Advance Research Trends in Medical and Clinical Sciences Volume-1

Editors

Porf (Dr.) Manju Chhugani

Dr. Neha Singh

Dr. Madhavrao C

Dr. Mythili Bai K

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Editors

Prof (Dr.) Manju Chhugani
Prof. & Dean
School of Nursing Sciences and Allied Health
Jamia Hamdard, Hamdard Nagar, New Delhi, India

Dr. Neha Singh
Senior Scientist
Virology Lab, Department of Microbiology,
Pt JNM Medical College, Raipur, Chhattisgarh

Dr. Madhavrao C
Associate Professor
Department of Pharmacology
AIIMS Mangalagiri, Andhra Pradesh

Dr. Mythili Bai K
Assistant Professor
Department of Physiology
Government Siddhartha Medical College
Vijayawada, Andhra Pradesh

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Preface

Current trends in clinical & medical sciences is a highly interdisciplinary research field is dedicated to disseminating in-depth information and insights into all areas of current medical and clinical sciences including neurology, cardiology, anaesthesia, gynecology, dentistry, nursing, gastroenterology, ophthalmology, orthopaedics, cancer, medical imaging, dermatology, anatomy, genomic medicine etc. Clinical research is that component of medical and health research intended to produce knowledge valuable for understanding human disease, preventing and treating illness, and promoting health. The importance of clinical research is that it brings basic biomedical discoveries to the bedside to address patient care from the physical, behavioral, and social perspectives.

The present volume is based on the contributions made by various authors on different important topic of **"Advance Research Trends in Medical and Clinical Sciences Volume-1"** and introduces the subject along the following topics: Role of Physiotherapy Interventions in Diabetes Peripheral Neuropathy; A SWOC Analysis of Health Politics in Globalized World; Impact of COVID-19 on perioperative management and outcomes of critically ill pregnant patients; Role of High Flow Nasal Cannula for Respiratory Support during Oral Feeding for COVID-19 Patients on Non-invasive Ventilation; Introduction to Spinal Cord Injury; Pharmacotherapy for Diabetic Neuropathy; Alzheimer's Disease - Paths for Treatment; Dengue Prevention; and Cancer and Smartphones: Fact or Fiction?

We must place on record our sincere gratitude to the authors not only for their effort in preparing the papers for the present volume, but also their patience in waiting to see their work in print. Finally, we are also thankful to our publishers **Mrs. Shweta Singh** M/S MKSES Publishers, Lucknow for taking all the efforts in bringing out this volume in short span time.

Editors

Contents

Chapter: 1
Role of Physiotherapy Interventions in Diabetes Peripheral Neuropathy

Manu Goyal[1]* and Kanu Goyal[2]
[1]Professor, Maharishi Markandeshwar Institute of Physiotherapy & Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana
[2]Assistant Professor, Maharishi Markandeshwar Institute of Physiotherapy & Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana
*E-mail: manugoyal1111@gmail.com

Abstract: Diabetes Peripheral Neuropathy (DPN) has found to be the most prevalent around 42% of all the peripheral neuropathies in the northern rural India. As an advanced microvascular complication of Diabetes Mellitus (DM), it leads to several chronic which hampers the quality of life of a sufferer and may progress to development of foot ulcer and later amputation or even fatal. Physiotherapy interventions in form of therapeutic exercises, electrotherapy agents, manual therapy, taping and gait training has proven too beneficial in patients with DPN. Physiotherapy helps in the improvement of clinical manifestations of DPN such as balance and gait disturbance, proprioception deficits, loss of muscle mass and bone strength, neuropathic pain, conduction and alteration in the mechanical sensitivity of the peripheral nerves. This chapter will elaborate on the mechanism of action of each intervention supported by the published literature in the management of DPN.

Keywords: Diabetes Peripheral Neuropathy, Balance, Quality of life, Exercise, Transcutaneous Electrical Nerve Stimulation, Nerve conduction velocity

Introduction

Diabetes Peripheral Neuropathy (DPN) is one of the common microcirculation complications seen in 60% - 70 % of individuals suffering from Diabetes Mellitus (DM) [1] and is 50% more prevalent in Type 2 DM than Type 1 DM. [2] In the rural population in northern India, DPN prevalence rate was found to be 42%. [3] With an advancement in age, DPN hampers the quality of life to a greater extent and contribute to higher morbidity and mortality rates. [4]

Pathomechanisms in DPN

Peripheral nerves affected by diabetes are devoid of adequate blood supply due to disruption of endothelial cells and thickening of the endoneurial vessels.[5] Uncontrolled sugar levels in blood

have found to be associated with an activation of various biochemical processes [6] as shown in table below.

S. No.	Polyol Pathway Hyperactivity	Oxidative and Nitrosative stress	Microvascular changes
1.	a) Depletion of glutathione leads to accumulation of toxic species. b) Builds upon oxidative stress and free radicals. c) Elevation of advanced glycation end products; diacylglcerol; protease kinase C activity.	a) Elevation in the free radicals. b) Development of DPN may also be due to Perioxynitrite.	a) Raised dysfunction of endothelial cells. b) Elevation in levels of nitric oxide and prostaglandins.

Classification of Diabetes Peripheral Neuropathy

Diabetes Peripheral Neuropathy (DPN) have been classified into four major types as described by Thomas. [7] Sensorimotor chronic polyneuropathy which is symmetrical in class and affecting the distal extremities and approximately 70% more common than other class and types. [8] The following figure delineates the classification of DPN.
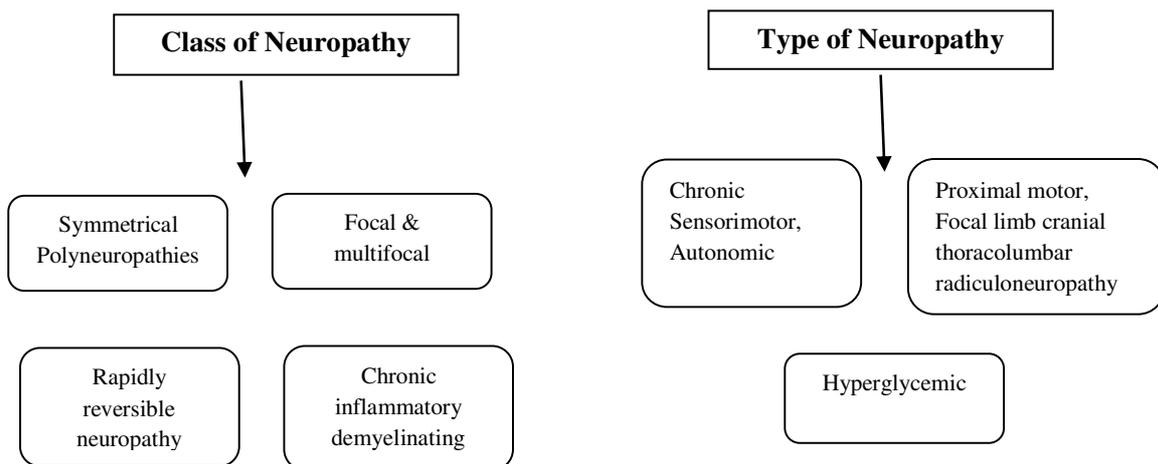
Figure 1: Classification and Types of DPN

Clinical Manifestations of Diabetes Peripheral Neuropathy

An increase in the rate of prevalence of chronic sensorimotor symmetrical polyneuropathy may be attributed to various factors such as duration of diabetes, age, gender (male), deranged lipid profile, poor percentage of HbA1C, and long term use of insulin. [9] The involvement of sensory nerves are more than the motor nerves [10] which are reflected through the symptoms such as stock and glove like distribution, numbness, progressive muscle weakness, cramps. Impairment in balance and risk of falls is twice or thrice more in patients with DPN. [11] Deficits in proprioception (joint position sense) and hampered viscoelastic behaviour (common in gastrocnemius complex) have found to be common in these patients. [12, 13] Neuropathic pain is 40% to 60% more prevalent [14] and is difficult to manage. [15]

Evidence on Physiotherapy interventions in treatment of Diabetes Peripheral Neuropathy

Exercise Therapy

In patients with diabetes mellitus, an exercise therapy has found to be beneficial in improving the sensitivity of cells to insulin, reduction of risk of hypertension and coronary artery disease, reduction of triglycerides, body fat and obesity, reducing risk of development of osteoporosis, optimizing HBA1C levels, in prevention of associated complications and coping with stress and anxiety.

Several forms of exercises such as aerobic exercises, strengthening exercises, resistance exercises, stretching exercises, balance training have been reported in the literature in patients with DPN. Exercise therapy parameters have been reported to be different among the published literature with a duration of exercise program ranges from 8 – 16 weeks.

Supervised aerobic exercises have shown the reduction in the pain interference with respect to activities of daily living. Pain interference with walking ($p = 0.016$), sleep ($p = 0.02$) and improvement in the VO2 max ($p = 0.028$) has been reported to be significantly improved. However, pain intensity as measured through Brief Pain Inventory – Diabetes Peripheral Neuropathy has shown no improvement following the 16 weeks supervised aerobic exercises in sedentary individuals having DPN. [16]

A moderate intensity aerobic exercise performed at 40% - 60% of heart rate reserve for 3-6 days per week for 8 weeks in patients with DPN have shown the disruption in the progression of DPN as measured through nerve conduction studies and Michigan Diabetes Neuropathy Score (MDNS). Conduction velocities in peroneal nerve ($p = 0.03$) and sural nerve ($p=0.00$) have reported to be statistically significant. MDNS was also reported to be statistically significant with $p<0.05$. [17]

A structured strength and balance (static and dynamic) training exercises advised once in a week for 8 weeks have reported the improvement in the functional status of the patients, with no significant improvement noted in the health-related quality of life. It has been suggested that longer duration and intensive exercises are needed to influence the health-related quality of life in such patients. [18]

Proprioception training in combination with conventional exercises such as "bilateral ankle range of motion (5 minutes), deep breathing (3 minutes), sit to stand (5 times), standing weight shifts (5 times), functional reach (sideways and anterior, 5 times each), bilateral heel raises for 20 seconds (5 times), single leg stance for 15 seconds (5 times) and single leg stance with knee flexion for 15 seconds (5 times each), wobble board training (6 minutes), tandem walking (5 minutes) and spot marching (5 minutes)", have shown the significant improvement in the functional balance in patients with DPN. [19]

Neural Mobilization & Neural massage

In DM, impairment in the excursion of nerve have been documented in the literature [20], which can contribute to adverse pathoneurodynamics. [21] Peripheral nerve exhibits the phenomenon of convergence and divergence in an attempt to counteract the physical stresses imposed on it during movement of the joint. [22] In response to mechanical stresses, neural tissue reveals the physiological defense mechanism i.e., mechanosensitivity. It is defined as the "local tenderness over nerve trunks and pain in response to limb movements that elongate the nerve." [23] Change in the mechanosensitivity may be attributed to the presence of intraneural edema due to repetitive injury, which is due to excessive secretion of substance - P and calcitonin – gene related peptide. [24] The accumulation of edema in the nerve leads to development of fibrosis and which further impair the movement of the nerve. [25]

Passive Neural mobilization (NM) along with nerve massage and transcutaneous electrical nerve stimulation has shown to be effective in the improvement of fractional anisotropy and apparent diffusion coefficient in a patient with DPN as reported in a case report.[26] Mobilization of the tibial nerve in patients with DPN have shown statistical improvement ($p<0.05$) in the nerve conduction velocity. [27] Nerve sliders and neural massage have found to be statistically significant ($p<0.05$) in improving the vibration pressure thresholds, cooling perception thresholds. [28]

Neuromuscular Taping

Neuromuscular taping (NMT) facilitates flow of lymph through the lymphatic channels, promotes flow in the blood vessels and produces relief in the pain. It is an application of adhesive tape which is elastic in nature, over the area of target without any stretch and it produces wrinkles on skin and enhances dilatation effect on the underlying body tissue. [29] In the previous literature, taping has shown to be effective in the improvement of dorsiflexors muscle strength in patients with DPN. [30] NMT has shown to effective in reduction of pain as reported in a preliminary report in patients with multiple sclerosis. [31]

Electrotherapy

Various electrotherapy modalities such as laser therapy (low level and deep tissue), transcutaneous electrical nerve stimulation (TENS), microcurrents, pulsed electromagnetic field (PEMF) have shown to be effective in reduction of neuropathic pain, improvement in nerve conduction velocities as reported in the published literature. [32,33,34,35,36]

Conclusion

It is concluded that physiotherapy interventions play a critical role in the treatment of DPN and should be used as ana adjunct to pharmacological treatment to further enhance the quality of life and prevention of falls and development of diabetic foot ulcer and later amputation in the sufferers.

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Chapter: 2
A SWOC Analysis of Health Politics in Globalized World.
Dr. Amar Raj and Dr. R.T Ankushe*
[1]Department of Community Medicine
SRTR Government Medical Collage, Ambajogai, Maharashtra
E-mail: dramarraj@gmail.com

Abstract: Public health is politics, as said in the oxford textbook of public health. Health is political because power is exercised over it as part of a wider economic, social and political system. Social determinants are amenable to political interventions and depend on political action or more usually, inaction. Health politics or politics of health is an interdisciplinary field of study concerned with analysing social and political power over the health status of individuals and societies. Factors such as housing, income and employment indeed many of the issues that dominate political life are key determinants of our health and well-being. Changing this system requires political awareness and political struggle.

Health politics requires the involvement of all human populations through a democratic process. It is important that the political process to improve the public's health be based on sound scientific evidence. Moving forward, political interference in medical decisions may become more common, but it may also be necessary in order to improve patient care. A nation's policies toward health care access tend to be broadly inclusive, even when other forms of inequality are tolerated, because health is a responsibility of the federal state. Nations worldwide should converge on a governance model for health products and health services that gives significant power to professionally and governmentally sanctioned scientists and healthcare workers who can serve natural justice and do equitable distribution of health system resources.

Keywords: Health Politics, SWOC Analysis, Globalized World.

Introduction

Public health is politics as said in the "Oxford Textbook of Public Health". Ultimately, health is political because power is exercised over it as part of a wider economic, social and political system. Health is political because its social determinants are amenable to political interventions and depend on political action or inaction. Health politics or politics of health is an

interdisciplinary field of study concerned with the analysis of social and political power over the health status of individuals[1,2]. Health determinants such as housing, income and employment indeed many of these issues dominate policy formulation in democratic countries indirectly by politicians. Making People-centric healthcare decisions requires political awareness and political struggle. The politics of health is not just constrained to a particular area of society, such as the state or government, but rather is a dynamic, ongoing social process that takes place ubiquitously throughout our levels of society[3].

Strength

➢ Globalization has increased economic interdependence, global communication, and international migration, creating a new sense of urgency to address global health issues and ushering in a new era of global health governance to replace the previous international health governance.

➢ A strong body of decision makers made up of scientists and their allies to work together and come to decisions through open, transparent, and rigorous debate. Public health and policymaking should be free from vested religious, economic, or political interests, according to modern reasoning and democratic methods of government.

➢ Intersectoral coordination through global political commitment is the ideal strategy for achieving universal health coverage, one health and health for all, since it will bring global health to improve population and planetary health.

➢ The decision to apply the equity principle in health is political; there is a crucial distinction between the decision to act or not to act, which is eminently political in nature.

Weakness

➢ Health politics requires the involvement of all human populations through a democratic process that excludes reflection of class politics. Decision-makers may neglect scientific evidence or in the worst cases, bend it to serve their own narrow interests.

- The weak commitment results in a lack of communication and coordination between the countries where public health emergency of international concern breaks out. There is no honest governing system at the global level.

- Political determinants of health are not set within the social determinants of health rather; emotional factors play an important role. Individuals are identified by nation, race, ethnicity or by religion, not as human beings.

- Political determinants of health are set within the social determinants of health, but acknowledges that political processes and contestation over power form a unique social phenomenon that requires a distinct conceptualisation to appreciate their impact upon health and healthcare[4]

- Health justice, is a fundamentally global concept and requires health equality within and across countries and regions. Problems confronting the global governance of international public health, such as limited functions of international organizations and difficulties in achieving objectives, poor collaboration between governance subjects and their limited performance, the overlapping legal basis of governance and blurred core function, and lack of solutions to special problems.

Opportunity

- With ongoing national and international debates on healthcare reform, women's access to reproductive health services, and immigration, physicians need to provide critical voices to discussions that will impact patients.

- Entanglement between politics and medicine may not only be an increasing reality, but a necessity. As the legendary German physician Rudolph Virchow noted over a century ago: "Medicine is a social science, and politics is nothing more than medicine on a large scale[5]."

