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Editorial

THE FUTURE OF THE FIGHT: THE EMERGING CHALLENGES AND FIGHT AGAINST OBESITY FOR MEDICAL SCIENCE

Dr. Balwinder Kaur Rekhi

ABSTRACT: The world is faced with perhaps one of the biggest challenges in today's medical world: that of the obesity epidemic. Obesity was perceived to relate to lifestyle issues; however, it has nowadays been acknowledged as a chronic and relapsing disease with multiple biologic and psychosocial components. It has widespread implications and is threatening to destabilize the healthcare system as a whole. Obesity is not only causing a significant increase in comorbidities but also breaking healthcare systems and economies as a whole. This note attempts to critically analyse and discuss challenging trends of obesity in the field of medical science.

KEYWORDS: Obesity, chronic disease, medical education, anti-obesity drugs, weight loss surgery, healthcare systems

I. INTRODUCTION: THE UNPRECEDENTED GLOBAL

"The belief that obesity is the consequence of individual 'failure,' 'weak willpower,' and 'dysfunction,' and thus something that an individual could, and perhaps should, control" is profound and has long roots in society at large and, indeed, healthcare itself. But new findings from the science of metabolism demonstrate that "obesity is caused by interactions between susceptibility, neuroendocrine regulation, gut microbiota, adipose tissue, and environment". [1]

Obesity is no longer a regional public health issue but rather a global pandemic that has never been witnessed before. According to the World Health Organization, more than a billion people across the world are actually suffering from obesity.[2] This pattern indicates drastic changes that affect the whole world in areas that include food habits, urbanization, mechanization, and the resultant lack of physical activity. It is essential to note at this stage that all age groups are now affected by obesity, including children.

The community of medical science is also faced with the task of coping with an ever-increasing incidence of obesity, while, at the same time, an ever-increasing spectrum of diseases is being attributed to it. While it was hitherto considered a risk factor, it is now increasingly perceived as a disease entity in its own right, contributing to morbidity, mortality, and health care utilization in an independent manner.[3] The strategy of coping with its downstream effects, like diabetes mellitus, hypertension, and cardiovascular disease, has proved ineffective.

Adipose tissue is considered to be a dynamic endocrine organ that secretes various mediators, including adipokines, cytokines, and inflammation mediators, which play a role in insulin resistance, endothelial damage, atherosclerosis, and carcinogenesis.[4] The pathways responsible for regulating the CNS involved in appetite, satiety, and energy expenditure are dramatically different in obese individuals to support the challenge to lose weight through behavioral interventions.

Such knowledge demands a paradigm shift in medical education and discussions in general. Obesity needs to be recognized as a chronic relapsing illness that requires chronic or individualized management rather than intermittent advice related to lifestyle changes.

II. CHALLENGES IN THE PHYSICIAN'S ROLE: BIAS, BURN

A. Weight Bias and Stigma in Clinical Practice

Weight bias has been persistent in the healthcare environment and has been formally recognized as an obstacle to optimal care in people who are obese.[5] For people who experience obesity, there may be stigmatizing talk, lack of empathy, and a tendency to attribute all symptoms to weight.

Doctors may inadvertently forsake a differential diagnosis or fail to fully utilize evidence-based treatments in obese patients. A change in anti-obesity bias requires a systematic change in educational efforts and institutional policy in supporting dignified language.

B. Lack of Proper Training and Time Constraints

Although the magnitude of the issue is great, education in anti-obesity medication is given relatively little place in university courses or higher degrees. Indeed, most specialists feel that they lack confidence when it comes to prescribing anti-obesity medicines or offering long-term advice.[6] Patient care is also hampered in primary health sectors due to time constraints and inappropriate payment structures.

The future of management of obesity might include obesity medicine certification programs, multi-disciplinary clinics, as well as payment systems that address obesity as a chronic disease.

III: THE THERAPEUTIC REVOLUTION AND LIMITATIONS

A. Anti-Obesity

Glucagon-like peptide-1 receptor agonists and dual incretin therapies have revolutionized current approaches for treating obesity. The efficacy of these drugs has been proved in randomized studies in terms of sustained weight loss of 10-20% with improvements in cardiometabolic risk factors. The action mechanism includes regulating appetite, gastric emptying, and central satiety components.

Nonetheless, concerns exist about its safety profile in the longer term, the definition of its treatment duration, gastrointestinal adverse reactions, and weight regain after stopping treatment. The high drug cost could further accentuate differences in therapeutic accessibility.

B. Bariatric and Metabolic Surgery

Bariatric surgery is currently the only definitive long-term solution for someone who is severely obese to achieve remission of metabolic conditions.[8] In spite of the strong evidence base showing declines in fatalities as well as cardiovascular events, there is a low rate of use of this procedure.

With an increasing trend of surgical candidates presenting with higher BMI's and more complex comorbid conditions, risk stratification, anesthesia optimization, and minimally invasive strategies have assumed key significance. Pharmacological management coupled with surgical interventions is the future of managing obesity.

IV. THE COMORBIDITY CASCADE: A MULTISYSTEM CRISIS

Among these risk factors, obesity is recognized as a major contributing or predisposing factor for various chronic illnesses such as type 2 diabetes mellitus, cardiovascular disease, obstructive sleep apnea syndrome, chronic renal disease, metabolic dysfunction-associated steatohepatitic liver disease, and osteoarthritis.[9] Furthermore, there exists a higher susceptibility and risk of death from various malignancies such as breast cancer, colorectal cancer, and endometrial cancer among obese patients.

This has led to a situation of highly complex patients, who require management approaches that involve multiple disciplines. Biomedical research needs to shift focus to mechanisms that are further upstream in order to prevent the progression of the diseases.

V. HEALTHCARE INFRASTRUCTURE AND ECONOMIC STRAIN

Obesity poses an enormous burden on healthcare infrastructure. More resources are required by the healthcare system, such as bariatric-rated beds, equipment, operation tables, and healthcare professionals.[10] Obesity has resulted in an increased proportion of healthcare expenditure on the healthcare system, with disability and loss of productivity impacting profoundly on the burden on society due to the syndrome.

VI. TECHNOLOGY AND DIGITAL HEALTH IN OBESITY TREATMENT

Digital healthcare innovations have scalable interventions in the management of obesity. Tele-health platforms, wearable technology, mobile apps, and artificial intelligence-powered risk stratification platforms allow for remote patient observation and management.[11] However, disparities in technology access and the lack of long-term data have impeded widespread and prudent application.

VII. PREVENTION, POLICY, AND PUBLIC HEALTH INTEGRATION

The obesity epidemic cannot be solved by medicine by itself. For prevention, a multifaceted public health strategy addressing food systems, advertising, urban design, education, and issues of socioeconomic inequality is necessary.[12] There comes a role for physicians as advocates, speaking from their experience to the public about what must be done at a population level.

VIII. CONCLUSION

The future of biomedical science is inevitably tied up with the answer that must be found to the epidemic of obesity. It is a challenge that demands a paradigm shift—instead of shame and a lack of knowledge that centers on treatment,

it is a challenge that demands a focus on integration and management. It will require more than just innovation but the ability to provide equitable care.

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Original Research Article

ADVERSE EVENTS DURING INTRA-HOSPITAL TRANSPORT : IMPACT OF TRAINED TEAM

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ABSTRACT: Caring for critically ill patients during intra-hospital transport is a high-risk task, and evidence regarding the effectiveness of specialized transport teams in this setting remains limited. We conducted a ambispective study in a multidisciplinary teaching hospital including all consecutive adult ICU patients transported for diagnostic or therapeutic purposes. A dedicated transport team comprising twenty nurses and six medical students were trained, and patients were accompanied by trained personnel. The patients were then divided into two groups for analysis, based on the pre and post training period to compare the incidence, type, and pattern of adverse events during transport. A total of 573 transports were analyzed, with 178 adverse events (31%) recorded, including physiological adverse events (39.8%), team failure (27.5%), equipment failure (21.5%), and delays (11.2%). There was a statistically significant difference in overall adverse events between the groups (p=0.003), particularly in events related to team failure (p=0.006) and equipment failure (p=0.001). These findings suggest that the use of a trained, specialized transport team, rather than a hybrid team drawn from sending units, can significantly reduce adverse events related to team and equipment failure during intra-hospital transport of critically ill patients, underscoring the importance of focused education and training to improve patient safety and team performance.

KEY WORDS : Intra Hospital Transfer, Adverse events, Equipment failure, Team failure

INTRODUCTION

The most secure place where the critically ill patient can be safely managed is the intensive care unit with multimodal monitoring facilities, organ support system and trained staff; all available at the bedside. However, there are situations when patients have to be shifted out of this secure environment to radiology or other departments for diagnostic or therapeutic interventions. This transport process involves shifting of the critically ill patients from advanced hemodynamic monitoring to portable devices, which may be associated with the high risk of adverse events. The incidence and pattern of adverse events depends on multiple factors such as severity of illness, duration of transfer and availability of experienced medical escort.[1-3] Studies have been conducted regarding the safety concerns of transferring of critically ill patients and the results show that timely transfer, hemodynamic stabilization before transfer, continuing monitoring and resuscitation during transfer are some factors that result in a smoother journey for critically ill patients.[4]

Despite the presence of guidelines for the transport of critically ill patients that emphasize the preparations before transfer, still the reported incidence of adverse events is up-to 70%.[5] This high incidence may be because of deviation from suggested standards. Even in our personal experience, there were of episodes of hypotension and desaturation of patients when transferred back to the intensive care unit following investigations. This inspired us to train our staff and residents for the transport of critically ill patients using a constructed model. Following model implementation, outcomes were compared before and after the structured training program.

METHODS

This ambispective study was conducted over a six-month period in the Intensive Care Unit (ICU) of a multidisciplinary, 1500-bed teaching hospital. The patients admitted to the ICU belonged to medical, surgical, and neurosurgical specialties. All ICU patients requiring intra-hospital transportation for either diagnostic or therapeutic purposes were included. The diagnostic category included transfer to radiology department for ultrasound, Computerized Imaging (CT) or Magnetic Resonance Imaging (MRI) or endoscopy room, whereas therapeutic category included transfer to operation theatre, intervention-radiology suite, or for invasive gastroenterological interventions. Patients younger than 18 years, whose stay in the ICU was less than 24 hours, or who did not consent were excluded from the study population. The study protocol was approved by the Institutional Ethics Committee (2018-277).

This prospective–retrospective study incorporated a structured model for intra-hospital transport of critically ill ICU patients. Initially, patient transfers were conducted by the primary care team trained in BLS and ACLS who have the privilege to do so as a part of their job responsibility. A dedicated transport team was later established, comprising 20 ICU nurses from various units and 6 junior residents (two each from medicine, anesthesia, and surgery). Team members underwent two weeks of structured training, delivered by certified Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) instructors, using video modules and presentations based on ISCCM guidelines for inter- and intra-hospital transfer.

Outcome Comparison: Pre- vs post-implementation

Outcome metrics were compared between the pre-intervention period (before training and protocol adoption) and the post-intervention period (after trained transport team deployment). Data collection was organized in a continuous and sequential way of all patients transferred from the ICU during the study period. The parameters collected consisted of demographic variables and clinical information which included diagnosis, prognostic scores, duration of hospital admission and presence of co-morbidities according to Charlson co-morbidity index.[6] Information regarding transport including indication for transport, procedure to be performed, vital in pre- and post-transport periods, presence of invasive devices (including vascular access, tubes, drains, infusion pumps),accompanying professionals, transportation time were recorded on the pre-structured proforma.

The incidence, type and severity of any adverse event (AE) during transport were also recorded. Adverse events were defined as any incident which influenced patient's stability and were divided according to the nature of the events into physiological alterations; team failures; equipment failures or delays. The severity was classified according to the International Classification of Patient Safety given by WHO[7] as: None-no symptoms detected and no treatment required; Mild-mild symptoms, loss of function or minimal or moderate damage with rapid duration, and only minimal interventions being required (extra observation, investigation, treatment review, and mild treatment); Moderate-symptomatic patient, requiring intervention as additional therapeutic procedure or treatment, increased hospitalization time, permanent or long-term damage or loss of function; Severe-symptomatic patient, need for intervention for life support, or major intervention, or long-term loss of function, or influence on life expectancy; and Death-with-in the probabilities, in the short term that the event caused or accelerated death.

Based on the model of transfer of patients, they were divided into two groups for comparison.

Group I: Patients who experienced an adverse event following completion of structured training and adoption of the transport model.

Group II: Patients who experienced an adverse event during transport pre-implementation of training model

The two groups were compared with respect to demographic and clinical characteristics, along with the incidence, type, and severity of transport-related adverse events.

Data Analysis- Descriptive statistics and frequencies were calculated for all data collected. Categorical data were compared using chi-square analysis. Statistical significance was adopted as 5% with 95% of the confidence intervals. The data were analyzed in the program Med Calc Statistical Software version 15.2.2 (MedCalcSoftware,Ostend, Belgium).

