JNSCCM January 2023 | Volume 1, Issue 1 | ISSN 2976-1212 (Print) | ISSN 2976-1220 (Online)

JNSCCM

Journal of Nepalese Society of Critical Care Medicine

A Peer Reviewed, Official Journal of NSCCM

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A Peer Reviewed, Official Journal of NSCCM

ISSN 2976-1212 (Print)
ISSN 2976-1220 (Online)

CONTACT US

Web address *nsccm.org.np/pages/journal*
Email address *jnsccm@gmail.com*
Phone Number *+977 9841248584*

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A PEER REVIEWED, OFFICIAL JOURNAL OF NSCCM

EDITORIAL

Unveiling of Journal of Nepalese Society of Critical Care Medicine (JNSCCM)

Sanjay Lakhey, M.D.

Author(s) affiliation:
Department of Internal Medicine
B and B Hospital
Lalitpur, Nepal

Corresponding author:
Sanjay Lakhey, MBBS, MD (Internal Medicine)
Email: sanjaylakhey@gmail.com

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HOW TO CITE THIS ARTICLE IN VANCOUVER STYLE?

Lakhey S. Unveiling of Journal of Nepalese Society of Critical Care Medicine (JNSCCM). Journal of Nepalese Society of Critical Care Medicine. 2023 Jan;1(1):

Submitted : 12 Nov 2022
Accepted : 26 Nov 2022
Published Online : 2 Dec 2022

Conflict of Interest : None
Source of Support : None

"A journey of thousand miles begins with a single step"
-Lao Tzu

The Nepalese Society of Critical Care Medicine (NSCCM) was established in 2010 AD. The history of Critical Care Medicine in Nepal dates back to 1973, when the first ICU was started at Bir Hospital as 5 bedded medical ICU.[1] This was the only ICU in the country for almost 20 years.[2]

The NSCCM, since its inception, has been striving to improve critical care services in Nepal by organizing continuing medical education (CME) programs and workshops in various parts of the country. It is now also holding its 4th Conference with 22nd Annual Congress of Asia Pacific Association of Critical Care Medicine.

The last decade saw a significant advancement in the field of critical care in Nepal. In parallel with development and expansion of critical care services, we saw increasing number of doctors and nurses trained in critical care, both from abroad and from Nepal. High quality research can foster the development of critical care services and critical care education. It can help to generate local epidemiological data and can also help to contribute to the global critical care research community. The need of high quality research was well perceived by the Nepalese critical care community.[3]

As another step forward, and as major source of information for improvement of medical care in critical care medicine and to serve as a platform to showcase quality research works, we are now publishing our first edition of the Journal of Nepalese Society of Critical Care Medicine (JNSCCM).

This biannual specialty journal will be publishing sound scientific articles focusing on topics that are of great importance to its readership. It is our aim to provide accurate and up to date scientific and clinical information to our readers.

Learning is a never-ending process and JNSCCM is, indeed, our next step in a journey of thousand miles.

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JOURNAL OF NEPALESE SOCIETY OF CRITICAL CARE MEDICINE
A PEER REVIEWED, OFFICIAL JOURNAL OF NSCCM

ORIGINAL ARTICLE

Comparison of airway pressure release ventilation with low tidal volume ventilation in patients with acute respiratory failure

Hem Raj Paneru[1], M.D., D.M., Subhash Prasad Acharya[1], M.D., Moda Nath Marhatta[2], D.A., F.C.P.S.

[1] Department of Critical Care Medicine, Maharajgunj Medical Campus, Kathmandu, Nepal;
[2] Department of Anaesthesiology, Nepal Medical College, Jorpati, Kathmandu.

Corresponding author:
Hem Raj Paneru, MBBS, MD,
DM Critical Care Medicine.
Lecturer, Department of Critical Care Medicine,
Maharajgunj Medical Campus, Kathmandu,
Nepal
Email: hem.paneru@gmail.com
Phone: +977 1 9851205051

ACCESS THIS ARTICLE ONLINE

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HOW TO CITE THIS ARTICLE IN VANCOUVER STYLE?

Paneru HR, Acharya SP, Marhatta MN. Comparison of airway pressure release ventilation with low tidal volume ventilation in patients with acute respiratory failure. Journal of Nepalese Society of Critical Care Medicine. 2023 Jan;1(1):2-6

Submitted : 13 Nov 2022
Accepted : 26 Nov 2022
Published Online : 2 Dec 2022

Conflict of Interest : None
Source of Support : None

ABSTRACT

Background and aims : Acute respiratory failure (ARF) frequently requires invasive mechanical ventilation. Though low tidal volume ventilation has improved outcome of these patients, mortality is still high. We aimed to assess whether the use of Airway Pressure Release Ventilation (APRV) results in better oxygenation compared to Low Tidal Volume (LTV) ventilation in patients with ARF.

Methods : Patients with ARF requiring mechanical ventilation were randomized into either APRV or LTV ventilation. PaO_2 and PaO_2/FiO_2 ratio were recorded and compared between the groups for the assessment of effect on oxygenation.

Results : Two hundred and two patients were included in the study with 101 patients in each group. Baseline oxygenation status, APACHE II scores, and demographic parameters were similar in both the groups. PaO2 values at the time of admission (73.73 ± 22.23 mmHg in APRV group and 75.13 ± 20.43 mmHg in LTV group; p = 0.643), at 24 hours (176.21 ± 50.70 vs 180.62 ± 53.19 mmHg; p = 0.547) and at 72 hours (208.17 ± 61.20 vs 211.36 ± 50.89 mmHg; p = 0.688) were similar between the groups. The mean values of PaO2/FiO2 ratio at 0, 24, and 72 hours were 178.67 ± 55.51 vs 186.09 ± 53.34, 285.87 ± 69.08 vs 290.95 ± 63.56, and 288.95 ± 71.51 vs 283.78 ± 59.13 mmHg respectively in APRV and LTV groups.

Conclusion : Both APRV and LTV modes improved oxygenation and had similar effects on oxygenation in patients with ARF.

Keywords : *acute respiratory failure, airway pressure release ventilation, low tidal volume ventilation, oxygenation.*

INTRODUCTION

Acute respiratory failure (ARF) is defined by the sudden onset of severe impairment of pulmonary gas exchange and is characterized by the inability of the lungs to meet the body's metabolic needs for the transport of oxygen (O_2) into the blood and/or removal of carbon dioxide from the blood.[1] More than half of the patients admitted to the ICU with stays of more than 48 hours have ARF at some point during their hospitalization[2]. And the overall mortality rates are well above 34%.[2-5] Many of these patients need ICU admission for respiratory support. With the overwhelming mortality reduction observed in ARDSNet trial,[3] positive pressure ventilation in the form of low tidal volume ventilation has been the mainstay of therapy for these patients. Despite these developments and advances, mortality in patients with ARF is still very high (35 to 46%).[4] Lately Airway Pressure Release Ventilation (APRV) has shown promising results. APRV has the following theoretical advantages:[5] a) minimizes ventilator-induced lung injury, b) improves hemodynamic profile, c) provides benefits from spontaneous breathing, d) decreases work of breathing, e) decreases need for sedation/neuromuscular blocker. Moreover, recent studies have compared APRV to ARDS net protocol ventilation and found improved efficacy and safety with APRV.[6,7] Animal models and retrospective human data have suggested that APRV may even prevent the development of ARDS.[8-10] However, despite its theoretically attractive advantages and positive results, APRV is still not routinely used in clinical practice. We aimed to assess whether APRV results in better oxygenation compared to Low Tidal Volume (LTV) ventilation in patients with acute respiratory failure requiring endotracheal intubation and mechanical ventilation.

METHODS

This was a quantitative, interventional, randomized clinical trial enrolling all eligible patients with ARF admitted to the ICU of TUTH between 2015 December to 2017 January. All patients, more than 16 years of age, requiring intubation and positive pressure ventilation for more than 72 hours were included. Exclusion criteria were: a) pregnancy, b) presence of bronchopleural fistula, c) immunocompromised state, d) cirrhosis of liver, e) terminal cancer, f) refractory hypoxemia and hypercarbia at presentation, g) patients extubated or deceased before 72 hours, and h) failure of a modality of ventilation. Randomization was done by lottery method. Sample size was calculated on the basis of a previous similar study,[16] to detect a difference in mean PaO_2 of 20mmHg, assuming that the common standard deviation is 40mmHg, with a 0.05 two-sided significance level ($Z\alpha$ =1.96), and a power of 90% ($Z\beta$ = 1.282). Considering 20% drop out rate, the final number of participants in each group was 101 patients.

Written informed consent was taken after obtaining ethical approval from Institutional Review Committee of Institute of Medicine. Demographic data, PaO_2, and PaO_2/FiO_2 ratio at 0, 24 and 72 hours of mechanical ventilation were recorded. $PaCO_2$ at 0, 24 and 72 hours, sedation requirement, inotrope requirement, length of ICU stay, duration of mechanical ventilation and all cause in-hospital mortality and baseline APACHE II score were also recorded. Patients were randomized into two groups: Low Tidal Volume (LTV) group and Airway Pressure Release Ventilation (APRV) group.

ORICARE™ V8800 Ventilator was used for all patients. Initial tidal volume was set at 6 ml/kg of predicted body weight while on VCV (Volume Control Ventilation) mode. Ventilator management in either group was as follows:

In APRV group, the initial high-pressure setting (P_{High}) was adjusted to equal the plateau pressure from the original VCV settings. The low-pressure setting was set at zero by convention. Time spent at P_{High} (T_{High}) was set based on spontaneous respiratory rate starting at 5 seconds (range 4 to 10 seconds). Duration of low pressure (T_{Low}) setting was adjusted, so that pressure release terminated at 25% to 75% of peak expiratory flow (range 0.2 to 1.0 seconds). FiO_2 was initially set at 100% and then gradually titrated down to 40% with the target SpO_2 of ≥92%. For hypoxic conditions (PaO_2 <60 mmHg and/or arterial oxygen saturation (SpO_2) <92%), P_{High} was increased by 2 cm of H_2O, followed by an increase in T_{High} by 0.5 seconds and then an increase in FiO_2 by 10% (Maximum limits of P_{High}, T_{High}, and FiO_2 were 35 cm of H_2O, 10 seconds and 100% respectively). If this did not correct even after maximum limits of P_{High}, T_{High}, and FiO_2, the patient was excluded from the study and managed with other modes of mechanical ventilation. If CO_2 was >50 mmHg and arterial pH <7.35, the P_{High} was increased by 2 cm of H_2O and T_{High} was increased by 1 second at a time. This was repeated every 60 – 120 minutes. If this did not correct even after three consecutive modifications, the patient was excluded from the study and managed with other modes of mechanical ventilation. Weaning was initiated when PaO_2 >70 mmHg, SpO_2 >92%, and pH <7.35. The primary method used to wean APRV was an alternate decrease in P_{High} by 2 cm of H_2O followed by an increase in T_{High} of 0.5 seconds to 1.0 seconds. This "drop and stretch" method was used to achieve a P_{High} of less than 10 cm of H_2O on 40% FiO_2, at which time patients were evaluated for extubation.