- Machenbach proposed an imaginary "ladder of political activism" with four rungs from which the global health practitioner can choose the level of political action they think would be most effective and appropriate (seen in fig:1). Public health professionals should consider the third rung of Machenbach's Imaginary Ladder of Political Activism[6].
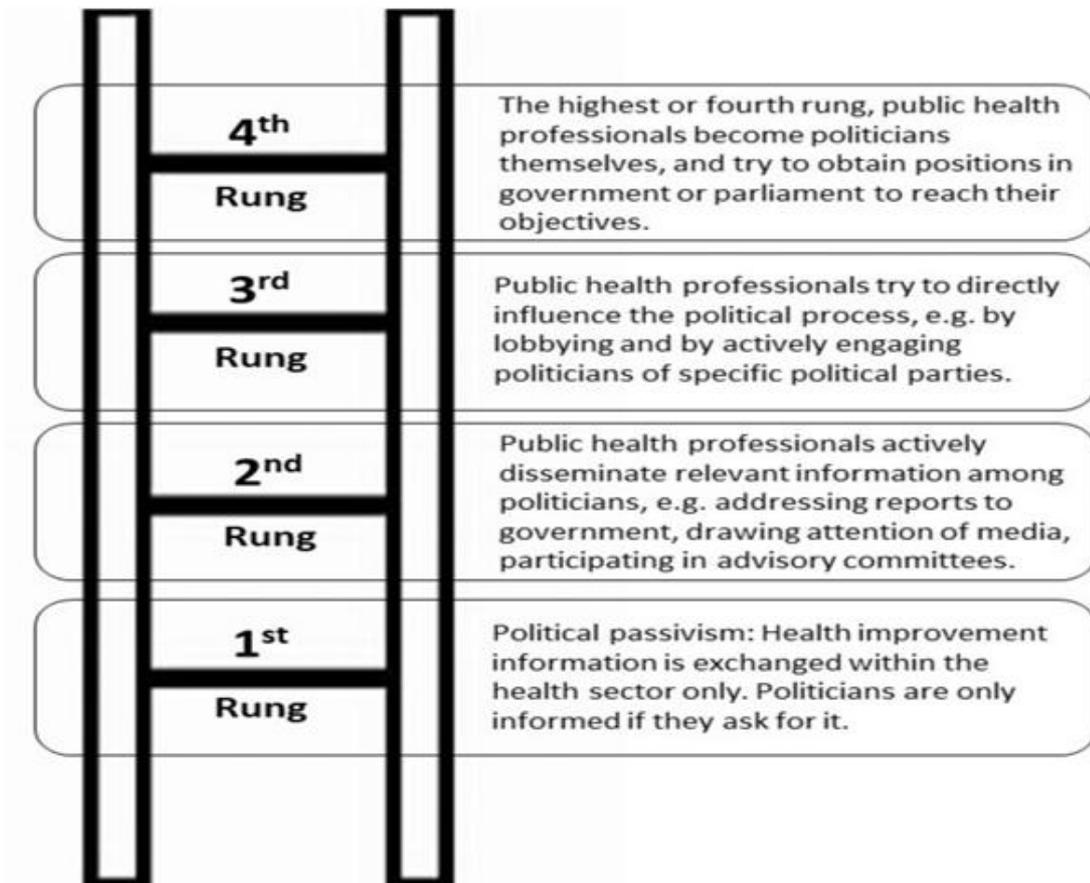
Figure 1: Machenbach's ladder of political activism[6]

➢ The political determinants of health are a conceptual framework that visualizes and frames the political factors that shape and control the health and wellbeing of people[7]. This places a sociological lens upon areas like medicine, treating it as a social science as much as an applied science to understand its political nature[8].

Challenges

➢ The growth of global corporations and their political power are exercised in health services provision, health products, and in national politics generally. Issues of federalism at which level of government should the health services or regulations be rendered, promulgated, and enforced. Transnational and cross-governmental diffusion and dependence in health politics.

- ➢ Improving the efficiency of the governance of global public health, including supporting the role of international organizations to achieve the objectives, enhancing coordination among international governance subjects to form synergy, promoting compliance with International Health Regulation 2005 to avoid conflict of law application and upholding the vision of a community with a shared future for humanity to jointly respond to the special problems[9].

- ➢ Licensure and legitimation of medical services, organizations, and professionals by government and nongovernment entities and the comparative political organization of hospitals, physicians, nurses, and other health service providers.

- ➢ The gatekeeping and conceptual powers of regulatory agencies governing medical products like drugs, devices, and traditional healing products. For example, the politics of tobacco and alcohol control globally and the disease burden caused by it.

Conclusions

Health politics requires the involvement of all human populations through a democratic process. It is important that the political process to improve public health be based on sound scientific evidence. Political biases favor the immediate gratification and gains of today rather than tomorrow[10]. Moving forward, political interference in medical decisions may become more common, but it may also be necessary in order to improve patient care. A nation's policies toward health care access tend to be broadly inclusive, even when other forms of inequality are tolerated, because health is a responsibility of the federal state. Nations around the world should converge a model of governance for health products and health services that gives significant power to professionally and governmentally sanctioned scientists and health care workers who can serve natural justice and do equitable distribution of health system resources.

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Chapter: 3
Impact of COVID-19 on perioperative management and outcomes of critically ill pregnant patients

Dr. Rajesh Raman and Dr. Rati Prabha
Department of Anesthesiology, King George's Medical University, Lucknow, UP
E-mail: ramanrajesh83@gmail.com

Abstract

Objective: We aim to describe the clinical course, perioperative management, and outcomes of critically ill pregnant patients with COVID-19 in this case series.

Methods: This was a hospital-based, retrospective case series. The case history and files of the patients were evaluated for preparation of this case series.

Results: The seven critical COVID-19 ill patients had acute respiratory distress syndrome, septic shock, hemorrhagic shock, ruptured uterus, preeclampsia with severe features or ruptured ectopic pregnancy. Initial resuscitation was done for patients who were in shock. All patients had to be operated within 24 hours of admission. Five patients needed general anesthesia and remaining required epidural anesthesia. Hypoxia, hypotension, and tachycardia were common intraoperative complications managed by optimizing oxygen therapy, fluid resuscitation and vasopressors. In absence of contraindications, remdesivir, low molecular weight heparin and steroids were used for management of COVID-19. Four patients expired within one week of admission, remaining patients were discharged. Three newborns were discharged within one week of birth, remaining three were stillborn.

Conclusions: Currently, the effect of COVID-19 on pregnancy and vice versa is yet to be determined. Differences in quality and access to healthcare facilities with evolving nature of COVID-19 and its management may result in wide variations in maternal and neonatal outcomes.

Keywords: COVID-19, pregnancy, anesthesia, critical illness, hemorrhagic shock, pre-eclampsia

Introduction

The COVID-19 pandemic has profoundly affected the management and outcomes of pregnant patients.[1-3] Most trials exclude pregnant patients from their study. At least some of the rapidly evolving research shows that maternal and newborn outcomes are adversely affected directly or indirectly by the SARS-CoV-2 infection.[4,5] Majority of the data of these studies are derived from patients with mild illness. Even less information is available about patients whose illness is critical. In this case series, we have described perioperative management and outcomes of COVID-19 positive pregnant patients who were critically ill and underwent major surgery.

Subjects and Methods:

The case history and files of obstetric patients at a tertiary care center were searched for preparation of this case series. Informed consent of the patients' or legal representatives was taken.

Results:

Table 1 summarizes the initial presentation and intraoperative management of the cases. Postoperative management and outcomes are summarized in table 2. Intraoperative heart rate and systolic blood pressure are depicted in figures 1 and 2 respectively.

Cases 1 and 2:

Both patients had full-term pregnancy with severe acute respiratory distress syndrome (ARDS) on admission. In addition, case 1 was in septic shock with arterial blood pressure (BP) of 78/52 mm Hg and heart rate of 159 per minute. Her respiratory rate was 40/minute and had initial arterial blood oxygen saturation (SpO$_2$) of 76% on 6 liters/minute oxygen by Hudson mask. Case 2 had a respiratory rate of 36/minute and SpO$_2$ of 81% on oxygen at 6 liters/minute by Hudson mask with heart rate 134/minute. Both patients were intubated immediately after arrival in our hospital and lung-protective mechanical ventilation was started. Case 1 had refractory hypoxemia and needed lung recruitment maneuver, neuromuscular blockers, and bronchodilators to achieve SpO$_2$ of $\geq$92%. She was also given crystalloids boluses and vasopressor (noradrenaline and vasopressin) infusion. Emergency lower segment caesarean section (LSCS) was done on both patients under general anesthesia. Case 1 had intraoperative hypoxemia (SpO$_2$: 82-86%%, managed by increasing inspired oxygen percentage to 100% and PEEP to 15 cm H$_2$O), prolonged hypotension (BP: 80/40 to 85/50 mm Hg for 15 minutes, managed by

intravenous fluids and increasing vasopressor infusion rate) and sustained tachycardia. Case 2 had transient intraoperative hypoxia which was managed by increasing inspired oxygen percentage to 100%.

After surgery, lung protective mechanical ventilation was continued in the intensive care unit (ICU) for both patients. Case 1 expired 16 hours after surgery. Case 2 was given injection remdesivir, hydrocortisone infusion and antibiotics. Low molecular weight heparin (LMWH) could not be started because of deranged coagulation postoperatively. She died on fourth day after admission due to septic shock and ARDS.

Cases 3 and 4:

Both these cases had a history of fever, cough for last four days and dyspnea for past one day. In addition to ARDS, both patients had ruptured uterus and were in hemorrhagic shock at the time of admission. Intravenous crystalloids and blood products were given, and infusion of noradrenaline and vasopressin was started. Their airway was immediately secured, and emergency hysterectomy was done under general anesthesia. Fluid resuscitation and vasopressors were continued intraoperatively. Both patients expired after surgery within 24 hours of admission due to hemorrhagic shock and disseminated intravascular coagulation, before any specific therapy for COVID-19 could be started.

Case 5:

The patient had moderate COVID-19 with fever, myalgia and cough for three days and dyspnea for one day. She had hemorrhagic shock with a heart rate of 127/minute and BP of 70/46 at the time of presentation due ruptured ectopic pregnancy. Her respiratory rate was 26/minute and SpO_2 was 90% on presentation, which improved to 95% with supplemental oxygen by Hudson mask. Crystalloids, blood products, and vasopressors were started, and emergency laparotomy under general anesthesia was undertaken to control bleeding. Intraoperative hypotension was managed with additional blood products, intravenous fluids, and vasopressor infusion. She was weaned off from mechanical ventilator and vasopressors the next day after surgery. For COVID-19, she was given dexamethasone and remdesivir for five days. LMWH was started two days after surgery. She was discharged on tenth day after admission.

Cases 6 and 7:

These patients had moderate COVID-19 with fever and cough for the last three (case 7) and four (case 6) days. Their SpO_2 was 90-92% on room air with normal respiratory rate and were given

oxygen using Hudson mask. Both had preeclampsia with severe features (SPE) with case 6 having BP of 180/116 mm Hg and case 7 having BP of 176/112 mm Hg at the time of presentation. The patients were given labetalol and magnesium sulphate and emergency LSCS was done under epidural anesthesia. The intraoperative course was uneventful. Postoperatively, both were given dexamethasone and LMWH for COVID-19 and supplemental oxygen by Hudson mask was continued. Case 7 was also given remdesivir for five days as she delivered stillborn baby. They were discharged on eighth (case 6) and eleventh (case 7) day after admission.

Discussion:

Management of sick obstetric patients poses unique challenges. Concurrent COVID-19 infection adds additional issues to their management.[1,2,6] The differences in the severity of COVID-19 and pregnancy outcome may be affected by physiologic and immunologic changes in pregnancy as well as by altered expression of angiotensin-converting enzyme 2 (which acts as a co-receptor for SARS-CoV-2).[3,7] We presented seven cases of pregnant patients with COVID-19. Out of these, the initial four cases had critical COVID-19 infection and the last five cases had severe/critical obstetric complications with COVID-19.

The contribution or effect of COVID-19 infection to pregnancy and various obstetric conditions or vice versa is a matter of debate and scientific literature is limited on this topic. Some studies indicate that the severity of COVID-19 is unaffected by pregnancy while others conclude that mortality and ICU stay is increased by COVID-19 infection, especially if caesarean delivery is done.[1,2,5-12] Adverse maternal outcomes also vary by the geographic location with studies originating from China and Brazil reporting worse outcomes compared to those from Europe and North American studies.[4,13] Maternal and neonatal morbidity and mortality (in non-COVID-19 patients) varies widely among countries, with developed countries generally having better outcomes. It is likely that this heterogeneity is reflected in pregnant patients suffering from COVID-19.

It must be stressed that a vast majority of patients described in the above studies had mild to moderate disease and their findings may not be applicable to more severe COVID-19. In their systematic review of 637 hospitalized pregnant patients, Turan et al found that patients with severe and critical diseases accounted for most of the adverse maternal and newborn outcomes.[14] Some outcomes, on which studies invariably agree are that COVID-19 increases

the need for ICU admission, caesarean delivery, and preterm birth. Newborn mortality is unaffected directly and vertical transmission appears to be extremely rare. Co-location of mother with newborn or 'rooming in' is advised by most guidelines unless contraindicated by maternal or newborn's medical condition.[2] Newborn should be placed at least two meters from mother. The mother should wear mask and wash her hands before feeding the baby. Expressed breastmilk can also be fed to the newborn.

Little research is available for the management of severe ARDS in pregnant patients with COVID-19. Important points that may help in managing these patients are:[15,16]

1. Lung protective invasive mechanical ventilation with use of PEEP, low tidal volume, and plateau pressure less than 30 cm of water.

2. Prone ventilation can be difficult in pregnant patients and very little evidence is available on this, but it has been used successfully.[15] Lateral positioning may also help, is easily achievable, and also helps in avoiding aorto-caval compression.

3. Use of neuromuscular blocking drugs and lung recruitment followed by inhaled nitric oxide and extracorporeal membrane oxygenation can be used if hypoxia is refractory to the above measures.

Current knowledge on pharmacotherapy of COVID-19 in pregnant patients is extremely limited as the vast majority of research has been done on non-pregnant patients.[17] Experts recommend that drugs that are likely to be effective in COVID-19 pregnant patients should not be denied based solely on potential adverse effects.[16] The decision to administer the drug should be decided after discussion between the patient and physician regarding advantages and potential adverse effects on mother and fetus. Steroids, lopinavir/ritonavir (category B), hydroxychloroquine, azithromycin (category B), and convalescent plasma have been used safely in pregnancy.[17] Favipiravir and ivermectin are teratogenic and embryotoxic in animals.[17-19] Remdesivir is not FDA approved in pregnancy but can be, and has been used in pregnancy on compassionate grounds.[20] Local availability of drugs can also be an issue in deciding the treatment.

COVID-19 and preeclampsia share overlapping clinical features, and both have an exaggerated immune response in their pathogenesis.[21,22] Abnormal placental development plays a central role in the development of preeclampsia. Pathological placental changes including infarction, thrombi, chorio-hemangioma, and mal-perfusion are seen even in mild COVID-19 disease.[23]

There is higher incidence of preeclampsia in COVID-19 patients and outcomes are worse in preeclampsia with severe COVID-19 infection.[24-26] Preeclampsia has the potential to worsen the respiratory impairment caused by COVID-19, but in our patients with SPE, the severity of COVID-19 was moderate. Both the patients recovered completely but one of them had intrauterine fetal demise.

Neuraxial anesthesia is the recommended technique for caesarean delivery of COVID-19 patients and should be used if there are no contraindications like severe respiratory compromise, coagulopathy, and infection at the site of block. The potential benefits of neuraxial anesthesia in COVID-19 pregnant patients are:

1. Reducing risk for Mendelson syndrome.

2. Avoidance of endotracheal intubation, which is an aerosol-generating procedure, reducing infection risk for operating room personnel.[27]

3. Reducing pulmonary complications by avoiding manipulation and alterations of the respiratory system, which is the predominant organ system affected by COVID-19 disease.[28,29]

4. Eliminating muscle relaxants and reduction in systemic opioid requirements further reduce the pulmonary compromise.

5. COVID-19 and pregnancy both are pro-coagulant states, hence increasing the risk for abnormal thrombosis- regional anesthesia potentially reduces these thrombo-embolic complications.[29-31]

6. Regional anesthesia provides better postoperative analgesia.

7. There is reduced need for drugs including sedatives, hypnotics and muscle relaxants.[27]

8. Potential suppression of the pro-inflammatory state by regional anesthesia and local anesthetics.[32]

A high incidence of intraoperative hypotension was observed by Chen et al in COVID-19 pregnant patients given neuraxial anesthesia, but no resulting organ damage or adverse neonatal outcome was present.[33] We did not observe hemodynamic instability in the two patients with SPE who were given epidural anesthesia.

If general anesthesia is necessary due to patient's hemodynamic, respiratory, neurological or hematological derangement, precautions must be taken to prevent the of COVID-19 spread to healthcare workers:[2,34]

1. Whenever possible, patient must wear surgical/N95 mask.

2. Use dedicated operating theatre and post-operative recovery room with negative pressure ventilation and dedicated pathway and elevators for patients' transport.

3. Minimize the number of personnel in the operating room. Use of personal protective equipment is mandatory for all healthcare workers in the operating room.

4. Rapid/modified rapid sequence intubation is recommended for all COVID-19 patients with normal airway. Use of rocuronium bromide is preferred over succinylcholine to prevent fasciculations and resultant aerosol generation.

5. Pre-oxygenate the patients with 100% oxygen for five minutes to avoid ventilation after induction of anesthesia. Cover the mouth and nose of patient with two layers of wet gauze to possibly trap the respiratory droplets and secretions.

6. Use adequate depth of anesthesia before intubation to avoid coughing and bucking.

7. Video-laryngoscope is preferred over the direct laryngoscope for intubation as it has higher first-pass success rate and the user can maintain greater distance between himself and the patient's airway to minimize exposure.

8. Most experienced anesthesiologist should intubate the patient to achieve successful intubation in first attempt.

9. Heat and Moisture Exchange filters should be placed between the endotracheal tube connector and the circuit to contain the SARS-CoV-2 virus within the patient's respiratory system.

10. Breathing circuit should be disconnected after clamping the endotracheal tube. Use closed suction for endotracheal suctioning.

11. The operating and post-operative room should be cleaned after every use.

General anesthesia was needed in five patients in our case series. Out of these, three patients were in hemorrhagic shock in our case series with two of them having ruptured uterus and one having ruptured eight-week ectopic pregnancy. The rapid spread of COVID-19 in a short period has led to scarcity of evidence-based guidelines for management of several conditions. In absence of guidelines, hemorrhagic shock was managed with blood component therapy, crystalloids and vasopressors, and emergency surgery was undertaken to control bleeding. It must be kept in mind that peripartum obstetric hemorrhage is frequently underestimated and failure to replace the lost blood volume to acceptable levels and delaying surgery to control

bleeding may worsen obstetric outcomes.[35] The ratio of heart rate to systolic blood pressure, the shock index, is a useful parameter for detecting hemorrhagic shock even in the early stages.[35]

Three out of six uterine pregnancies resulted in intrauterine death, with two resulting from uterine rupture and one due to SPE. Remaining three newborns needed resuscitation and ICU stay but were discharged from our hospital within few days. As discussed earlier, the rate of preterm birth and ICU stay is increased but newborn mortality is unaffected. The intrauterine demise in at least two of the three cases can be attributed directly to the obstetric complications.

