PCSK9 gene in the liver through the CRISPR-based gene-editing technology thereby reducing LDL-C. The PCSK9 gene plays a key role in regulating the LDL receptor and therefore cholesterol metabolism. Increased activity of the PCSK9 gene leads to higher levels of LDL- or the 'bad' cholesterol.

A year-long preclinical study published earlier this year first demonstrated the potential of VERVE-101 as a long-term treatment for raised LDL-C levels wherein a single dose of VERVE-101 resulted in 69% reduction in LDL-C and 83% decrease in PSCK9 levels. It was also well-tolerated. Significantly, these results persevered for 2.5 years after just one dose.[4]

The present study is the first human trial of VERVE-101, in patients with HeFH and ASCVD. These are interim data and are the "first reported results for any *in vivo* DNA base editing medicine administered to human trial participants". This was a small clinical trial with just 10 patients and since all received the investigational treatment, no direct comparison could be performed with another treatment, which according to the authors is a limitation of their study. Also, "the results were measured by reductions in LDL-C, not changes in the occurrence of heart attacks". The trial is ongoing and recruitment of patients for the highest two doses of VERVE-101 is still on. The US FDA mandates a long-term follow-up of participants for up to 15 years after administration of human gene therapy products. Participants of this trial would also be subjected to this long-term follow up after a year of observation.

These are certainly exciting results for mankind and have the potential to drastically alter the landscape of treatment. They come with lot of hope for patients with devastating genetic diseases. Recently, UK's Medicines and Healthcare products Regulatory Agency (MHRA) for the first time approved Casgevy, a therapy that utilizes the CRISPR gene editing tool for the treatment of beta-thalassemia and sickle cell disease.

In addition to the evident safety concern, which is of the utmost importance, gene editing also raises ethical concerns. Many questions come to mind. What will be its impact on the generations to come? Since this will obviously be an expensive therapy, will it be accessible to just the well-off, who can afford the high costs further adding to the existing disparities in access to health care. What will be the scope of its application? And so on. These are difficult to foresee. Such innovations not only call for stringent policies and regulations, but also immense self-regulation on the part of the scientific community. Are we ready?

Nevertheless, these results are promising and pave the way for a revolutionary novel treatment option, "a single-course therapy that may lead to deep LDL-C-lowering for decades" instead of large number of daily medications, which the patients are required to take and therefore may not comply with.

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Collective Consciousness

Consciousness is an energized field of information with powers to do everything in the universe. Collective consciousness is the internet of the collective souls of many people in a group.

Collective consciousness is the strongest super power ever available in the universe. As per the Vedic texts, whatever is the intent of collective consciousness will become a reality. Scientifically, collective consciousness is based on the principle of critical mass. Vedic literature has shown it to be 1% of the defined population under study.

The origin of the critical mass comes from 100th monkey phenomenon. The story goes as under: long ago in Japan a monkey called Emo used to eat dirty apples picked up from the ground everyday. One day by accident the apple fell down in a river, the dirt got washed off and he ate the washed apple. Obviously it tasted delicious. He started washing the apples thereafter every day before eating. His fellow monkeys started following the same. The process of following went on. A time came when the 100th monkey washed the apple and ate it. A strange phenomenon was noticed. All monkeys in and around that state started washing the apple before eating. The no. 100 was the critical mass.

Once this mass is crossed the information will spread like a wild fire and the intent becomes a universal reality. Vedic literature has also shown if 1% of the public of any area meditates together, the crime rate of that area goes down. It also talks about the role of critical mass in prayers in achieving miracles.

Thus principle of critical mass is often used in designing and organizing an event. In a movie hall of 1,000 people if 10 people clap sitting in different areas everybody will clap. The same is true for hooting at a particular scene. Most politicians use this principle when they organize election rallies. For a gathering of 10,000 they need 100 and for a gathering of 1,000 people they only need 10 supporters who are supposed to sit in different areas and shout or clap on given directions. The Mexican way of hooting or clapping in cricket grounds also follows the same principle. For a ground like Eden Gardens with a capacity of 75,000 people you only require 750 people to control the mood of the people. Most successful leaders used this technology to lead.