After initial ventilator setup, patients in LTV group remained on VCV mode. Initial minute ventilation was set at 100 mL/kg and the ventilator rate was determined by dividing this amount by the set tidal volume. Positive end expiratory pressure was set at 6 cm of H_2O. FiO_2 was initially set at 100% and then titrated down to less than 50% at a gradual decrement of 10% every half an hour with the aim to maintain SpO_2 ≥ 92% or PaO_2 ≥ 70 mmHg. If spontaneous respirations were >25 breaths per minute, the ventilator rate was readjusted. For hypoxic conditions, PEEP was increased in 2 cm of H_2O increments, repeated twice as necessary, followed by an increase in FiO_2 of 10%. This cycle was repeated as necessary until PaO_2 ≥70 mmHg or SpO_2 ≥92%. At maximum, PEEP will be increased up to 24 cm of H_2O and FiO_2 up to 100%. Weaning

from LTV was conducted on a time-based protocol similar to the APRV group. The set ventilator rate was weaned as long as spontaneous respirations are <30 breaths per minute. When weaned off LTV, patients were placed on CPAP and pressure support. When CPAP was reduced to less than 10 cm of H_2O and pressure support to 8 cm of H_2O, patients were evaluated for extubation.

Arterial blood gas analysis was done within half an hour of presentation to ICU (time 0), and at 24 hours and 72 hours and at other time points as necessary. PaO_2 and PaO_2/FiO_2 ratio, pH and $PaCO_2$ were recorded.

Data were entered into Microsoft Excel 2010 and then imported to and analyzed by using Statistical Package for the Social Sciences (SPSS) software version 17.0 (SPSS Ltd, Chicago, IL, USA). Independent t test was used to compare age and height of patient, baseline APACHE II score, PaO_2 at 0, 24 and 72 hours, PaO_2/FiO_2 ratio at 0, 24, and 72 hours, $PaCO_2$ at 0, 24, and 72 hours, duration of mechanical ventilation, and the duration of ICU stay. Chi-square test was used to compare gender differences, in-hospital mortality and incidence of ventilator associated pneumonia. Oxygenation and ventilation were also compared within the group at 0 hour and 72 hours to look for the effectiveness of intervention using paired t test. Mann-Whitney U test was used to analyze the use of analgesia and sedative drug doses between the groups.

RESULTS

A total of 360 patients were assessed for eligibility, of which 202 patients were enrolled in the study and included for the final analysis. Graphic outline of our study design is presented in Figure 1(Figures in brackets are the number of patients).

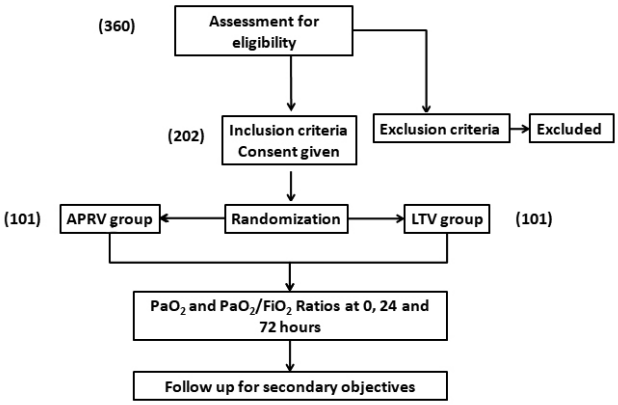

Figure 1: Graphic outline of the study design

Baseline demographic parameters were similar in both the APRV and LTV groups (Table 1). Hospital acquired pneumonia was the most common cause of acute respiratory failure requiring invasive mechanical ventilation (Table 2).

Table 1: Demographic and baseline characteristics of patients

Parameter	APRV group	LTV group	'p' value
Age (years ±SD)*	49.84 ± 18.62	52.08 ± 20.35	0.416
Gender (Female)	44.6%	41.6%	
Height (Inches ± SD)*	69.11 ± 2.17	69.32 ± 2.42	0.521
APACHE II Score	23.90 ± 4.12	24.69 ± 4.18	0.177
PaO_2 (mmHg ± SD)*	73.73 ± 22.23	75.13 ± 20.43	0.643
PaO_2/FiO_2 (mmHg ± SD)*	178.67 ± 55.51	186.09 ± 53.34	0.334

**Data are Mean ± Standard Deviation*

Table 2: Cause of Respiratory Failure at ICU Admission

Cause of Respiratory Failure	APRV [(Number of Patients (%)]	LTV [(Number of Patients (%)]	Total Number of Patients (%)
Hospital Acquired Pneumonia	49 (48.51)	37 (36.63)	86 (42.57)
Community Acquired Pneumonia	20 (19.80)	25 (24.75)	45 (22.27)
Sepsis	18 (17.82)	22 (21.78)	40 (19.80)
Trauma	2 (2)	6 (6)	8 (3.96)
Pulmonary Aspiration	6 (6)	4 (4)	10 (4.95)
Postoperative Respiratory Failure with Pneumonia	2 (2)	5 (5)	7 (3.46)
Disseminated TB	1 (1)	1 (1)	2 (0.9)
Severe Acute Pancreatitis	3 (3)	1 (1)	4 (1.9)

Oxygenation was similar and followed similar trend over time in both the groups (Table 3). Changes in oxygenation over time within the group are shown in Table 4 and 5.

Table 3: Comparison of PaO_2 and PaO_2/FiO_2 values (mmHg ± SD) at various time points

Time point	APRV group	LTV group	'p' value
PaO2 at Admission (0 hour)	73.73 ± 22.23	75.13 ± 20.43	0.643
PaO2 at 24 hours	176.21 ± 50.70	180.62 ± 53.19	0.547
PaO2 at 72 hours	208.17 ± 61.20	211.36 ± 50.89	0.688
PaO2/FiO2 at Admission (0 hour)	178.67 ± 55.51	186.09 ± 53.34	0.334
PaO2/FiO2 at 24 hours	285.87 ± 69.08	290.95 ± 63.56	0.587
PaO2/FiO2 at 72 hours	288.95 ± 71.51	283.78 ± 59.13	0.576

Table 4: Change in oxygenation at 0 hour and 72 hour in APRV group

Parameter	Mean ± SD	p value
PaO2 at 0 hour (mmHg)	73.73 ± 22.23	<0.001
PaO2 at 72 hour (mmHg)	208.17 ± 61.20	
PaO2/FiO2 at 0 hour	178.67 ± 55.51	< 0.001
PaO2/FiO2 at 72 hour	288.95 ± 71.51	

Table 5: Change in oxygenation at 0 hour and 72 hour in LTV group

Parameter	Mean ± SD	p value
PaO2 at 0 hour (mmHg)	75.13 ± 20.43	<0.001
PaO2 at 72 hour (mmHg)	211.36 ± 50.89	
PaO2/FiO2 at 0 hour	186.09 ± 53.34	< 0.001
PaO2/FiO2 at 72 hour	283.78 ± 59.13	

Mean duration of mechanical ventilation in APRV and LTV groups was 9.24 ± 4.87 days and 8.64 ± 3.75 days respectively (p=0.332). Duration of ICU stay was 11.63 ± 5.71 days and 11.07 ± 4.16 days in APRV and LTV groups respectively.

The most common complication was ventilator-associated pneumonia (VAP) with an incidence of 19.8% in APRV and 21.8% in LTV group (p=0.729). One patient in APRV and two in LTV group had pneumothorax. Two patients in APRV group and 3 patients in LTV group had unplanned extubation. All-cause mortality during hospital stay was 25.7% in APRV group whereas it was 23.8% in LTV group. ICU mortality was 25 cases (24.5%) in APRV group and 21 (20.5%) in the LTV group. (p = 0.086).

DISCUSSION

The major findings in our study are consistent improvement in oxygenation status compared to baseline values in all patients in both the groups. But there was no statistical difference in the oxygenation indices when compared between the two groups at various specified time points of 0, 24 and 72 hours.

Use of both APRV and LTV ventilation improved oxygenation at 24 and 72 hours when compared to baseline values signifying effectiveness of both the strategies to optimize oxygenation status of patients. But neither of the two strategies was found to be superior over each other in improving oxygenation measured in terms of PaO_2 and PaO_2/FiO_2 at 24 and 72 hours. Similar findings were noted in various other studies.[9,10,11,17] Improvement in oxygenation in APRV mode is probably because of favorable increase in mean airway pressures at relatively lower peak and plateau pressures compared to conventional mechanical ventilation. This increased mean airway pressure then helps better aerate recruitable alveoli and improves oxygenation[12]. On the other hand some other studies have shown largely similar oxygenation between APRV and conventional mode of mechanical ventilation.[13] Another mechanism of improvement in oxygenation in APRV mode is that it allows spontaneous breathing at both high and low pressure levels that helps improve gas exchange through the optimization of ventilation/perfusion matching in dependent lung regions.[14]

Regarding adequacy of ventilation, mean $PaCO_2$ values were slightly higher in APRV group compared to LTV group at the time of admission but values did not reach the level of statistical significance. The $PaCO_2$ values were similar at 24 hours and at 72 hours. Maxwell et al. also observed the $PaCO_2$ values for initial five days in trauma patients and found $PaCO_2$ values to be comparable.