One of the contributors to poor outcomes in our cases was their late presentation to the hospital. The clinical condition of case number one to five was already in critical at the time of admission. Four of them expired, with three dying within 48 hours of admission. The systemic pro-inflammatory state caused by major surgery, and to some extent by mechanical ventilation may add to the already pro-inflammatory state in COVID-19. This can also negatively affect the prognosis of patients with severe/critical COVID-19.

Conclusion:

In pregnancy, COVID-19 can have an ominous outcome for mother and neonate if the disease is severe/critical or if the patient has any concurrent obstetric complication. However, scientific data related to COVID-19 continues to grow at a fast pace and any conclusive statement regarding this will be relevant only after reviewing appropriate good quality studies after they become available.

Table 1: Initial presentation and intraoperative management of cases

Case No.	Age	Diagnosis	Symptoms & abnormal clinical findings	Abnormal investigations	Pre-operative management & drugs	Anesthesia Details	Complications
1	30 years	G3P2, 38W pregnancy with severe ARDS, septic shock & obstructed labor	Fever, dyspnea, B/L crepitations, HR:159, BP:78/52, RR:40, SpO$_2$:76 % on oxygen by Hudson mask	Leukocytosis, lymphopenia, ↑PCT, ↑CRP, ↑ferritin, ↑D-dimer, ↑IL-6, ↑LDH, ↑lactate deranged LFT, KFT, ↑INR	Invasive ventilation, lung recruitment, bronchodilator, antibiotics, fluid bolus, NA & vasopressin	Induction: ketamine, rocuronium, Maintenance: sevoflurane, fentanyl, rocuronium	Hypoxia, hypotension, tachycardia
2	40 years	G5P4, 38W6D pregnancy with severe ARDS with fetal distress	Dyspnea, RR:36, SpO$_2$:81% on oxygen by Hudson mask, HR:134, B/L crepitations,	Leukocytosis, lymphopenia, ↑PCT, ↑CRP, ↑ferritin, ↑D-dimer, ↑lactate, ↑IL-6, ↑INR, ↑LDH, deranged LFT, KFT	Invasive ventilation, fluid bolus, antibiotics,	Induction: propofol, rocuronium Maintenance: sevoflurane, fentanyl, rocuronium	Hypoxia, tachycardia
3	35 years	G4P3, 37W3D pregnancy with ruptured uterus severe ARDS, hemorrhagic shock and IUD	Fever, cough, pallor, dyspnea, B/L crepitations, HR:165, BP:80/52, RR: 38, SpO$_2$: 84% on oxygen by Hudson mask	Hb:5.4, Leukocytosis, ↑CRP, ↑lactate, ↑LDH, ↑ferritin, ↑D-dimer, ↑IL-6 ↑INR	Invasive ventilation, crystalloid and blood products, NA & vasopressin infusion	Induction: ketamine, rocuronium, Maintenance: sevoflurane, fentanyl rocuronium	Hypotension, tachycardia
4	35 years	G4P1, 33W2D pregnancy with ruptured uterus, ARDS, hemorrhagic shock	Fever, cough, dyspnea, pallor BP:74/40, HR:163, RR:40, SpO$_2$:86% on oxygen by Hudson mask	Hb: 4.6, leukocytosis, ↑LDH, ↑INR, ↑CRP, ↑lactate, ↑D-dimer, ↑CRP, ↑ferritin, ↑IL-6	Invasive ventilation, crystalloid and blood products, NA & vasopressin infusion	Induction: ketamine, rocuronium, Maintenance: sevoflurane, fentanyl rocuronium	Hypotension, tachycardia
5	26 years	G3P1, 8W ruptured ectopic	Cough, myalgia, fever, dyspnea, BP:70/46 on NA	Hb:5.6, Leukocytosis,	Invasive ventilation, crystalloid and	Induction: ketamine,	Hypotension, tachycardia

		pregnancy & hemorrhagic shock	infusion, HR: 127, RR:26, SpO$_2$: 90% on room air, pallor	lymphopenia, ↑lactate, ↑LDH ↑D-dimer, ↑INR ↑CRP, ↑ferritin,	blood products, NA & vasopressin infusion	rocuronium Maintenance: sevoflurane, fentanyl rocuronium	
6	30 years	G3P2, 35W3D pregnancy with SPE and previous 2 LSCS	Fever, cough, BP: 180/116, RR:22, SpO$_2$: 90% on room air	Leukocytosis lymphopenia, ↑CRP, ↑LDH, ↑lactate, ↑D-dimer, ↑CRP, ↑ferritin	Magnesium sulphate, labetalol	Epidural anesthesia with 0.5% bupivacaine	Nil
7	25 years	G2P1, 36W5D pregnancy with SPE, previous LSCS and IUD	Fever, cough, fever, BP:176/114, RR:20, SpO$_2$:92% on room air	Leukocytosis lymphopenia, ↑lactate, ↑D-dimer, ↑CRP, ↑ferritin, ↑LDH	Magnesium sulphate, labetalol		Nil

G: gravidity, P: parity, W: weeks, D: days, ARDS: acute respiratory distress syndrome, B/L: bilateral, ↑: Raised, HR: heart rate in beats per minute, RR: respiratory rate per minute. BP: blood pressure in mm Hg, SpO$_2$: Oxygen saturation, PCT: procalcitonin, CRP: C-reactive protein, NA: noradrenaline, IL-6: interleukin 6, LDH: Lactate dehydrogenase, IUD: intrauterine fetal death, Hb: hemoglobin in g/dL, SPE: preeclampsia with severe features, LSCS: lower segment caesarean section.

Table 2: Postoperative course and outcomes

Case No.	Postoperative management	Maternal outcome	Newborn birth details	Newborn outcome
1.	No specific COVID-19 therapy	Expired on D1	Weight:2.7 Kg, Apgar:2,6. Needed resuscitation	Discharged on D4 of ICU stay
2.	Remdesivir, hydrocortisone infusion, antibiotics	Expired on D4	Weight:2.8 Kg, Apgar:5,7. Needed resuscitation	Discharged on D2 of ICU stay
3.	No specific COVID-19 therapy	Expired on D1	Stillborn	Not applicable
4	No specific COVID-19 therapy	Expired on D1	Stillborn	
5	Remdesivir, Dexamethasone, LMWH	Discharged on D10	Not applicable	
6	LMWH, dexamethasone	Discharged on D8	Weight:3.1 Kg, Apgar:7,8	Discharged on D6
7	Remdesivir, LMWH,	Discharged on D11	Stillborn	Not applicable

dexamethasone			

Apgar score recorded at 1 and 5 minutes, D: days after admission, ICU: intensive care unit, LMWH: Low molecular weight heparin
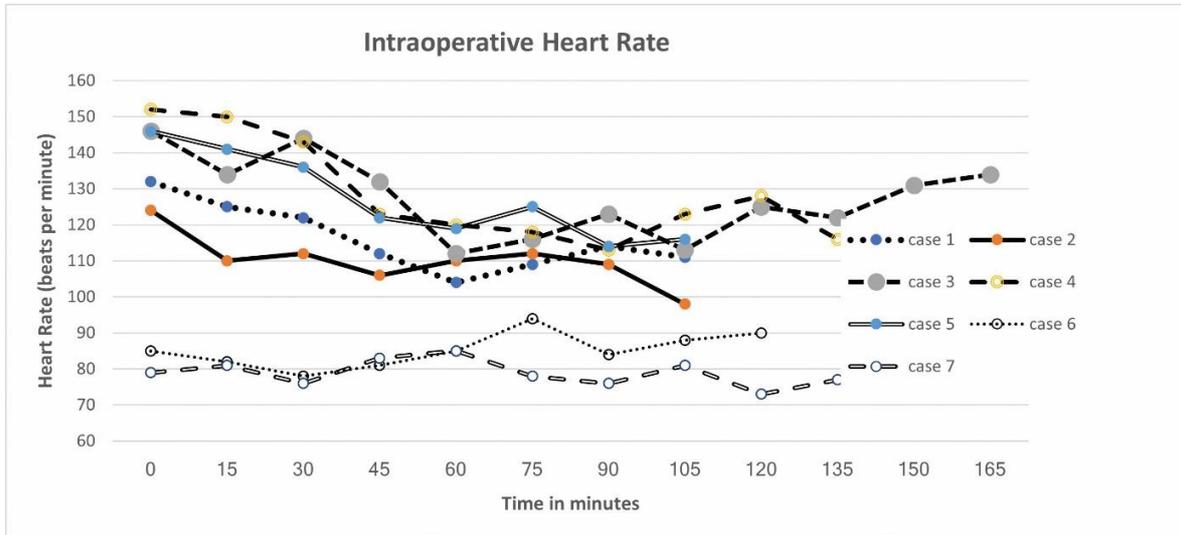
Figure 1: Intraoperative heart rate
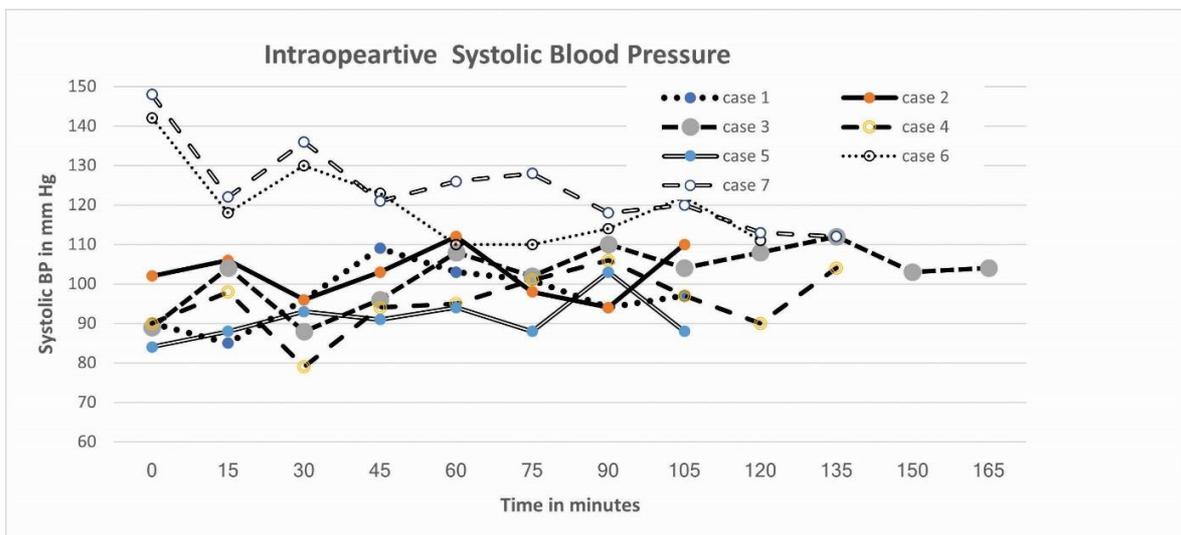
Figure 2: Intraoperative systolic blood pressure

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Chapter: 4
Role of High Flow Nasal Cannula for Respiratory Support during Oral Feeding for COVID-19 Patients on Non-invasive Ventilation

Dr. Rati Prabha and Dr. Rajesh Raman
Department of Anesthesiology, King George's Medical University, Lucknow
E-mail: ratiprabh83@gmail.com

Abstract: If feasible, oral route should be chosen for nutrition of patients admitted in intensive care unit. COVID-19 patients on non-invasive ventilation (NIV) are frequently unable to take oral feed due to risk of hypoxemia and/or respiratory distress on removal of the NIV mask for feeding. High flow nasal cannula (HFNC) supports respiration by variety of mechanisms and can potentially substitute NIV in selected cases. We aim to establish that NIV can be substituted by HFNC for respiratory support during oral feeding. Hospital based, prospective case series. Ten patients with severe COVID-19 disease requiring NIV with inspiratory pressure of <10 cm H2O, positive end-expiratory pressure of <6 cm H2O and FiO2 <0.6 were included in this study. Patients underwent HFNC trial for ten minutes and were screened for risk of dysphagia and aspiration using a 3-ounce water swallowing test. Then, HFNC was used for supporting the respiration during oral feeding for up to twenty minutes. The HFNC support for oral feeding was successful in eight patients without desaturation/respiratory distress during oral feeding. Six patients, previously on enteral nutrition, were successfully switched to oral feeding with help of HFNC. Four patients were directly started on oral diet with help of HFNC support. HFNC could not support respiration adequately in two of these four patients. HFNC can be used to support respiration during oral feeding in selected severe COVID-19 patients requiring NIV support.

Keywords: High flow nasal cannula, Nutrition, Intensive care unit, Non-invasive ventilation

Introduction

Malnutrition is one of the common issues with COVID-19 patients admitted to intensive care unit (ICU) due to the catabolic state induced by COVID-19, inadequate diet intake, and prolonged ICU stay.[1-3] This problem is compounded in the patients requiring non-invasive ventilation (NIV) due to inadequate diet intake.[4,5] Oral feeding, despite being the route of choice for nutrition, is not feasible in most of these patients due to risk of hypoxemia and/or respiratory distress on the removal of the NIV mask. Removal of NIV mask results in rapid desaturation of

the patient.[6] Nasogastric or nasojejunal tube is inserted for enteral nutrition but these can lead to gas leak around the NIV mask, compromising the ventilation and may also cause discomfort.[4,5,7] High flow nasal cannula (HFNC) delivers heated and humidified oxygen mixed with air at high flows that provides respiratory support in patients with acute respiratory failure. [8,9] We describe here a case series of ten patients for which we used HFNC for respiratory support during the oral feeding of patients on NIV.

Subjects and Methods:

This case series was conducted on ten patients on NIV support in a tertiary care hospital. The patients included were those admitted to intensive care unit with severe COVID-19 pneumonia and were stable on NIV support with oronasal mask requiring FiO_2 <0.6, positive end-expiratory pressure (PEEP) <6 cm H_2O, inspiratory pressure of 5-10 cm H_2O and respiratory rate 20-30 per minute with arterial oxygen saturation ≥90% and arterial partial pressure of carbon dioxide between 30-50 mm Hg. Patients with altered consciousness, circulatory failure, or worsening acidosis were not included in the study.

The procedure was explained, and consent was taken from all the patients included in the study. The patients were given a trial of HFNC for 10 minutes with a flow of 60 L/minute and FiO_2 of 0.1 more than their requirement on NIV. The patients were observed for hypoxemia (SpO_2 <88%) or signs of respiratory distress e.g., increase in respiratory rate (>35/minute), labored breathing pattern, use of accessory muscle of respiration, heart rate (>20% change), blood pressure (>20% change), perspiration and anxiety. The trial was considered successful if none of the above sign or symptom was present. This trial was repeated every day in the morning. The patients were then screened for risk of dysphagia and aspiration using 3-ounce water swallowing test.[10] HFNC was then used for respiratory support during the oral feedings. During oral feeding, the above observations were repeated. The duration of feeding was limited to 20 minutes. Daily three major and three minor meals were given with a target to achieve total daily caloric intake of 20-30 Kcal/kg/day with 50:50 energy ratio of fat and carbohydrate, protein intake of 1-1.3 mg/kg/day. Micronutrient supplementation including vitamin A, D, E, B_6, B_{12}, zinc, magnesium, phosphate, calcium, and selenium was also done. Number of calories required, and intake of calories were calculated by a nutritionist. Feeding was started with hypocaloric target on starting day and was increased progressively as per European Society for Clinical Nutrition and

Metabolism guidelines to the target estimated caloric requirement.[6] All the patients were given pantoprazole. Intolerance to oral feeding was defined as presence nausea, vomiting, bloating and abdominal pain or diarrhea in absence of any other cause. Prokinetic drug in form of erythromycin or metoclopramide was given if needed.

Results:

Case 1: This 70-year male patient was admitted to ICU for severe COVID-19 disease with co-existing chronic obstructive pulmonary disease (COPD). He was put on NIV, and bronchodilators were started, on which there was rapid clinical improvement. On the second day of ICU stay, HFNC trial for feeding was given, to which there was no respiratory deterioration. He was then started on oral feed which was gradually increased to 90% of daily requirement by day five of ICU stay. He was switched completely to HFNC for respiratory support on day ten of ICU and then to Hudson mask on day 17. He was discharged on day 20 of ICU stay.

Case 2: This 45-year male with severe COVID-19 disease required NIV on admission to ICU. Enteral feed using nasogastric tube was started on the second day of admission. There was clinical improvement in respiratory function, and on day ten of admission, HFNC trial for feeding was given which was successful. After this, oral feed was started and increased progressively. He was weaned off the HFNC on the 18th day and switched to Hudson mask and transferred to post-COVID ICU due to anemia and thrombocytopenia on 25th day. He was subsequently discharged after 32 days of hospital admission.

Case 3: This 45-year female patient admitted with severe COVID-19 pneumonia, had obesity (BMI: 32 kg/m^2) and type II diabetes mellitus (DM). NIV was initiated on day one of admission. HFNC trial for feeding was given the next day which was successful, and oral diet was started. Oral diet was well tolerated, and the amount of oral diet was gradually increased to 85% of daily requirement. On the 14th day, she was weaned off from NIV and shifted to HFNC and then Hudson mask. She was discharged after 25 days of ICU admission.