RESULTS

During the study period, 963 patients were admitted to the ICU out of which 141 patients were excluded as 67

patients remained in the ICU for less than 24 hours, 12 were under 18 years of age, and 62 patients had missing data. Also, 304 did not require any transportation during their stay in ICU. The study included 518patients with573 transportations, as some patients were transported more than once during their course of treatment in ICU (Figure1)

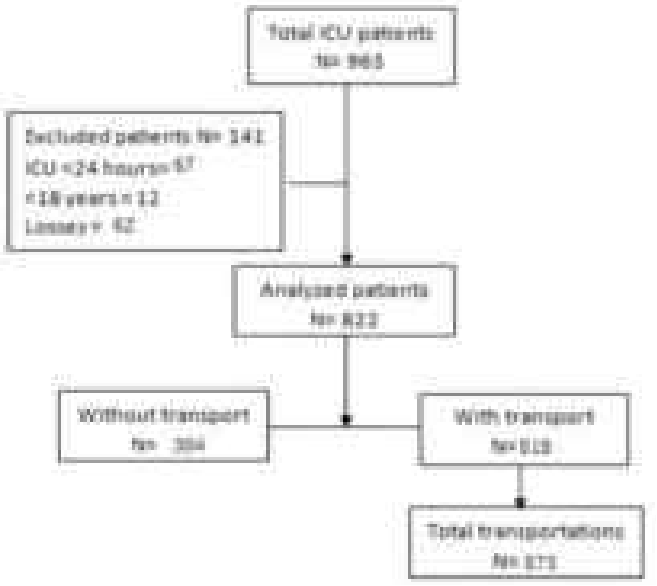

Figure-1 : Flow chart of study patients

Cohort characteristics- In this cohort, 390 (68%) patients were males. The mean age of the cohort was 53.5years, with range 24–78years. There were 240 (42%) patients that belonged to neurosurgical unit; 178(31%) and 155 (27%) patients belonged to medical and surgical specialty, respectively. All the patients during transportation had one or more invasive devices including endotracheal/tracheostomy tube, central venous/ arterial catheter, intercostals tubes or external ventricular/abdominal drains. Tracheal tube (endotracheal/tracheostomy-ETT/TT) was in-situ in 386(67.3%) patients, of which 256 were ventilated and remaining 130 had spontaneous breathing. The number of the devices for each patient was distributed as: 24% had one device, 51.2% had two devices (ETT/TT + CVC), 11.2% had three, 10.3% had four, and 3.3% had five devices in place during transfer. On 82 occasions (14.3%) patients were receiving one or more medications via continuous infusion pumps. The common medications used in decreasing order of frequency were vasopressors (7.8%), sedatives (4.4%)and others including amiodarone, insulin, adrenaline, 2.1% each. The duration of transport in our study ranged from 20-140minutes (mean-43 minutes).

Transport characteristics- On analyzing the pattern of transport, 300(52.3%) patients were transported for diagnostic purpose and 273 (47.7%) for therapeutic reasons. Transport for imaging studies was done in 181 (31.6%) patients while 152 (26.4%) were transported for surgical or neurosurgical procedures, 133 (23.1%) for endoscopic procedures, 67 (11.7%) to intervention radiology suite and 40(7.1%) to other units within the hospital.

Adverse events (AE)-During 573 transportations, there were 178 (31%) adverse events and more than one adverse event occurred in 34 (5.9%) patients (Table1).

Out of all the transports adverse events, most common were physiological variations. They occurred in 71 (39.8%) transports with alterations in heart rate being the most frequent event. Equipment failure occurred in 38(21.5%) occasions with kinking of the breathing circuit being the most common. Failure of the team coordination occurred in 49(27.5%) transports followed by delays in

Table 1 : Frequency distribution of adverse events observed during intra-hospital transport of critically ill patients.

Adverse events	N=178 (31%)
Physiological alterations	*71 (39.8)*
Variation in HR ≥20BPM	22
Arrhythmias	9
Hypotension	15
Variation in RR≥10 breaths	10
Saturation drop <90%	5
Agitation	5
Hypertension	4
Vomiting	1
Equipment failures	*38 (21.5)*
Exhaustion of infusion pump battery	*13*
Kinking of breathing circuit	*12*
ETT dislodgement	*9*
Accidental extubation	*2*
Exhaustion of 02 cylinder	*2*

Team failures	*49 (27.5)*
Secretions in tracheal tube	*9*
Lack of communication to target location	*7*
Interrupted ventilation < 1 minute	*7*
02 mask misplaced	*6*
Infusion medication need to be refilled	*5*
Loss of venous access	*3*
Returned without procedure done	*4*
Failure to carry required medications	*4*
Failure to carry required documents	*4*
Delays	*20 (11.2)*
Wait time >20mins at target location	*9*
Lift delay >5mins	*5*
Obstacle on the transport path	*4*
Bed not compatible with the lift	*2*

20(11.2%) occasions (Figure2). With regard to severity, 58(32.6%) AEs caused no damage, 67(37.7%) events resulted in mild damage, and 53(29.7%) resulted in moderate damage. There were no record of serious injury or death in this study (Figure3).

Out of 573 transportations, 339(59%) transports were performed post training and remaining 234(41%) transports were performed prior to the training model implementation. We compared the occurrence of AEs of the two groups. AEs occurred in 80 patients (23%) in group I and in 98(43%) patients in group II. This difference in adverse events between the two groups was statistically significant (p=0.003). The demographic and clinical characteristics of both the groups were

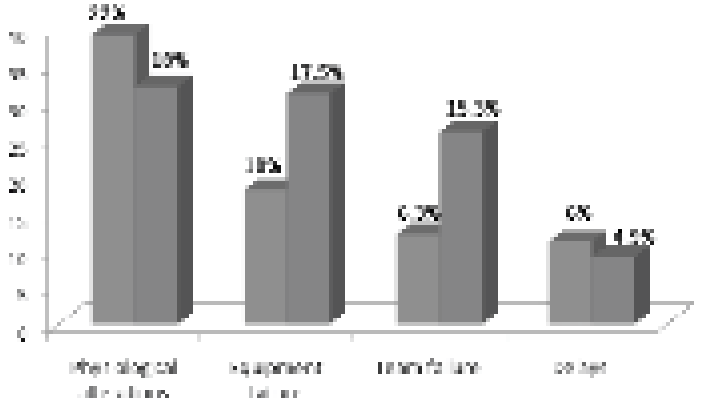

Figure2. Frequency of adverse events observed during intra-hospital transport of critically ill patients broadly divided into categories as - physiological alterations, team failure, equipment failure and delay

comparable and are shown in Table2. However, the mean SOFA score of group I was much higher (8.5) than in group II (3.2). as was the number of in situ devices (as central

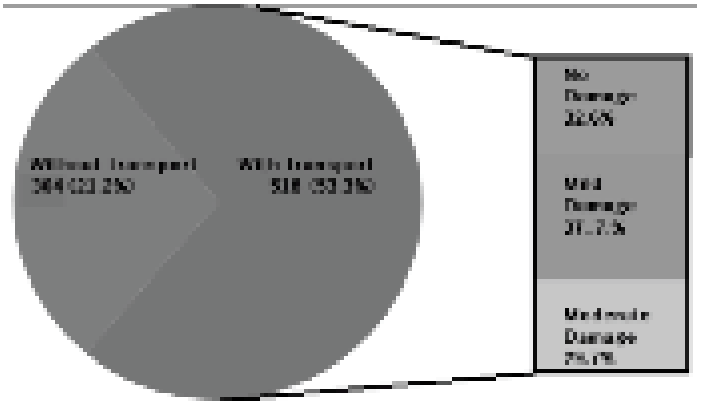

Figure3. Distribution of adverse events according to the International Classification of Patient Safety given by WHO

lines, arterial lines, drains) which was higher in group I compared to group II. Also, in groupI,65 (81.8%) patients were on ventilator as compared to 23(23.5%) patients in group II. Mean duration of transport in group I was

Table2: Comparison of demographic data and clinical characteristics of patients with adverse events requiring intra-hospital transport

Characteristic	***Group I n=80***	***Group II n=98***	***p value***
Age, mean (years)	*52.5*	*56.7*	
Sex, No. (n,%)			
Male	*21 (48.8)*	*28 (45.9)*	
Female	*22 (51.1)*	*33 (54)*	
Initial vital signs (mean ± SD)			
Glasgow Coma Scale	*9.8 +3.4*	*12.8 + 2.8*	
Systolic blood pressure, mm Hg	*120.8 + 22.8*	*134.7 +12.3*	
Diastolic blood pressure, mm Hg	*64.4 +15.9*	*73.4 + 10.6*	
Pulse, beats per minute	*103.5 + 23.7*	*96.1 + 16.8*	
Respiratory rate, breaths per minute	*23.5 + 9.9*	*13.8 + 4.7*	
Oxygen saturation	*94.2 +7.1*	*96.7 + 2.3*	
Devices			
Central venous line	*63*	*51*	*0.0002*
Intra-arterial catheter	*25*	*10*	*0.0004*
Vasopressor/inotropic drugs	*37*	*24*	*0.002*
Three or more invasive devices	*46*	*32*	*0.001*
SOFA Score	*8.5*	*3.2*	*0.001*
Mechanically ventilated (n,%)	*65 (81.3)*	*23 (23.5)*	*0.001*
Oxygen by Mask/ T-piece (n,%)	*22 (27.5)*	*30 (30.6)*	*0.64*

94.2+7.6 minutes as compared to 110+5.4 minutes in group II. Table 2 shows that there was statistically significant difference between the two groups when compared for adverse events based on invasive devices, vasopressor use, mechanical ventilation and SOFA score.

On comparison of type of AEs, there was statistically significant difference between the groups in relation to team failure (p=0.006) and equipment failure (p=0.001). The incidence of physiological adverse events were more in group I but the difference was not statistically significant(p=0.79). On the other hand, delays were more common in group II but difference was not statistically significant(p=0.19) (Table3).

DISCUSSION

Intensive care patients who are transported within the hospital for imaging or upgraded treatment are at risk of adverse events. This is because they have deranged physiology and require intensive monitoring devices. Guidelines suggest that transport of such patients should be supervised by experienced medical staff, with appropriate equipment and careful preparation so as to establish the safety of the patient during transit.[8]We adopted a model for training for intra-hospital transfer of critically ill patients at a tertiary care hospital and studied the impact of the presence of trained medical personnel during transit.

Table 3: Comparison of observed adverse events during intra-hospital transport of critically ill patients between two groups

Type of adverse event	Post implemen tation	Pre implemen tation	p value
Physiological alterations	39	32	0.79
Team failure	18	31	0.006
Equipment failure	12	26	0.001
Delays	11	9	0.19
Total	80	98	0.003

The results of this study show that about 59.5% patients needed transport during ICU stay, with approximately 2-3 transports occurring daily, and all patients had at least one invasive device in situ. We observed AEs in 31% patients, with 5.9% having more than one event when transferred for diagnostic (52.3%)or therapeutic (47.7%) procedure. This is much lower than data found in the literature where global incidence of AEs has known to reach about 68%.[9,10]

In this study, among all AEs the incidence of physiological alterations was the maximum (39.8%) but much lower than previously reported in literature.[11] As there was no significant difference of physiological alterations between the study groups (p=0.79), it highlights the fact that physiological changes are not solely due to transport but are related to the critical condition of the patient. However, The presence of a trained personnel can anticipate problems in advance and reduce the incidence of AEs in-spite of having higher SOFAs score and multiple invasive devices in situ. There is evidence in the literature that dedicated transfer teams improve the outcome of critical patients transferred between hospitals. Patients transferred by specialized teams demonstrated significantly better arterial blood gas despite having higher APACHE-II scores than standard transfer groups.[12] Hence, severity of illness is an important determinant of the occurrence of AEs during transfer but can be reduced by the presence of specialized teams that continuously monitor the compromised cardio-respiratory and neurological status of the patient during transfer. Knight et al. report that when patients were not monitored due to the limitation of human and technological resources in low-income countries, AEs were detected at destination.[13] Though it is recommend to have minimum mandatory monitoring of electro-cardiogram and pulse-oximetry continuously, and periodic measurement of blood pressure, pulse rate, and respiratory rate during intra-hospital transfer,[14]but it may not be sufficient for critically ill patients who require more intense monitoring even during intra-hospital transfer.

In this study, AEs second in frequency were related to equipment failures, most commonly being the exhaustion of equipment batteries (34.2%) and were significantly higher in group II as compared to group I. Shirley et al. reported that more than half of AEs during transfer are related to ventilation and airway problems while one-fourth are associated with tubes, drains or monitoring line malfunction.[15] A prospective observational study in the Netherlands evaluated AEs during Mobile Intensive Care Unit (MICU) transfers,

comparing specialized retrieval team to standard ambulance transfer. The incidence of AEs decline from 34% to 12.5%, with all being related to equipment failure.[16] Reports from literature also suggest that the incidence of adverse events is not only related to severity of patient's condition, but also number of various supportive care measures.[17] Hence, the number of invasive lines in any patient is directly proportional to equipment-related risk factor. This is of major concern because such incidents are avoidable and use of checklists of hardware before transfer by trained personnel can decrease the AEs related to equipment malfunction significantly.

Similarly, statistically significant difference in the team-related AEs in our study suggests inter-team communication failures. Up to 61% of AEs related to team failures have been reported.[18] Kwack et al. reported that trained personnel and dedicated team reduced unexpected problems related to team and equipment.[19] Such unexpected situations affect not only the patient but also staff and can easily be avoided by training professionals involved in transfer with emphasis on bilateral communication with the destination site and effective planning. Reduction in the frequency of such events will shorten transfer time and ensure safety to the patient.

Another advantage of adopting specialized transport teams is that physicians and staff in the ICU continue to focus on other patients and their responsibilities within the ICU. Lastly, use of specialized trained teams makes it possible to obtain diagnostic investigations and procedures for critically ill patients, safely and quickly, as they bridge the gap of ongoing care and monitoring. Hence, the successful model for the transport of critically ill patients by specialized and trained teams within the hospital should be based on models as for out-of-hospital transport environment focusing on i) careful planning and efficient execution, ii) qualified personnel iii) appropriate equipment iv) minimum mandatory monitoring v) bilateral communication.

Limitations of the study are that we did not analyze data of patients in the ICU who were not transported and hence, it is difficult to state if transport was beneficial for patient survival. Secondly, the small number of the study cohort may have underpowered the analysis of the adverse events. Another limitation is training to team was non-formal without any certification. Strength of the study is that we prospectively tried to rate the clinically significant adverse events specific to our institutional setting and formulate corrective measures accordingly.