Ventilator-Associated Pneumonia (VAP) was the major complication in both the groups. One study from India reported by Gadani et al. found the incidence of early onset VAP (within 96 hours) to be 27% and the late-onset type (>96 hours) to be 73% which is quite high as compared to our study. In other studies incidence of VAP is reported to be 9 – 27%.[15, 16] One patient in APRV group suffered pneumothorax as a complication of central venous catheterization. The other two cases of pneumothorax were in LTV group, one as a complication of central venous catheterization and the other had spontaneous pneumothorax, probably ventilator associated, secondary to high PEEP requirement. Incidence of pneumothorax is, reportedly, 14 – 87% depending on severity and duration of ARDS and mode of ventilator used.[17]

There are some limitations of this study. It was a single center study. Blinding was not feasible because of the nature of the study using two different modes of mechanical ventilation. The patient population was heterogeneous including patients with primary pulmonary disease as well as patients with pulmonary manifestations of other diseases like severe sepsis, burn, pancreatitis etc. Non-availability of esophageal manometer devices precluded measurement of transpulmonary pressures.

CONCLUSION

APRV and LTV ventilation strategies are equally effective to improve oxygenation in patients with ARF requiring endotracheal intubation and mechanical ventilation.

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JOURNAL OF NEPALESE SOCIETY OF CRITICAL CARE MEDICINE
A PEER REVIEWED, OFFICIAL JOURNAL OF NSCCM

ORIGINAL ARTICLE

Effect of intravenous administration of 20% Mannitol on optic nerve sheath diameter in patients with raised intracranial pressure

Shiva Poudel[1], M.D., Ankit Rimal[2], M.D., Ninadini Shrestha[1], M.D., Arjun Gurung[3], M.D., Anil Shrestha[1], M.D.

[1] Department of Anaesthesiology, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal;
[2] Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal;
[3] Department of Cardiothoracic and Vascular Anaesthesiology, Manmohan Cardiothoracic Vascular and Transplant Center, Maharajgunj, Kathmandu, Nepal

Corresponding author:
Dr. Shiva Poudel
M.D. Anaesthesiology
Tribhuvan University Teaching Hospital,
Maharajgunj, Kathmandu, Nepal
Email: rockaice@gmail.com

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HOW TO CITE THIS ARTICLE IN VANCOUVER STYLE?

Poudel S, Rimal A, Shrestha N, Gurung A, Shrestha A. Effect of intravenous administration of 20% Mannitol on optic nerve sheath diameter in patients with raised intracranial pressure. Journal of Nepalese Society of Critical Care Medicine. 2023 Jan;1(1):7-13

Submitted : 13 Nov 2022
Accepted : 26 Nov 2022
Published Online : 2 Dec 2022

Conflict of Interest : None
Source of Support : None

ABSTRACT

Background and aims : Mannitol is commonly used to reduce elevated intracranial pressure (ICP) in patients with traumatic brain injury, intracranial hemorrhage and acute cerebrovascular accident. Optic nerve sheath diameter (ONSD) has high sensitivity and specificity in diagnosing raised ICP. This study aims to evaluate effect of Mannitol on ONSD in patients with raised ICP.

Methods : This was a prospective cohort observational study of adult patients receiving osmotherapy for increased ICP admitted to the ICU. Baseline ONSD (T1) was recorded bilaterally followed by administration of Mannitol. ONSD was remeasured bilaterally at 30 (T2), 60 (T3) and 120 (T4) minutes after completion of administration of mannitol. Peak inspiratory pressures and PEEP were recorded for patients on mechanical ventilation.

Results : Of the 40 patients included in the study, the mean age of patients was 54.03 ±19.15 years. Among them 26 were mechanically ventilated. Compared to the baseline values of 6.1 ± 0.74 mm, the mean ONSDs at T2, T3 and T4 were significantly lower after administration of 20% Mannitol with all p values < 0.001. A statistically significant correlation between change in ONSD (ΔONSD) at each time point and the dose of Mannitol administered was observed.

Conclusion : ONSD can be used for monitoring effectiveness of osmotherapy on a point-of-care basis in patients with elevated ICP.

Keywords: *mannitol, osmotherapy, ONSD, raised ICP*

INTRODUCTION

Osmotherapy with mannitol to reduce the intracranial pressure (ICP) in patients with elevated ICP is a common practice. The effect of mannitol on ICP can be monitored by various invasive and non-invasive methods with variable sensitivity and specificity. Optic nerve sheath diameter (ONSD) has been shown to have high sensitivity and specificity in diagnosing raised ICP based on its correlation with invasively measured ICP. However, its clinical applicability to monitor changes brought about by osmotherapy remain to be studied. Our study aims to explore the utility of this noble modality to evaluate ICP changes during osmotherapy.

Raised intracranial pressure is a common complication in patients with traumatic brain injury (TBI), intracranial hemorrhage, intracranial tumors and ischemic stroke.[1] Prompt diagnosis and treatment of elevated intracranial pressure is one of the primary cornerstones in the management of these conditions. The incidence of elevated ICP is more than 50% and ranging as high as 80% in patients with TBI.[2,3] The fundamental goal of management in TBI is based on managing the ICP and maintaining an adequate CPP in the background of an impaired cerebral autoregulation in order to prevent secondary insults to the injured brain. Similarly, incidence of raised intracranial pressure in patients with intracranial hemorrhage ranges from 36% to 80%.[4] Malignant cerebral edema leading to raised intracranial pressure is a major cause of adverse outcome in patients with acute ischemic stroke with an incidence of 10-20%.[3]

The current standard of care for diagnosing raised ICP involves intracranial placement of a variety of invasive monitoring devices. These techniques have the distinct benefit of providing continuous, real-time monitoring, with some allowing therapeutic interventions as well. They, however, are generally limited to patients in a neurocritical care or intensive care units.[3,4] Disadvantages of invasive ICP monitoring include the risk of hemorrhage, infection, catheter misplacement and the requirement of trained individuals to place the device, monitor, interpret findings and provide targeted therapy.

Various non-invasive techniques have been explored to avoid inherent disadvantages of invasive procedure and improve early detection of an elevated ICP, with variable results. The opportunity to diagnose a raised ICP earlier using an appropriate non-invasive technique makes the applicability of such a method more valuable. However, despite several promising advances, no single non-invasive method of assessing ICP has been accurate enough as a quantitative measure of ICP to replace invasive monitoring.[5,6]

Recent advances in application of ultrasonography, image quality and point-of-care techniques have stimulated the use of this modality as a diagnostic and monitoring utility.[6,7] The benefit of having a portable, cost-effective, quick modality in a resource-limited environment makes the prospect of its utility more attractive. Among the sonographic techniques utilized for measurement of ICP, ONSD and Trans-cranial Doppler (TCD) have been shown to have high positive and negative predictive values.[8]

The optic nerve has a length of about 40 – 50 mm, and an average diameter of about 4 mm.[5] This nerve is a white matter tract of the central nervous system that originates from within the diencephalon. The optic nerve is surrounded by CSF within the subarachnoid space and enveloped by the nerve sheath, which is a continuation of the intracranial dura mater. The subarachnoid space surrounding the optic nerve is a heterogeneous, cul de sac, which holds about 0.1 ml of CSF.

The sheath surrounding the optic nerve is made up of three layers, which are in continuity with the leptomeninges of the brain. The two layers of the dura are attached within the optic canal, but split at the orbital end of the canal, with the outer layer forming the orbital periosteum and the inner layer forming the dural optic nerve sheath.

An increase in ICP results in an increase in CSF within the space surrounding the optic nerve leading to expansion of the nerve sheath. The region of the nerve sheath located 3 mm posterior to the lamina cribrosa of the retina is considered the most distensible and recommended as the most consistent region to acquire the ONSD measurement.[9] Changes in the ONSD can be visualized using images from ultrasound, MRI and CT scans. Several studies have demonstrated a strong association between distension of the ONSD and an increase in ICP.[10,11]

Mannitol is a naturally occurring sugar alcohol used clinically as an osmotic diuretic. Various theories and mechanisms have described the effects produced by mannitol in the CNS and other organs. According to the osmotic theory, at the higher end of clinically relevant doses, mannitol generates a substantial blood-brain osmotic gradient and exerts at least some of its ICP lowering effect by direct removal of water from the parenchyma.[12] Mannitol is believed to induce a decrease in total cerebral blood volume not only by decreasing hematocrit, but by decreasing the volume, rigidity and cohesiveness of RBC membranes and thereby decreasing mechanical resistance to passage through microvasculature.[12,13] Through its osmotic diuretic effect, it contributes to a reduction in the total circulating blood volume.[12,13]

A rebound elevation in the ICP is seen sometimes following accumulation of osmotically active particles in the brain parenchyma with prolonged use of mannitol.[12]

This study was designed to evaluate the effect of intravenous administration of 20% mannitol on the ONSD in patients with raised ICP. In order to do so, we compared the changes in the ONSD from baseline and at 30, 60 and 120 minutes. Additionally, we compared and correlated the changes in between right and left eye, in relation to the dose of mannitol and the mean arterial pressure (MAP). Also compared were the changes in ONSD in patients on mechanical ventilation against those not on mechanical ventilation. We hypothesized that serial ONSD monitoring with a cut-off value of 5.0 mm can reflect changes following IV administration of 20% mannitol in patients with raised ICP.

METHODS

Study Design and Setting

The was a prospective cohort observational study of patients receiving osmotherapy for increased ICP presenting to the multidisciplinary Intensive Care Unit (ICU) of Tribhuvan University Teaching Hospital. The study was conducted following approval by the Institutional Review Committee.

Participants

Adult patients more than 18 years of age, diagnosed with traumatic brain injury or intracranial hemorrhage or acute stroke with a mean optic nerve sheath diameter of more than 5mm and receiving osmotherapy with 20% mannitol were included in the study.

Patients with a history of ocular surgery, ocular pathology at baseline and who had undergone a decompressive cranial surgery were excluded from the study.

The IRC waived the requirement for written informed consent given the observational nature of the study. A verbal informed consent, however, was taken from the legal guardian.