Case 4: This 35-year patient with obesity (BMI: 35 kg/m^2) and severe COVID-19 pneumonia required NIV since the day of admission. She was started on enteral feeding on day one. Her respiratory condition improved and with consequent reduction in ventilatory support from NIV, a trial of HFNC for oral feeding was given on the seventh day. Oral diet was started after the

successful trial. She was shifted completely to HFNC on the 15th day. She was shifted to ward on Hudson mask on 18th day and subsequently discharged.

Case 5: This 70-year-old male had severe COVID-19 disease with acute exacerbation of COPD was put on NIV immediately on arrival at ICU. A nasogastric tube was inserted, and enteral feeding was started on day one of ICU admission. With clinical improvement, on fifth day of admission, HFNC trial for feeding was given. After the successful trial, oral diet was started, and full daily dietary requirements could be given to the patient. He was completely switched to HFNC for respiratory support on day ten and was discharged on 15th day on room air.

Case 6: This 65-year-old male patient with severe COVID-19 disease with type II DM was put on NIV. For five days, an enteral route was used for nutrition. Trial of HFNC for respiratory support during feeding was done on sixth day, which was successful. After this oral feed was started with the HFNC support. Complete transition to HFNC support took place on day seven of ICU admission. HFNC was continued for ten more days. He was shifted on Hudson mask to post-COVID-19 ICU and subsequently discharged.

Case 7: This 45-year-old male with severe COVID-19 patient with coronary artery disease was on NIV support with enteral nutrition for three days. On the fourth day, a trial of HFNC support for oral feeding was given which was successful. An oral diet was started, and he achieved 100% of his daily requirement on day five after the trial. He was successfully discharged on the 20th day after admission.

Case 8: This 55-year-old patient with severe COVID-19 with co-existing dilated cardiomyopathy with 35% left ventricle ejection fraction was put on NIV for ten days with enteral nutrition. After his clinical improvement, a trial of HFNC support for oral feeding was given. The trial was successful, and his oral diet was started. He was completely shifted to HFNC on the 13th day and to nasal prongs on 21st day. He was subsequently shifted to the post COVID ward and discharged.

Case 9: This 65-year female was diagnosed with severe COVID-19 pneumonia with type II DM and obesity. She was started on NIV at admission. Two days after admission, her respiratory condition improved and HFNC trial for oral feeding was given on which she had rapid arterial

oxygen desaturation within 1-2 minutes with tachypnea. Her nutrition was continued using the enteral route.

Case 10: This 55-year female patient with obesity (BMI: 37 Kg/m^2) and severe COVID-19 disease was put on NIV at admission. Next day trial of HFNC support for oral feeding was successful and her oral diet was started. But her oxygen and ventilatory requirements increased progressively and the trial of HFNC for oral feeding failed on the fifth day. After this, enteral nutrition was started using nasogastric tube.

Table 1 depicts the pre-HFNC trial caloric intake and post-HFNC trial caloric intake of the patients.

Discussion:

We hereby presented a case series of ten patients requiring NIV due to COVID-19 induced acute respiratory insufficiency whose respiration was supported using HFNC at the time of oral feeding. Out of these ten patients, the HFNC support for oral feeding was successful in eight with adequate diet delivery. Of these, six patients were already on enteral feeding, and they were successfully switched to oral feeding with help of HFNC during the feeds. Four patients were directly started on oral diet with help of HFNC support. Out of these four, one patient failed the HFNC trial on the initial attempt and thus was not found suitable for continuation of HFNC support. Another patient failed the trial on the fourth day after initiation of oral feed due to decline in the respiratory condition.

Malnutrition and reduced nutritional intake predict raised morbidity and mortality in patients admitted to ICU.[11,12] Deficiency of nutrients reduces immune function, which can decrease outcome of the patients.[13-16] HFNC can be used temporarily to substitute NIV as it supports respiration by several mechanisms including:

1. Delivery of a desired fixed fraction of oxygen.[17-20]
2. Positive end expiratory pressure due high flow of oxygen results in re-expansion of collapsed alveoli, reducing respiratory work.[8,17-20]
3. Mixing of dead-space gas with gas of HFNC oxygen results in increased fraction of oxygen of dead-space gases.[8,18-19]
4. HFNC improves flow of gases through the airway.[18]

5. Moist gases help clear the pulmonary secretions and decrease bronchial constriction.[18,19]

6. Improves lung compliance by raising positive end expiratory pressure.[19,21]

Overall, studies have found that use of HFNC in acute respiratory failure results in improved oxygenation and compliance, decreased respiratory rate and inspiratory effort.[21,22] Additional advantages of HFNC over NIV include better ability for communication and decreased pressure and discomfort caused by NIV mask over face.[8] Other options during oral feeding are use of low flow nasal cannula, Hudson mask or non-rebreathing mask. These devices can only increase the fraction of inspired oxygen, but they lack the additional mechanisms by which HFNC supports the respiration. Hence, HFNC seems to be the most suitable device for supporting respiration while feeding. We increased the FiO_2 by 0.1 and used the maximum flow of gas (60 liter/minute) to the patients to ensure good respiratory support during the feeds. HFNC supports patient's respiration only when the patient's mouth is closed as the inspiratory gases escape through the open mouth.[19] So, it is particularly important to ensure that patient chews the food with mouth closed for better support of respiration.

Another advantage of this HFNC trial is that it augments our decision making to completely shift the patient to HFNC if it is well tolerated. All the eight patients in whom the HFNC was successfully used for feeding, were eventually weaned off NIV and switched to HFNC for respiratory support.

Limitations:

We recruited patients with low pressure and FiO_2 requirements on NIV as we expected these patients to tolerate the brief periods of HFNC successfully. The tolerability and feasibility of HFNC support for feeding patients requiring higher respiratory support is uncertain and further studies are needed to determine this. Removal of nasogastric tube after initiation of oral feed should have resulted in better NIV mask seal with improved mask seal and decreased loss of minute ventilation. This, however, was not evaluated in our case series. The patients in the present case series predominantly had type I respiratory failure due to COVID-19. The results of the study may not be applicable to patients with type II respiratory failure. This method requires two devices (NIV and HFNC) for a single patient. This may not always be feasible in a resource-limited COVID-19 pandemic era.

Conclusion:

Based on our case series, using daily screening trial of oral feeds with HFNC support in selected patients of severe COVID-19 pneumonia on NIV seems thought provoking and should be explored for its potential in improving patient's nutrition with positive impact on outcome.

Table 1: Caloric intake of patients before and after HFNC support during oral feeding

Case No.	Pre-HFNC caloric intake	Post-HFNC D1 Caloric intake	Post-HFNC D2 Caloric intake	Post-HFNC D3 Caloric intake	Post-HFNC D4 Caloric intake	Post-HFNC D5 Caloric intake
1	30	45	55	70	90	90
2	70	70	80	85	90	95
3	30	42	50	70	70	85
4	60	60	65	70	74	90
5	60	62	74	80	88	100
6	55	60	60	70	80	80
7	70	70	70	80	90	100
8	65	74	75	75	75	80
9	35	Trial failed				
10	30	40	60	45	Trial failed	

The caloric intakes are presented as a percentage of estimated daily caloric requirement. HFNC= High flow nasal cannula, D= day.

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Chapter: 5
Introduction to Spinal Cord Injury

Simranjeet Kaur and Nidhi Sharma*

[1]**Assistant Professor, Maharishi Markandeshwar Institute of Physiotherapy & Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana**
[2]**Professor, Maharishi Markandeshwar Institute of Physiotherapy & Rehabilitation, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala, Haryana**
E-mail: simranjeetkaursaini825@gmail.com; sharmanidhiphysio@gmail.com

Abstract: Spinal cord injury (SCI), which damages the spinal cord running from the foramen magnum to the cauda equina, can be brought on by an incision or trauma. Distant from the level of injury, the spinal cord regular functions are hampered by the injury. Severe disability is experienced by SCI patients. Clinical presentation may vary according to the level of lesions and hence the assessment and management are individualistic for each patient. Still a general assessment Performa can be followed and a comprehensive management of the patient can be undertaken.

Keywords: Injury, spine, traumatic, non-traumatic

Introduction

Definition: An impairment of motor or sensory function in the cervical, thoracic, or lumbar regions of the spinal cord caused by damage to neuronal components within the spinal canal is known as a spinal cord injury (SCI).

The insult to the spinal cord caused by an incision or contusion that occurs between the foramen magnum and the cauda equina is known as a spinal cord injury (SCI). The spinal cord's ability to conduct its duties distally from the site of lesion is disrupted as a result of the injury. SCI leaves people with the most severe disability. (1) About 40 million people globally experience SCI each year. Although 1% of them are children, the majority of them are young men, often between the ages of 20 and 35. [2] The majority of spinal injuries among school-age children are caused by traffic collisions and sports-related injuries, with the cervical area accounting for 60 to 80 percent of these injuries and the thoracic and lumbar regions accounting for the remaining 20 to 40 percent. (4) Traffic accidents, gunshot wounds, knife wounds, falls, and sports injuries are the leading causes of SCI in adults worldwide. The most frequent athletic injury involving the spinal

cord is believed to be diving. Injury is typically brought on by mechanisms including flexion, compression, hyperextension, or flexion-rotation. This is referred to as "primary harm," and it is brought on by these mechanisms. Secondary damage is the term used to describe the actions taken by the body to repair the primary harm, such as haemorrhage, inflammation, and chemical release. (5)

Level of injury and Classification: It is majorly classified into three levels depending upon the region involved: cervical spine region, thoracic spine region, lumbar spine region. The motor and sensory functions are taken into account when defining spinal cord injuries by the American Spinal Injury Association (ASIA). In 2011, the ASIA Impairment Scale underwent its most recent version. Deep anal pressure is used in place of the former phrase "deep anal sense." Due to the fact that skeleton level is not always present in spinal cord lesions, it was left out of the most recent "International Standards for Neurological Classification of Spinal Cord Injury (ISNCSC)" components. (6)The ASIA scale is listed in Table:

Complete Spinal cord injury can be defined as no motor and sensory function is preserved below

Grades	Type of injury	Definition of type of injury
A	COMPLETE	S4-S5 segments do not retain any sensory or motor function.
B	INCOMPLETE	No motor function is protected from three levels below the motor level at each side of the body, and there is motor deficit without sensory loss below the neurological level, including the S4-S5 segments (mild touch, pin feeling, or deep anal pressure at S4-S5).
C	INCOMPLETE	More than half of the muscles below this level have strength lower than 3/5, while motor function is preserved below the neurological level 1.
D	INCOMPLETE	Below the neurological level 1, motor function is intact, and at least half (or more) of the muscles have strength greater than 3/5.
E	NORMAL	All segments of sensory and motor function as determined by ISNCSC are normal, and "E" degree ASIA is present in patients who already have impairments.

the level of injury. However, in an 'incomplete injury' there is a partial involvement of the cord with some sparing (of motor cord sensory functions) depending upon the site of cord involvement. Four types of incomplete spinal cord injury have been reported:

- Brown Sequard syndrome
- Central cord syndrome
- Anterior cord syndrome
- Posterior cord syndrome[6][7]

Clinical Presentation:

Causes: There are two types of injuries to spinal cord i.e. traumatic and non-traumatic. Traumatic injuries can stem from a sudden, traumatic blow to the spine that causes fractures, dislocates, crushes or compresses one or more vertebrae, fall from height, sports and recreational injury. It can also result from a gunshot or knife wound that penetrates and cuts spinal cord. A non-traumatic spinal cord injury can be caused by any kind of spinal infections, inflammations, cancerous cells or reduced bone density or degenerative changes in the spine.[16] Clinical features depend upon the involved area of spinal cord.

➢ General clinical presentation of a patient includes –

- Severe pain

- Paralysis according to the level of lesion

- Tingling , numbness and loss of sensation in involved area

- Respiratory problems

- Balance problems

- Difficulty in walking

- Loss of bowel and bladder

- Difficulty in sexual activity [17]

➢ Clinical features according to the level of lesion are as follows –

C1-C4 levels

Patients needing ventilator support have injuries at the C3 and higher levels. Patients at the C4 level can control spontaneous breathing but are totally functionally reliant. Mouth bars can be utilised for several tasks, like writing and page turning. Adjustable spinal stabilizers and a safety belt that can steady the body and be adjusted for tilting or reclining are required for wheelchairs. Wheelchairs powered by batteries must feature a control for the head, tongue, breath, or jaw. Patients with C4 levels have fairly strong deltoid and elbow flexion muscles, allowing them to perform personal care tasks while wearing a balanced forearm orthosis. The likelihood of contractures and abnormalities can be decreased by using a static wrist orthosis to keep the hand and wrist in their usual position.

C5 level

Elbow flexor muscle strength is adequate at this point. Exercises that increase range of motion and flexibility are crucial during the acute stage to prevent elbow flexor and supinator contractures. The hand orthosis' static posture protects the wrist extensors from overstretching. Patients can manoeuvre a manual wheelchair with appropriate gloves or utilise a battery-powered wheelchair with a remote adaptation. Transferability depends on everything. Even though they might be able to eat with a customised splint, the majority of these patients require assistance with daily chores.

C6 level

Hand grasp can be attained with a tenodesis effect, and dynamic wrist extension is conceivable. Most of the time, these patients can take care of themselves in areas like nourishment, personal cleanliness, and upper body clothing. When the proximal muscles are weak and the distal muscles are strong, an active triceps-driven orthosis is beneficial for tasks like reading, eating, brushing one's teeth, and caring for one's hair. The hand grip can be performed using the hand/wrist driven brace. The aid of the transfer board is used to facilitate transfers. By connecting a knob to the circle, a conventional wheelchair can be utilised, but for longer trips, a

battery-powered wheelchair is required. Men can care for their bladders independently with a few changes, including clean intermittent catheterization, while women frequently require assistance.

C7-C8 levels

The strength of the finger flexor muscles at the C7 level and the elbow extension at the C8 level is adequate. Most transfers and activities of daily living are performed independently by patients. When clothing their lower extremities, they may need assistance. Wheelchair transfer is effective and a conventional wheelchair is available. Cars with specialised equipment can be used.

T11-T12 levels

Patients are competent in their everyday tasks, including utilising a manual wheelchair, caring for their bowels and bladders, and transferring. The goal is restorative ambulation in patients with upper thoracic injuries. They are unable to ambulate socially. Patients with lower thoracic injuries have good body control, and they may be able to walk around their homes with the aid of a walker and lower extremity orthoses.

L1-L2 levels

In terms of personal care and everyday living activities, patients are completely independent. For short distances, they may be mobile with a long-legged walking aid, but for longer trips, they require a wheelchair.

L3-L4 levels

Patients can fully bend their ankle dorsiflex and lock their knees completely. With ankle foot orthoses and elbow crutches, patients can socially ambulate. They can care for their bowels and bladder on their own.

L5 and lower

Patients are competent in every action, including daily tasks and functional activities. [15]

➢ Broadly SCI can be categorized as –

Paraplegia: The word "paraplegia" describes the loss or impairment of motor and/or sensory activity in the thoracic, lumbar, or sacral (but not cervical) regions of the spinal cord as a result of neuronal components within the spinal canal being damaged. Upper extremity function is preserved in paraplegia, but depending on the severity of the injury, the trunk, legs, and pelvic organs may also be affected. The term is used to describe injuries to the cauda equina and conus medullaris, but not to the lesions of the lumbosacral plexus or to peripheral nerves that are not inside the neural canal. Diplegia is another name for paraplegia. Depending on the severity of the lesion, the body and/or the limbs may not be impacted. In many paraplegia cases, sensory loss, bladder and anal sphincter dysfunction, as well as loss of motor function, would be found in the distal stages of injury. [9]

Tetraplegia: In this condition, commonly known as quadriplegia, neurological impairment affects the trunk and all extremities. When the C1-C8 spinal segments are injured, tetraplegia results. Tetraplegia is not defined to encompass damage to the brachial plexus or nerves outside the neural canal. Tetraplegia as formerly defined is no longer used, and incomplete tetraplegia is preferable. The posterior ligament tear and dislocation, the most frequent type of spinal cord injury in the neck, results in serious neurological disorders, particularly because it is connected to destruction and ischemia of the cord's grey matter. Ischemia can result from direct damage to the circulatory system or through vasospasm-induced neurogenic shock. Depending on the size and localisation, the SCI produces different results.[10]

Tetraparesis and Paraparesis: The usage of these terminology is discouraged because they inaccurately depict incomplete lesions and falsely indicate that tetraplegia and paraplegia should only be applied to neurologically full injuries. The ASIA Impairment Scale (AIS) instead offers a more accurate method of describing the completeness of the SCI. [8]

Complications

The effects of SCI not only impair independence and physical ability but also lead to numerous complications. Frequent sequelae following SCI include bladder and bowel incontinence, urinary tract infections, pressure sores, postural hypotension, fractures, circulatory disorders, spasticity, heterotrophic ossification, contractures, autonomic dysreflexia, pulmonary and cardiovascular issues, and depressive disorders. The patient's life expectancy and quality of life are directly

correlated with these problems. Pressure ulcers, bladder infections, and autonomic dysreflexia in particular isolate the sufferer from society. (11,12) Complications from SCI lead to negative alterations in the patient's impression of their health. Pressure ulcers, stiffness, contractures, bladder and bowel issues, in particular, hamper societal integration and cause patients' mental discomfort. Due to these difficulties, SCI patients must spend a lot of time in the hospital and are limited in many daily tasks. The reduction in sexual dysfunction can also lead to low self-esteem, which has a detrimental impact on the patient's perception of their body.[13]

Patients who have experienced spinal cord damage as children are at risk for developing diabetes and metabolic illnesses during the growth phase. Common paediatric problems include obesity, insulin resistance, dyslipidemia, decreased glucose transfer, and spasticity. Workouts that are passive, active-assisted, active, resistive, cycling, and water exercises must be appropriate for the severity of SCI and the comorbidities. These workouts will lessen bone fractures, decubitus ulcers, inactivity, and muscular atrophy.[14]

- Special precautions are necessary in patients with spinal injuries, as they are associated with high rates of complications:

1. **Pneumonia**: Pneumonia is defined as inflammation of the lung tissue and is usually caused by infection. The higher the level of spinal-cord damage, the more severe are the respiratory impairment and the risk of Pneumonia.