Lessons learnt

1. *Transfer of critically ill patient by trained team rather hybrid team that includes different providers makes a difference in the frequency and pattern of adverse events.*
2. *Education and training should be a major focus as it enhances patient care during intra-hospital transfer.*
3. *In spite of best efforts commonest adverse events are respiratory or cardiovascular in nature.*
4. *Skills and training should focus on issues of transport of critically ill patients including airway and vascular access, understanding deranged patho-physiology and pharmacology.*

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Original Research Article

MASSIVE TRANSFUSION AND BLOOD PRODUCT DYNAMICS IN OBSTETRIC HYSTERECTOMY: A ONE-YEAR PROSPECTIVE STUDY FROM A TERTIARY CARE CENTRE IN NORTH INDIA

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ABSTRACT: Obstetric hysterectomy (OH) is a maternal near-miss event most often required for catastrophic obstetric hemorrhage, with blood transfusion being unavoidable. This prospective observational study conducted over one year (February 2023–January 2024) at a tertiary care center in North India evaluated blood and blood product utilization and maternal outcomes in women undergoing OH. Among 3,759 deliveries, 37 women underwent OH (incidence 9.84/1,000), with placenta accreta spectrum being the leading indication (64.8%). All patients required packed red blood cell transfusion (mean 4–6 units), while fresh frozen plasma, platelets, and cryoprecipitate were used in 50%, 20%, and 6.6% of cases, respectively. Maternal deaths occurred only in cases requiring massive transfusion (>10 PRBC units), predominantly associated with PAS. The study emphasizes that optimal transfusion support, early activation of massive transfusion protocols, and blood bank preparedness are critical for improving outcomes in obstetric hysterectomy, especially in resource-limited settings.

KEY WORDS: Obstetric hysterectomy, Post partum hemorrhage, Placenta accreta, Blood transfusion practice

INTRODUCTION

Obstetric hysterectomy (OH) remains a radical yet often lifesaving procedure, performed when conservative measures fail to control catastrophic hemorrhage. The most frequent indications include placenta accreta spectrum (PAS), uterine rupture, and severe postpartum hemorrhage (PPH). Hemorrhage continues to be the leading cause of maternal death worldwide and contributes to nearly one-third of maternal deaths in low- and middle-income countries (LMICs).[1] In such situations, survival depends not only on the timeliness and skill of surgical intervention but also on the availability of blood and blood products. In PAS, for instance, blood loss may exceed five liters, underscoring the indispensable role of transfusion support in maternal survival. [2]

Although several Indian and international studies have reported the incidence and clinical profile of OH, relatively few have systematically addressed transfusion requirements [3,4]. This represents a critical gap in the literature, particularly given the logistical challenges of ensuring timely blood availability in LMICs. The present prospective study was designed to evaluate transfusion dynamics in OH over a one-year period in a tertiary referral center in North India, with particular focus on patterns of blood and blood product use and their influence on maternal outcomes.

MATERIALS AND METHODS

This prospective observational study was conducted at the Department of Obstetrics and Gynecology, Government Medical College and Rajindra Hospital, Patiala, from February 2023 to January 2024. All women undergoing OH during the study period were included, irrespective of delivery route or whether hysterectomy was performed intrapartum or postpartum.

For each patient, demographic details, obstetric history, and indication for hysterectomy were recorded. Intraoperative blood loss was estimated by measuring suctioned blood, weighing blood-soaked drapes, and visual assessment. The number and type of blood and blood products transfused including PRBCs, FFP, platelets, and cryoprecipitate were documented.

Transfusion reactions and maternal outcomes, including survival and complications, were also assessed.

Data were analyzed using SPSS version 21. Results were expressed as mean, range, and percentages.

RESULTS

During the study period, a total of 3,759 deliveries were conducted, among which 37 required obstetric hysterectomy (OH), giving an overall incidence of 9.84 per 1,000 deliveries. The mean maternal age of these women was 30.3 years (range: 24–42 years). Nearly all were multiparous, and 62% were gravida three or above. A significant majority (73%) were either unbooked or referred cases.

The most frequent indication for OH was placenta accreta spectrum (PAS), contributing to 64.8% of cases. The next common cause was intractable postpartum hemorrhage (PPH), seen in 24.3%, while uterine rupture accounted for the remaining 10.8%.

The average blood loss during surgery ranged between 2.5 and 3 liters, although in patients with PAS, losses often exceeded 5 liters. Blood transfusion was universally required. All 37 women received packed red blood cells (PRBCs), the number varying from 2 to 14 units, with a mean requirement of 4–6 units. Fresh frozen plasma (FFP) was administered in 50% of cases, mainly in those who developed coagulopathy or disseminated intravascular coagulation (DIC), with an average of 3–4 units. Platelet concentrates were transfused in 20% of women, usually in the context of DIC and massive hemorrhage, with a mean of six units. Cryoprecipitate was required in 6.6% of patients, largely for refractory hypofibrinogenemia.

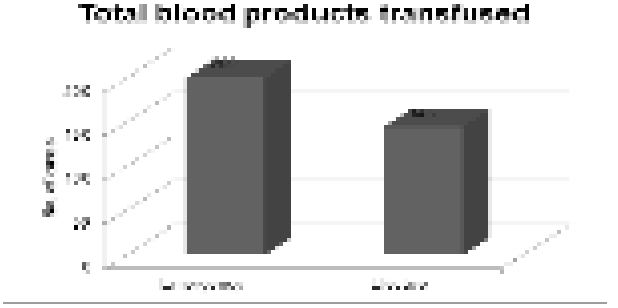

Figure 1:- Transfusion of blood products during Emergency vs Elective OH.

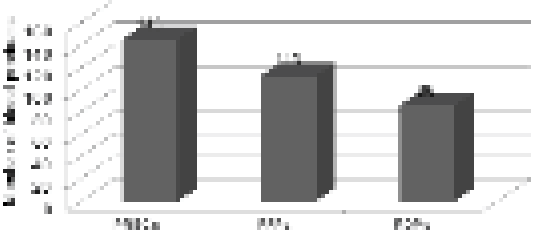

Figure 2: The figure depicts utilisation of blood products during OH.

Transfusion-related complications were rare. Only one patient experienced a febrile non-hemolytic transfusion reaction, and no major adverse events were documented. Maternal mortality was noted exclusively in PAS cases, particularly among those who required transfusion of more than 10 units of PRBCs.

DISCUSSION

The findings of this study highlight that transfusion support is inevitable in obstetric hysterectomy and often substantial. Although the average PRBC requirement was 4–6 units, PAS cases frequently demanded more than 10 units, emphasizing the massive nature of hemorrhage associated with this condition.

The incidence of OH in the present study (9.84 per 1000 deliveries) was markedly higher than that reported from high-income countries, where rates range between 0.2 and 0.7 per 1000 deliveries. [1] However, the findings are consistent with those from other LMICs, where late referrals, higher cesarean rates, and limited access to conservative measures or interventional radiology are common.[4]

Patterns of transfusion in this study were also consistent with international literature. Approximately half of the women required FFP and one-fifth required platelets, which aligns with reports from Western studies where 40–60% of OH cases need component therapy.[2] Although cryoprecipitate use was relatively infrequent, it proved essential in the management of refractory hypofibrinogenemia, highlighting its critical role in obstetric blood banks. [5]

Importantly, maternal mortality was observed only among PAS patients requiring more than 10 PRBC units, underscoring the fact that survival depends as much on blood bank preparedness as on surgical expertise. In LMICs, where component availability is often limited, early requisition and rapid-release systems are crucial. From a systems perspective, implementation of massive transfusion protocols (MTPs) tailored to obstetrics is urgently needed, along with pre-emptive mobilization of blood products in antenatally diagnosed PAS cases. [6,7]

The implications of this study extend beyond individual

patient management. Anticipating transfusion requirements, involving blood banks early in cases of suspected PAS, and strengthening component availability at peripheral centers may significantly reduce maternal mortality. Future research should focus on multicenter audits of transfusion practices, cost-effectiveness analyses, and training programs to improve obstetric hemorrhage response systems.

CONCLUSION

This study demonstrates that blood transfusion is universal and central to the management of obstetric hysterectomy. The mean requirement of 4–6 PRBC units, frequent need for FFP and platelets, and occasional use of cryoprecipitate reflect the scale of transfusion support required. Maternal mortality was confined to PAS patients requiring massive transfusion, reaffirming that outcomes depend as much on blood bank preparedness and transfusion protocols as on surgical skill. Strengthening blood bank infrastructure, implementing obstetric-specific MTPs, and ensuring timely component availability are critical steps toward reducing maternal morbidity and mortality in high-burden, resource-limited settings.

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Original Research Article

YOGA AS A NON-PHARMACOLOGICAL TREATMENT MODALITY FOR PATIENTS OF COPD

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ABSTRACT : Chronic obstructive pulmonary disease (COPD) is a major health problem worldwide. Various non pharmacological modalities are being investigated for the management of COPD, in addition to medical and surgical treatment. Yoga training is one such adjuvant therapy. A study was hence conducted to determine the effectiveness of yoga training in patients of COPD. It was a prospective study conducted on 50 COPD patients diagnosed as per GOLD 2021 guidelines. They were divided into two groups of 25 patients each. The yoga group received adjuvant yoga therapy along with medical management. The control group received medical management only. At baseline, forced expiratory volume in first second (FEV1), forced vital capacity (FVC) and FEV1/FVC, saturation of peripheral oxygen (SpO2), modified medical research council dyspnea scale (mMRC), six-minute walk distance test (6MWD) and COPD assessment test (CAT) score was noted in both the groups and the same parameters were studied at follow-up at 1st month and 3rd month. The FEV1, FVC, 6MWD and CAT score improved significantly in both the groups from baseline to 3rd month ($p < 0.001$). The FEV1/FVC also improved significantly in both yoga ($p = 0.001$) and control group ($p = 0.012$) from baseline to 3rd month. mMRC improved in both the groups from baseline to 3rd month but the improvement was significant in the yoga group only ($p = 0.002$). No significant improvements from baseline to 3rd month were seen in SpO2 in either of the two groups. Yoga group showed statistically significant additional improvement in mMRC ($p = 0.002$), 6MWD (p value <0.001) and CAT score (p value <0.001) from baseline to 3rd month, when improvements in both the groups were compared with each other. There was no additional benefit of yoga on FEV1 (p value = 0.051), FVC (p value = 0.165), FEV1/FVC (p value = 0.167) and SpO2 (p value = 0.650). We concluded that 3 months of yoga training is an effective adjuvant to medical management in patients of COPD.

KEY WORDS: Yoga, Pulmonary Rehabilitation, COPD

INTRODUCTION:

Validated non-pharmacologic approaches to combat dyspnea and exercise intolerance in patients of Chronic obstructive pulmonary disease (COPD) include pulmonary rehabilitation, smoking cessation and immunization.[1–3] Like pulmonary rehabilitation, yoga, which is a mind and body technique is being recently studied for its role in COPD as an adjuvant therapy.[4] Few studies have been conducted in India to evaluate the role of yoga in patients of COPD and have shown varied results.[4–7] The yoga practices included a prayer of 1 min duration, asanas (ardhakatichakra asana, ardh-achakra asana, shashankasana, ardha ushtra asana, bhujangasana, shalabhasana: 12 mins), breathing (shashank asana breathing and hujanga asana breathing: 12 mins), pranayam (kapalabhati, surya bhedi pranayama, ujjayi pranayama, bhramari pranayama, bhastrika pranayama, anuloma villoma: 25 mins), meditation (nadaanu sandhana and om chanting: 5 mins) and deep relaxation techniques / Quick relaxation techniques (5 mins).

This study was undertaken to assess the effectiveness of 3

months yoga training practice in COPD patients, by evaluating its effect on spirometeric parameters: (FEV1), forced vital capacity (FVC) and FEV_1/FVC; oxygenation status: saturation of peripheral oxygen (SpO_2), level of breathlessness: modified medical research council dyspnea scale (mMRC), exercise capacity: six-minute walk distance test (6MWD) and health status: COPD assessment test (CAT) score.

MATERIALS AND METHODS

It was a prospective study carried out from July, 2021 to October, 2022. Patients of stable COPD aged more than 18 years and diagnosed as per GOLD 2021 guidelines were counselled for 3 months yoga as an adjuvant therapy. Those who agreed for the same were taken up in the yoga group and those refusing for the same were taken up in the control group, till the sample size of 25 was reached in each group. The yoga group received adjuvant yoga therapy along with medical management as per GOLD guidelines. The control group received medical management only. (Figure 1). Spirometry (performed using spirometer - EasyOne Connect, ndd Medical technologies) was used to diagnose and classify COPD as per GOLD 2021 guidelines.[8] The mMRC score, 6MWD and CAT score of all the patients was noted at baseline.[8]

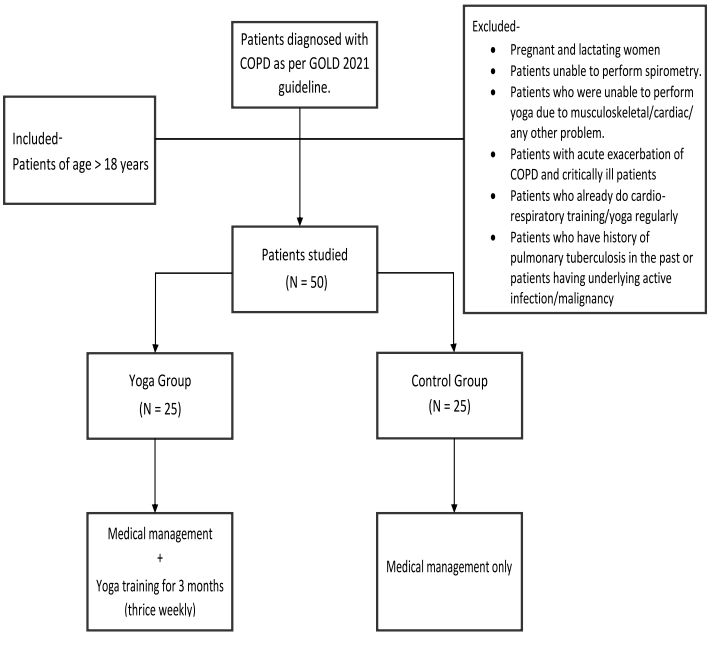

Figure 1: Patient enrolment criteria. COPD, Chronic obstructive pulmonary disease; GOLD, Global initiative for chronic obstructive lung disease.