Variables

Demographic parameters and diagnosis were documented. The baseline (T1) ONSD measurement of the right eye, left eye and MAP were recorded. The dose of 20% mannitol was noted. In patients on mechanical ventilation, the peak inspiratory pressure (PIP) and PEEP were documented. Thereafter, the prescribed dose of 20% mannitol was administered intravenously via a dedicated line over 20 minutes.

ONSD measurements of both eyes at 30 (T2), 60 (T3) and 120 (T4) minutes after the completion of administration of the prescribed dose of 20% mannitol were recorded along with the corresponding MAP at each examination. Each measurement of ONSD was performed by a single investigator using a 6-10 Hz linear array USG probe (SonoSite M-Turbo®) with the head of the patient elevated at 30 degrees, in supine position. A transparent dressing and adequate jelly coupling the ultrasound probe was placed over both eyes. Measures were taken to ensure hygiene and safety during all examinations.

Sample size determination

The sample size was determined based on a previous study which showed a mean difference (δ) and standard deviation of difference (σ) of ONSD at baseline and 60 minutes to be 0.24 and 0.49 respectively. In order to detect a significant difference in ONSD at T1 and T3 with a power of 80% (β=0.2[illegible]t a significance level of $p < 0.05$ ($\alpha = 0.05$), the minimal sample size required was calculated to be 35. A sample size of 40 patients was taken to account for an assumed dropout of 10%.

RESULTS

A total of 48 patients admitted to the ICU of TUTH were screened for eligibility and 40 patients were enrolled as they fulfilled the inclusion criteria. The flow of participants in the study is shown in Figure 1.

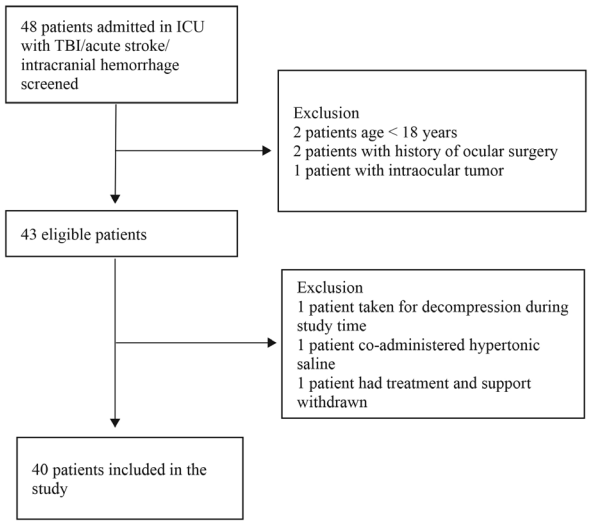

Figure 1. Flow of patients in the study

Baseline characteristics along with the dose of mannitol are described in Table 1. Table 2 shows the ONSD values and MAP values at baseline (T1), 30 (T2), 60 (T3) and 120 (T4) minutes. Compared to the baseline values of 6.1 ± 0.74 mm, the mean ONSDs at T2, T3 and T4 were significantly lower after administration of 20% mannitol with all p values < 0.001. The mean ONSD was lowest at T3, 60 minutes after administration of 20% mannitol.

Table 1. Baseline characteristics of patients, data presented as mean ± SD or number of patients.

Variables	Values
Age	54.03 ±19.15
Sex (M/F)	25 (62.5%) / 15 (37.5%)
Weight (kgs)	62.58 ±11.30
BMI (kg/m^2)	23.28 ± 3.31
Mechanically ventilated/non-ventilated	26/14
Dose of 20% mannitol (gm/kg)	0.5 ± 0.13

Table 2 : ONSD values at different time points, p value < 0.05 considered statistically significant compared to baseline. Data presented as mean ± SD

Variables	T1 (baseline)	T2 (30 minutes)	T3 (60 minutes)	T4 (120 minutes)
MAP (mmHg)	96.4±12.7	101.5 (p < 0.001)	104.3 (p <0.05)	97.7 (p > 0.05)
RT ONSD (mm)	6.13 ± 0.74	5.72 ± 0.73 (p < 0.001)	5.54 ± 0.71 (p < 0.001)	5.83 ± 0.72 (p < 0.001)
LT ONSD (mm)	6.08 ± 0.77	5.63 ± 0.75 (p < 0.001)	5.49 ± 0.74 (p < 0.001)	5.82 ± 0.77 (p < 0.001)
Mean ONSD (mm)	6.10 ± 0.74	5.68 ± 0.73 (p < 0.001)	5.51 ± 0.71 (p < 0.001)	5.82 ± 0.73 (p < 0.001)

Comparison of right ONSD and left ONSDs showed no statistically significant difference at any point of the study time as shown in Figure 2. Compared to the baseline value, mean arterial pressure was significantly raised at 30 minutes (T2) and 60 minutes (T3). Though significantly lowered compared to T3 (p < 0.05), MAP at 120 minutes (T4) was non-significantly changed while compared to baseline (T1). Analysis showed no statistically significant correlation between MAP and change in ONSD at any time point in the study.

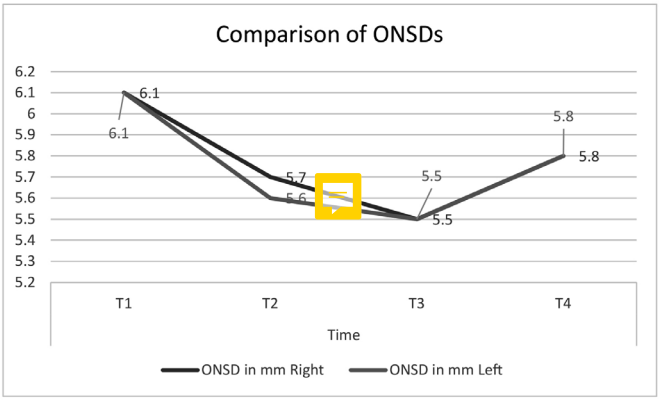

Figure 2. Comparison of ONSD at different time points

There was a statistically significant correlation between change in ONSD (ΔONSD) at each time point to the dose of mannitol administered. ΔONSD was positively correlated with dose of mannitol at 30 minutes (Pearson's correlation, r= 0.359, p < 0.05), 60 minutes (r= 0.424, p < 0.01) and 120 minutes (r= 0.582, p < 0.001) (Figure 3).

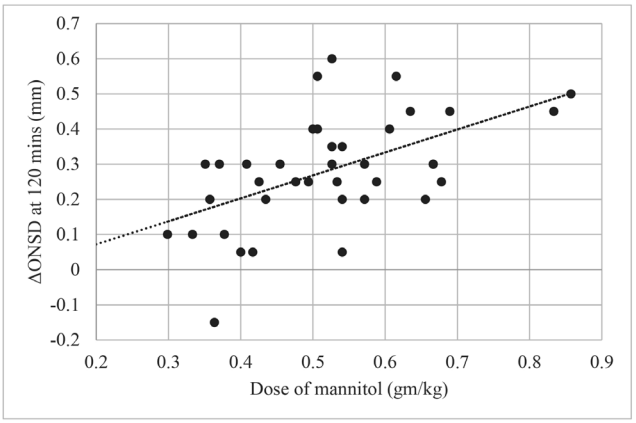

Figure 3. Correlation between dose of mannitol to ΔONSD at 120 minutes

DISCUSSION

Our study showed significant changes in ONSD values after administration of mannitol at 30, 60 and 120 minutes from baseline (6.1 ± 0.7mm) with the highest changes at 60 minutes (5.51 ± 0.7 mm, p < 0.001).

In congruity with our study, a study by Jun et al. observed similar changes in ONSD after administration of mannitol to patients undergoing robot assisted laparoscopic prostatectomy.[14] The highest changes occurred at 90 minutes, well under the time to peak action of mannitol. However, the rise in ICP among these patients was attributed to positioning and establishment of pneumo-peritoneum under anaesthesia rather than TBI, intracranial hemorrhage or acute stroke.

Similar changes were shown in the study by Launey et al. where changes in ONSD were compared to invasively measured ICP prior to and after osmotherapy with 20% mannitol in 13 cohorts similar to our study population.[10] There was a significant decrease in ONSD values after only 20 minutes following administration of 20% mannitol. On the basis of the correlation established by this study between ONSD and invasively measured ICP (R2 = 0.54, p < 0.002) and several other studies it can be assumed that the changes in ONSD in our study were reflective of the concomitant change in ICP brought about by the administration of 20% mannitol.[11,15]

Another study has also studied the changes in ONSD brought about by osmotherapy.[16] Though this study aimed at comparing change in ONSD with the use of mannitol and hypertonic saline at various time points different than those used in our studies, it found significant decrease in ONSD, reflecting a reduction in ICP.

Our study showed a statistically significant positive correlation between dose of mannitol administered and ΔONSD at 30 minutes (r = 0.359, p = 0.023) 60 minutes (r = 0.424, p = 0.006) and at 120 minutes (r = 0.582, p < 0.001).

In a subgroup analysis, variation of the dose of mannitol was studied and an analysis on change in ONSD (ΔONSD) in correlation with the dose administered was done in

two groups with a cut-off value of 0.5gm/kg. ΔONSD was significantly higher among patients in the dose > 0.5gm/kg group at 60 minutes ($p < 0.05$) and 120 minutes ($p < 0.001$). On linear regression analysis a significant positive correlation was found between change in mannitol ONSD and dose of mannitol. There are no studies directly comparing these variables. However, taking the strong correlation between ICP and ONSD into consideration, our results are similar to the results of the study by Sorani et al.[17] In their study they explored the dose-response relation in patients with TBI and found a linear relation between dose of mannitol and change in ICP indicating that an additional 7 g of mannitol (0.1 g/kg for 70-kg person) achieves an additional reduction of approximately 1.0 mmHg in ICP. Though our study did not explore such parameters, a higher degree of decrease in ONSD values were sustained for a longer period of time in patients with doses higher than 0.5 mg/kg as compared to those receiving lower doses.