■■■■

Common Causes of Acute Poisoning in Young Children

Nonpharmaceutical agents were the most common cause of acute poisoning in young children, aged 1 to 5 years, with medications as the second most common cause, according to a study from Vietnam published in the *International Journal of Pediatrics*.[1] Most of these poisonings occur unintentionally. A retrospective analysis was carried out at Haiphong Children's Hospital in Vietnam over a 10-year period from 2012 to 2021 to evaluate data on acute poisoning in children. During this period, 771 children were hospitalized on account of acute poisoning. Children aged 1 to 5 years had the largest percentage of hospital admissions at 506 (65.6%) with mean age of 4.5 years. There were 1.2 males for every female. The most prevalent cause of acute poisoning were nonpharmaceutical substances in 331 cases (42.9%) followed by medications in 290 cases (37.6%). Among the nonpharmaceutical substances were cleaning products (n = 63, 19.0%), rat poison (n = 60, 18.1%) and petrol (n = 42, 12.7%). The commonly implicated medications were paracetamol (n = 60, 20.7%) and sedatives (n = 40, 13.8%). Majority of cases of acute poisoning in children between the ages of one and five are accidental, whereas in older children, they are mostly intentional as also shown in this study. Nearly 70% of the accidental poisonings were in children aged 1 to 5 years; they are more exposed to dangerous substances and needed to be watched more closely. Almost ~90% of intentional poisonings (suicide attempts) were in children aged 11 to 15 years. Acute poisoning in young children is a public health problem, which is avoidable and therefore has public health implications as also corroborated by the authors who write "our study may offer information that public health officials might utilize to organize useful initiatives". Identification of the causes and frequency of acute poisoning may help formulation of programs for prevention of acute poisoning.

Reference

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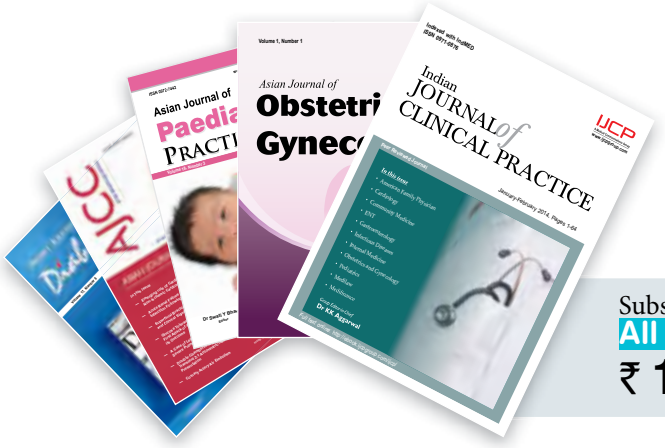

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Lighter Side of Medicine

INSPIRATIONAL STORY

TWO MONKS AND A PRETTY LADY

Once upon a time a big monk and a little monk were traveling together. They came to the bank of a river and found the bridge was damaged. They had to wade across the river.

There was a pretty lady who was stuck at the damaged bridge and couldn't cross the river.

The big monk offered to carry her across the river on his back to which the lady accepted.

The little monk was shocked by the move of the big monk and was thinking "How can big brother carry a lady when we are supposed to avoid all intimacy with females?" But he kept quiet.

The big monk carried the lady across the river and the small monk followed unhappily. When they crossed the river, the big monk let the lady down and they parted ways with her.

All along the way for several miles, the little monk was very unhappy with the act of the big monk. He was making up all kinds of accusations about big monk in his head. This got him madder and madder. But he still kept quiet. And the big monk had no inclination to explain his situation.

Finally, at a rest point many hours later, the little monk could not stand it any further; he burst out angrily at the big monk. "How can you claim yourself a devout monk, when you seize the first opportunity to touch a female, especially when she is very pretty?"

All your teachings to me make you a big hypocrite.

The big monk looked surprised and said, "I had put down the pretty lady at the river bank many hours ago, how come you are still carrying her along?"

Moral: This very old Chinese Zen story reflects the thinking of many people today. We encounter many unpleasant things in our life, they irritate us and they make us angry. But like the little monk, we are not willing to let them go away. There is no point in remaining hurt by the unpleasant event after it is over. Learn to move on in life!