The yoga group was taught yoga exercises by the yoga instructor/candidate. The total duration of yoga practice was 60 minutes for 3 days/week for a period of 3 months. The patients did yoga under the supervision of yoga instructor/candidate for three days/week during the first two weeks. After that the patients practiced yoga at their home. The patients were given a yoga record sheet to keep a record of their yoga sessions, symptoms, hospitalization, and medications. All patients were asked to visit the outpatient department after one month and then after three months to report about their health status and for reassessment of their study parameters. The changes in FEV_1, FVC, FEV_1/FVC, SpO_2, mMRC, 6MWD and CAT score were noted at both the follow ups in both the groups. Patients who had an exacerbation during the study period or who left yoga training in between were excluded, and additional patients were recruited to reach the desired sample of 25 patients in each of the two groups.

Exclusion criteria: Pregnant and lactating women, patients who were unable to perform yoga due to musculoskeletal/ cardiac/any other problems, had recently undergone surgery, patients who were already doing cardio-respiratory training/yoga, patients who had history of pulmonary tuberculosis in the past and patients having underlying active infection/malignancy were excluded.

The study was approved by the institutional ethical committee.

Statistical analysis: Normality of quantitative data were checked by measures of Kolmogorov Smirnov tests of normality. Normally distributed quantitative data was given as mean ± SD and range, and Student t-test was applied to compare two groups. Non -normally distributed (skewed) was represented as median and interquartile range; comparisons for the two groups were made by Mann-Whitney U test. For time related variables of different timings Wilcoxon Signed rank test was carried out for comparison of events at different timings. Changes were calculated by subtracting value of each subject T0 (baseline) - T1 (1^{st} and 3^{rd} month) and then its mean/medians were calculated. Comparisons for two groups were made by Mann-Whitney U test. Spearman correlation coefficient were calculated to see relation between variables. A p value <0.05 was considered significant. Analysis was conducted using IBM SPSS STATISTICS (version 22.0).

RESULTS

The study subjects in the two groups were uniformly distributed in terms of demographic factors like age,

Table-1
BMI, body mass index; GOLD, global initiative for chronic obstructive lung disease
Baseline patient characteristics

Parameter	Yoga group (n=25)	Control group (n=25)	p value
Age (years)	58.92 ± 11.79	61.04 ± 9.43	0.486
Gender			
Male (n)	23	24	0.552
Female (n)	2	1	
Weight (kg)	60.20 ± 16.19	56.64 ± 11.97	0.381
Height (cm)	165.20 ± 9.31	165.88 ± 7.45	0.777
Mean BMI (kg/m^2)	21.98 ± 5.26	20.56 ± 3.89	0.790
GOLD Grade			
GOLD Grade 1 (n)	0	1	
GOLD Grade 2 (n)	6	7	0.414
GOLD Grade 3 (n)	14	9	
GOLD Grade 4 (n)	5	8	
ABCD Group			
A (n)	3	2	
B (n)	12	17	0.494
C (n)	2	2	
D (n)	8	4	

gender, weight, height, BMI, locality, occupation, GOLD grade and ABCD grouping at the baseline (p>0.05). (Table 1)

In both the groups, the FEV_1, FVC, 6MWD and CAT score improved significantly at 1st month and 3rd month as compared to baseline (p value < 0.001). At 3rd month FEV_1/FVC improved significantly in the yoga group (p value <0.001) and control group (p value = 0.012) as compared to baseline. The mMRC improved significantly only in the yoga group at the end of 3 months (p value = 0.002) as compared to baseline. (Table 2)

At the end of 3 months, it was seen that yoga had an additional significant benefit, as seen by the improvement in mMRC (p =0.002), 6MWD and CAT score (p <0.001), in the yoga group, when improvements in both the groups were compared. Yoga didn't have any additional significant benefit on FEV_1, FVC, FEV_1/FVC and SpO_2. (Table 3).

No patient developed any adverse effect because of yoga sessions.

DISCUSSION

The pharmacotherapy has been established to influence the various lung function parameters. In a developing and resource limited country like India, the most common reason for non-compliance to inhaled medications was patients belief that medications were not needed during symptom free period, followed by forgetfulness, social

Table-2
Patient Characteristics at baseline, one month and three months in yoga group and control group

	Yoga Group						Control Group					
Parameter	**Baseline**	**1st month**	**3rd month**	**p value**			**Baseline**	**1st month**	**3rd month**	**p value**		
				B - 1	**B - 3**	**1 - 3**				**B - 1**	**B - 3**	**1 - 3**
FEV_1 (L)	1.16 ± 0.43	1.32 ± 0.48	1.52 ± 0.56	<0.001*	<0.001*	<0.001*	1.27 ± 0.63	1.42 ± 0.68	1.52 ± 0.70	<0.001*	<0.001*	0.001*
FVC (L)	2.21 ± 0.67	2.37 ± 0.65	2.60 ± 0.69	<0.001*	<0.001*	<0.001*	2.32 ± 0.81	2.53 ± 0.84	2.62 ± 0.81	<0.001*	<0.001*	0.005*
FEV_1/FVC	0.51 ± 0.08	0.54 ± 0.08	0.57 ± 0.10	<0.001*	<0.001*	0.024	0.52 ± 0.09	0.54 ± 0.09	0.55 ± 0.08	0.185	0.012*	0.053
SpO_2(%)	95.92 ± 0.95	96.00 ± 0.70	96.20 ± 0.57	0.593	0.166	0.166	95.84 ± 0.89	95.92 ± 0.95	96.00 ± 0.81	0.564	0.346	0.617
mMRC score	2.12 ± 0.72	2.08 ± 0.81	1.72 ± 0.93	0.317	0.002*	0.003*	2.04 ± 0.61	2.04 ± 0.61	2.00 ± 0.57	1.00	0.317	0.317
6MWD (m)	283.36 ± 45.03	324.64 ± 59.11	373.68 ± 67.77	<0.001*	<0.001*	<0.001*	282.68 ± 40.54	299.80 ± 41.84	311.92 ± 43.65	<0.001*	<0.001*	<0.001*
CAT score	22.16 ± 7.57	18.48 ± 7.13	14.92 ± 6.06	<0.001*	<0.001*	<0.001*	23.68 ± 7.62	21.56 ± 6.75	19.28 ± 6.59	<0.001*	<0.001*	<0.001*

B-1: Baseline – 1st month B-3: Baseline – 3rd month 1-3: 1st month – 3rd month

Table - 3
FEV1, forced expiratory volume in first second; FVC, forced vital capacity; Sp02, saturation of peripheral oxygen; mMRC, modified medical research council dysnea scale; 6MWD, six minute walk distance; CAT, COPD assessment test
Mean change in characteristics after one month and three months of intervention

	Yoga group			Control group			p value		
Parameter (Mean change)	B - 1	B – 3	1 – 3	B – 1	B – 3	1 – 3	B - 1	B – 3	1 – 3
FEV_1(L)	-0.16 ± 0.10	-0.36 ± 0.21	-0.20 ± 0.18	- 0.15 ± 0.12	- 0.25 ± 0.17	-0.09 ± 0.12	0.705	0.051	0.217
FVC(L)	-0.16 ± 0.20	-0.39 ± 0.29	-0.23 ± 0.21	-0.21 ± 0.21	-0.29 ± 0.27	-0.08 ± 0.21	0.277	0.165	0.057
FEV_1/FVC	-0.03 ± 0.02	--0.06 ± 0.06	-0.02 ± 0.05	-0.01 ± 0.05	-0.03 ± 0.06	-0.01 ± 0.04	0.213	0.167	0.448
SpO_2(%)	-0.08 ± 0.75	-0.28 ± 0.98	-0.20 ± 0.70	-0.08 ± 0.70	-0.16 ± 0.85	-0.08 ± 0.81	0.983	0.650	0.495
mMRC score	0.04 ± 0.20	0.40 ± 0.50	0.36 ± 0.49	0.00 ± 0.00	0.40 ± 0.50	0.04 ± 0.20	0.317	0.002*	0.005*
6MWD(m)	-41.28 ± 16.79	-90.32 ± 29.30	-49.04 ± 16.59	-17.12 ± 6.47	-29.24 ± 9.99	-12.12 ± 6.94	<0.001*	<0.001*	<0.001*
CAT score	3.68 ± 1.14	7.24 ± 2.04	3.56 ± 1.44	2.12 ± 1.20	4.40 ± 2.02	2.28 ± 1.48	<0.001*	<0.001*	<0.001*

B -1: Baseline – 1st month, B -3: Baseline – 3rd month, 1-3: 1st month – 3rd month

stigma in using inhalers, difficulty in using inhalers and inadequate instructions.[9] There have been studies in the past exploring the role of adjuvant therapies. We evaluated the role of one such adjuvant therapy i.e., yoga in patients of COPD.

In both yoga and control group, FEV_1 and FVC at 1st month and at 3rd month improved significantly as compared to baseline ($p < 0.001$). FEV_1 improved significantly in yoga and control group from baseline to 3rd month ($p<0.001$ and 0.012 respectively). It also improved from baseline to 1st month in both the groups, however the improvement was statistically significant in only yoga group ($p<0.001$). On comparing the change in mean of FEV_1, FVC and FEV_1/FVC amongst yoga and control group, there was no additional benefit of yoga over pharmacotherapy when comparison of change in FEV_1, FVC and FEV_1/FVC from baseline to 1st month, from baseline to 3rd month and from 1st month to 3rd month was done.

Thus, there was no additional significant benefit of yoga on the spirometry parameters of COPD patients versus control group. The duration of yoga in our study may not have been adequate to bring out spirometerically significant outcomes. Other contributing anatomical factors like bullae and emphysematous changes may have caused non-significant improvements in the spirometry parameters. Similar results were obtained in the past by some authors.[10,11] In contradiction, study by Jessy John et al, reported an improvement in FEV_1/FVC, whereas studies by Thokchom SK et al, Artchoudane S et al and Niu R et al, reported an improvement in FEV_1 only.[4, 12–14]

As seen in previous studies, the saturation of peripheral oxygen (SpO_2) did not show any significant improvement in any of the two groups at any of the follow-ups.[14,15]

mMRC improved significantly from baseline to 3rd month and 1st to 3rd month in yoga group only (p value 0.002 and 0.003 respectively). The improvement in mMRC in control group was non-significant at both the follow-ups. There were statistically significant additional improvements in mMRC from baseline to 3rd month ($p = 0.002$) and from 1st month to 3rd month ($p = 0.005$) in patients practicing yoga vs controls. Beneficial effect of yoga on mMRC in COPD patients was also observed in the past.[16,17] There was no statistically significant improvement in the yoga group as compared to control group after 1 month of yoga training (p value = 0.317). In our study, significant improvement in mMRC score in the yoga group highlights that the patient has decreased

perception of breathlessness at follow up. While performing yoga there is expansion and descent of the lungs that stimulates the release of surfactant and prostaglandins in the alveolar spaces which leads to expansion of the surface area of the lungs. This leads to improvement in respiratory function and decreases dyspnea.[18] One month of yoga training in our patients was found to be insufficient to decrease the perception of breathlessness, and have an impact on mMRC. However, yoga sessions of three months duration improved the mMRC significantly. Though no time limit has been specified in the past for duration of yoga practice, we suggest the patients to be motivated and persistent in their efforts and continue their yoga sessions before any clinical improvements become appreciable.

In both the groups, the 6MWD improved significantly from baseline to 1st month, baseline to 3rd month and 1st to 3rd month (p value <0.001). On comparing the change in mean 6MWD amongst yoga group and control group, there was significant additional benefit of yoga over pharmacotherapy alone when comparison of change in 6MWD from baseline to 1st month, baseline to 3rd month and 1st to 3rd month was done (p <0.001). The 6MWD is an indicator of exercise capacity. The improvement depicted that the patients practicing yoga had an improved ability to perform daily activities. The increase in 6 MWD could be due the effect of yoga on musculoskeletal and cardio-respiratory system. Yoga has been found to increase oxidative capacity, skeletal muscle strength, flexibility and endurance, and thus justifies our results.[19] Appreciable improvement in 6MWD has been observed by a number of studies in the past.[20–25]

CAT score improved significantly from baseline to 1st month, baseline to 3rd month and 1st to 3rd month (p= <0.001) in both the groups. On comparing the change in mean CAT score amongst yoga and control group, there was significant additional benefit of yoga over pharmacotherapy seen at baseline to 1st month, baseline to 3rd month and 1st to 3rd month (p <0.001). Yoga reduces stress and anxiety through better regulation of hypothalamic-pituitary axis, suppressing sympathetic activity and balancing the autonomic nervous system responses.[20] Thus it may directly have an impact on CAT score which actually is a tool to assess symptom control, health status and wellbeing. The same has been reported by few authors in the past as well.[11,20]

CONCLUSION

The present study showed that yoga is effective as an adjuvant to pharmacotherapy in patients with COPD. Three months of yoga training improves the perception of dyspnea, exercise capacity and health status. We hence propose that yoga as a form of pulmonary rehabilitation should be offered to patients of COPD unless contraindicated.

LIMITATIONS OF THE STUDY

The study was conducted at a single centre and had a small sample size with a follow up period of three months only. In addition, the effect of yoga on other etio-types of COPD was not studied as all the patients has smoking related COPD. The different co-morbidities were not thoroughly evaluated. Studies with larger sample size, different etio-types of COPD and longer follow-ups are needed to explore the role of yoga in day-to-day practice.

