Original Article

A study to evaluate effect of PEEP and end-tidal carbon dioxide on optic nerve sheath diameter

Address for correspondence:
Dr. Jyoti Sharma,
H. No. 313, Sector 14,
Rohtak, Haryana, India.
E-mail: doctorjyotisharma@yahoo.in

Renu Bala, Rajesh Kumar, Jyoti Sharma
Department of Anaesthesiology and Critical Care, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

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ABSTRACT

Background and Aims: PEEP is commonly used to improve postoperative respiratory outcomes in surgical and ICU patients. It is thought to increase ICP by impending CSF outflow and cerebral venous drainage. Hyperventilation is used to decrease ICP in patients having intracranial hypertension. We investigated the effect of various levels of PEEP and $EtCO_2$ on ONSD as an indirect predictor of ICP in patients undergoing surgery under GA. **Methods:** After induction, different levels of PEEP and $EtCO_2$ were applied to 50 patients. Sonographic ONSD was measured 5 minutes after stabilization of each new setting. Haemodynamic parameters like pulse, SpO_2, BP were also recorded. Quantitative variables were expressed as Mean ± SD and compared across between follow-ups using paired *t*-test. Qualitative variables were expressed in number and percentage. **Results:** Baseline ONSD was 0.44 ± 0.06 cm. It increased significantly to 0.45 ± 0.07 cm, 0.47 ± 0.07 cm and 0.49 ± 0.07 cm after applying PEEP of 8, 12 and 15 cm H_2O PEEP, respectively. It significantly decreased to 0.42 ± 0.06 cm, 0.41 ± 0.06 cm and 0.40 ± 0.06 cm after hyperventilation, $EtCO_2$ range 35–37, 32–34 and 29–31 mm Hg. Results were statistically significant but clinically not significant. **Conclusion:** We conclude that there are acute and dynamic alterations in ONSD in response to hyperventilation and presence of PEEP in anaesthetised patients. Ocular sonography may be used as a reliable indicator of acute variations in ICP.

Key words: Carbon dioxide, hyperventilation, intracranial hypertension, optic nerve

INTRODUCTION

Intracranial pressure (ICP) monitoring is one of the important components of neuro monitoring. Although invasive methods of ICP monitoring are considered as the gold standard but limitations like risks of infection and haemorrhage have led to search for non-invasive techniques.[1] Amongst all, ultrasonographic assessment of optic nerve sheath diameter (ONSD) has sparked significant interest in recent years as a valuable tool for estimation of ICP.[2]

Positive End-Expiratory Pressure (PEEP) is a commonly employed manoeuvre to improve oxygenation by preventing end–expiratory collapse of alveoli and by recruiting non-ventilated (shunt), or poorly ventilated (low V/Q) alveoli.[3] Effect of PEEP on ICP is controversial. The increase in intracranial pressure (ICP) with application of PEEP has been reported by several investigators, but there are few studies which refute it.[4-6] Carbon dioxide (CO_2) which is a potent vasodilator may contribute to ICP change. Short-term hyperventilation by decreasing CO_2 level causes cerebral vasoconstriction and prevents acute increase in ICP. The end-tidal carbon dioxide ($EtCO_2$) has been reported to be a non-invasive parameter to estimate $PaCO_2$ indirectly and shows a good correlation with $PaCO_2$, even in those with severe brain trauma.[7]

The present prospective study was conducted to evaluate the effect of various levels of PEEP and $EtCO_2$

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on ONSD as a surrogate marker for ICP in non-brain injured patients undergoing surgery under general anaesthesia.

METHODS

This prospective, cross-over trial was conducted between January 2017 and February 2018. The study protocol was approved by the Institutional Ethics Committee. Fifty-four patients of either sex between age group 18-60 years belonging to American Society of Anesthesiologists (ASA) physical status I and II, scheduled to undergo elective surgery under general anaesthesia requiring tracheal intubation were assessed for enrollment. A written informed consent was obtained from each patient. Patients with orbital tumour, hyperthyroidism, optic neuritis, pregnancy/lactation, glaucoma, abnormal liver functions, respiratory dysfunctions, central nervous system (CNS) dysfunctions, hypotension or laparoscopic surgeries were excluded.