2. **Atelectasis**: Atelectasis occurs frequently in patients with spinal cord injury (SCI). Impaired cough leads to ineffective clearance of secretions. If the secretions cannot be cleared and become thick and purulent, atelectasis may occur.

3. **Pressure sores on sacrum and heel:** Below the neurological level of injury, patient have lost some or all skin sensations. Due sensation loss or injury to skin resulting from prolonged pressure. [18]

4. **GI ulceration:** is common in chronic spinal cord injury patients.[19]

5. **Bowel and bladder problem**: In SCI, bladder will work normally and store urine from kidneys. However, brain does not send proper signal to control bladder and message carrier of the spinal cord due to injury. [20]

6. **Associated problems with Bowel and bladder**: The likelihood of urinary tract infections rises as a result of changes in bladder control. Infections of the kidneys and kidney or bladder stones may also result from the alterations.

7. **Circulatory control:** Hypotension due to swollen limbs, blood clots like thromboembolism, and a life-threatening increase in blood pressure are all possible complications of a spinal cord injury (autonomic dysreflexia).[20]

8. **Respiratory system: If the abdomen and intercostal muscles are injured, a serious injury may make it harder to breathe and cough. The extent of the neurological damage will determine the type of breathing issues present. Pneumonia and other lung conditions are more likely to occur after cervical and thoracic spinal cord injuries**.

9. **Bone density:** Osteoporosis and fractures below are more likely after spinal cord damage below the level of injury.

10. **Muscle tone:** Spasticity, an uncontrollable tightening or motion of the muscles, or limp, soft muscles with no muscle tone are the two main muscle tone issues associated with spinal cord injury (flaccidity).

11. **Strength and conditioning**. Atrophy of the muscles and weight loss are frequent issues. A sedentary lifestyle brought on by limited mobility raises the likelihood of obesity, cardiovascular disease, and diabetes.

12. **Reproductive health:** After a spinal cord injury, males experience problems getting erections and having ejaculations, and female reproductive systems experience alterations in lubrication.

13. **Pain**: Overusing certain muscle groups can result in joint or muscle pain. Following a spinal cord injury, nerve discomfort is possible, particularly in cases of incomplete injuries.

14. **Psychosomatic disorder**: Living with pain can contribute to depression in some people, as can adjusting to the changes brought on by a spinal cord injury.

15. **Muscle atrophy**: There are two types of muscle atrophy related in SCI one is denervation atrophy another one is disuse atrophy. Denervation atrophy occurs when there is an injury to a nerve that connects to the muscle. After SCI, the communication between the brain

and muscle can be lost, resulting in the inability to voluntary contract that muscle. Disuse atrophy occurs from a lack of physical activity. Though communication between the brain and muscle is not completely lost, muscle atrophy can occur by not using the muscles enough. [21]

16. **Contractures**: Contractures occur due to loss of motion in a joint, resulting in shortening of muscles, ligaments, and tendons. Contractures can occur due to a complete lack of movement at a joint, or when there is an imbalance between muscle groups at a particular joint. Spasticity also can contribute to the development of contractures. The loss of movement can result in deformity and often lead to difficulty with functional mobility. [21]

17. **Osteopenia/Osteoporosis**: It is a decreased bone density, or a thinning of bone mass, caused by more bone breakdown than bone creation. Osteopenia is the stage of bone loss before osteoporosis. These are occurred because of a lack of weight bearing. [21]

Assessment

General Assessment Performa: Although the assessment of a patient suffering from SCI should be performed as per ASIA scale yet general assessment can be done by keeping the following points into consideration.

General Assessment Performa
Subjective assessment : • Name • Age • Gender • Occupation • Date of assessment • Chief Complaint • History
Observation/Inspection:

Palpation: Examination: Myotomes/ Dermatomes				
Sensory Examination:	Superficial sensations	Deep sensations	Combined cortical sensations	
	R	L	R	L	R	L
Reflex examination	Superficial Reflexes	Deep tendon reflexes	Bulbocavernosus reflex	Cremasteric reflex
Motor measurement	Muscle Girth	MMT	ROM	Muscle tone

Management

Objectives:

- Teach respiratory regimen to manage respiratory conditions and lung complications.
- To maintain the full range of movement of all joints within the limitations determined by the stability of the fracture
- To monitor and manage the neurological status.
- To maintain and strengthen all innervated muscle groups
- To facilitate functional patterns of activity
- To support and educate the patient, family and caregiver

Treatment: This stage, which lasts 6 to 12 weeks while the patient is receiving acute phase treatment, starts when they are admitted to the hospital and the patient's neurological condition is stabilized. The purpose of therapy during this time is to avoid potential long-term consequences.

- Passive exercise should be done to avoid contractures and to maintain range of motion of the joint, avoid muscle atrophy and pain. [22]
- Breathing exercises: help in reduction of pain as well as in help in respiration.

- Strengthening of specific group of muscles: to regain the strength of involved muscle

- Stretching exercise: Stretching exercises should be beneficial for individuals who don't actively extend their wrists and have partially stretched fingers in order to protect the tenodesis effect.[23].)

- Gait training and ambulation: This is preferably done in parallel bars. In this, the patient is taught the correct method of balancing while standing from a wheelchair and transferring the weights properly. Gait training is also commenced within the parallel bar for patients with lesions below T6 level. Above this level walking may not be possible. Patient is taught within the parallel bars how to balance on a single leg placing the feet properly, moving the hands correctly, avoiding dragging of the feet, lifting the body, etc. in a continuous long and repeated practice session

- Positioning: Rolling routines, mobility, sufficient skin hydration, nutrition, and supervision are all necessary to prevent bedsores. Additionally, it aids in maintaining the ideal level of muscle tone and protecting the articular structure. Pillows and sand bags are both good for positioning. Plaster splints or more stiff orthotics can be used to position the patient if cushions and sandbags are unable to do so (spinal orthosis).

- Bed mobility and transfers: C6 and lower level SCI have the ability to attain 5 motor skills: rolling (using momentum) -1.mobilizing from supine to long-sitting 2. Unsupported sitting (short- & long sitting) 3. Lifting vertically 4. Transfers

- If you experience excessive weariness while exercising your muscles and to recuperate muscle power, electrical stimulation may be a good choice.[24]

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Chapter: 6
Pharmacotherapy for Diabetic Neuropathy

Dr. Chaitali A Chindhalore* and Dr. Ganesh N. Dakhale
Department of Pharmacology, AIIMS Nagpur, Maharashtra
*E-mail: drchaitali@aiimsnagpur.edu.in

Abstract: Diabetes mellitus, the largest pandemic across the globe, affected approximately 425 million people worldwide according to The International Diabetes Federation with India ranking second to China. The global epidemic of prediabetes and diabetes has led to a corresponding epidemic of macrovascular and microvascular complications. The most prevalent complication is neuropathy caused by diffuse and focal nervous system damage and occurs in up to half of all individuals with diabetes. Types of neuropathy include peripheral neuropathy, autonomic neuropathy, focal neuropathy and proximal neuropathy.

Painful diabetic peripheral neuropathy occurs in approximately 25% of patients and significantly affects quality of life. It typically causes burning pain, paraesthesia, and numbness in a stocking-glove pattern that progress proximally from the feet and hands. Drug therapy like α lipoic acid and aldose reductase inhibitors, like epalrestat targeting the pathogenesis of peripheral neuropathy have limited evidence of efficacy. Drug categories used to treat painful neuropathy are anticonvulsants (pregabalin, gabapentin), tricyclic antidepressants (amitriptyline), selective serotonin reuptake inhibitors (fluoxetin), serotonin-norepinephrine reuptake inhibitors (duloxetine), opioid-like medications (Tramadol, tapentadol) and opioids.

Diabetic autonomic neuropathy (DAN) encompasses a group of disorders caused by impairment of the sympathetic and parasympathetic nervous system affecting various organs systems like cardiovascular system, gastro-intestinal system, urogenital system etc.

Cardiovascular autonomic neuropathy (CAN), an important form of DAN is caused by the impairment of the autonomic nerve fibres that innervate the heart and blood vessels and leads to abnormalities in cardiovascular dynamics. It causes a wide range of cardiac disorders, including resting tachycardia, arrhythmias, intraoperative cardiovascular instability, asymptomatic myocardial ischemia, infarction, and increased rate of mortality after myocardial infarction. Pathogenesis oriented interventions may promote some degree of reversal of established CAN. Various researchers explored different medication approach to treat CAN which ranges from strict glycemic control, α lipoic acid, aldosterone inhibitors, CCBS etc. whose results were not

much promising. Recently the EMPA-REG outcome trial in T2DM demonstrated improvement in sympathetic tone along with reduction in cardiovascular events. Contrary, Liraglutide, a GLP-1 receptor agonist had reduced HRV with decrease in parameters of parasympathetic activity suggesting negative impact on sympathovagal balance. Considering neurovascular insufficiency as one of the etiology. Various studies reported beneficial effect of quinapril, ramipril in reversing CAN through increases in nerve blood flow by promoting vasodilation. Different therapeutic agents are emerging for treatment of diabetic neuropathy. While considering particular agent, evidence based approach should be followed.

Keywords: Diabetic autonomic neuropathy, cardiac autonomic neuropathy, duloxetine, pregabaline

Introduction

Diabetes mellitus, the largest pandemic across the globe, affected approximately 425 million people worldwide according to The International Diabetes Federation with India ranking second to China.[1-3]

According to 2019 estimates, 77 million individuals had diabetes in India, which is expected to rise to over 134 million by 2045 due to the increasing prevalence of overweight/obese persons and unhealthy lifestyles.[4,5]

The global epidemic of prediabetes and diabetes has led to a corresponding epidemic of macrovascular and microvascular complications. The most prevalent complication is neuropathy caused by diffuse and focal nervous system damage and occurs in up to half of all individuals with diabetes. Types of neuropathy include peripheral neuropathy, most commonly distal symmetric polyneuropathy manifesting with a "stocking and glove" distribution, autonomic neuropathy, focal neuropathy, and proximal neuropathy.[6]

Diabetic Peripheral neuropathy

Diabetic peripheral neuropathy (DPN) occurs in approximately 50% of patients with diabetes mellitus who are treated in the OPD setting. Furthermore, up to half of them suffer from painful neuropathy which often leads to depression, anxiety, and sleep disorder with compromised quality of life.[7] DPN leads to degenerative and atrophic changes throughout the peripheral and

central nervous system like; demyelination of myelinated nerve fibres, axonal degeneration and necrosis, Schwannopathy, and microangiopathy.[8,9]

Some proposed molecular mechanisms include polyol pathway activation, oxidative stress, protein kinase C activation, and advanced glycation end-product formation. However, the exact causal links between hyperglycemia and clinical DPN are uncertain. Our current understanding is that hyperglycaemia, as well as vascular risk factors; activate detrimental pathways ultimately leading to downstream injury to the microvascular endothelium, nerve support cells, and nerve axons.[10]

It typically causes burning pain, paresthesias, and numbness in a stocking-glove pattern that progress proximally from the feet and hands. Less than 20% of patients with diabetes experience dynamic mechanical allodynia (pain in response to stroking lightly), thermal hyperalgesia (increased sensitivity to pain by thermal stimuli), or pain attacks.[11]

Management

Glycaemic control: improved glycaemic control plays a role in preventing the onset and progression of diabetic neuropathy in patients with T1DM. A Cochrane review of two randomized controlled trials involving 1,228 patients reported that enhanced glucose control significantly reduced the risk of developing DPN in patients with type 1 diabetes (risk difference = 1.84%; 95% confidence interval [CI], –1.11 to –2.56). A similar analysis of four RCTs in patients with type 2 diabetes, however, did not show a statistically significant reduction in the rate of DPN with enhanced glucose control. [12]

Disease-modifying therapy: Drug therapy like α-lipoic acid and aldose reductase inhibitor, epalrestat targeting the pathogenesis of peripheral neuropathy have limited evidence of efficacy.[13]

Pain Management

Symptomatic pain management remains the cornerstone of therapy. Drug categories used to treat painful neuropathy are as follows

- Anticonvulsants: Pregabalin, Gabapentin, Topiramate, Valproate, Oxcarbazepine, Lamotrigine, Lacosamide

- Tricyclic antidepressants: Amitriptyline, Imipramine, Desipramine, Nortriptyline
- Selective serotonin reuptake inhibitors (SSRIs): Escitalopram, Paroxetine
- Serotonin-norepinephrine reuptake inhibitors (SNRI): Duloxetine, venlafaxine, Desvenlafaxine
- Opioid-like medications: Tramadol, Tapentadol
- Opioids: methadone, levorphanol, morphine

Anticonvulsants

Anticonvulsants, like topiramate, valproate, oxcarbazepine, lamotrigine, and lacosamide, as well as the newer calcium channel α-2-δ ligand class anticonvulsants (gabapentin and pregabalin), have been studied for the treatment of painful DPN. Based on a recent meta-analysis, the American Academy of Neurology and Toronto guidelines recommend pregabalin as the first-line medication for painful DPN, with gabapentin as the first-line alternative.[14]

Pregabalin is a GABAergic drug primarily used in the treatment of neuropathic pain and is approved for use in over 120 countries. Pain relief usually occurs within 1 week of initiating therapy and is thought to be mediated via high-affinity binding to the alpha2-delta subunit (a2δ) of voltage-gated calcium channels at the presynaptic terminals. This results in modulation of the release of excitatory neurotransmitters such as glutamate through the glutamate synthesising enzyme, branched chain amino acid transaminase.[15]

Metanalysis involving a total of 2056 participants showed that pregabalin was significantly superior to placebo for improving mean pain scores [mean difference (MD) = -0.79, P < 0.001]. Pregabalin reduced pain below baseline by at least 50% in a significantly greater proportion of patients than placebo did [relative risk = 1.54, P < 0.001].[16]

Monotherapy with gabapentin, duloxetine, or pregabaline produced a clinically and subjectively meaningful pain relief in patients with DPNP with onset of pain relief being faster and superior with PGB.[17]

Tricyclic antidepressants

Among TCA, amitriptyline is highly effective. 2015 Cochrane review of four RCTs including 382 patients with all causes of neuropathic pain showed that amitriptyline use led to a

statistically significant benefit (relative risk = 2.0; 95% CI, 1.5 to 2.8; NNT = 5).[18] However, use of amitriptyline is associated with adverse effects due to significant anticholinergic properties, especially in older adults.

Serotonin-norepinephrine reuptake inhibitors (SNRI)

Duloxetine is a first-line medication that received FDA approval in 2004 for treating painful DPN. A 2014 Cochrane review of eight studies (n = 2,728) showed that duloxetine at 60 mg daily led to at least 50% pain reduction at 12 weeks (NNT = 5; 95% CI, 4 to 7) vs. placebo. However, duloxetine shows comparable efficacy and tolerability to gabapentin and pregabalin in DPNP.[19]

Venlafaxine and desvenlafaxine are considered second-line medications, but they have better safety and tolerability profile as compared to TCA.

Centrally-acting opioid-like medication, tramadol and tapendalol has evidence to support their efficacy in painful neuropathy. However, the risk-benefit analysis of these drugs required further studies. One can consider Isosorbide dinitrate spray, lidocaine 5% patch or plaster, and capsaicin 0.075% cream as an alternative.[13]

To summarise findings from available shreds of evidence, pregabalin, Gabapentin, duloxetine, amitryptiline and tapentadol have good efficacy in the treatment of DPN pain and are commonly used for the clinical treatment of painful DPN at present. [Table 1]

Table 1: Commonly prescribed medications for painful Diabetic peripheral neuropathy

Name of medication	Dose	Common adverse effects
Pregabalin	300 mg-600 mg/day	Somnolence, dizziness
Gabapentin	1200 mg-3600 mg/day	Somnolence, dizziness
Amitriptyline	10 mg/day	Dry mouth, insomnia
Duloxetine	60 mg-120 mg/day	Nausea, somnolence, dizziness
Tramadol	200 mg-400 mg/day	Constipation, nausea, drowsiness

Extended release Tapentadol	200 mg-500 mg/day	Nausea, dizziness, diarrhoea
Lidocaine 5% patch	1-3 patch/day	Irritation at site of application

Diabetic autonomic neuropathy (DAN)

DAN encompasses a group of disorders caused by impairment of the sympathetic and parasympathetic nervous system affecting various organ systems like the cardiovascular system, gastrointestinal system, urogenital system, etc. Clinical symptoms depend on the organ system affected by neuropathy.

Cardiovascular autonomic neuropathy (CAN)

CAN is caused by the impairment of the autonomic nerve fibres that innervate the heart and blood vessels and leads to abnormalities in cardiovascular dynamics. It causes a wide range of cardiac disorders, including resting tachycardia, arrhythmias, intraoperative cardiovascular instability, asymptomatic myocardial ischemia, infarction, and increased rate of mortality after myocardial infarction. Reduced heart rate variation (HRV) is the earliest indicator of CAN. HRV is beat-to-beat variation in heart rate (i.e., in R-R intervals) which occurs due to continuous changes in the sympathetic and parasympathetic outflow to the heart. It is non-invasive and objective in the evaluation of cardiac autonomic function. [20]

The aetiology of CAN is multifactorial, ranging from metabolic insult, neurovascular insufficiency, increased oxidative stress, reduction in neurotrophic factor, or formation of advanced glycosylation end products. [21]

Management

Pathogenesis-oriented interventions may promote some degree of reversal of established CAN. Various researchers explored different medication approaches to treat CAN.