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Review Article

RECENT ADVANCES IN ALZHEIMER'S DISEASE MANAGEMENT

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ABSTRACT: Alzheimer's disease is very common type of dementia in old age which is slowly progressive neurodegenerative disease associated with loss of cognitive functions. It is caused by several pathological pathways like amyloid-β (Aβ) deposition, hyperphosphorylated tau protein, excessive glutamatergic stimulation, cholinergic disorder, and neuroinflammation and oxidative stress. Currently, most of the drugs available for the management of Alzheimer disease, like cholinesterase enzyme inhibitors (*donepezil, rivastigmine, galantamine*) and N-methyl d-aspartate (NMDA) antagonist, *memantine*, are effective in treating the symptoms but do not cure the disease. Various research projects on Alzheimer's disease have failed or have been abandoned in the past decade due to adverse effects or lack of the efficacy. This can be due to starting of therapy in the late stages of disease, inappropriate drug doses or an inadequate understanding of the pathophysiology of AD. Recently there have been success in disease management with the approval of adacanumab and donanemab-azbt, which have been recently approved by FDA. Furthermore, there are many ongoing trials which are currently in various phases of development which, if successful, would provide multiple options to choose from, for better management of AD. This review highlights such recent advances as well as future targets in the disease treatment, which would aid physicians in optimizing patient care.

KEYWORDS : Alzheimer, Amyloid, Dementia, Cholinergic, Glutamatergic

INTRODUCTION

Alzheimer's disease, named after the German psychiatrist, Alois Alzheimer is the most common type of dementia in the old age.[1] It is a slowly progressive neurodegenerative disease which leads to impairment of cognitive functions due to various pathological pathways like amyloid-β deposition, hyperphosphorylated tau protein, cholinergic disorder, neuroinflammation, excessive glutamatergic stimulation and oxidative stress[2].

Alois Alzheimer, in 1906, noticed the presence of amyloid plaques and a massive loss of neurons while examining the brain of his patient that suffered from memory loss and change of personality before dying and described this condition as a serious disease of the cerebral cortex.[3] Emil Kraepelin named this medical condition as Alzheimer's disease for the first time in the 8th edition of his psychiatry handbook.[4]

About 55 million people have dementia worldwide and it is estimated that this number may increase to 139 million by 2050 due to population aging. Also, among these patients, 44% are 75 to 84 years old patients and 38% are 85 years or older in age.[2]

Amyloid β is produced by the cleavage of its precursor, amyloid precursor protein (APP), by α-secretase and γ-secretase. Dysregulated accumulation of Aβ leads to the formation of senile plaques, subsequent phosphorylation, and aggregation of tau protein, resulting in the generation of neurofibrillary tangles (NFTs), neuronal loss, and synaptic dysfunction. Also, deposition of Aβ triggers mitochondrial dysfunction, initiating endoplasmic reticulum (ER) stress and ultimately causing neuronal cell death.[5] (Figure 1)

Besides, other factors can cause neurodegeneration such as neuroinflammation, oxidative stress, and injury of cholinergic neurons.[6] In the last decade, several

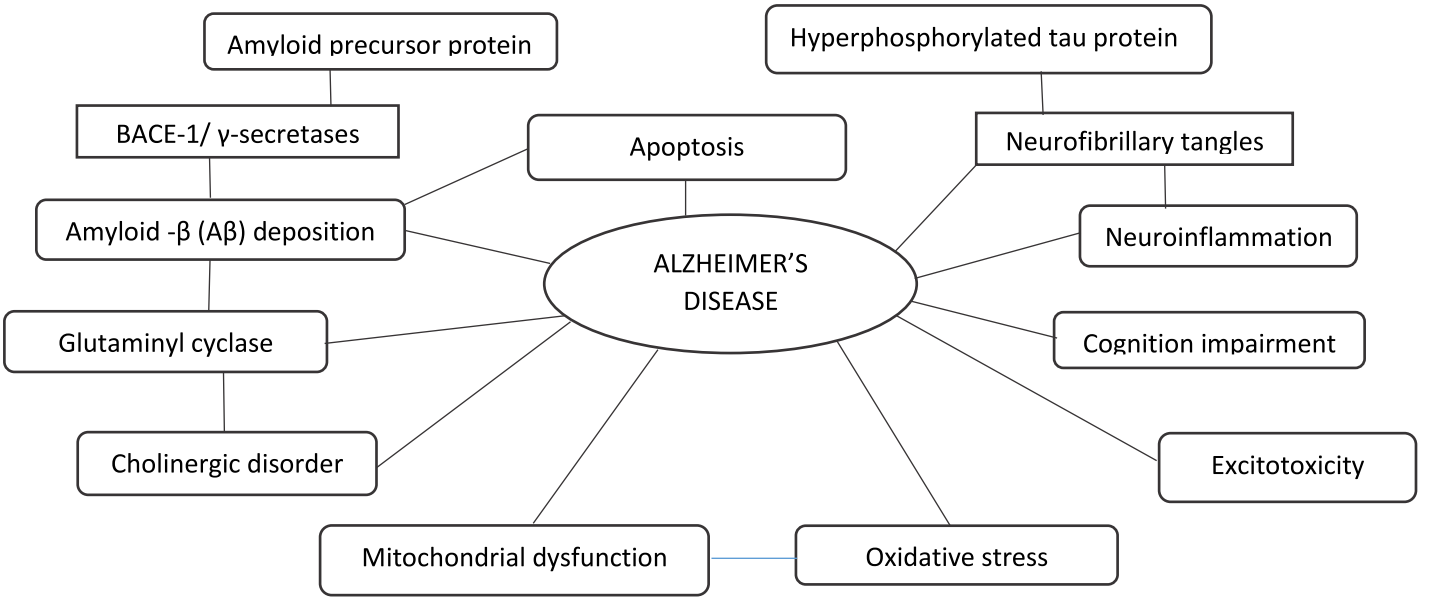

Figure 1: ***Mechanisms related to pathogenesis and progression of Alzheimer's disease***

research projects on Alzheimer's have been failed or have been abandoned due to lack of efficacy or adverse effects.[7] This can be due to starting of therapies in late stages of disease, inappropriate drug dosage, wrong main target of the treatment, or incomplete understanding of the pathophysiology of AD.

Only two classes of drugs, including inhibitors to cholinesterase enzyme (donepezil, galantamine, rivastigmine) and antagonists to N-methyl d-aspartate (NMDA) - memantine, were approved for treatment of Alzheimer's disease by FDA till 2021, which are effective only in treating the symptoms of AD, but do not cure or prevent the disease.[8] In 2021, **monoclonal antibody (Anti Aβ),** Adacanumab was approved, and on July 6, 2023 Lecanemab and recently, on July 2, 2024, Donanemab-azbt was approved by US FDA.

Therefore, this review, mainly focuses on future theories for the development of new therapies for AD.

Current Landscape in Treatment Research for AD

Potential targets:

1. **Amyloid Beta and Tau protein:** Cleavage of amyloid precursor protein (APP) by β-secretases (BACE-1) or γ-secretases produces insoluble Aβ protein. So, the therapeutic approach is to disassemble and degrade amyloid plaques chemically or by recruiting microglia and activating phagocytosis to stop the neuronal damage elicited by the protein accumulation. Active or passive immunotherapies are the most widely studied strategies due to their precise response, although some adverse effects like autoantibodies induction, edema or hemorrhage have been reported. [9]

a) **Reduction of Aβ42 production** (γ-secretase inhibitors, β-secretase inhibitors, α-secretase potentiation)

- ***γ-secretase inhibitors:*** These drugs inhibit γ-secretase, which processes APP as well as the Notch receptor—an essential regulator of cell differentiation and signaling. Interference with the Notch pathway has led to adverse effects and failures in clinical trials. For instance, **Semagacestat** was associated with cognitive decline, increase in infection rate, and increased skin cancer incidence; Avagacestat caused dose-dependent toxicity; and **Tarenflurbil** exhibited poor brain penetration and clinical inefficacy.[5]
- ***β-secretase inhibitors:*** The β and γ-secretase leads to the generation of shorter insoluble peptide fragments (~39-43 amino acids) known as Aβ-fragments by cleaving APP in neuronal cells which possess a distinct neurotoxic effect leading to neurodegeneration, amyloid angiopathy, mitochondrial dysfunction and inflammation. Drugs in pipeline are: Verubecestat: oral BACE-1 inhibitor, Lanabecestat: decreased plasma and CSF Aβ, Elenbecestat , and Umibecestat.[10]

- ***α-secretase potentiation:*** Agents that activate the PI3K/Akt pathway or act as selective GABA receptor modulators are assumed to activate α-secretase also, so suggested as potential therapeutic drugs for AD

b) Reduction of Aβ-plaque burden: aggregation inhibitors, drugs interfering with metals

Aggregation inhibitors (anti-amyloid aggregation agents): directly interact with the Aβ peptide to inhibit Aβ42 fiber formation. Drugs include scyllo-inositol (ELND005) and Peptidomimetics (KLVFF, γ-AA)

Drugs interfering with metals: Abnormal accumulation of metal ions such as iron, copper, and zinc has been associated with the pathophysiology of AD. In a phase 2 study of 3 months, PBT2 succeeded in13% reduction of CSF Amyloid β and an cognition function improvement in patients with early AD. Drugs in pipeline include Deferiprona and PBT2.[10]

c) Promotion of Aβ clearance (active or passive immunotherapy):

Active immunotherapy: This approach involves immunization with Aβ or phosphorylated tau peptides, or synthetic peptides such as polymerized ABri-related peptide (pBri). These antigens elicit a B-cell–mediated antibody response against pathogenic epitopes. Vaccines under investigation include UB-311 (targets Aβ1–14 and demonstrated strong immunogenicity in phase II trials), CAD106, CNP520, ABvac40, GV1001, ACC-001, and AF20513.[5]

Passive immunotherapy: Passive immunotherapy involves the passive inoculation of monoclonal antibodies (mAbs) or polyclonal antibodies that act against Aβ peptides, making the inflammatory process developed by T cells unnecessary. Drugs in pipeline includes Crenezumab, Gantenerumab, LY3002813.[5]

2. **5-HT receptors:** 5-HT6R and 5-HT7R are the most extensively studied serotonin receptors due to their brain distribution and cognitive properties reported in vivo. 5-HT6R induces signaling that changes cholinergic, glutamatergic and monoaminergic brain signaling with least peripheral adverse effects.[11]
3. **Glutaminyl cyclase:** Glutaminyl cyclase plays a vital role in synaptotoxic Amyloid β oligomer formation with pro-inflammatory potential. It converts glutamate residue to AβpE3 peptide at position 3 of the N-terminal of truncated Aβ that may contribute to tau hyperphosphorylation. Drugs in pipeline includes Belinostat, Amlexanox and Acipimox.[12]
4. **Neuroinflammation:** TNF-α (Tumor necrosis factor-α) plays a significant role in neuronal excitotoxicity, synaptic loss and inflammation. Drugs in pipeline are NE3107, AL002: Monoclonal antibody targeting TREM2 receptors to promote microglial clearance of Aβ, TB006: Monoclonal antibody targeting Galactin 3, Edicotinib (JNJ-40346527): Colony-stimulating factor-1 receptor (CSF-1R) inhibitor and Pepinemab: Monoclonal antibody directed at semaphorin 4D to reduce inflammation. [13]
5. **Growth factor promotion:** growth factors have the role to regenerate neurons. Drug in pipeline is ATH 1017 (fosgonimeton)
6. **Stem cell therapy:** Stem cells have capacity to differentiate and proliferate throughout the lifetime of the organism. So, these cells can serve as the most appropriate choice for cell replacement therapies. These includes hNSCs (human Neural Stem Cells), hUC-MSCs (human Umbilical Cord Mesenchymal Stem Cells) and Autologous ADSCs (AstroStem).[14]
7. **Natural compounds:** In recent years, bioactive compounds derived from plants, animals, and fungi have shown therapeutic potential due to their anti-inflammatory, antioxidant, and neuroprotective properties. These natural agents may modulate key molecular pathways implicated in AD pathology. [15]
8. **Nanoparticle based delivery systems:** NPs enter the brain by crossing or disrupting the BBB. Diverse systems, including liposomes, polymeric NPs, solid-lipid NPs, and inorganic NPs, micelles, and NP based immunotherapy have been investigated to relieve AD symptoms, target AD hallmarks, and target moieties to diagnose AD.[16]

   Liposome : Osthole, Galantamine HBr,
   Micelles: Resveratrol, curcumin,
   Solid Lipid NPs: Rivastigmine, Donepezil
   Polymeric-NPs: Quercetin, Memantine
   Nanoemulsions: Huperazine A
   Magnetic NPs: Quercetin, SiRNA

Table-1: Trials in their various phases of development for the treatment of Alzheimer's disease

ANTI-AMYLOID THERAPY			
NAME	**COMPANY**	**THERAPY TYPE**	**STATUS**
Donanemab (LY3002813)	Eli Lilly & Co	Passive Immunotherapy	Approved on 3rd July 2024
Remternetug (LY3372993)	Eli Lilly & Co	Passive Immunotherapy	Phase 3
Valiltramiprosate (ALZ-801)	Alzheon	Small molecule	Phase 3
ABBV_916 (N3pG_Abeta mAb)	AbbVie	Passive Immunotherapy	Phase 2
CT1812 (SHINE (COG0201) Study)	Cognition Therapeutics	Small molecule	Phase 2
ANTI-TAU THERAPY			
Bepranemab (UCB0107)	Hoffmann-La Roche, UCB S.A	Passive immunotherapy	Phase 2
BIIB080 (ISIS 814907)	Biogen, IONIS Pharmaceuticals	Tau DNA/RNA-based	Phase 2
Posdinemab (JNJ-63733657)	Janssen	Passive immunotherapy	Phase 2
LY3372689	Eli Lilly & Co	Tau small molecule	Phase 2
NEUROPROTECTIVE AGENTS/ Synaptic plasticity			
Fosgonimeton	Augment the activity of hepatocyte growth factor and its receptor		Phase 2/3
Buntanetap	suppress the translation of the mRNAs of neurotoxic aggregating proteins		Phase 3 completed
Hydralazine hydrochloride	Activate the Nrf2 pathway, Restore mitochondria, Activate autophagy		Phase 3
COGNITIVE ENHANCERS			
AR1001	Inhibit phosphodiesterase 5 protein		Phase 3
KarXT(xanomeline_trospium)	Muscarinic receptor agonist		Phase 3
Metformin	Antidiabetic		Phase 3
Piromelatine	Melatonin MT1 and serotonin 5-HT-1A receptor agonist		Phase 3
Tricaprilin	Semisynthetic medium chain triglyceride		Phase 3
DRUGS TARGETTING NEUROINFLAMMATION			
Masitinib	Tyrosine kinase inhibitor		Phase 3
NE3107	Inhibits NFκB/ERK pathway		Phase 3
Canakinumab	Anti-IL-1β antibody		Phase 2
AL002 (Biological)	Monoclonal antibody targeting TREM2 receptors to promote microglial clearance of Aβ		Phase 2
Pepinemab (Biological)	Monoclonal antibody directed at semaphorin 4D to reduce inflammation		Phase 1/2
REPURPOSING TRIALS			
Escitalopram Oxalate	Selective serotonin reuptake inhibitor		Phase 4
Sodium Oligomannate Capsule	Neuro-inflammation inhibitor, Amyloid β formation inhibitor		Phase 4
Spironolactone	Mineralocorticoid receptor antagonist (Anti neuroinflammation)		Phase 4
leucine methylthioninium	Inhibition of tau-hyperphosphorylation		Phase 3
Thalidomide	Regulation of β-secretase enzyme, BACE-1 modulator		Phase 3
Etazolate	α-secretase stimulation, GABAA-receptor modulator		Phase 3
Rilapladib	cPLA2 inhibitor, Inhibits LOX and COX pathway		Phase 2
Bexarotene	Activates RXR receptors		Phase 2
Riluzole	Inhibition of glutamate release Inactivation of voltage dependent sodium channels		Phase 2
Saracatinib	Inhibition of Src/Abl family of kinases and Fyn kinase, Inhibition of Aβ formation.		Phase 1