A meta-analysis analyzed 18 studies which explored the correlation between the dose of mannitol and changes in ICP.[18] The aggregated data analysis showed that mannitol invariably reduced ICP, however the quantitative relationship between dose and response was inconsistent. This inconsistency was credited to the variations among protocols and patients included in those studies. Similar to the studies included in the meta-analysis, a weak linear dose-response relation was found in our study. This highlights the need for a consensus of methods and results required to determine this relationship. However, it can be concluded that sonographic measurement of ONSD is sensitive to detect the subtle changes attributed to the dose-response relationship.

Although differences were present among individual patients, our study did not find significant difference in left and right eye measurements of mean ONSD at baseline or at any point of time after administration of mannitol. Significant difference between right and left eye ONSD were noted in a study by Skoloudik et al.[19] They reported a statistically significant difference in ONSD on the side ipsilateral to the lesion among 31 patients presenting in the hyperacute phase of intracranial hemorrhage. The findings in our study can be attributed to the heterogenous pathology involved and timing of evaluation and is consistent with various other studies.[10,11,20]

Our study did not find a significant correlation between the MAP and ONSD. Correlation analysis was also performed between changes in MAP and ONSD which showed no significant statistical correlation (p value > 0.05 at every time point). Our study result is in concordance with the findings of various studies where investigators have failed to show any significant correlation between MAP (ΔMAP) and ONSD (ΔONSD) or ICP. [10,14,21]

A subgroup analysis in our study compared the changes in ONSD between mechanically ventilated patients and those not on mechanical ventilation. Comparison of means using the independent t-test showed no significant difference in ONSD among these groups. Change in ONSD in relation to PEEP/PIP was not found to be significant at any point ($p > 0.05$ at every time point).

In a study performed on 33 patients with TBI by Cooper et al., the application of a PEEP of 10 cm H2O raised ICP from a baseline of 13.2 ± 7.7 mmHg to 14.5 ± 7.5 mmHg ($p < 0.005$).[22] However, this rise in ICP was considered to be clinically non-significant. Similar result was obtained among a pediatric patient cohort with TBI in a study by Khandelwal et al.[23] Application of PEEP ranging from 0-3 cm of H2O was not associated with any rise in ICP. But when PEEP was raised from 3 to 5 cm H2O there was a statistically significant but clinically non-significant rise in ICP.

Similarly, in a study by Bala et al. which evaluated the effects of variable PEEP and EtCO2 in non-brain injured patients undergoing surgery under general anaesthesia, a statistically significant increase in ONSD following stepwise increment in PEEP from 0 cm H_2O at baseline to 8, 12 and 15 cm H_2O was found.[24]

Our study did not detect a significant difference in change in ONSD in mechanically ventilated patients with various values of PEEP when compared to non-ventilated patients. This can be attributed to use of minimal PEEP (median: 5 cm H_2O) among most patients in our study. Further studies with adequate power will be required to establish a relation between PEEP and its effects on ONSD.

There are certain limitations of our study. The decision to use mannitol and the dose were decided on the judgment of raised ICP by the treating physician rather than with the use of invasive monitoring. Another limitation is attributable to the inherent limitation of using the ONSD to detect an elevation in ICP. It is an operator dependent entity but, in our study, only one investigator was responsible for all measurements which would have circumvented this limitation to a certain degree. Measurements of serum osmolality was not done.

CONCLUSION

In patients with an acutely elevated ICP, administration of 20% mannitol caused a significant change in the sonographically measured ONSD which can be correlated with concomitant change in ICP among patients with raised ICP. ONSD can be used for monitoring such changes and effectiveness of osmotherapy on a point of care basis. However, larger studies are warranted to validate the use of ONSD as a reliable surrogate to invasively monitored ICP.

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JOURNAL OF NEPALESE SOCIETY OF CRITICAL CARE MEDICINE
A PEER REVIEWED, OFFICIAL JOURNAL OF NSCCM

REVIEW ARTICLE

Critical Care Nutrition in Nepal: Where do we stand?

Sushil Khanal, M.D., Sarobar Upadhyaya, M.D., Ashesh Neupaney, B.Sc., Subhash Prasad Acharya, M.D.

Department of Critical Care Medicine, Grande International Hospital, Kathmandu, Nepal

Corresponding author:
Dr. Sarobar Upadhyaya,
Department of Critical Care Medicine,
Grande International Hospital,
Kathmandu, Nepal
Email: usarou@gmail.com

ABSTRACT

Critical care nutrition is a vastly unexplored domain when it comes to managing critically ill patients admitted to the hospitals in Nepal. Patients who are critically ill require a holistic approach in their management and as such the nutritional part of their care cannot be overstated. The lack of regulatory bodies and practice guideline has been a long-standing problem. It is high time for nutrition to come to the forefront in a clinical scenario and play an equal part when it comes to treating critically ill patients, as they are more likely to be undernourished.

Keywords: *critical care nutrition, guidelines, Nepal.*

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HOW TO CITE THIS ARTICLE IN VANCOUVER STYLE?

Khanal S, Upadhyaya S, Neupaney A, Acharya SP. Critical Care Nutrition in Nepal: Where do we stand? Journal of Nepalese Society of Critical Care Medicine. 2023 Jan;1(1):13-16

Submitted	: 20 Nov 2022
Accepted	: 27 Nov 2022
Published Online	: 2 Dec 2022
Conflict of Interest	: None
Source of Support	: None

BACKGROUND

The speciality of critical care medicine began to develop in the late 1950s with development of first ICU. Since then, major advances have been made in terms of understanding of disease process, technology and development of human resources. Patients in need of critical care require multidisciplinary approach. Management of the dietary and nutritional needs of these patients is crucial, and the evidence-based input of specialists in nutrition and dietetics is central to their care. Optimal nutrition therapy is essential to improve the long-term outcome and to reduce the likelihood of getting complications during and even after ICU stay.[1]

Malnutrition is very common in acutely ill patients, occurring in 30 to 50% of hospitalized patients.[2] Malnutrition in hospitalized patients also increases hospital costs[3] and is associated with increased long-term mortality. In the last few years, there has been notable development in critical care nutrition in terms of guidelines and technology around the world. In this review, we highlight the current scenario of critical care nutrition in Nepal.

Where we stand?

Before talking about nutrition in critical care, let us look into the history of critical care facility of Nepal, which in itself is quite short. The very first ICU was a five bedded medical ICU established at Bir hospital in 1973. That is nearly a half decade later than the first ICU of the world was started. The numbers of intensive care beds and advanced respiratory support (ventilators) in Nepal are limited to 1395 and 480 respectively.[4] ICUs of Nepal have fewer resources and manpower for the diagnosis and treatment of critical illness than ICUs in high income countries.[5] Furthermore, there are no governing bodies that monitor the services, quality and facilities required to run an ICU.[6] However, we might have come long way since 1973, but still as for critical care nutrition in Nepal, it remains in low priority of clinicians.

Malnutrition within the critical care setting is a global issue where prevalence in developing and developed countries can be as high as 78.1% and 50.8%, respectively.[7] In the study conducted in India, 39.6% of patients were found to be malnourished in ICU.[8] However, during the review of articles for this paper, no such studies were found to be conducted in Nepal. The report of Department of Health Services (DoHS) regarding the nutrition are only limited to prevalence of malnutrition on under-five children, pregnant women and adolescent girls. In contrast, no data is available about the malnutrition rates in hospitalized patients (of any settings). In addition to that, the programs related to nutrition are found to be implemented in community settings only. Till date, adequate focus has not been made by governing bodies in the sector of critical care nutrition. Nutritional problems have only considered as public health problems but not clinical problems.

Critical care medicine is a super speciality service which is provided by an inter-professional team of clinicians.[9] In such type of interdisciplinary team, intensivists along with other types of attending physicians collaborate with and share their inter-professional expertise of bedside nurses, respiratory therapists, clinical pharmacists, dieticians, and clinical psychologists.[10] Dietetic professionals are placed to provide best advice to the interdisciplinary team on the optimal way to manage the nutritional needs of patients who are critically ill.[11] In relation to this, it is very unfortunate to report that, there are no dedicated and specialized critical care dieticians till date in Nepal. Nevertheless, there are few dieticians who look after diet and nutrition of the patient in critical care settings in some of the tertiary level hospitals.

Nepalese Society of Critical Care Medicine (NSCCM), an association of critical care specialist formed on 2010 A.D is one of the pioneering organizations that have been working on the development of critical care medicine in Nepal. However, it seems that there are only critical care specialists as members (medical doctors) in this society and no paramedical members such as clinical pharmacist, physiotherapist and dieticians, despite the fact that critical care is a multidisciplinary and integrated approach.

There is non-uniformity of nutritional practice and protocol in ICUs of Nepal. This could have led to under-nutrition of patients, thereby leading to higher morbidity /mortality and prolonged hospital stay in our patient's population. Among countries of south-east Asia, only Sri Lanka, India and Pakistan have published their own nutrition guidelines for ICU.[12] The guideline that are mostly referenced as a critical care nutrition guideline in ICU's of Nepal are those developed by American Society of Parenteral and Enteral Nutrition (ASPEN) and European Society of Clinical Nutrition and Metabolism (ESPEN). However, the guidelines of those societies may not be applicable in every context to Nepalese population. To address this issue, NSCCM along with Nepal Dietetic Association (NDA) and Critical Care Nurses Association of Nepal (CCNAN) have started drafting for nutrition guideline for ICU practice in Nepal. Nepal Critical Care Development Foundation (NCCDF), NSCCM has also conducted various workshops and short training courses in partnership with CCNAN and NDA. Furthermore the NSCCM has published its working guidelines in critical care nutrition, which can be accessed via the society website. This must be considered a significant step in the right direction, but still much remains to be done.

Where do we stand internationally?

The role of clinical nutritionist or dietician is one of the important aspects of improved outcomes in critically ill patients. The dieticians working in critical care need to have clinical privileges such as automatic referral, ability to order oral, enteral and parenteral nutrition and ordering of relevant laboratory tests. Despite the above fact, the dieticians are not still considered as part of multidisciplinary team in the majority of ICUs. Doctors working in ICU are still making the prescriptions for the nutritional requirements and diet of the patients. From 2017, in the UK, Health and Care Professions

Council (HCPC) - registered advanced dieticians can now undertake non-medical supplementary prescribing training to allow them to prescribe interventions as parenteral nutrition (PN), vitamin and mineral supplementation and pancreatic enzyme therapy rather than relying on junior doctors to sign off prescriptions for patients that they have not nutritionally assessed.[13] In context to mentioned situations, limited dietician in Nepal working in ICU have no such privilege. There needs to be a strong mutual understanding between ICU consultants and dieticians while planning for nutrition care process of ICU patients.