- **Strict glycemic control**: Eighteen years of follow-up of a group of type 1 diabetic individuals demonstrated that fair long-term glycemic control (i.e. glycosylated hemoglobin 8.4%) was associated with preserved cardiovascular autonomic function, whereas lack of fair glycemic control was associated with dysfunction. [22]

- **Antioxidants**

    During chronic hyperglycemia, the metabolism of glucose also results in the generation of free radicals. α -Lipoic acid, an antioxidant that reduces free radical formation, appears to slow the progression of CAN. [23]

    - **Angiotensin converting enzyme inhibitors**

Considering neurovascular insufficiency as one of the aetiology, it was postulated that ACE inhibitors had a beneficial effect in reversing CAN through increases in nerve blood flow by promoting vasodilation. ACEIs act by preventing the generation of angiotensin II and also inhibit the breakdown of bradykinin. Angiotensin II, in addition to its role as a vasoconstrictor, stimulates aldosterone release and promotes sympathetic outflow as aldosterone affect the autonomic nervous system with sympathetic activation and parasympathetic inhibition and impairment of the baroreflex response. Treatment with quinupril for 2 years improved DCAN (mainly parasympathetic dysfunction) in diabetic patients.[24] Similarly, the administration of ramipril had a positive effect not only on myocardial hemodynamic parameters, but also restored the autonomic balance. The predominance of parasympathetic activity has been observed in patients with decompensated DM type 2.[25]

Angiotensin type 1 receptor blockers

Angiotensin type 1 (AT1) receptor mediates all potentially deleterious effects of angiotensin II. Improved cardiovascular autonomic function was, however, shown in a study, in which 23 diabetic individuals were treated with 100 mg of losartan for 1 yr.[26]

Various researchers evaluated role of aldosterone inhibitors, CCBS, beta blockers in improving autonomic flow in diabetes whose results were not promising.[27-29] Recently the EMPA-REG outcome trial in T2DM demonstrated that empagliflozin causes improvement in sympathetic tone along with reduction in cardiovascular events.[30] Contrary, Liraglutide, a GLP-1 receptor agonist had reduced HRV with decrease in parameters of parasympathetic activity (RMSSD and HF power) suggesting negative impact on sympathovagal balance.[31]

Diabetic autonomic Neuropathy of the gastrointestinal tract leads to development of numerous symptoms such as: escalation of gastro-oesophageal reflux disease (GERD), gastroparesis,

diarrhoea, habitual constipation and faecal incontinence. Instituting a short-term course of prokinetic agents (metoclopramide, Itopride) can be tried for gastroparesis. However, It is recommended that patients should follow a low-fibre and low-fat diet, preferably semi-liquid meals divided in small portions.[32]

Urogenital autonomic neuropathy is a diagnosis of exclusion, with multiple medications, low hormone levels and infections being the main three differential diagnoses to consider before attributing dysfunction to diabetes. Urogenital autonomic neuropathy is responsible for urinary dysfunction like frequency, excessive urinating at night, urgency, stress incontinence, retention, hesitancy and sexual dysfunction like erectile dysfunction, vaginal dryness, and decreased libido. A symptomatic approach can be adopted like use of bethanechol for overactive bladder and phosphodiesterase type 5 inhibitors for the treatment of male erectile dysfunction.

The topical antimuscarinic drug glycopyrrolate can be used for the treatment of gustatory sweating, whereas daily moisturizing lotions provide relief for dry skin.[13]

Conclusion

Different therapeutic agents and approaches had been evaluated by researchers for treatment of diabetic neuropathy with a mixed outcome. Results might be influenced by various existing comorbidities also. Management of painful DPN involves symptomatic approach with use of various drug categories to get relief from pain. Evidence suggested that ACEIs has a promising role in treating CAN. However, while considering a particular agent, an evidence-based approach should be followed.

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Chapter: 7
Alzheimer's Disease - Paths for Treatment

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Rajnish Raj and Jasmin Garg*
Department of Psychiatry, GMC and RH, Patiala, Punjab
*E-mail: jasmin.arneja@gmail.com

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Abstract: Alzheimer's Disease (AD) is a common neurogenerative disease of old age. It is characterized by progressive memory loss and functional decline. It has complex and multifactorial etiopathology. There are depositions of amyloid plaques and neurofibrillary tangles in brain. It is diagnosed on the basis of history, clinical examination and neuropsychological testing. Amyloid PET scans and CSF biomarkers are used for establishing confirmatory diagnosis in research trials. There is no cure for this disease so far. Some interventions such as exercise, lifestyle and dietary modifications can prevent the onset of AD. The available treatment options include Acetylcholinesterase Inhibitors and a NMDAR receptor antagonist which help in managing symptoms of the disease, but do not slow the disease process. Research is going on in different parts of the world to find a successful Disease Modifying Therapy (DMT) for AD. These research regimens include monoclonal antibodies, vaccines and small molecules with antioxidant, neuroprotective, anti-inflammatory or anti protein aggregation properties. This chapter describes in detail about the contemporary treatment paths for AD under research.

Keywords: Alzheimer's Disease, Dementia, Amyloid, Tau, Disease Modifying Therapy

Introduction

Mrs. Y 70 years of age was living with her son, daughter-in-law and two grandchildren in an urban area of North India. She would manage the household work well and take care of her grandchildren. She would occasionally forget minor things e.g. turning off taps, closing doors, taking her medication etc. Initially family members thought this was normal for her age. But this gradually increased over next few years as she would ask questions again despite being replied to. She had forgotten how to use washing machine. She wouldn't work in home as before, and would keep sitting at one place for long. She would sometimes cook chapatis but the quality of her preparation had deteriorated. It was increasingly becoming difficult for family members to leave her alone at home as there were incidents in which she forgot to turn off gas stove knobs.

She was then taken to a psychiatrist who diagnosed her to be suffering from Alzheimer's disease. Her caregivers were explained about the lack of a cure and availability of just symptomatic treatment for this. They were devastated to know that they would be slowly losing their family member.

Like Mrs. Y, millions of patients around the world are waiting for the discovery of a successful treatment of Alzhemer's Disease (AD). As of now, AD has a chronic deteriorating and highly disabling course. The illness usually begins after the age of 65 years with short-term memory loss (forgetting recent/ day to day activities) and gradually becomes associated with a plethora of symptoms. These can be aphasia (problems in speech), apraxia (inability to perform known activities), agnosia (problems in recognizing objects/persons), apathy (lack of motivation for activities, decreased facial expressions), personality changes (either withdrawn or uninhibited), behavioural disturbances (agitation or irritability), psychosis (delusions and hallucinations) and so forth. The patients increasingly become dependent on others for their activities of daily living (self-care).[1, 2] According to WHO, over 55 million people are suffering from dementia worldwide and AD is the most common cause of dementia accounting for 60-80% of cases. [3] In India, the estimated prevalence is 20 per thousand population.[4]

Although there is no cure at present, research in the management of AD is rapidly progressing. Currently, there are about 150 agents in clinical trials for AD.[5] Disease Modifying therapies (DMTs) have not been successful so far. This chapter will describe the existing treatment modalities for AD and important forthcoming pharmacological agents under research.

Etiopathology

Several risk factors are known to be associated with AD such as increasing age, female gender, genetic factors, cardiovascular disease, diabetes, head injury, history of depression, low level of education, environmental pollution etc. AD is a multifactorial, progressive and complex neurodegenerative disease. It was first described over a century ago by Alois Alzheimer who conducted brain autopsy of his patient with a history of late age onset forgetfulness. The histopathological findings typically reveal accumulation of extracellular amyloid plaques and neurofibrillary tangles (NFT). Amyloid plaques are deposits of beta-amyloid protein (Aβ). These are formed from abnormal cleavage of transmembrane Amyloid Precursor Protein (APP) by β

secretase and γ secretase enzymes. Aβ deposition is believed to be the reason behind the neurotoxicity, synapse loss, cortical atrophy and cognitive impairment of AD. It is also hypothesized to be the reason for neurodegeneration and loss of cholinergic neurons in Nucleus Basalis of Meynert. Another type of protein depositions mostly found in patients with AD is NFT. These are intracellular deposits of hyperphosphorylated tau protein which lead to disruption of cytoskeletal microtubules and consequent neuronal loss. [1, 6]

Pathophysiology of AD also involves overstimulation of N-methyl D-aspartate Receptor (NMDAR). NMDAR plays an important role in long term potentiation (LTP) and formation of memory. In AD, there is excessive stimulation of NMDAR by glutamate resulting in massive Ca^{++} influx which hinders the process of LTP. Glutamate is excitatory amino acid and via NMDAR it leads to excitotoxity and neuronal death. [1, 6]

Apart from these etiological hypotheses, some gene alterations have been found to be strongly associated with AD. These are genes coding for APP, Presenelin 1, Presenilin 2, Apolipoprotein E4 (APOE4) and many others. APOE4 alleles and multiple susceptibility genes are frequently found in late onset AD. The variant APOE4 is thought to be involved in increasing oxidative stress, neurotoxicity and impairing mitochondrial activity in AD. [1, 6]

Impaired glucose metabolism in cerebral cortex is also found in brains of patients with AD. These factors may hinder the delicate balance of pro-inflammatory and anti-inflammatory signalling in brain resulting in chronic neuroinflammation. Chronic neuroinflammation may in turn lead to accumulation of tau and Aβ. There are intracellular regulatory systems to remove toxic protein accumulation mediated by chaperone proteins.[1,6] On all the above etiological pathways, there are different pharmacotherapies under investigation.

Stages and Diagnosis

The clinical stages of AD are divided into the following:[1, 6]

A) Preclinical stage: There is mild memory impairment without functional problems. The neuropathological changes of AD have begun.

B) Mild AD: Memory problems surface with apparent decline in function.

C) Moderate AD: Increasing memory loss with evidence of other symptoms such as personality change, behaviour problems, agnosia, apraxia etc.

D) Severe AD: There is widespread accumulation of Aβ and NFT in cortex. The patient maybe bedridden, has declining self-care and may not be able to perform basic activities of living.

Diagnosis of AD is usually established clinically by history taking, neurological examination and neuropsychological testing. Reversible causes of cognitive decline are ruled out by MRI brain and blood tests for thyroid hormones, vitamin B12 and homocysteine levels. [1] Research criteria for AD have also been recently defined by The National Institute on Aging-Alzheimer's Disease. These criteria require the presence of biomarkers of Aβ deposition either in Cerebrospinal fluid (CSF) or positron emission tomography (PET) for establishing a confirmed diagnosis of AD. Three radioligands (F-florbetapir, F-flutemetamol, F-florbetaben) for amyloid PET have been approved in USA and UK for diagnosing AD. Levels of CSF Aβ42 and Aβ42/40 ratio has been found to be highly concordant with gold standard amyloid PET. Tau biomarkers (Flortaucipir F18) for PET have also been approved in USA. Plasma biomarker for detection of Aβ42/40 are under the approval stage and studies assessing plasma levels of tau biomarkers e.g. p-tau181, p-tau217 are emerging.[7]

Digital technologies for early detection

In old age homes in some regions of USA, digital health technologies are used to monitor cognition, sleep, mobility and social engagement of elderly. Wearable mobile devices such as smartphones and smartwatches are used to collect continuous data. Digital health technologies (including mobile applications) are under development to detect change in function and cognition. Subtle signs associated with mild AD such as speech and language changes, oculomotor problems and mobility may also become detectable via technology in future and these might serve as digital biomarkers. Early detection of AD is important because the upcoming Disease Modifying therapies have claimed efficacy in mild cognitive impairment or mild AD stages only, before the neurodegeneration becomes irreversible.[7]

Prevention of Dementia

In a famous Finnish study (FINGER), interventions in the form of dietary modifications, exercise, cognitive training and vascular risk monitoring were carried out for elderly at risk of dementia. It was demonstrated that these lifestyle modifications led to improvements in cognitive functioning of elderly at 2 years follow-up. [8] On these lines, to decrease the risk of development of AD, worldwide wide trials of FINGER models have been launched in over 25 countries including India. These trials are for testing, adapting and optimizing lifestyle interventions concordant with different geographical regions and cultures.[9] Doing regular physical exercise can prevent occurrence of AD through multiple pathophysiological and molecular pathways such as decreasing neuroinflammation, oxidative stress, neurotoxicity, improving synaptic plasticity and metabolism etc.[10] Studies have also showed that learning a new language in old age can delay the onset of AD by several years by increasing cognitive reserve and neuroplasticity.[11]

Treatment

Cognitive Enhancers

Currently, there are only two classes of drugs approved for symptomatic treatment of memory impairment. These are Cholinesterase inhibitors and a NMDAR antagonist. These cognitive enhancers do not slow the progression of AD or reverse the memory loss.

Cholinesterase inhibitors

Acetylcholine (ACh) plays an important role in regulation of cognitive functions including memory. Due to neurodegenerative process of AD, there is decrease in cholinergic transmission in brain. Acetylcholinesterase (AChE) degrades ACh to choline in synaptic clefts. AChE inhibitors (AChI) prevent the breakdown of ACh. Increase in cholinergic neurotransmission and improves cognitive functions. There are four approved AChIs globally[1] and three in India:[12]

Tacrine was the first AChI approved for the treatment of AD but seldom used now-a-days because of hepatotoxicity.

Donepezil is the most commonly used drug in the treatment of AD. It is reversible inhibitor of AChE associated with mild and transient gastrointestinal side effects.

Rivastigmine is a pseudo irreversible inhibitor of AChE and Butyrylcholinesterase inhibitor (BuChE). BuChE is found in glial cells and accounts for about 10 percent metabolism of ACh in normal brains. However, in AD it accounts for more than 50% metabolism of ACh. Inhibition of both enzymes could theoretically enhance the cognitive functions better than Donepezil, but studies have not demonstrated any additional benefit. Rivastigmine is associated with somewhat higher gastro-intestinal adverse effects such as nausea, vomiting, dyspepsia, decrease in appetite etc. on oral administration. It is also available in transdermal patch forms which avoid gastro-intestinal side effects.

Galantamine is a competitive inhibitor of AChE. It also acts as positive allosteric modulator of alpha subunit of nicotinic ACh receptors which may contribute in improving cognition. It is also available in patch form.

NMDAR antagonists

Memantine is the only approved drug in this category for management of moderate to severe AD. It is a low affinity uncompetitive antagonist of NMDAR. It prevents massive Ca^{++} influx from NMDAR and excitotoxicity. It doesn't block the normal glutaminergic neurotransmission due to low affinity. It is generally safe and well tolerated. It can be administered either alone or in combination with Donepezil.[1, 12]

Cognitive enhancers under phase 3 clinical trials

Memogain (Alpha 1062): It is a prodrug of galantamine developed to enhance its CNS bioavailabilty. It is either delivered through nasal spray or administrated orally and it has shown better tolerability and CSF levels.[13]

KarXT: It is a combination of Xanomeline and Trospium. Xanomeline is M1/M4 Ach receptor activator and Trospium is peripheral Ach receptor inhibitor. Xanomeline improves cognitive functions by directly stimulating muscarinic ACh receptors while Trospium counteracts the gastric side effects of muscarinic receptors.[13]

Management of behavioural problems and psychological symptoms

Behaviour problems in the form of agitation frequently accompany memory loss in AD. They can range from agitation, restlessness, stereotypic movements, easy irritability, apathy and so forth. Agitation and psychotic symptoms can be managed by off-label use of antipsychotics in low doses (Risperidone, Olanzapine, Aripirazole or Quetiapine). Use of antipsychotics in elderly is associated with increased mortality due to cardio-vascular events.[2]

Drugs under clinical trials for behaviour problems of AD

AVP-786: It is a combination of dextromethorphan and quinidine. Dextromethorphan is a weak NMDA receptor antagonist and sigma-1 receptor agonist. Quinidine is an anti-arrhythmic drug, however when it is added to dextromethorphan, it inhibits its metabolism. AVP-786 also contains deuterium instead of hydrogen atom to prolong its liver metabolism.[5, 13]

Brexpiprazole: It is a dopamine receptor (D2) partial agonist and an atypical antipsychotic. Phase 3 Studies have shown improvements in agitation and good tolerability. It is currently under FDA review for management of agitation associated with AD.[5, 13]

Trazodone: It is an antidepressant which is agonist and antagonist at serotonin receptors. It is used off-label for management of insomnia as it improves and deepens slow wave sleep. Disruption of slow wave sleep due to amyloid and tau deposition may be the cause behind cognitive decline. Phase 3 trials are going on for evaluation of effect of trazodone on sleep parameters and cognition.[13]

Nabilone and other cannabinoids: Nabilone is a synthetic compound related to 9-tetrahydrocannabinol. Nabilone is partial agonist of cannabinoid receptors. Cannabinoids have mildly sedative, anxiolytic, appetite stimulant and pain-relieving properties. These are currently under testing for relieving agitation in advanced AD.[5, 13]

Disease Modifying Therapies

Several DMTs are under development to prevent AD or slow its progression. Most research studies recruit patients in mild stage of AD having PET/CSF biomarkers. DMTs are classified as biological therapies and small molecules. Biological therapies can be further divided into those targeting Aβ and tau. Biological therapies include passive immunotherapies, active

immunotherapies and oligonucleotides whereas small molecules include therapeutic agents of small molecular weight administered orally.[5]

Biological therapies for Aβ

These include passive and active immunotherapies. Most passive immunotherapies for Aβ are associated with development of Amyloid Related Imaging Abnormalities (ARIA) as cerebral edema or microhemorrhages.[14, 15]

Passive immunotherapies:

- *Aducanumab* is a human IgG1 monoclonal antibody which binds to Aβ plaques and oligomers and breaks them down to amino acids. It received accelerated approval from FDA in 2021 for management of mild AD. It demonstrated modest efficacy when used in high doses by decreasing amyloid deposition in one trial whereas it failed in other trials. One year therapy of Aducanumab costs around $56000 for each patient. The patients have to undergo PET CT scans periodically with additional cost. The drug also led to development of ARIA in 35% of study participants. The neurological side effects may outweigh the benefit of mild improvements in cognition. [16, 17]

- *Other passive immunotherapies on Aβ pathway: Lecanemab* (monoclonal antibodies for Aβ protofibrils) and *Donanemab* (monoclonal antibody for pyroglutamate form of Aβ) have also demonstrated some improvement in clinical trials and are currently under FDA review. *Gantenerumab* (for Aβ plaques and oligomers), *Solanezumab* (for Aβ monomers) and *Crenezumab* (monoclonal antibody for soluble Aβ oligomers) are also under Phase 2 or 3 clinical trials. [1, 5, 13]

Active Immunotherapies

Vaccines against Aβ are under development from over 2 decades. Initial vaccines showed good response in animal models but led to development of serious neurological side effects and autoimmune reactions in humans. [15] Recently some vaccine against Aβ have demonstrated good tolerability in Phase 1 trials and have entered Phase 2 and 3 trials which are as follows.