DISCUSSION

A wide range of old and novel therapeutive targets are currently being explored in the drug development pipeline of Alzheimer's disease. Although there are various advancements in the knowledge of Alzheimer's pathogenesis, but still the most common outcome of new drug clinical trials is the lack of efficacy. This can be due to the late disease stage of patients under trial because earlier therapy yeilds better results in AD. Data from studies involving 5-HT6 antagonists, tau inhibitors, and nicotinic agonists have also been disappointing. On the other hand, agents such as anti-Amyloid β vaccine, BACE inhibitors, and drugs that targets neuroinflammation have shown better results in text of clinical improvement and minimal toxicity.

The effectiveness of anti-amyloid monoclonal antibodies reinforces amyloid plaques as a valid therapeutic target in AD therapeutics. Similarly, the success of tau antisense oligonucleotides indicates that therapies decreasing abnormal protein production may be effective. Growing insights into neuroinflammation have also found several promising molecular pathways which could serve as targets for both monotherapy as well as combinations therapy

Recent AD drug therapies have incorporated multiple innovative features such as novel biomarkers, refined neuropsychological assessment tools, early stage patient recruitment , and innovative trial designs. In the near future, treatment is likely to move toward a 'precision medicine' approach, where customized treatment regimens are tailored to individual patients based on aberrant biomarkers, accompanied with characteristic neuropsychological and neuroimaging findings.

Treatment of the diverse disease population of moderate to advanced stages of AD also remains a major concern. Even some of the existing therapies do not provide, even a symptomatic relief, in moderate to advanced stages of AD. The lack of an effective therapy for these populations underscores a critical opportunity of further drug discovery and development.

To identify, validate, and include rationalized efficient clinical biomarkers as end-points is the another key requirement for AD drug development. Such specific biomarkers would enable objective measurement of disease severity in order to set a clinical end-point and also help to predict the results of clinical trial more accurately.

At the same time, continuous effort is being made towards drug repurposing/repositioning to modify the disease's molecular pathophysiology. Due to high attrition rates and lack of funds, the pharmaceutical industries have diverted their focus from the new drug discovery and

development programs to drug repurposing approaches. This approach is more cost-effective, easier and faster as compared to the traditional drug discovery process particularly with the help of modern computational and screening technologies.

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Review Article

RE-IRRADIATION IN GLIOBLASTOMA MULTIFORME

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ABSTRACT

This review article addresses the role of re-irradiation in recurrent cases of previously treated Glioblastoma multiforme (GBM). The article particularly focuses on patient selection, imaging, dose fractionation regimens, radiation delivery techniques and follow up assesement, survival benefits and toxicities, when re-irradiation is used to treat local recurrences.

KEY WORDS : Reirradiation, Image guided radiotherapy IGRT, Glioblastoma multiforme

INTRODUCTION

Glioblastoma multiforme (GBM) is the most aggressive and common primary malignant brain tumor in adults, characterized by rapid progression and poor prognosis. The standard initial treatment includes maximal safe surgical resection followed by concurrent chemoradio therapy with temozolamide and adjuvant chemotherapy. [1] Despite aggressive management, most patients experience recurrence, typically within 6 to 9 months after initial therapy.[2] The therapeutic options for recurrent GBM are limited and often palliative. Re-irradiation has emerged as a potential salvage therapy for selected patients.[3] However, concerns regarding cumulative radiation toxicity, particularly radiation necrosis, had limited its widespread application. With advances in radiation delivery techniques such as stereotactic radiosurgery (SRS), stereotactic radio therapy (SRT), and intensity-modulated radiotherapy (IMRT), reirradiation has regained interest as a viable treatment modality. Systematic reviews for endpoints like progression-free (PFS) or overall survival (OS) with the use of newer treatment modalities, have indicated a benefit with regards to PFS, but the benefit in terms of OS has still not been seen. [4-7]

MATERIALS AND METHODS

A literature search was conducted using PubMed, Scopus, and Google Scholar databases to identify peer-reviewed studies on re-irradiation in GBM from 2000 to 2024. Search terms included “re-irradiation,” “glioblastoma,” “recurrent glioma,” “stereotactic radiotherapy,” and “radiation necrosis.” Inclusion criteria were studies reporting clinical outcomes, toxicity, and survival following re-irradiation in histologically confirmed recurrent GBM patients. Studies involving pediatric gliomas or those not differentiating GBM from other gliomas were excluded.

A total of 52 studies were reviewed, comprising retrospective analyses, prospective cohorts, and a few phase I/II trials. Key data extracted included patient selection criteria, radiation technique, total dose, fractionation schedule, time interval between initial and second irradiation, concurrent systemic therapies, survival outcomes, and toxicity profiles.

Patient Selection:

Careful patient selection is crucial for the success of re-irradiation. Factors influencing selection include age, Karnofsky Performance Status (KPS), tumor location and volume, interval since initial radiotherapy, repeat surgery and presence of symptoms. Typically, patients with KPS ≥ 60, and a progression-free interval of ≥ 6 months from initial treatment, independent of age and MGMT methylation status are considered suitable candidates [8,9]; with KPS being considered as a strongest predictor of OS, as it appears to be the single most common factor in multivariate analysis of prospective trials and in large retrospective cohorts. [4-7, 10]

Imaging required to assess recurrence post primary treatment

Often, serial imaging (typically, MRI) and clinical evaluation form the basis for classifying treatment response and defining recurrence.

The Macdonald criteria, published in 1990, based on the product of maximal cross-sectional dimensions of enhancing foci, provided an objective methodology for tumor measurement and comparison over time. [5] These criteria standardized nomenclature for response assessment (i.e., complete response, partial response, stable disease, or progressive disease) according to changes in tumor size, while taking into account neurologic status and steroid use.

Over time, identification of limitations of the Macdonald criteria resulted in the development of the RANO criteria. [11] for treatment response assessment and definition of tumor recurrence, which took into account the non-enhancing disease, and addressed pseudoprogression and pseudoresponse. The RANO criteria defines recurrence as any of the following: at least 25% increase in sum of the products of perpendicular diameters (SPD) of well-defined and "measurable" enhancing lesions or significant increase in T2/FLAIR non-enhancing lesion while on stable or increasing corticosteroid doses, development of a new lesion, clear progression of "nonmeasurable" disease (i.e., unidimensional, ill-defined or <10 mm), or clinical deterioration not attributable to causes apart from tumor.

Pseudoprogression should be strongly considered if the enhancing lesion grows within 12 weeks of chemo-radiation.[8] The RANO criteria only consider such growth "progression" if the majority of new enhancement lies outside the high-dose region (i.e., 80% isodose line) or if there has been pathologic confirmation of disease.

Pseudoresponse should be considered in patients receiving anti-angiogenic therapy, which may cause rapid reductions in enhancement in tumors that subsequently demonstrate increased T2/FLAIR signal reflecting infiltrative tumor. [7]

Post contrast T1 weighted images are required to particularly assess in- field recurrences seen as 'contrast enhanced tumors' in GBM.[8,9] Additionally conventional T2 weighted/T2 FLAIR images can detect non enhanced tumor progression or edema seen as 'hyperintense signals'. To differentiate tumor recurrence from treatment induced changes such as radiation necrosis/ pseudoprogression, advanced imaging techniques (i.e., perfusion MRI, MR spectroscopy, AA-PET) are recommended as they can more accurately detect tumor-associated processes (neovascularisation, metabolic changes, cell proliferation). AA-PET imaging could be [11C]Methionine (MET) PET , [18F] fluoro-L-3,4-dihydroxyphenylalanine (FDOPA) PET, or [18F] fluoroethyltyrosine (FET) PET . The additional value of PET for target volume delineation needs to be revisited and cannot be unequivocally recommended at present. [12]

Re-imaging after an interval of four to eight weeks may elucidate the underlying pathology (stable/subsiding changes indicating pseudoprogression/radiation necrosis versus continued increase indicating recurrence).

In addition, the imaging finding should be correlated with the previously irradiated volume The prior radiation dose distribution and dosimetry can serve as a guidance in addition to imaging to decide for or against tumor progression.

Optimal target definition

Simulation CT (slice thickness 1–3 mm) should be performed using an individualised immobilisation thermoplastic mask and images should be acquired encompassing the entire cranium. MRI images for planning purposes similar to simulation CT (1 mm slice thickness, orthogonal plane) should be acquired and fused with the CT images. Target selection should include lesions not exceeding 5–6 cm in largest diameter, while larger lesions, multi-focal and leptomeningeal disease should be excluded from reirradiation.

Critical organs at risk should be contoured, especially the brain, brainstem, optic nerves, chiasm, and eyes. The data for Hippocampal sparing in reirrdiation of GBM is limited. Most GBMs are not near the hippocampal region, therefore sparing hippocampus can help preserve neuroocognitive functions. But GBM being diffusely infiltrative tumor, any attempt to spare hippocampus may lead to hippocampal region harbor microscopic disease. Therefore, decision to spare hippocampus should be

individualized based on tumor location, expected survival, prior cognitive function status and priority of local control rather than perseverance of neurocognitive function. Therefore hippocamal sparing can be attempted in select patients only, but not generally recommended.

GTV is typically defined as the visible lesion on MRI contrast- enhanced T1-weighted sequences as well as suspected new / progressing T2-weighted/T2-weighted FLAIR abnormalities or AA-PET avid regions [8].There is no consensus whether to include or not the perfusion suspect regions into the GTV. In the published literature there is no standard GTV to CTV margin; in the majority of studies the GTV corresponds to the CTV but others used margins ranging from 3 to 5 mm. A PTV margin should be created by a geometrical expansion of the CTV using a margin of up to 3 mm. [9]

Radiation Techniques:

Modern techniques have enabled precise targeting of recurrent lesions while sparing surrounding healthy brain tissue. Advanced IGRT techniques are recommended for reirradiation purposes. Common modalities include:

Stereotactic Radiosurgery (SRS):

Delivers a high radiation dose in a single fraction. Suitable for small lesions (< 3 cm).Median doses range from 15–20 Gy.

Stereotactic Radiotherapy (SRT):

Fractionated stereotactic radiation over 3–5 sessions (e.g., 25–35 Gy in 5 fractions). It offers a balance between efficacy and safety for larger lesions.

Hypofractionated IMRT/VMAT:

Used for larger or irregular lesions. Typical regimens include 30–40 Gy in 10–15 fractions.

Proton and Carbon Ion Therapy:

These modalities are under investigation and show promise due to their Bragg peak property and reduced exit dose.

On board CBCTs should be used prior to treatment delivery.

Radiation dose fractionation schedules

Data suggests improved PFS with doses above BED10 of 40 Gy for SRS and BED10 of 45 Gy for conventional fractionation.[13] The evidence for any additional gains of increasing the biologically effective dose much beyond 40–55 Gy appears rather weak.

ESTRO guidelines recommend to use a dose fractionation regimen that delivers a biological equieffective dose (corresponding to a EQD2Gy above 36 GY in 18 fractions to the target (using an a/b value of 3 Gy).[8] They also recommend to use few treatment fractions and the preferred use of radiosurgery (single fraction) for smaller tumors (< 3cm) The safe dose fractionation regimens followed for re irradiation are:

For tumor > 6 cm : Conventionally fractionated regimens to the dose of 40 Gy in 20 fractions are used.

For tumors > 3- 6 cm or tumors < 3cm but near critical organs like chiasm and brainstem: High-dose hypofractionation (27–30 Gy in 3–5 fractions) are preferred. Moderate Hypofractionation (35 Gy in 10 fractions of 3.5 Gy each) are used for larger and irregular lesions. Longer courses should be reserved for patients with longer expected OS.

For tumors < 3 cm: Single-fraction SRS (16 Gy -24 Gy) can be used.

Dose accumulation calculation:

PTV prescription for reirradiation should follow the primary goal of respecting safe or acceptable OAR dose limits . Thus, a PTV compromise is reasonable to keep OAR safe or acceptable and PTV prescription should only be adjusted if this is not achieved even with a significant PTV compromise. Tissue recovery is still a matter of debate and subject to investigation.[14] The minimum set of organs at risk (OAR) to be evaluated after biological dose acculmulation include brain, brainstem, optic nerves and chiasma,, cranial nerves in close proximity to PTV. Consistent recovery has been described for brain and spinal cord and thus should be considered when assessing cumulative doses to these organs. The dose recovery of optic nerves and tracts however is still uncertain, therefore careful asseseement is required before calculating dose accumulation. Two dose accumulation methods that can be employed: a) Same OAR constraints are used for reirradiation as were for the first course with dose discount for first course. b) Cumulative OAR constraints are used.