Status of current academic nutrition courses and opportunities in Nepal:

Educational programs and formal trainings about the nutrition among the ICU nurses and dieticians have significantly updated the quality of critical care services. Inadequate knowledge about critical care nutrition can lead to negative outcome such as increased morbidity.[14] To overcome this problem, comprehensive educational program regarding the critical care nutrition needs to be incorporated in the curricular activities of different levels of educational activities of nutrition. To our knowledge, the syllabus of nutrition, that are being run by different institutes in Nepal have not mentioned about the critical care nutrition. The Bachelors and Masters in Science in Nutrition and Dietics offered by Tribhuvan University and others since 2006 has started to provide the country with much needed professionals with a strong background in science. Where the stage was once filled with professionals without much academic training in the sciences, these University courses have paved way for a new batch of dieticians and nutritionists to flourish.

In Nepal, a number of dieticians are being graduated every year but there are no vacancies for permanent positions that have been announced till date by Public Service Commission (PSC), which is involved in selecting meritorious candidates required by government of Nepal for various vacant posts of the civil service. This is creating discouragement to students and professionals who have studied the course of nutrition in their graduate and post graduate level and for those who are seeking their career in the same field. Those professionals who have completed their academic studies, are generally working as contracted temporary staff.

Hospitals, being a place of care and treatment, a clinically practicing professional needs accreditation or should be registered in their respective council. In United Kingdom, for instance, to be qualified as a dietician, dietetics programme approved by Health and Care Profession Council (HCPC) needs to be undertaken.[13] In our context, none of the dieticians are registered under health councils of Nepal. As Nepal Health Professional council gives accreditation to other paramedical professionals such as pharmacist, physiotherapist, lab technologist etc., it has not yet started giving accreditation to dieticians.

CONCLUSION:

To summarize, although ICU services and critical care medicine in Nepal has developed to a considerable stage in the last few decades, critical care nutrition also needs to be considered as an integral part of this area of medicine. Stakeholders should envision to incorporate nutrition as one of the important factors in management of critically ill patients. The responsible health council should not delay to recognize clinical nutritionist/dieticians and should provide them with the council accreditation or registration. In addition, the government needs to appoint council registered clinical nutritionist/dieticians in every tertiary level hospital, for optimal management of nutritional needs of critically ill patients.

The role of dieticians in nutritional management of critically ill patients need to be well appreciated. They need to be commissioned by PSC as permanent staffs in government hospitals, should be registered under respective health council and get involved during multidisciplinary management of patients in ICU. Critical care nutrition in Nepal is an area with in critical care medicine, that is yet to be explored and that needs to get nurtured.

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JOURNAL OF NEPALESE SOCIETY OF CRITICAL CARE MEDICINE
A PEER REVIEWED, OFFICIAL JOURNAL OF NSCCM

REVIEW ARTICLE

Red cell transfusion in critical care: Could less be more?

Bipin Karki, M.D.[1], Shirish Shakti Maskay, M.D.[2], Ashad Shaheed Mohammad, M.D.[2], Aryan Neupane, M.B.B.S.[1]

[1] Department of Critical Care Medicine, Maharajgunj Medical Campus, Institute of Medicine, Tribhuvan University, Maharajgunj, Kathmandu, Nepal;
[2] Indira Gandhi Memorial Hospital, Male, Maldives.

Corresponding author:
Dr. Bipin Karki, MD
Department of Critical Care Medicine
Maharajgunj Medical Campus
Institute of Medicine, Tribhuvan University
Maharajgunj, Kathmandu, Nepal
Phone: +977 9841701269
Email: karki_bipin@yahoo.com
ORCID ID: 0000-0001-6218-9716

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HOW TO CITE THIS ARTICLE IN VANCOUVER STYLE?

Karki B, Maskay SS, Mohammad AS, Neupane A. Red cell transfusion in critical care: Could less be more? Journal of Nepalese Society of Critical Care Medicine. 2023 Jan;1(1):17-22

Submitted : 20 Nov 2022
Accepted : 27 Nov 2022
Published Online : 2 Dec 2022

Conflict of Interest : None
Source of Support : None

ABSTRACT

Blood transfusion has a very important place in ancient medicine where it is associated with vitality. In the era of modern medicine, it still holds an important place. Critical events in the history led to the development of the physiological knowledge of blood flow and pathological processes associated with anemia. These still have a strong foothold in the practice of transfusion medicine which until very recently led physicians to liberally transfuse red blood cells to patients. However, the past few decades have revealed the darker side associated with transfusion of red blood cells. Recent evidences strongly suggest that the arbitrary transfusion triggers that had been historically set might have been too high, possibly causing unnecessary harm. Here, in this narrative review, the authors have tried to explore the evidences favoring lower transfusion threshold and without added adverse events thus supporting the notion – less is more.

Keywords: *critical care, red blood cells, transfusion.*

INTRODUCTION

Blood has been referred to as the "river of life". Almost all cultures and religions have a special place when it comes to blood. Be it regarding the purity of blood which leads to blood being rejected by Jehovah's witnesses once it gets out of the body, it's vitality which led the Roman emperors to bathe in it to increase the vitality or the blood-letting done in various cultures to release the impurities.[1]

The first documented transfusion of blood to a human was done by Blundell in 1818 when a female with post-partum hemorrhage was salvaged by transfusing blood from her husband. But when a particular patient succumbed, although later found to be murdered by his wife by poisoning him with arsenic, led him to stop doing experiments with blood transfusions altogether.[2] However, this was the first time when both the importance and the adverse effects of blood transfusion was noted.

Further works by various authors have allowed for safer transfusion practices including the works of Landsteiner who discovered the major RBC antigens and Lewisohn which led to the possibility of storage of blood for days. World War I saw the development of "blood depot" while World War II was a major milestone in the history of development of blood transfusion when the program "Plasma for Britain" was started by the US government for its troops in the British Isles which no doubt had led onto saving thousands of lives. The value of blood transfusion was ever so increasing.[2] But, a major spectrum of adverse effects of blood was seen with the discovery of transfusion related infections especially with the HIV epidemic. Many other infectious complications were being reported and various guidelines were being formulated to screen for increasing number of diseases including Creutzfeldt-Jakob Disease, hepatitis B and C, HTLV infection, syphilis and so on.[3] Various non-infectious complications were also being reported and newer terms were also being coined which included Transfusion Associated Circulatory Overload (TACO), Transfusion Related Acute Lung Injury (TRALI) and Transfusion Related Immunomodulation (TRIM).[4,5] The notion of "less is more" was being revived.

The optimal transfusion trigger for red blood cell

Oxygen delivery to the tissue by blood is calculated as

$$DO_2 = CO \times CaO_2$$

(where CaO_2= Hb X SaO_2 X 1.34 ml).

Where DO_2 is the total oxygen delivery by the heart to the tissues; CO is the cardiac output; CaO_2 is the arterial oxygen content; SaO_2 is the arterial oxygen saturation and 1.34 is the amount(ml) of oxygen carried by a gram of hemoglobin molecules.[6,7]

It is clear here that hemoglobin is an important factor determining the oxygen delivery to the tissues. Increasing the hemoglobin content thus increases the oxygen delivery to the tissue. Different organs have different extraction ratios (EO_2) for oxygen which ultimately in conjunction with the degree of anemia culminate to the final effect in the tissue/organ system.

$$EO_2 = (SaO_2 - SvO_2)/ SaO_2,$$

where SvO^2 is the venous oxygen saturation.

In cases of decreased oxygen delivery, oxygen extraction increases and thus the SvO_2 decreases albeit differently across different tissue/organ systems.[8] A final marker of this is also seen as a decrease in the central venous oxygen saturation ($ScvO_2$). If the maximum extraction of oxygen along with the increase in CO associated with anemia is not able to meet the oxygen demand, tissue hypoxia ensues.[9] Red blood cell transfusion is aimed thus at increasing the oxygen content, delivery and thus improve the tissue oxygenation.

Table 1: Possible triggers for transfusion of red cells

SN	Triggers	Comments
1.	Generalised oxygenation impairment triggers	
	a. Hemoglobin/ hematocrit	a. Most commonly used transfusion trigger.
	b. SvO_2 and $ScvO_2$	b. Denotes venous and central venous oxygen saturation which reflects increased oxygen extraction and decreased delivery
	c. Serum lactate	c. Denotes the product of anaerobic metabolism suggesting decreased oxygen delivery
2.	Myocardial oxygenation impairment triggers	
	a. SBP X HR (Target <1200)	a. Higher product reflects increasing myocardial oxygen extraction
	b. ECG changes	b. Denotes myocardial oxygen extraction and delivery
3.	Cerebral oxygenation impairment triggers	
	a. Digit symbol subtraction test	a. Delayed memory
	b. P300	b. Reaction time
	c. NIRS	c. Measures transcranial oxygen saturation

However, though adequate delivery of oxygen is no doubt very important for maintaining the physiological oxygen demands of tissues, the arterial content and delivery are not linearly related with the uptake at all tissue levels. Various physiological and microcirculatory changes occur which lead to redistribution of blood from less to more vital organs including the heart, brain and kidneys.[6,8] Anemia is also associated with stress responses and hemodilution which cause increased cardiac output further offsetting the linear relationship between hemoglobin concentration and tissue oxygenation making hemoglobin based transfusion trigger too empiric rendering the classical rule of 10/30 (hemoglobin of 10 and hematocrit of 30%) inaccurate.[10] Based on the above pathophysiological concepts, various other physiological transfusion triggers have been put forward (Table 1). Many of these transfusion triggers are however yet to find their place in clinical practice. Furthermore, optimal triggers may be different for individual patient groups.