- *ABvac40* is a conjugate vaccine targeted against C terminal of Aβ 40 is under phase 2 trials as it was well tolerated in phase 1 trial. [1, 5, 13, 18]

- *UB-311* is a synthetic Aβ1-14 peptide vaccine that couples with helper T cell epitope. It was well tolerated, had good immunogenic response and slowed the progression of mild AD in Phase 2 trials. It has entered phase 3 trials currently. [13, 19]

Biological therapies for Tau aggregation

Passive immunotherapy

- *Bepranemab* is a monoclonal antibody which binds to middle of tau protein and prevents its aggregation. It was found safe in phase 1, so it entered phase 2.[5, 13]
- *Semorinemab*, another monoclonal antibody in Phase 2 which binds to extracellular tau. It was safe but not much efficacious in decreasing tau accumulation and did not prevent the cognitive decline much. Two more monoclonal antibodies *E2814* and *JNJ-63733657* which bind tau protein are in phase 2 trials.[5, 13]

Active immunotherapy

Vaccines against tau tangles have showed small clinical benefits. Also, obtaining rigorous immune response in elderly remains a challenge. [16] Some vaccines acting on Tau pathway are:

- *AADvac -1* acts against non-phosphorylated tau. In phase 1 trials it was found safe and well tolerated. It triggered high IgG response and it slowed the neurodegeneration by 30%. There was 58% reduction in accumulation of Tau tangles. Frequent booster doses of this vaccine are required to be administered to sustain immune response. It is currently in Phase 2 trials. [13, 16]
- *ACI-35* that works on phosphorylated tau is under investigation in phase 1a/2b. In phase 1 trials it was found to be safe and immunogenic.[5, 13, 16]

Oligonucleotides

Ionis Maptrx (BIIB080): It is MAPT RNA Inhibitor, i. e. it is an Antisense nucleotide for mRNA of tau protein. It prevents tau translation. It is injected intrathecally and is currently in Phase 2 trials. [5, 13]

Small molecules under clinical trials

These are some DMT small molecules with different mechanisms of action in Phase 2 and 3 trials:

- *Methylene blue:* It was originally used for malaria, but it has been found to disrupt tau aggregation. It showed some efficacy in improving cognition in Phase 2 trials and is currently in phase 3 trial.[1, 5, 13]

- *Valiltramiprosate:* Prodrug of Tramiprosate and homotaurine, inhibits aggregation of toxic Aβ oligomers. It was found to be effective in AD patients with APOE4 gene copies in phase 2 trials.[5, 13, 16]

- *Blarcamesine:* It is intracellular sigma 1 receptor agonist, a type of chaperone protein which has potential to prevent tau hyperphosphorylation, decrease oxidative stress, protein misfolding and mitochondrial dysfunction. It was well tolerated and slowed the cognitive decline in 47% patients.[5, 13]

- *PU-AD*: It is Heat shock protein 90 inhibitor (chaperone). It prevents aggregation and hyperphosphorylation of Tau and is currently in phase 2 trials.[5, 13]

- *Simufilam:* It is inhibitor of a protein filamin which is regulates cytoskeleton. Filamin aids in binding of Aβ42 with α7 nicotinic receptors which in turn triggers tau hyperphosphorylation. There was improvement in levels of biomarkers and memory tests in research trials and there were no safety issues reported.[5, 13]

- *GV-971:* It is a mixture of acidic oligosaccharides derived from brown algae. It is believed to work on gut brain axis by restoring the normal gut flora and thereby decreasing brain inflammation, amyloid deposition and tau hyperphosphorylation. No significant adverse effects were reported and it demonstrated slowing of cognitive decline in mild AD patients.[5, 13]

- *Hydralazine:* It is an antihypertensive drug that has demonstrated improvement in cognitive decline owing to its antioxidant properties.[5, 13]

- *Icosapentetheyl and omega 3 fatty acid DHA* have also demonstrated benefit by decrease oxidative stress and reducing inflammation.[5, 13]

- *Mastinib:* It is protein kinase C inhibitor used in the management of some cancers. It regulates the activity of mast cells and it is hypothesized to modulate the functions of microglia in AD. In Phase 2 trials it improved the cognitive functioning of patients with AD yet the side effects were twice as high as those in placebo group.[1, 5, 13]

- *Metformin:* It is an oral hypoglycaemic with antioxidant and anti-inflammatory properties. It may have a role in improving cerebral glucose metabolism. It was administered to

nondiabetic persons with mild cognitive impairment and it showed improvements in neuropsychological test batteries while no change in biomarkers.[5, 13]

- *Semaglutide:* It is a synthetic glucagon like peptide used in the management of diabetes. It improves insulin signaling in brain which is thought to be impaired in AD. The preclinical data indicated that it reduced the risk of developing dementia by 53%.[5, 13]

- *NE3107:* It is a derivative of beta-androstenetriol without androgenic or oestrogenic properties. It has anti-inflammatory and insulin sensitizing properties. There was improvement in cognitive decline and biomarkers in about 60% patients.[5, 13]

Other therapies involving alternative medicines

Stem cell therapy: Allogenic human mesenchymal stem cells are under investigation for their role in management of mild to moderate AD. These clinical trials are in phase 1 and 2.[5]

Ayurvedic medicines: Certain ayurvedic medicines derived from *Curcuma Longa, Gingko Biloba, Centella asiatica, Bacopa monnieri* and other plants may have a role in cognitive impairment due to their hypothesized neuroprotective effects.[20]

Chinese traditional medicine: Bryostatin, derived from *Bryozoan Bugula Neritina* has showed decrease in Aβ production in AD mice models. It is claimed that many traditional Chinese medicines have potential in the management of cognitive decline.[1, 21]

Conclusion

Due to increasing life expectancies, there is increase in prevalence of chronic diseases including AD. Yet AD is underdiagnosed across the globe. [7] Many research molecules are under development which can halt the progression of disease or prevent its occurrence. Early detection of AD is the need of the hour as failure of many DMTs in past was due to administration in late stages.. Use of digital technologies may aid in early identification of patients at risk of developing AD. Other reasons for failures have been due to unknown multifactorial aetiology, drugs used on wrong pathways and serious treatment emergent side effects. But still the research is progressing at a rapid pace and a successful DMT might become available very soon in the near future.

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Chapter: 8
Dengue Prevention

Shilpa Nandan Singh * Kalpana Singh
Laboratory of Applied Zoology,
Department of Zoology, University of Lucknow
***E-mail: singh_kalpana@lkouniv.ac.in**

Abstract: Dengue fever is one of the world's fastest spreading viral diseases, causing severe mortality all over the world. Globally, dengue has become a dangerous and economic challenge for human health, though so many techniques have been used to stop this disease. That's why few techniques have been used to suppress dengue that is cost-effective, environmentally friendly, and efficient. To control dengue, vaccines and immunotherapy have been developed, which are more effective. In the present study, the main focus is on dengue control strategies. To control dengue, biotechnology techniques such as paratransgenesis, sterile insect techniques, the production of genetically modified vectors, and the development of a few new vaccines have been used in this study, which claims to be effective. The dengue tetravalent (CYD-TDV) vaccine has been the most effective in preventing dengue infection to date. Though advances in the dengue virus vaccine are being made, we cannot expect a better future unless the virus is eradicated.

Keywords: Dengue virus, infection, vaccine, Techniques

Introduction:

Dengue is a mosquito born disease, which spreads by biting of female *Aedes aegypti* mosquito vector. Due to Dengue there is continuous effect on health, social life, and economy worldwide (Dengue Prevention and Control 2016). Incidence of Dengue has increased 30 fold over the last 5 decades. Due to dengue disease almost 2.5 billion people get affected throughout the world. (koeh *et al*., 2008). In 2012 WHO had reported that Dengue outbreak in worldwide has become burden in tropical countries on communities, healthcare systems and economic conditions. According to WHO Africa, Asia, Americans and the Mediterranean, these all regions are affected due to emergence of DENV. (WHO, 2012). Recently Bhatt *et al*. had guessed that 390 million people get infected by DENV and 96 million people apparently come in evidence yearly. (Bhatt *et al*.2013). Dengue fever infection starts from mild fever and gradually increases. A different type of vector control has been developed to prevent from DENV, like physical control,

chemical control & biological control but rather than these control methods, other vaccines is also being developed so that we can use to control & prevent against Dengue. (DeRoeck *et al*. 2003).

Prevention and control Strategies:

There are three types of prevention & control strategies, which are as follows:

Physical control of Dengue by GIS mapping:

GIS is a very good technique for mapping of DENV location. GIS easily founds seri-positive areas of Dengue transmission and so it can be easily treated by using different control strategies. (Gandhi *et al.*, 2017). GIS mapping not only provides better surveillance & suppresses Dengue but it also successfully determines rate of control mapped area. GIS surveillance was used to determine *Aedes aegypti* major breeding sites. (Kittayapong *et al*.,2008).

Effective Surveillance:

Surveillance provides fundamental information by doing assessment of Dengue risk and this surveillance response delivers timely in system about Dengue control & prevention. (Wilder-Smith *et al.*, 2012). Surveillance is enabled to understand number of dengue cases at same time & same place and it also provides link for better planning of entomological & epidemiological (WHO, 2012; Scarpino *et al.,* 2017). But on other hand these surveillance programmes are not this much focussed that it may eliminates dengue vectors (Abbas *et al.,* 2014).

Determination of Oviposition sites:

Female *Aedes aegypti* laid eggs in water container & jar to survive (Morrison *et al.,* 2004). If we wish to decrease *Aedes* mosquito vector population then it is necessary to identify the behavioural pattern of them. After complete study, it has been reported that oviposition pattern behaviour of *Aedes aegypti* shows strong intra-specie affinity. Rather than this if we find oviposition site then strategies can be planned to control *Aedes* mosquito population in developmental stage (Wong *et al.,* 2011). Recently it has been introduced that oviposition –based technology is most intensify in controlling *Aedes* mosquito vector (Johnson *et al.,* 2017).

Community-based mosquito control programmes:

Aim of this programme is to study about extermination of Dengue vector breeding sites at large scale. In this programme peoples of community are divided into various groups on the basis of their education & understanding (Abbas *et al.,* 2014). Elimination programme of Dengue in Kerela district (George *et al.,* 2017), Mexico (Tapia-conyer *et al.,* 2012) & Cuba (Valerberghe *et al.,* 2010) had proved that awareness of Dengue elimination among these communities is of high level and by involvement of these communities, new techniques are integrated to control Dengue vectors (Heintze *et al.,* 2007; Perez-Guerra *et al.,* 2009; Shriram *et al.,* 2009).

Education of Prevention Strategies:

Education plays an important role in peoples of community to increase awareness at serious note that how to use techniques & strategies for prevention of Dengue vector and also have to provide better measures so that habitat of dengue vectors can be eliminated (Madeira *et al.,* 2002).

Biological control by Paratransgenesis:

Nowadays, paratransgenesis is a popular method to control *Aedes aegypti* genetic (Araujo *et al.,* 2015; Ogaugwu & Durvasula, 2017). In this process, genetically modified symbiotic bacteria are introduced again in Dengue vectors, so that they may grow Dengue vector population but in these Dengue vectors there is the limitation of transmission of disease (Araujo *et al.,* 2015; Wilke & Marrelli, 2015). Due to these genetically modified bacteria, in body of Dengue vectors there is no proper function of sexual cycle, competence of development process is reduced and Dengue vector population suppresses (Wilke & Marrelli, 2015).

Use of Larvivorous fish:

When Dengue vectors larvae resides in open water bodies then larvivorous fish like *Poecila reticulata* (guppy fish) (Seng *et al.,* 2008) & Crustacean *Mesocyclops formosanus* (Kalimuthu *et al.,* 2017) are used to control *Aedes* mosquito vector population. This is eco-friendly & cost effective method and it's a most simple & innovative strategy (Abbas *et al.,* 2014; Han *et al.,* 2015; Warbanski *et al.,* 2017).

Species Genetic Modification:

Genetic modification is used to reduce *Aedes* vector population. This is designed, so that due to induced effector genes may hinder the transmission of disease (Reis-Castro, 2012; Carvalho *et al.,* 2014; Jupatanakul *et al.,* 2017). In Brazil genetically modified mosquitoes are released in field, due to which 85% population of *Aedes aegypti* mosquito has been declined (Pan American Health Organization, 2014). Genetically modified vector is most innovative way to control transmission of mosquito born disease (Fraser, 2012; Favia, 2015).

Chemical control by using of Insecticides:

Chemical insecticides are used since many decades to control mosquito and this results negative impact on environment (Araujo *et al.,* 2015).

Use of Insect Growth Regulators (IGRs):

Like other chemical compounds Insect Growth Regulators (IGRs) is also an innovative & feasible method to control growth & development of insects. Insect Growth Regulators (IGRs) kills insects at early stage only. Many types of IGRs like diflubenzuron, endotoxins & methoprene are used to control viral infection of Aedes aegypti (Abbas et al., 2014). In some studies it has been found that cyromazine shows effective results in reducing population *Aedes aegypti* (Lau *et al*., 2015).

Use of plant derivatives:

To control *Aedes* vector population researchers had developed plant based derivatives. Plant derivatives are safest method for environment, there is no impact on non targeted animals and plant derivatives are developed by plant parts (leaves, stems & roots) (Ramkumar *et al.,* 2015). There are many plants which has been used for medicines like *Erythrina indica & Asparagus racemosus* (Govindrajan & Sivakumar, 2015), *Callistemon rigidus* (Pierre *et al.,* 2014). These plants prove their efficiency as a repellent against *Aedes aegypti* (Araujo *et al.,* 2015; Govindrajan & Sivakumar, 2015).

Development of vaccines and Immunotherapies:

Among improvised vaccines, live development vaccines called ChemariVax-Dengue of bivalent & tetravalent based vaccines was effective against DENV in a test held in Mexico (Dayan *et al.,*

2014). The study on group stated that a bivalent & tetravalent vaccine exhibits different results (Dayan *et al.,* 2014). Proven result of assured random studies have underlined the grandness of CYD-TDV vaccine in Latin America (Villar *et al.,* 2015), Thai (Sabchareon *et al.,* 2012), Asian (Capeding *et al.,* 2014) and children plus adults in Singapore (Sin Leo *et al.,* 2012). Even so, in study it has been found that there is modest risk of CYD in CYD-TDV vaccinated kids of age above 2 years to 16 years old, than controlled group without vaccination (Hadinegoro *et al*., 2015), antibody counteraction have reaction with Dengue serotypes & secure visibility of CYD-TDV (Qiao *et al.,* 2011; Villar *et al.,* 2013). Despite endure/faded vaccines, demobilized and non-repeated vaccines also has been practiced. The formulating non-repeating vaccines assesses centre on recombinant DENV antigens, demobilized viruses & practice of non-repeating transmission factor developed specifically to induce Dengue virus DENV antigens in *vivo*. Practicing demobilized vaccines also lowers the risk of infection by confabbing hurdles. Also, fractional monetary unit vaccines & inherited vaccination have been formulated to answer the demobilized viruses (Sawaminathan & Khanna, 2010). Across many region of the world holocene eruption of Zika virus has aroused a developing pertain. Even so, by practicing vaccination many viral diseases have been insured. Even so, no vaccines have been made yet for most of the arthropod communated viral diseases. Hence, researching possible transmission blocking vaccines (TBV) could freeze the viral infection in homo and may be implemented to almost arboviruses, admitting chikungunya, DENV & ZIKV.

Challenges & limitations to Dengue prevention strategies:

In new planning, Dengue vaccine has been differentiated for DENV prevention & its control. There is always something missing in challenges & limitation when we go to perfectly apply such planning (Achee *et al.,* 2015). Whatever strategies has been introduced for Dengue control & prevention has not given satisfactory result & utilization of vaccine is cost-effective for public health and the vaccines which are present use to face various challenges (Ghosh & Dar, 2015).

Conclusion:

Dengue pandemic has increased so much in today's world, due to which cost efficient & safe control measurement are being practiced to reduce the infection of Dengue. The method which has been used like physical control, biological control & chemical control and among other

developed vaccines, live attenuated tetravalent vaccines are safe, tolerable and helpful against dengue protection.

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Chapter: 9
Cancer and Smartphones: Fact or Fiction?

Monika Monika[1*], Sanjeev Gupta[2]

[1]Department of Zoology, Kurukshetra University, Kurukshetra, Haryana 136119, India

[2]Department of Zoology, Institute of Integrated and Honors Studies, Kurukshetra University, Kurukshetra, Haryana 136119, India

[*]E-mail: monikay167@kuk.ac.in

Abstract: Mobile phones have revolutionized the modern telecommunications industry by using wireless communication technology, and they have surpassed the global population in terms of their number. An upsurge in smartphone use created a notion in the media and public that smartphones are associated with cancer. Since the use of mobile phones and exposure is rapidly increasing, even minor elevated risks can have serious implications on public health. To get a full picture of their impact on human health, umpteen investigations have been conducted over a period of 10 years or longer. In this chapter, numerous studies are reviewed regarding the impact of smartphones on human health, as well as preventive measures to minimize harmful effects.