Table 1: Shows the dose constraints for OAR to be used for reirradiation via conventional fractionation, SRT and SRS (per QUANTEC [15], AAPM TG-101 [16])

Organ at risk	Conventional fractionation (40 Gy in 20 fractions)	Stereotactic Radiotherapy (27-30 Gy in 5 fractions)	Steretactic Radiosurgery (16-24 Gy in 1 fraction)	Function preserved
Brainstem	Dmax < 20-25 Gy Cumulative dose < 100Gy EQD2	<31 Gy	< 12.5 Gy	To avoid necrosis
Optic nerves/chiasm	Dmax < 20-25 GY Cumulative dose < 100Gy EQD2	<25 Gy	< 8 10 Gy	To avoid neuropathy
lens	Dmax < 7 Gy Cumulative dose < 12 Gy EQD2	<10 Gy	<2-4 Gya	Cataract threshold
Cochlea	Dmean < 30 Gy	<30 Gy	<9 Gy	To prevent Hearing loss
Normal brain	V40 < 30-50 cc Avoid large V40	V25 Gy < 10 cc	V12 Gy < 5 10 cc	To avoid radionecrosis
Hippocampus (if sparing)	Dmean < 10 Gy			For neurocognitive sparing

Combined modality treatment

There is no need to change target definition, dose and fractionation when considering combined modality treatment. [8]

Most studies reporting on combined modality reirradiation use conventional (36 Gy in 18 fractions) and moderately hypo-fractionated (35 Gy in 10 fractions) treatment and show that the addition of either alkylating agents (Temoolamide) or bevacizumab (an anti-VEGF monoclonal antibody) is well tolerated reporting OS and PFS times of around 9–12 months and 4–7 months, respectively. [17,18] But no prospective trial has indicated that the combined modality is superior to reirradiation alone in terms of PFS or OS. There is also insufficient data to suggest specific role of maintenance systemic treatment post irradiation.

Follow up schedule post re-irradiation

Follow up for early acute toxicity should be done at 6 weeks, however follow up standard MRI is recommended every 3 months post reirradiation completion. In case of suspicion and to differentiate tumor progression from radiation necrosis/pseudoprogression, advanved MRI (perfusion and spectroscopy) or AA PET are re-commended. [8]

In case of further tumor progression and after exclusion of pseudoprogression/radiation necrosis, if there are no further reasonable treatments options, transition to best supportive care should be considered and further imaging follow-up is not beneficial.

Efficacy:

Survival after re-irradiation varies across studies. Reported median overall survival (OS) from the time of

reirradiation ranges from 6 to 12 months. Progression-free survival (PFS) typically ranges from 3 to 6 months. [4-7] A meta-analysis by Kazmi et al.[19] of 28 studies reported a pooled median OS of 9.3 months after re-irradiation.

Table 2 : Shows the Studies showing local control and survival benefits with Re-irradiation in GBM Tumors

Study	N	Technique	Dose/Fractionation	Median OS	Median PFS	Key Findings
Combs et al., 2011 [20]	172	FSRT	36 Gy / 2 Gy x18	8 months	5 months	Smaller volume and higher KPS better outcome
Minniti et al., 2012 [17]	86	SRT	30 Gy / 2.5 Gy x12	9 months	5.2 months	Favorable outcomes with limited toxicity
Navarria et al., 2011 [21]	53	FSRT + TMZ	36 Gy / 2 Gy x18	7.7 months	4.5 months	ReRT with TMZ safe, well tolerated
Gutin et al., 2009 [5]	25	SRT + Bev	30 Gy / 5 Gy x6	11 months	6 months	Bevacizumab may lower necrosis risk
Fogh et al., 2010 [22]	147	SRS	15–24 Gy single fraction	8.6 months	NR	Good for small lesions (<3 cm)
Fogh et al., 2012 [22]	71	Hypo - IMRT	35 Gy / 5 Gy x7	10.3 months	5.6 months	Safe and effective with IMRT
Kazmi et al., 2019 [19]	2095	Mixed	Median 35 Gy	9.3 months	4.6 months	Larger tumor, short interval worse
Niyazi et al., 2014 [7]	198	FSRT	36 Gy / 2 Gy x18	7.5 months	4 months	Scoring system developed
Tsien et al., 2012 [10]	47	IMRT + Bev	35 Gy / 5 Gy x7	9.9 months	4.4 months	Bev may enhance reRT effect
Navarria et al., 2014 [21]	42	SRT	25–35 Gy / 5 –7 Gy x5	11.1 months	6.3 months	Excellent local control

Toxicity:

Re-irradiation carries risks of both acute and late toxicities. [17,18] Acute side effects include fatigue, headache, and worsening of neurological symptoms, usually transient. The most feared late toxicity is radiation necrosis, occurring in up to 20% of cases. The risk is influenced by cumulative dose, interval between treatments, and volume irradiated. Strategies to minimize toxicity include conformal planning, fractionation, and judicious dose constraints to organs at risk.

Prognostic Factors:

Favorable prognostic indicators for survival post re-irradiation include: Younger age (< 60 years), High KPS, Smaller tumor volume, Longer interval (> 12 months) since initial radiotherapy, MGMT promoter methylation, IDH1 mutation.[12-16] Some prognostic scoring systems, such as the Heidelberg and Combs scoring systems, have been proposed to guide clinicians in selecting patients and estimating outcomes.

Emerging Strategies:

Novel approaches including re-irradiation with immune checkpoint inhibitors, tumor-treating fields, and personalized dosing based on genomic profiles are under investigation. Integration of radionomics and artificial intelligence in predicting response and toxicity is also gaining traction.

CONCLUSION

Re-irradiation is a feasible and moderately effective salvage option for selected patients with recurrent GBM, especially with advances in radiation delivery techniques. While it offers symptomatic relief and a modest survival benefit, the risk of toxicity, particularly radiation necrosis, mandates careful patient selection and planning. Prospective randomized trials are needed to define optimal dosing strategies, fractionation schedules, and combinations with systemic therapies. With an individualized approach, re-irradiation can play a meaningful role in the multidisciplinary management of recurrent GBM.

DISCUSSION

Radiobiological aspect of re-irradiation in recurrent GBM

Recurrence within 6 to 9 months following standard radiation doses of 60 Gy in 30 fractions over 6 weeks in GBM tumors, indicates the high proliferative capacity, hypoxia and dominance of radioresistant clones in the recurrent disease. Considering the concept of 4 Rs of radiobiology in re irradiation of recurrent GBM tumors, we can see that normal brain tissue has some capacity to repair sublethal damage over time, however late responding tissues (white matter, brainstem) are vulnerable due to slower repair kinetics. Accelerated repopulation in GBM starts 3 – 4 weeks into radiotherapy. Re-irradiation aims to counter the fast tumor regrowth, along with sparing of normal tissue.

But the recurrent GBM tumors tend to be hypoxic and have tumor cells in radioresistant phases (S- Phase). So unlike radiosensitive rapidly proliferative cells in primary GBM which has high α/β ratio (~10 Gy) , the recurrent GBM tumor has low α/β ratio (~2 Gy), similar to the normal brain tissue. So the tumor is sensitive to change in dose per fraction. Therefore hypofractionated stereotactic radiotherapy regimens tend to offer better tumor control rates, along with sparing of normal brain tissue.

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Review Article

SUGAMMADEX : A REVOLUTION IN NEUROMUSCULAR BLOCKADE REVERSAL

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ABSTRACT: Sugammadex represents a significant advancement in anesthetic pharmacology, offering a rapid, safer and more reliable method for reversing NMB. Its unique pharmacologic profile, mechanism of action, favorable pharmacokinetic profile, and clinical efficacy make it a valuable tool in modern anesthesia practice and enhances patient safety and operating room efficiency. While it offers several advantages over traditional reversal agents, including reduced risk of residual NMB and PONV, clinicians should be aware of potential adverse effects and carefully consider patient-specific factors, including renal function and cardiovascular status, when using sugammadex to optimize its use and minimize potential risks.

KEY WORDS : Sugammadex, Neuromuscular block reversal

INTRODUCTION

Sugammadex is a selective relaxant binding agent (SRBA) that has transformed the practice of anesthesia, particularly in the reversal of neuromuscular blockade (NMB) induced by aminosteroid non-depolarizing neuromuscular blocking agents like rocuronium and vecuronium during general anesthesia. Unlike traditional reversal agents which are acetylcholinesterase inhibitors, such as neostigmine, which work indirectly by inhibiting acetylcholinesterase, and increasing acetylcholine levels to counteract NMB; sugammadex acts by directly encapsulating the NMB agent, effectively removing it from the neuromuscular junction and inactivating the neuromuscular blocking agent. This novel mechanism allows for a rapid, predictable, and complete reversal of moderate to deep neuromuscular blockade, making it a valuable tool in anesthetic practice.[1,2]

Its onset of action is typically within 2 to 3 minutes, regardless of the depth of blockade, making it particularly valuable in cases requiring quick recovery, such as short surgical procedures or unanticipated needs for rapid extubation.

Mechanism of Action

Sugammadex is a modified γ-cyclodextrin with a hydrophobic core and a hydrophilic exterior. The hydrophobic core allows it to encapsulate the steroidal

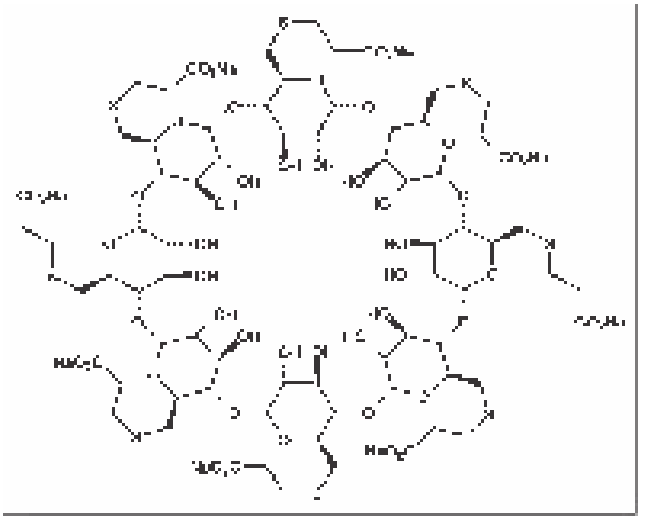

Figure 1 : Chemical Structure3

structure of aminosteroid NMBDs, forming a stable, water-soluble inclusion complex. This binding effectively reduces the free concentration of the NMBD at the neuromuscular junction, leading to the dissociation of the drug from nicotinic acetylcholine receptors and rapid restoration of neuromuscular function. The affinity of sugammadex for rocuronium is particularly high, with an association constant of approximately $1.79 \times 10^7\ M^{-1}$, indicating a very tight and stable complex formation .[4,5]

PHARMACOKINETICS

Sugammadex exhibits linear pharmacokinetics within the recommended dosing range. It has an estimated

volume of distribution of 11–14 liters and a plasma clearance rate of approximately 88 mL/min in healthy adults. The drug is not metabolized and is excreted unchanged by the kidneys, with more than 90% eliminated within 24 hours . This renal excretion pathway underscores the importance of dose adjustment in patients with renal impairment.[6]

Clinical Efficacy

Clinical studies have demonstrated that sugammadex provides rapid and effective reversal of NMB. In patients receiving rocuronium-induced deep NMB, sugammadex administered at a dose of 16 mg/kg can achieve recovery of the train-of-four (TOF) ratio to 0.9 within 3 minutes. Even at lower doses, such as 4 mg/kg, sugammadex facilitates recovery within 5 minutes. These outcomes are significantly faster compared to traditional reversal agents like neostigmine, which may take 10–30 minutes to achieve similar effects .[7]

Table 1 : Dose[8] of Sugamadex

TOF: train-of-four, PTC: post-tetanic counts.

KEY ADVANTAGES

- **Rapid and Complete Reversal:** Sugammadex provides quick recovery from NMB, which is particularly beneficial in surgeries requiring prompt patient emergence from anesthesia.
- **Reduced Incidence of Residual NMB:** Studies indicate that one of the major clinical advantages of sugammadex is that it is associated with a lower incidence of residual NMB compared to traditional reversal agents, which is a significant cause of respiratory complications in the post-anesthesia care unit (PACU). By providing a more reliable reversal, sugammadex helps minimize risks such as airway obstruction, hypoxia, and the need for extended mechanical ventilation.
- **Lower Risk of Postoperative Nausea and Vomiting (PONV):** Some evidence suggests that sugammadex was associated with a lower incidence of PONV during the first 24 hours following general anesthesia compared to neostigmine, which contributes to enhanced patient comfort and faster recovery.[9]
- Sugammadex also tends to have fewer side effects than neostigmine. Acetylcholinesterase inhibitors can cause bradycardia, increased salivation, and gastrointestinal symptoms, often requiring co-administration of anticholinergic drugs like atropine or glycopyrrolate. In contrast, sugammadex does not increase acetylcholine levels and thus avoids many of these adverse effects.

SAFETY CONSIDERATIONS

Despite its benefits, sugammadex is not without concerns. While sugammadex is generally well-tolerated, its use is associated with certain adverse reactions. A comprehensive analysis of the World Health Organization's pharmacovigilance database identified 94 adverse drug reactions (ADRs) with a positive signal for sugammadex. The most frequently reported ADRs include recurrence of neuromuscular blockade, laryngospasm, bronchospasm, and bradycardia.

- **Hypersensitivity Reactions:** Albeit rare, hypersensitivity reactions, including anaphylaxis, can occur. These reactions typically manifest within minutes of administration and require prompt treatment.[2]
- **Cardiovascular Events:** There have been reports of coronary vasospasm and acute coronary syndrome associated with sugammadex use, potentially due to hypersensitivity reactions.[2]
- **Pulmonary Complications:** Cases of upper airway obstruction, laryngospasm, and bronchospasm have been reported following sugammadex administration, particularly when used in combination with certain anesthetic agents.[2]
- Cases of bradycardia and even cardiac arrest have occurred, usually shortly after administration. Therefore, clinicians are advised to monitor cardiovascular status closely during use. Notably, the incidence of bradycardia and other serious cardiovascular events has raised concerns, particularly in patients with underlying heart conditions.
- Additionally, because sugammadex binds steroidal compounds, it may interfere with the efficacy of hormonal contraceptives for up to seven days, necessitating patient counseling postoperatively.