HUMOR

FOR CRYING OUT LOUD

With all the new technology regarding fertility, an 88-year-old woman was able to give birth to a baby recently. When she was discharged from the hospital and went home, various relatives came to visit. "May we see the new baby?" one of them asked. "Not yet," said the mother. "I'll make coffee and we can visit for a while first."

Another half hour passed before another relative asked, "May we see the new baby now?"

"No, not yet," said the mother. A while later and again the guests asked, "May we see the baby now?"

"No, not yet," replied the mother.

Growing impatient, they asked, "Well, when can we see the baby?"

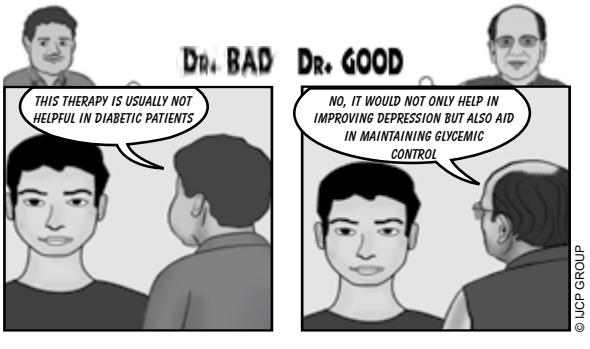
"When it cries!" she told them.

"When it cries?" they gasped. "Why do we have to wait until it cries?"

"Because, I forgot where I put it."

Dr. Good and Dr. Bad

SITUATION: A 14-year-old boy with T1DM presented with some depressive symptoms. He was advised cognitive behavioral therapy.



LESSON: The findings of a randomized controlled trial has shown the benefits of cognitive behavioral therapy in terms of maintaining glycemic control and psychological well-being in patients with T1DM. When compared with nondirective supportive counseling, it is an effective option.

Pediatr Diabetes. 2018;19(1):106-13.

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

Books

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

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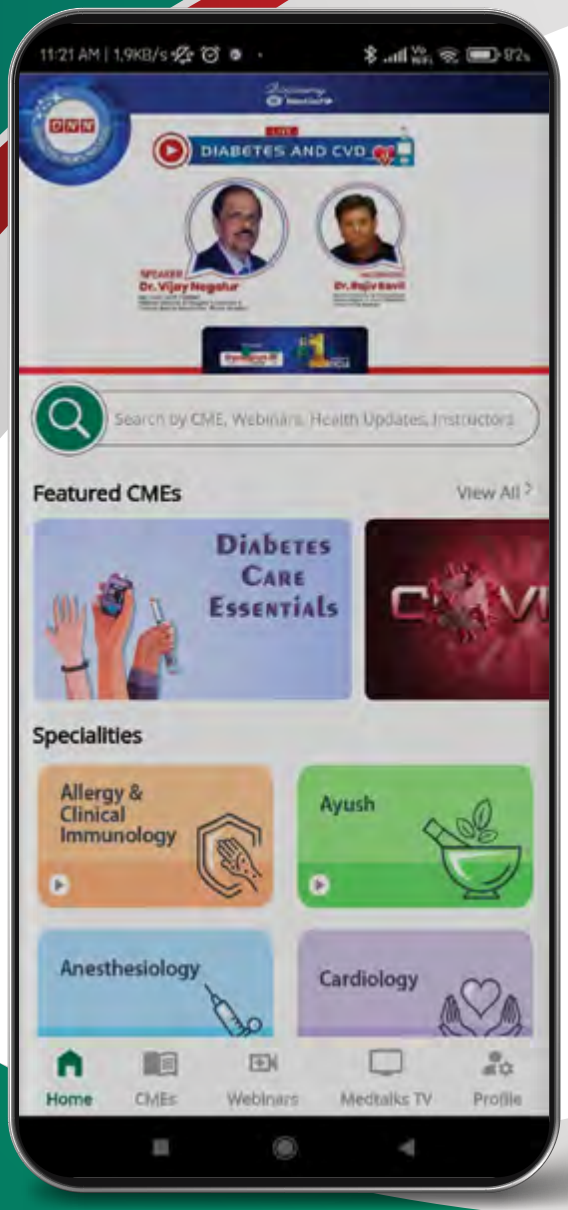

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