Critically ill patients

As much as 50% of critically ill patients have hemoglobin level in the anemic range if defined as per the World Health Organization.[11,12] Anemia in the ICU can be present pre-ICU admission.[13] A drastic drop even in non-bleeding patients is seen in the first week more so within the first three days.[14] This can be attributed to a majority of cases which can be grouped as being either related to decrease production or increased losses (Table 2). Decreased production has been linked to the infectious and inflammatory processes which produce a state of relative iron deficiency and cause a blunted marrow response to erythropoietin.[13] In addition, the iatrogenic blood loss has a significant role positively correlating with the sickness, with more iatrogenic losses in sicker patients.[15] This is probably related to the fact that sicker patients have a far higher number of blood samplings and vascular related procedures like central venous cannulations and renal replacement therapies.[14] These were reflected in the findings by a large observational study across the United States which showed that almost half of the patients admitted to the ICU were transfused with at least one unit of red cell product during their stay. Another important finding noted in this study was that the number of red cell units transfused was an independent risk factor for a poorer clinical outcome.[16] The landmark study by Rivers et al., targeted a higher CVP and hematocrit among others.[17] Both have a physiological background on improving the tissue delivery of oxygenated blood to counteract the effects of tissue hypoperfusion brought about by septic shock. In contrast to the proposed beneficial effects, other studies were finding higher risks of transfusion which led to various other studies being designed and conducted to find a lower transfusion trigger to minimize the adverse events. Two major trials, TRISS and TRICC both found that a restrictive strategy was non-inferior to a liberal strategy of transfusion in terms of mortality or the length of hospital stay but resulted in far lesser transfusions.[18,19] In addition, TRICC had found a significant difference (13% vs 21%) in the incidence of major cardiac events and even found a mortality benefit by transfusing less in a subgroup of lesser sick patients.[18] The TRIPICU trial on pediatric critically ill patients also came to a similar conclusion of a hemoglobin trigger of 7 g/dL, reducing transfusion requirements without any increase in adverse events.[20] Even lower hemoglobin levels could well be tolerated by these patient population so much so that red cell transfusion guidelines for pediatric critically ill patients recommend a transfusion trigger of <5g/dL.[21] A recent Cochrane review has found the restrictive strategy of transfusion comparable with liberal transfusion strategy.[22]

Table 2: Causes of anemia in critically ill patients

1. Decrease production
a. Blunted erythropoietin response
b. Lack of substrates (Iron, Vitamin B12, Folate)
c. Presence of renal failure
2. Increased losses
a. Disease related
i. Traumatic blood loss
ii. Coagulopathy
iii. Haemolysis
iv. Gastrointestinal losses
b. Secondary- iatrogenic
i. Sampling¶
ii. Others- vascular cunnulations, RRT, surgeries
¶May account for upto 40ml/day and one unit/week of blood loss.

Patients undergoing surgeries

A very famous publication in JAMA was a case series of 542 consecutive patients in 20 years who underwent cardiovascular surgery without any transfusion. This case series included Jehovah's witnesses with age of the patients being between one day to 89 years. The reported mortality in this series was 9.4%. A thing to be noted here is that this was published in the year 1977 before many medical advances were yet to be made. Nevertheless, anemia was attributed as a cause of death in only 12 patients, remaining being secondary to surgical complications.[23]

With an increase in the life expectancy and improved health care systems all over, increasing number of surgical procedures are being performed globally, which can be expected to increase further. In addition, the age and cardiovascular comorbidities of the patients undergoing surgery are also expected to increase both of which can lead to bleeding and transfusion peri-operatively especially in major orthopedics and cardiovascular surgeries. The changing physiology of an aged morbid patient supports the notion that anemia should be aggressively treated especially during an acute loss as in the perioperative period. The FOCUS study which enrolled

2016 patients with documented coronary artery disease undergoing hip surgeries of an average age of >81 years compared a restrictive vs liberal transfusion strategy. They found no difference whatsoever between the two cohorts receiving transfusion at 8 or 10g/dL in terms of mortality, length of stay or functional outcome.[18]

Surgery is one of the most important situations which accounts for upto 70% of all transfusions.[24,25] Yet contradicting reports about the actual clinical role and possible harm has led transfusion to undergo scrutiny over the past few decades. The concept of "Patient Blood Management" has been coined and interventions to decrease peri-operative transfusion have been devised.[26] Preoperative use of erythropoietin, autologous transfusion, use of tranexamic acid and allowable hemodilution, all have found a role in the perioperative blood management.[27–30] The aim here is to manage the patient and not the blood product since even a single unit of red blood cell transfusion has been shown to be associated with harms.[31,32]

Patients with myocardial ischemia

Myocardial ischemia is related to supply and demand of oxygen in the cardiac tissue. Electrocardiographic changes with induced anemia have been demonstrated in numerous animal and healthy volunteer studies.[33] So the generally accepted idea is to transfuse at a higher hemoglobin level as compared to other patients not having an ischemic event and so is the clinical practice. A large study including almost 79,000 patients had found that anemia was associated with an increase in 30 day mortality which however was severely biased. This study was a retrospective record based observational study and could only correlate anemia with increased mortality. This study was not designed to study the effects of transfusion.[34] The recent REALITY trial shows improved outcomes with transfusion at 8 gm/dL when compared with 10g/dL in patients with ongoing myocardial ischemia.[35] Though, the restrictive threshold in this study is still higher than that in non-cardiac patients, this again should make us ponder if a lower than the generally accepted threshold for transfusion should be sought for.

Acutely bleeding patients

Hemorrhagic shock is the most important cause of shock in trauma patients. Six people out of 10 die within three hours because of hemorrhage.[36] Nowhere else is the role of blood more important than an acutely bleeding patient. But the harms have equally been documented leading to the recommended target of 7-9 g/dL in even an acutely bleeding trauma patient. Similar is the finding in patients with an upper gastrointestinal bleed where too bleeding is a common cause of death in patients with chronic liver disease. More harm of transfusion has been seen in less sicker patients with Child Pugh class A and B.[37]

Neurological patients

Cerebral blood flow is autoregulated by various mechanisms. Anemia increases carotid output by activation of carotid and aortic chemoreceptors by increasing both the heart rate and stroke volume. In the cerebral microcirculation, release of nitric oxide ensues which causes vasodilatation to improve the cerebral blood flow. As discussed earlier, oxygen extraction also increases which prevents the brain cells from undergoing hypoxic injury. Brain pathology disrupt these compensatory mechanisms which make the brain suffer secondary insult if oxygen delivery is compromised.[38] Nevertheless, despite the existence of physiological basis for benefit, definite advantage has been seen only in a few reports while many other studies report harm including an increased risk of mortality.[39,40]

CONCLUSION

With the evolution of the evidence based medicine, harms associated with red blood transfusion are being discovered. Majority of recent evidences point towards limiting the use of blood to the bare minimum. An exact transfusion trigger in different clinical scenarios is yet to be determined. The most rudiment but time tested trigger, hemoglobin, is on the test at the moment. Individual patient groups and furthermore individual patients may have different factors at play which may be the cause for inability to set a specific transfusion trigger. Precision medicine may be the answer for the individualized transfusion trigger. Developments of an ideal oxygen carrier can be an alternative to transfusion and thus to prevent adverse effects of red cell transfusion. Till then, as has been proven in many fields of medical sciences, in transfusion medicine too, less could be more.

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JOURNAL OF NEPALESE SOCIETY OF CRITICAL CARE MEDICINE
A PEER REVIEWED, OFFICIAL JOURNAL OF NSCCM

CASE REPORT

Sildenafil induced seizures in a patient treated for pulmonary hypertension: A case report.

Sunti Barahi[1], M.D., Hem Raj Paneru[2,3], M.D., D.M.

[1] Fellow, St. Michael's Hospital, Toronto, Canada
[2] Department of Critical Care Medicine, Maharajgunj Medical Campus, Kathmandu, Nepal
[3] Department of Pulmonary and Critical Care, HAMS Hospital, Mandikatar, Kathmandu, Nepal

Author(s) affiliation:

Corresponding author:
Dr. Sunti Barahi
MBBS, MD
Fellow, St. Michael's Hospital, Toronto, Canada.
Email: sunti.barahi@gmail.com
Phone: 1-437-240-6448

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HOW TO CITE THIS ARTICLE IN VANCOUVER STYLE?

Barahi S, Paneru HR. Sildenafil induced seizures in a patient treated for pulmonary hypertension: A case report. Journal of Nepalese Society of Critical Care Medicine. 2023 Jan;1(1):23-25

Submitted : 20 Nov 2022
Accepted : 27 Nov 2022
Published Online : 2 Dec 2022

Conflict of Interest : None
Source of Support : None

ABSTRACT

Sildenafil is one of the common drugs used to treat pulmonary hypertension. We report a rare case of a life-threatening adverse effect of Sildenafil. The patient was admitted to our intensive care unit for the management of urosepsis with obesity hypoventilation syndrome with pulmonary hypertension. After administration of the first dosage of Sildenafil, the patient developed generalized tonic-clonic seizure. She had no previous history of seizure disorder. She was investigated for the possible cause of seizure, but none were conclusive. Sildenafil was discontinued and she remained seizure free after discontinuation of it. Sildenafil can increase the effects mediated by nitric oxide and can thus affect the seizure threshold. Though rare, seizure as an adverse effect of Sildenafil should be considered before initiating this drug.

Keywords: *generalized tonic-clonic seizures, pulmonary hypertension, Sildenafil.*

INTRODUCTION

Pulmonary Hypertension (PH) is classified into five main categories, one of which is a sequelae of sleep disordered breathing.[1] Hypoxia induced pulmonary vasoconstriction is reversible when acute whereas chronic hypoxia cause structural remodeling, proliferation and migration of vascular smooth muscle and an increase in deposition of vascular matrix.[2]

The availability of drugs to treat PH has resulted in improvement in quality of life and mortality. Amongst the different Food and Drug Administration (FDA) approved drugs, Sildenafil is the most widely used agent in our part of the world. Although extremely rare, we report a life-threatening adverse effect of Sildenafil in a patient treated for severe PH.