Special Populations

- **Patients with Myasthenia Gravis:** A systematic review suggests that sugammadex may be a reasonable option for reversing NMB in patients with myasthenia gravis, with rapid recovery and a low incidence of serious complications. However, further large-scale studies are needed.[10]
- **Patients with Neuromuscular Disorders:** Case reports indicate that sugammadex can effectively reverse NMB in patients with conditions like polymyositis and dermatomyositis. However, variability in onset time and recovery have been observed, possibly due to disease-related factors, and altered neuromuscular physiology in these patients.[11] Caution and individual assessment remain critical in these contexts.
- **Renal Impairment:** Given its renal elimination, sugammadex should be used with caution in patients with renal impairment. Dose adjustments are necessary, and its use is generally not recommended in patients with severe renal dysfunction or end-stage renal disease requiring dialysis.[12]
- **Pediatrics:** Sugammadex has been shown to be effective in pediatric populations, with similar efficacy and safety profiles as in adults. However, dosing considerations and monitoring are essential due to differences in pharmacokinetics and the potential for age-related variations in drug response.
- **Pregnancy and Lactation:** The safety of sugammadex during pregnancy and lactation has not been well-established. As with all medications, its use should be considered only when the potential benefits justify the potential risks to the foetus or neonate.

From a pharmacoeconomic standpoint, sugammadex is more expensive than neostigmine, which can be a limiting factor in resource-constrained settings. However, its cost may be offset by shorter recovery times, decreased postoperative complications, and reduced length of stay in the PACU or hospital.

CONCLUSION

In summary, sugammadex represents a significant advancement in anesthetic pharmacology, offering a rapid, safer and more reliable method for reversing NMB. Its unique pharmacologic profile, mechanism of action, favorable pharmacokinetic profile, and clinical efficacy make it a valuable tool in modern anesthesia practice and enhances patient safety and operating room efficiency. While it offers several advantages over traditional reversal agents, including reduced risk of residual NMB and PONV, clinicians should be aware of potential adverse effects and carefully consider patient-specific factors, including renal function and cardiovascular status, when using sugammadex to optimize its use and minimize potential risks. As clinical experience continues to grow, sugammadex is likely to become the standard of care for NMB reversal, particularly in high-risk or time-sensitive situations. Ongoing research and clinical experience will continue to refine its role in anaesthesia and perio-operative care and its optimal use in various patient populations.

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Case Report

FETAL NECK MASS AS A CAUSE OF OBSTRUCTED LABOUR - AN ANAESTHESIOLOGIST'S AND OBSTETRICIAN'S NIGHTMARE

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ABSTRACT : Fetal neck masses cause a nightmare for obstetrician and anaesthesiologist when delivery is conducted. The techniques and methods of the delivery vary with experience of the surgeon and it is a real emergency when there is an obstruction and foetus is not delivered in time. It may cause hypoxia and cardiac arrest or aspiration to the baby to be delivered. Appropriate experienced team of obstetrician, anaesthesiologist and neonatologist is required to conduct these deliveries. Giant fetal mass is most common indication where Ex-utero intrapartum treatment can be done in experienced hands. Here we present a case where a giant neck mass was delivered by turning the foetus to breech position and was delivered smoothly.

KEY WORDS : Fetal neck mass, Exit procedure, Caesarean section

INTRODUCTION

Delivery of foetus with large neck mass is a nightmare for both obstetrician and anaesthesiologists. Large neck masses in the foetus can lead to difficulty in the delivery and the anaesthesia technique may vary according to the size of the neck mass. Generally, neck masses in children fall into 1 of 3 categories: congenital, inflammatory, or neoplastic. 1 Although malignancies do occur, most neck masses in children are benign in nature. Large foetal neck masses can make it difficult or impossible to secure airways at birth, with associated risks of hypoxia, brain injury, and death.[2] The delivery of foetus causes obstruction and the vaginal delivery may become very difficult. Also, the delivery through caesarean section is a difficult task and anaesthesia technique may vary in these types of cases. [1]

Here we discuss a rare case of massive cystic hygroma in the foetus and the difficulties faced in the delivery of a foetus with anaesthesia challenges are discussed here.

CASE REPORT

A 28-year-old, G3P2L2 at term (37 weeks) was admitted in the obstetric ward of a tertiary hospital of north India in emergency area. The chief complains were labour pains and leaking per vaginum for 12 hours. The patient was dehydrated and exhausted. The pulse rate was 110/mt. and BP was 150/100 mm Hg; respiratory rate was 19/minute and was afebrile. The per abdomen size uterus, with lower uterine segment over stretched with Bandl's ring was observed. The fetal heart rate was 156/min., regular, uterine contractions of 35-40 sec duration occurring at 1 min. interval. Per vaginum examination revealed dryness, loose hanging cervix and edematous 8 cms dilated caput ++, cephalic at -3 station. Pelvis was gynecoid. The investigations showed Hb 9 gm%, blood group A+ve. The patient was immediately shifted to operation theatre for obstructed labour. On searching the previous ANC checkups, there was no ultrasound scan available and the patient was taken for emergency caesarean.

Detailed quick pre-anaesthetic checkup was done on the operation table that revealed tachycardia and hypertension of the mother. The history revealed nothing significant and the patient was fasted for 5 hours. Adequate blood units were arranged and appropriate consent was obtained. The patient was scheduled for spinal anaesthesia in view of 5 hours fasting and the drugs for general anaesthesia were made ready.

Intravenous cannulation was done with an 18 guage i.v

cannula. Preloading was done with normal saline @10 ml/kg and oxygen was started. Senior most anaesthesiologist administered spinal anaesthesia in a single prick after achieving asepsis and with appropriate spinal space identification. Total of 2 ml. of 0.5% bupivacaine heavy was given at L3-L4 intervertebral space after receiving csf using 25G spinal needle. Adequate block till T6 was obtained and lower segment caesarean section was started. On opening the lower abdomen, it was over stretched and myometrium thinned out. When the uterus was opened by the obstetrician, it was a huge dismay. A large cystic swelling was observed in the neck region and the baby was delivered as breech instead of normal method. The technique was changed by obstetrician at that moment during delivery of baby. The baby head was stuck for 5-6 seconds and finally delivered by breech delivery. The APGAR score was 9/10 and 2.8 kg male baby cried in a while. A 20x 14 cm size cystic swelling was seen on left side of neck which was probable cause of obstruction. There were no visible veins or pulsations over the swelling and it was translucent. (Figure-1) A differential diagnosis of teratoma neck / cystic hygroma was made and the baby was transferred to the paediatric surgery unit for further management. The final diagnosis could not be made as the baby was not operated upon due to parents' refusal of consent. Translucency test was positive for cystic hygroma and most probable diagnosis was giant cystic hygroma of the fetal neck. Caesarean section was completed and abdomen stitched. The mother's postoperative surgery was uneventful.

The patient, both mother and child, were managed and they were discharged home after 7 days of hospitalization. The patient did not follow up in the hospital further.

Figure 1: showing the foetus delivered

DISCUSSION

Large foetal neck masses can present a major challenge to securing an airway at birth, with associated risks of hypoxia, brain injury, and death.` The authors report a case of a giant neck mass, diagnosed in a foetus of 37 weeks, delivered through caesarean section but with change of technique of delivery of foetus. This obstructed labour was unanticipated and in emergency LSCS and in unbooked referred patient in obstetric emergency area. The anaesthesia was planned for regional anaesthesia because of anticipated full stomach and the safety of patient was kept in the mind. Although the foetal heart rate was more and thus senior most anaesthesiologist administered the anaesthesia in the patient. The senior obstetrician who had more than 20 years experience conducted the delivery (LSCS) where the normal technique of baby out was abandoned due to obstruction of head was anticipated after abdominal incision. The baby was turned to breech and then delivered breech with increase in the incision.

There have been reports of obstructed labour due to congenital swellings of the foetal neck. Huge swellings can be congenital teratoma or cystic hygroma.[3] This patient most probably had cystic hygroma in the fetal neck and it was larger in size. This cystic hygroma is due to dysplasia arising from the sequestration of lymphatic tissue that fails to communicate with the lymphatic tree. It is present in the posterolateral aspect of neck.[2] The antenatal diagnosis of these swelling can be made by ultrasound and the delivery has to be done with utmost care not to injure the foetus. The neonatal complications may arise due to tracheal compression and it should be dealt with as the emergency LSCS. The surgical management needs a team effort with obstetrician, anaesthesiologist and neonatologist. These cases if are already anticipated then these need multi-disciplinary approach as a team work. Patients' counselling is another component of management. The neonatal outcome depends on the expertise of the surgeon or obstetrician , anaesthesiologist foresightedness and skills of management of such patients and neonatologists alertness in the fast management in resuscitation if

required. The appropriate and adequate equipment may be required at that moment and the skill of its use is equally important.

Fortunately, according to the present set up the delivery can be conducted after conversion to breech otherwise Ex utero Intrapartum Treatment (EXIT) Procedure would have been a viable choice keeping in view that the expertise of doing this procedure is there or not.[4]

It is a rare and high-risk operation done before birth to help a baby breathe once born. This procedure ensures that the baby can get air to their lungs, while still being connected to the placenta and supported by their mother. It's typically done for babies in the uterus who have problems with their airways or the lower respiratory system (the parts of the body involved in breathing). The main goal of the procedure is to make sure the baby can breathe during a Caesarean section before the umbilical cord is cut. This allows obstetricians' to use the mother's blood supply to support the baby during the procedure.[4] The most common indication for an EXIT procedure is due to a growth in the neck area. Like in this patient but it needs expertise to conduct through this technique. Other reasons may include problems with the baby's diaphragm or respiratory system, or in rare cases, needing to separate conjoined twins.

In general, the procedure involves making an incision in the mother's abdomen and uterus and safely delivering the baby's head, neck, and upper body until the problem area is exposed. The necessary procedure is then done, which can range from a simple intubation to removing the problematic growth. Once the surgery is complete, the baby is safely delivered. This was difficult to conduct in this case as the patient was obstructed due to huge swelling of the neck . It was not possible to take neck out with head during the conduct of delivery in LSCS.

In well-equipped advanced centres this could have been treated through ex utero intrapartum treatment procedure to assist in securing an airway followed by excision of the mass on the day after delivery. A multidisciplinary team approach, combined with an accurate prenatal diagnosis obtained through foetal ultrasound magnetic resonance imaging examination, should have been the key to a successful outcome. The role of the paediatric surgeon could be initially to secure the airways through airway life saving skills followed by excision of the mass when the infant's vital parameters had been stabilized. Open discussions with the family and all involved care teams need to happen regularly in these situations. Our patient was not followed up as the patient did not visit again.

Conclusion

Delivery of foetus with giant neck mass needs experience, expertise and multidisciplinary approach. Obstetrician, anaesthesiologist and neonatologist as a team with prenatal diagnosis of type of neck swelling plays an important role in safe outcome of both mother and foetus. The EXIT procedure is another approach if the neck swelling is smaller and needs expertise in performing this. An expert obstetrician can change the techniques during the delivery of foetus and can perform the safe delivery .

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79.	LM/S-2/2016	Dr. Sarabjit Kaur - Gynecology
80.	LM /S-3/2017	Dr. Seema Goyal - Skin
81.	LM /S-4/2017	Dr. Sanjay Goyal - Medicine
82.	LM/S-5/2017	Dr. Sanjeev Bhagat - ENT
83.	LM/S-6/2017	Dr. Sangeeta Aggarwal - Gynae (Couple-H2)
84.	LM/S-7/2017	Dr. Shelly Jetly - Transfusion Medicine
85.	LM/S-8/2020	Dr. Satinder Pal Singh - Forensic Medicine
86.	LM/S-9/2020	Dr. Sudesh Kumari - Chest & TB
87.	LM/S-10/2021	Dr. Satinder Pal Kaur - Obs. & Gynae.
88.	LM/S-11/2021	Dr. Sanjeev Gupta - Surgery
89.	LM/T-01/2021	Dr. Tripat Kaur - Anesthesia
90.	LM/T-02/2022	Dr. Tanveer Singh Kundra - Anesthesia
91.	LM/ V-1/2016	Dr. Vishal Chopra - Chest & TB
92.	LM/V-2/2016	Dr. Vinod Dangwal - Radiotherapy
93.	LM/V-3/2016	Dr. Vijay Bodal - Pathology (Couple S-2)
94.	LM/V-4/2016	Dr. Vijay Sehgal - Pharmacology
95.	LM/V-5/2017	Dr. Vandna Singla - Clinical Pathology

Format of Application for Membership

To
The Editor
Journal Club Government Medical College Patiala Punjab India

Dear Sir/Madam

I wish to become a Life Member/Annual Member of the Journal Club GMC Patiala. I am furnishing the required particulars below with a request to enroll me in the Journal Club.

The fee of Rs. 5000/ Rs. 8000/- Rs 1000/- for Life Membership (Single/Couple)/ Annual Membership is enclosed as a Demand Draft/ Cheque with No._____of _____Bank, in the name of Journal Club Government Medical College Patiala along with my two passport size photographs.

I have gone/will go through the rules and regulations of the Journal Club and I agree to abide by the same.

PARTICULARS
1. Full name (in block letters)
2. Father's/Husbands' name
3. Qualification
4. Official Designation & Place of Posting
5. Permanent Address
6. Phone No. & Email

Place Yours Sincerely

Date (Signature)

For Use of Journal Club GMC Patiala

Membership accepted with life/Annual Membership No.....

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(Year 2017-2018)

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Founder Team: Editorial Board

N,B. This is the permanent page for the Founder Team (Editorial Board)