Keywords: smartphones, radiations, cancer, human health

Introduction: In 1899 the first telegraphic message was sent from New York harbor to Twin lights in highlands. The first commercial mobile phone was launched in 1983 since then this technology rapidly increased over time with addition of new features. 21st century is the era of cell phones (9). The mobile phone network is powered by base stations that produce 200 and 2000 watts of effective radiated power, while some old base stations produce up to 10000 watts (23). Mobile phones are two-way system: can send or receive the communication, possibly because of EMR (Electromagnetic radiations) and EMF (Electromagnetic field) (10). EMR consist of electric and magnetic field, can travel in air and vacuum. These radiations have wavelength 1mm-100km and frequencies from 3kHz to 300GHz (11). Smartphones technology uses 2nd generation global system (GSM) that includes 3G/4G/5G universal mobile telecommunications system (12). In the public health and research community, these mobile phone radiations and cancer issues received adequate attention. Cancer risk assessment is complicated when it comes to smartphones. Identifying weak carcinogens and their epigenetic mechanisms is extremely difficult. Over the last three decades, numerous scientific studies have

been conducted to check the biological effects of these radiations on human health and their associated risks. Childhood leukemia, brain tumors, genotoxic effects, neurological impacts, neurodegenerative illnesses, immune system dysregulation, allergy and inflammatory responses, infertility, and certain cardiovascular problems are among the health endpoints linked to radiations (30). Electromagnetic radiations interfere with brain signals and causes neurodegenerative disorders, hearing disabilities, diabetes, congenital abnormalities. EMR affects neurons by reducing the neuronal reactivity, increasing the neural membrane conductivity, increased the refractory period (32). Mobile phones increased the death rate by increasing risk of vehicle collision and affect the medical devices like pacemakers under certain conditions (26).

Smartphones and radiations: Smartphone definition is whimsical but oxford provided a solid definition i.e., "a mobile phone that performs many of the functions of a computer, typically having a touchscreen interface, internet access, and an operating system capable of running downloaded apps". Smartphones came into existence in 1990s and become an integral part of our lives (4). In last three decades, the use of smartphones has increased drastically. Globally, 5.3 billion subscribers are available for cell phones. There will be 2 billion 5 G connections till 2025 (34). This wireless technology made communication very easy, but it created a notion in media that it is related to increased risk of cancer and various health issues. Smartphones generates electromagnetic radiations which get absorbed by our body known as specific absorption rate (SAR). SAR causes heating effect of skin, ear, head near which phone is held. The adverse effects of radiations depend on time of exposure, frequency of radiation, distance between user and emitting source and the orientation of radiations (5). To avoid direct radiation effects, hand free kits were used. Hand free kits reduce the overall exposure of head to SAR 5 times but still provide a very low and continuous exposure to ear (6). The council of European union set SAR 2 watts/kg for cellphones. When SAR value is 1-2 watts/kg, it results in to increase of body temperature by 1˚C. SAR values can be calculated when you are speaking at ear level or when your phone is in pocket at body level. Different smartphone company cellphones have different SAR values (35).

Smartphones and diseases: Smartphones not only get popularity in media just only for its features but also for its impacts on human health. Various studies provided evidence against

negative effects of smartphone radiations. The low frequency radiations produced by smartphones short exposure causes headache, fatigue, dry eyes, tinnitus, sleep disorders, hormonal imbalance disorders (8).

Effect on DNA damage: Smartphones radiations impact on DNA and chromosomal structure was studied. A large number of in vitro studies provided negative results, but a few provided positive results which was argued to be possibly because of thermal effects. So, it still unclear that radiations had any direct effect on DNA damage (20).

Effect on plasma membrane: Electromagnetic radiations from smartphones had adverse effects on plasma membrane like calcium efflux from membrane, impact on channels or gap junction, increase in stress proteins, increase in ROS, decrease in protein kinase C activity, altered blood brain barrier (29).

Effect on salivary gland, vestibular system: A meta-analysis study included 5087 subjects; cell phones seemed to be associated with salivary gland tumor (33). Several reports speculate that a reasonable suspicion of mobile phone risk that exists based on clear evidence of bio-effects with prolonged exposures may reasonably be presumed to result in health impacts (30). Study was done to study the effects of smartphone radiation on auditory and vestibular system showed that acute exposure does not affect cochlear outer cells and vestibular system but had controversial results regarding acoustic neuroma (24).

Effect on thyroid gland: Mobile phone radiations were found associated with thyroid gland insufficiency, histopathological changes in thyroid follicles, alteration in serum thyroid levels, disruption in hypothalamus-pituitary-thyroid axis (25). In between 2010-2011, a study was conducted in Connecticut to study the association between smartphones and thyroid cancer in human population. This study included 440 thyroid cancer cases and 465 controls to study the association between Single nucleotide polymorphism variants and smartphones. This study proved that genetic susceptibility modifies the associated risk of thyroid cancer with smartphone use (19).

Effect on reproductive system: Excessive exposure to EMF for a longer duration affected male and female reproduction. Cell phone radiations causes increased reactive oxygen species (ROS) in testicular follicles which harm sperm motility, sperm count, morphological abnormalities, and

hormonal imbalance (16). In contrast to this, one study conducted in Denmark and USA human volunteers who kept their phones in pocket had no adverse effects on semen quality (17).

Smartphones and cancer: A popular French study, CERENAT findings showed a relation between use of smartphones for a decade or more than a decade and increased risk of meningioma. They classified smartphone radiations as Group 2A probable human carcinogen (7). A Sweden human study with age group 18-75 years revealed that ipsilateral and contralateral use of cell phones is related to higher risk of tumors (13). A person with increased cell phone timing from 30 minute/day to 8-10 h/day has double to quadruple increased risk of tumors (14). USA study from 2010-2017 showed that from birth to 24 years age group has increased incidences of neuroepithelial brain tumors in children, adolescents, and young adults. In the age group from 20-85 years has increased risks of pituitary tumors and nerve sheath tumors in UK (15). A meta-analysis study was done which included 11 studies, 6028 cases and 11488 controls. This study found that there was a positive association between glioma risk and increased use of mobile phones for longer period (minimum 10 years) (21). One study proved that radiofrequency increased case of lymphoma in mice (23). Positron emission tomography studies showed that smartphone radiations changes blood flow in cerebellum, trigger double strand DNA damage, misbalance in double strand break repair, which leads to various types of leukemia and tumors. Stem cells were more sensitive to EMR's (27). Levis and co-workers review study showed that use of mobile phones for 10 or more years is 100% related with increased risk of glioma and told that there was a clear relation between ipsilateral head tumors and mobile phones usage for 10 years in INTERPHONE study (28).

New Zealand study conducted between 1995-2010 showed no consistent increase in brain cancers in the age group 10-69 years but glioma increased cases over the age of 70 (18). Largest case study INTERPHONE conducted by group of 14 countries researchers coordinated by IARC international agency for research on cancer showed no significant results with increased cancer risk and overuse of mobiles (22).

Effect on survival: The literature consisted of 18 studies with survival data, and 16 of these have information on cancer. In one study, a significant decrease in lifespan was observed at 6.8 W/kg but not at 2 W/kg. Thermal stress appears to be the causal factor for the effect on lifespan

because the higher dose rate, unlike the lower dose rate, was estimated to increase body temperature significantly (31).

NIC report: According to national cancer institute (NIC) cell phones are emitting radiations of low frequency falling in the range of 0.7-80 GHz. Numerous studies revealed that radiations in the range 0-300 GHz does not causes harm at genetic level as they do not increase the number of micronuclei or any chromosomal aberrations (8). These radiations have very low energy which is not sufficient to create any DNA damage. The body absorbs these radiations, and since we hold cell phones close to our heads, brain cancer is one of the major concerns. But According to NIC report, there is no change in the incidences of adult gliomas, acoustic neuroma, and pediatric brain tumors in the United States from several decades. (36)

Expert organization's views: International agency for research on cancer (IARC) categorized cell phones as possibly carcinogenic to humans based on the confined authentication of different studies (2). National Institute of Environmental Health Sciences (NIEHS) and FDA stated current reports do not justify the link between cell phone and health issues, but more scientific studies required for a clear picture. Federal Communications Commission (FCC) mentioned that malignant diseases including child cancer cases were not increased after cell phone usage (3).

Protective measures:

FDA (US Food and Drug Administration) provided some guidelines to reduce the exposure of radiations generated by cellphones (1):

1. Use the cellphones for shorter conversations.
2. Use device with hand free technology, like headphones.
3. Keep a proper distance between cell phones and body.

Conclusion: Smartphones have become an integral part of our lives, but the notion of their harmful effects on the body has not disappeared. A high number of users means a minimum number of negative effects must also be considered as a serious concern. Studies linking cancer and smartphones have not shown conclusive results, so it is imperative to increase research in this field in order to get a clearer picture and ensure the health of mobile users. Due to the short duration of studies, the lack of rigid exposure measurement, and recall and response errors,

studies have limited results. Health impacts must be studied in more depth to provide a clearer picture. There is no evidence that smartphones increase risk of brain cancer, but their negative effects on eyes, ears, and thyroid glands are well documented. To minimize the side effects of this technology, we should use it with the necessary preventive measures. The purpose of technology is to improve our lives, not to make them worse, so we should be aware of its effects on human health at each level.

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Chapter:10

Music: A curative medicine for Hypertension

Simran and *Kalpana Singh
Laboratory of Applied Zoology, partment of Zoology, University of Lucknow
Email: singh_kalpana@lkouniv.ac.in

ABSTRACT

One of the problems people face today is hypertension. It is also known as a "silent disease" because people are unaware they have high blood pressure before checking. Music therapy generally tries to reduce people's stress and make their hearts healthy and happy. Music Therapy is the use of music and musical interventions to restore, maintain, and improve emotional, physical, physiological, and spiritual health and well-being. These are the key elements which define interventions as music therapy. Music Therapy is goal oriented and provides a system to work towards a specific therapeutic goal and objective. Music may prevent the hypertension with non-medication therapy which shows a positive effect on autonomous nervous system. It reduces the blood pressure both systolic as well as diastolic and stabilizes irregular heart rate and increases the parasympathetic activity. They have the ability to promote relaxation, as seen with the alpha level of brain waves.

INTRODUCTION

Today, music plays a significant role in every person's life. People listen to music to relax due to the heavy workload. Music has positive psychological and physical impacts on people. Music is the art and science of controlling tones or sounds. Good music encourages vitality, impulsivity, happiness, and attentiveness. Every cell in the body is given energy, and there is a rise in vitality and mental peace. We can lead more fulfilling lives with the support of music. It is beneficial to listen to certain types of music at different times of the day to maintain person's health. Indian music is well known for its therapeutic benefits due to the variety of Ragas. It appears that music has a therapeutic effect via influencing hormonal and glandular systems, which produce secretions that maintain the body's equilibrium and promote healing. Music is considered to stimulate the pituitary gland, whose secretions have an impact on the neurological system and blood flow. The metabolic processes in the human body are accelerated by music.

Music therapy is a specialized field that uses music to treat people with specific needs for their physical and mental well-being, rehabilitation, and other purposes. Music is a non-

medication therapy like drugs; it has no negative side effects. It is a simple, cost-effective, and easy-to-use method of relaxation. The general goal of music therapy is to make people happy and entertained, as well as to lessen the burden of their suffering(8). Three months of active music treatment showed a considerable increase in verbal and spatial memory(3). Indian classical music has developed a unique therapy based on the 72 ragas. A raga is a series of selected notes that provide appropriate 'mood' or 'emotion' in a selected combination. Raga is composed of melody, notes, and scales. A raga's ability to induce joy or sorrow, violence or calmness, depending on its character, serves as the basis for its musical application. Indian ragas can help with a variety of conditions such as indigestion, arthritis, epilepsy, insomnia, hypertension, asthma, chronic headaches, haemorrhoids, arrhythmia, ulcers, and cancer rehabilitation, among others. Indian music has emotions, and it unites us with an unseen divine power (2).

Effect of music on hypertension

Hypertension is a health problem that needs to be considered. It is the biggest culprit of stroke both systolic and diastolic blood pressure. Managing Blood pressure is critical for maintaining health and reducing the risk of the dangerous conditions. Listening to appropriate music lowers blood pressure, stabilises irregular heart rate, reduces anxiety and depression and related mental illnesses, improves concentration, and decreases the need for sedatives and pain medications. Raga Bhimpalasi, a type of Indian classical music, has been shown to significantly reduce anxiety levels and hypertension. It is mainly affecting concentration and memory related problems. Listening to Raga Bhimpalasi makes feel upbeat, joyful, relaxed, peaceful, and confident. It exhibited a beneficial impact on brain neurons. This in turn helps in releasing stress, while it stimulates the cells. The heart rate parameter reflects changes in autonomic response to the pleasurable experience of music listening.(7)

Blood pressure changes according to activity; in a stressful environment, blood pressure rises; in a restful and relaxing environment, blood pressure falls. Music therapy has a beneficial effect that can help to relax the mind and the heart rate slowly combines with the beat of the music, causing blood pressure to decrease. It reduces the blood pressure both systolic as well as diastolic and stabilizes irregular heart rate and increases the parasympathetic activity. It has the ability to induce alpha waves in the brain. Due to its slow tempo or rhythm, classical music is

utilised in music therapy to lower blood pressure since it promotes relaxation. In addition to calming the mind, it helps ease mental, emotional, physical stress (2).

Conclusion

People can benefit physically and mentally from music therapy. Music relaxes and improves the mood of the listener. A passive listening to a particular Indian music raga Bhimpalasi produced a mild arousal response. The benefits of listening to appropriate music include lowering blood pressure, regulating irregular heartbeat, easing pre-treatment anxiety, treating depression and other mental illnesses, improving focus, and reducing the need for sedatives and painkillers. Certain types of music can lower systolic blood pressure; as a result, music therapy is used successfully as an alternative and efficient means of treating hypertension. A simple, secure, and successful method has been discovered to be music.

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About The Editors

Prof (Dr.) Manju Chhugani is Dean, School of Nursing Sciences and Allied Health at Jamia Hamdard, Hamdard Nagar, New Delhi, India, and Head, Department of Paramedical Sciences and Department of Obstetrics and Gynecological Nursing. She is prodigious leader, trainer, researcher and an influential academician with more than 30 years of extensive hands-on experience in area of maternal and child health and university teaching. She is a certified assessor of National Assessment and Accreditation Council (NAAC), nodal head of National Skills Training Centre "Daksh", member of Central Review Mission (CRM), Government of India, steering group member at State of world's midwifery WHO 2021. She is notable member of University Grant Commission (UGC) expert committee for comprehensive and holistic review of functioning of universities and review more than 21 universities. She is external assessor at NHSRC and dynamic member of 25 national and international organizations and has completed various projects with UNICEF, UNFPA, ICHA, Centre for Development of Population Activities (CEDPA), and Ipas Development Foundation (IDF). She has been expert, resource person chairperson, and organizer and participated in more than 360 workshops/ seminar and conferences. She has received 16 awards and appreciation in her field. She is the first Indian to receive the prestigious Marie Goubran Agent of Change Award by ICM for the year 2020. She has a total of 65 publications, 7 book chapters, 5 books, 16 guidelines under her umbrella. She has led more than 12 research projects funded national and international organizations.

Dr. Neha Singh, working as a Senior Scientist, Virology Lab, Department of Microbiology, Pt JNM Medical College, Raipur, Chhattisgarh. She is Ph.D., Postdoc in Microbiology. Her area of interest is Antimicrobial compounds, Drug resistance, Infectious diseases, Molecular virology. She is having around 11 years of research experience. She is active *Member of ISC* (Institutional Scientific Committee) of medical college and running various institutional & ICMR research projects. She has contributed in disaster management of ongoing global pandemic of *COVID-19* since last two years as *operational **In-charge*** of state virology lab of medical college. She is one of the member of *State Advisory Committee* of establishment of molecular virology labs in Chhattisgarh. She is certified, *Master Trainer* for newly recruited HR for molecular virology labs, from USAID, RISE in association with London School of hygiene and tropical medicine. She is *Principal contributor* for operational manual for BSL-II virology laboratory for state of Chhattisgarh.

Dr.Madhavrao C (MBBS, MD) is currently working as Associate Professor in the Department of Pharmacology, AIIMS Mangalagiri (India). He has 12 years of enriched teaching experience for both undergraduate and postgraduate levels. His field of research is Neuropharmacology, Bioethics and Medical Education. He has completed several 'Preclinical and Clinical' research funded projects. He has more than 15 publications to his credit in peer reviewed indexed journals. He has been recognized 'Guide' for MD, PhD and ICMR-STS related research proposals. He is currently the 'Editor and Reviewer' of several reputed national and international journals in the field of medicine. He is also a 'Member of Institutional Ethics Committee (IEC) and IAEC (Institutional Animal Ethics Committee)'at several institutions(s).

Dr. MythiliBai K (M.B.B.S, M.D, PDCR, and ACCR) is currently working as Assistant Professor in the Department of Physiology, Government Siddhartha Medical College, and Vijayawada. She has 9 years of teaching experience for MD, MBBS, BDS and BSc Nursing students at tertiary care institution(s). Her areas of interest include 'Ethics in Clinical Research, Neurophysiology, Pulmonary Function Tests and Medical Education. She is a Principal Investigator as well as Co-Investigator for several Institution funded research projects. She has 10 publications including a chapter to her credit in national and international reputed journals. She is actively involved as 'Editor and Reviewer' of many national and international journals in the discipline of medical and allied sciences. She has been awarded for best oral presentation(s) in both national and international conferences.

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