CASE REPORT

A 49-year-old lady with BMI of 37.10 (weight 88 kilograms, height 1.54 meters) was brought to our intensive care unit with complaints of burning micturition, fever and chills. She was on inotropic support with noradrenaline and vasopressin. She was managed in the line of urosepsis and pyelonephritis. The patient had a history of hypertension and episodic shortness of breath for the past 10 years and was being treated with antihypertensives, inhalers and domiciliary oxygen. In addition, she had symptoms of sleep apnea, suggested by snoring during the sleep followed by frequent awakenings and associated with drop in SpO_2.

During the treatment, her symptoms of urinary tract infection subsided, but she still had high oxygen requirements. Initially, oxygenation and ventilation were maintained with BiPAP and later continued with High Flow Nasal Cannula. Vasopressor support was gradually tapered and then stopped. High Resolution Computed Tomography of chest showed bilateral calcified nodules with mild ground glass appearance and some emphysematous changes. Her blood gas panels slowly corrected and she was shifted to a high care unit. An echocardiography was done, which showed mild concentric left ventricular hypertrophy, minimal pericardial effusion and grade I left ventricular diastolic dysfunction with severe pulmonary hypertension (pulmonary artery systolic pressure of 121 mm of Hg), so she was started on Sildenafil 50 mg once daily, considering PH being contributory cause for her high oxygen demand. She was not hypercapnic. Patient was improving and shifted to the ward.

On the next day in ward (also the next day of initiation of Sildenafil), she had the first episode of generalized tonic-clonic seizure (GTCS). Immediate management was done with injection midazolam and the patient was transferred to the ICU. After a few hours, the patient developed another episode of tonic-clonic seizure lasting 15-20 seconds. She was started on Levetiracetam. All possible causes of seizures were explored, including dyselectrolytemia, dysglycemia, metabolic derangements, organic brain lesion, etc., all of which were within normal range. There were no signs and symptoms of meningitis. Sildenafil was suspected as a possible offending agent and was stopped. The patient did not have any seizures then after. Levetiracetam was stopped after five days and she has been seizure-free for the subsequent 9 months. Neurology opinion was also sought for evaluation of possible cause. After excluding all the causes and seizure cessation after stopping Sildenafil, it was concluded that the seizures were drug induced.

DISCUSSION

PH is defined as mean pulmonary artery pressure>25 mmHg at rest or >30 mmHg with exercise. Patients present with symptoms of breathlessness, weakness, fatigue, chest pain or syncope. The most common cause of death in these patients is due to decompensated right heart failure. The propensity to diagnose patients with PH is frequent, as it is often associated with common disorders like asthma or chronic obstructive pulmonary disease. Although only a screening test, with the advent of wide availability and frequency of performing echocardiography, more patients have been diagnosed and managed early, with significant improvement in quality of life and longevity.[3]

PH was previously classified as primary or secondary, but with increased understanding about the disease pathophysiology, now it has been classified according to similarities in pathophysiologic mechanisms and clinical presentation. The fifth world symposium on PH classified it into five categories: Pulmonary artery hypertension, PH owing to left heart disease, PH owing to lung disease, chronic thromboembolic pulmonary hypertension and PH with unclear multifactorial mechanisms. The symptoms of PH are non-specific and overlap or co-exist considerably with many common conditions, including asthma, other lung diseases and cardiac disease.

Although PH associated with sleep disorder is known to be of milder form, severe PH in this patient might be due to sleep related cause and underlying lung pathology. Several pharmacologic treatments for PH has been approved including direct acting drugs (Hydralazine, Nitroglycerin), α-adrenoceptor antagonists (Tolazoline, Phentolamine), β-adrenoceptor agonists (Isoproterenol), calcium channel blocker (Nifedipine, Diltiazem), prostaglandins (PGE1, Prostacyclin), adenosine, endothelin receptor antagonists, indirect acting vasodilators (Acetylcholine) and phosphodiesterase 5 (PDE5) inhibitors (Sildenafil and Tadalafil). Among these drugs, PDE5 inhibitor Sildenafil is commonly used in our part of the world. By inhibiting PDE5 enzyme, this drug inhibits cyclic GMP metabolism, leading to prolonged vasodilatory effect of nitric oxide, especially within the pulmonary arterial bed where high concentrations of cGMP are found.

The onset time of Sildenafil is 15 minutes and peaks at 2 hours with a half-life of 4 hours. The most commonly reported adverse events of Sildenafil are headache (16%), flushing (10%) and dizziness (2%). Incidence of severe adverse events like life-threatening hypotension, orthostatic hypotension and syncope is below 2%.[4] Seizure has recently been ascribed to as one of the rarest yet serious adverse events of Sildenafil. Various case reports have been published where patients, without any prior seizure disorder, have had an episode of GTCS after a single dose of the drug. In one of the case reports, all investigations were normal and Sildenafil was stopped. On resuming Sildenafil after three months, patient developed another episode of GTCS.[5]

The cause of seizure in our patient was unlikely to be a manifestation of any other disease, as a complete evaluation was done to rule them out. The GTCS occurred immediately (within 24 hours) following intake of the drug and the patient never had another episode of GTCS even after antiepileptic drugs were put on hold once Sildenafil was stopped.

Although the exact mechanism of seizure caused by PDE5 inhibitors is unknown, recent studies have shown that PDE5 inhibitors may increase the effects mediated by nitric oxide. Nitric oxide and cGMP may have effects on the seizure threshold.[6] Sildenafil has also been shown to interact with both exogenously and endogenously released nitric oxide.[7]

To conclude, though uncommon, seizure need to be considered as a possible side effect of Sildenafil in clinical practice.

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JOURNAL OF NEPALESE SOCIETY OF CRITICAL CARE MEDICINE
A PEER REVIEWED, OFFICIAL JOURNAL OF NSCCM

CLINICAL IMAGE

Double doughnut sign in dengue encephalitis

Sachit Sharma, M.D., D.M., Gentle Sunder Shrestha, M.D.

Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal

Author(s) affiliation:

Corresponding author:
Dr. Sachit Sharma
MD, DM in Critical Care Medicine
Clinical Lecturer, Department of Critical Care Medicine
Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal
Consultant in Critical Care Medicine
Upendra Devkota Memorial National Institute of Neurological and Allied sciences, Bansbari, Kathmandu, Nepal
Email: sachitrupakhetee@gmail.com
Phone: 977-9852049450

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HOW TO CITE THIS ARTICLE IN VANCOUVER STYLE?

Sharma S, Shrestha GS. Double doughnut sign in dengue encephalitis. Journal of Nepalese Society of Critical Care Medicine. 2023 Jan;1(1):26-27

Submitted	: 21 Nov 2022
Accepted	: 22 Nov 2022
Published Online	: 2 Dec 2022
Conflict of Interest	: None
Source of Support	: None

Key words: *dengue encephalitis, double doughnut sign.*

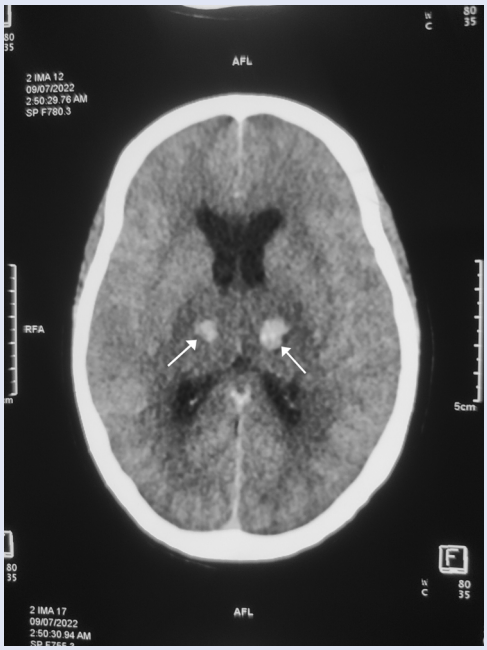

Figure A: Arrowheads indicating hyperdense lesion surrounded by hypodensity involving bilateral thalamus and basal ganglia regions (Double Doughnut sign) suggestive of Dengue encephalitis.

A 38 year old female with no known co-morbidities presented with the complaints of fever, abdominal pain and altered consciousness of 4 days duration. At presentation, her GCS was 7/15; eye opening to pain, flexor response to pain and incomprehensible sounds. Her vitals were stable with a SpO_2 of 92% with O_2 via nasal cannula at 2 L/min, blood pressure 110/70 mmHg, heart rate 100/min and temperature 99 degree Fahrenheit. Petechial rashes were present over multiple areas of the body. In the background of a low GCS score, the patient was intubated. Plain CT scan of head (Fig A) revealed hyperdense lesion surrounded by hypodensity involving bilateral thalamus and basal ganglia regions. Patient had leukopenia and thrombocytopenia (3,800/cu mm and 40,000/cu mm respectively) and elevated liver enzymes (ALT/AST- 120/86 IU/L). The patient tested positive for Dengue IgM antibody, Dengue IgG antibody and NS1 antigen. Evaluation for other tropical infections including Scrub typhus, Leptospirosis, Malaria, Brucellosis and Japanese encephalitis were negative. Lumbar puncture was performed which revealed total white cell

counts of 10 with 20% neutrophils and 80% lymphocytes, sugar of 50 mg/dl and protein of 90 mg/dl. A diagnosis of dengue encephalitis was made and supportive treatment was initiated. Viral isolation in CSF could not be performed because of unavailability of the test. The patient gradually deteriorated over the next three days and finally succumbed on the fourth day of ICU admission because of refractory septic shock.

Neurologic complications of dengue fever include encephalopathy, encephalitis, Guillain-Barre syndrome, transverse myelitis, and neuromuscular disorders.[1] In our patient, acute febrile illness with encephalopathy, positive dengue IgM serology, suggestive lumbar puncture findings and exclusion of differentials satisfied the diagnostic criteria of dengue encephalitis.[2] Various pathogenic mechanisms have been implicated for these complications which include direct viral invasion, systemic inflammatory response, and immune-mediated mechanisms. Dengue virus inflicts direct neuronal injury leading to cerebral edema and hemorrhage secondary to vascular leak, which usually involves bilateral basal ganglia and thalamus complex and manifests neuro-radiologically as "double-doughnut" sign.[3] This imaging finding is unique to dengue encephalitis and is rarely seen in other central nervous system infections.

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Journal of Nepalese Society of Critical Care Medicine

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