All patients received premedication in the form of oral alprazolam 0.25 mg and ranitidine 150 mg before sleep and 2 hours before surgery with sips of water. In the operating room, routine monitors (three-lead electrocardiogram, non-invasive blood pressure and pulse oximetry) were applied and intravenous access was achieved with appropriate size cannula. Baseline heart rate (HR), oxygen saturation (SpO_2), non-invasive blood pressure (NIBP) and mean arterial pressure (MAP) were recorded. All patients received standardised general anaesthesia with intravenous fentanyl (2 μg/kg) thiopental sodium (3-5 mg/kg), vecuronium bromide (0.1 mg/kg). After tracheal intubation with appropriate sized endotracheal tube, lungs were mechanically ventilated with Drager'Primus anaesthesia workstation SW 4.5 n using volume controlled mode with a tidal volume of 8 ml/kg ideal body weight and a respiratory rate 8-20 breaths per minute to maintain end-tidal CO_2 pressure ($EtCO_2$) in different ranges from 29 to 42 mmHg by increasing the respiratory rate by 2 per minute at a time. Anaesthesia was maintained at 1–1.2 MAC (Minimum Alveolar Concentration) with isoflurane and 67% N_2O in O_2. Maximum airway pressure (P_{max}) was kept at 30 cm of H_2O and baseline PEEP at zero. Heart rate (HR), oxygen saturation (SpO_2), non-invasive blood pressure (NIBP) and MAP were recorded before induction, after induction and again after intubation.

The sequence of interventions was generated using computer from website www.openepi.com and the order of interventions was kept in a sealed envelope. It was disclosed to the anaesthesiologist carrying out changes on the anaesthesia machine parameters. The changes in anaesthesia workstation (ventilator as well as monitor) were concealed by a screen from person doing sonography so as to ensure blinding.

Patients were placed in the supine position with their eyes closed with a tegaderm ensuring that there was no air bubble in between. A thick layer of sterile coupling was applied to the closed upper eyelid and the probe was placed gently on the gel on the superior and lateral aspect of the upper eyelid without exerting any pressure on the eyeball. Then, the probe was angled slight caudally and medially until an axial view of the orbit was obtained displaying the entry of the optic nerve into the globe. Depth and gain were adjusted accordingly. The image was frozen, and the cursors were placed on the outer contours of the dural sheath, at a retrobulbar position, 3 mm behind the globe and perpendicularly to the optic nerve axis. The ONSD was calculated as the horizontal distance between the 2 cursors [Figure 1]. A trained person having performed more than 25 ocular ultrasounds conducted all the measurements using a 7.5-MHz linear-array probe of Sonosite M-Turbo ultrasound machine. All measurements were done by the same person so that there were no inter observer variability.

Initially, we planned to measure ONSD by averaging the three values obtained from each eye in transverse and sagittal sonographic planes. After conducting the examinations and measurements as per this protocol in few patients, we found no differences in ONSD measured in two eyes or in axial versus sagittal planes. However, it was delaying the start of the surgical procedure and also exposing the patients to

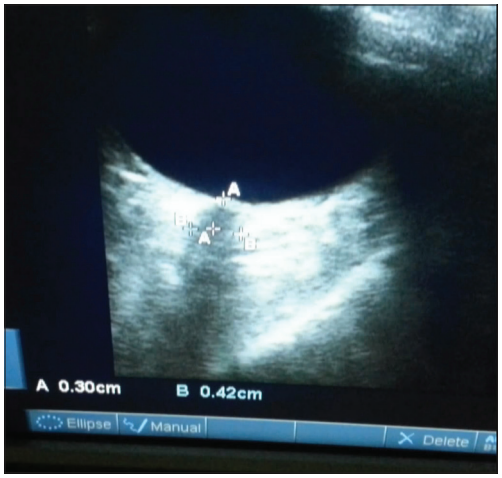

Figure 1: Optic nerve sheath sonography

prolonged anaesthesia time, therefore, further ONSD measurements were performed in only one eye in transverse plane and only single reading was taken. The ethical committee approval was taken for this change in method duly before the start of actual study after observing initial pilot cases. All the observations were made in similar manner.

Baseline ONSD was measured after 5 minutes of $EtCO_2$ value between 38 and 42 mm Hg with PEEP at zero. This reading was taken as T_0. various PEEP levels were applied (8, 12 and 15 cm H_2O) as per randomization sequence and ONSD was measured likewise 5 minutes after each new PEEP setting (T_1, T_2 and T_3, respectively). The basic parameters like HR, NIBP, MAP, SpO_2 and $EtCO_2$ were recorded with each new level of PEEP. All patients were temporarily hyperventilated from 8 to 20 breaths per minute by increasing 2 breaths per minute at a time with a fixed tidal volume to keep the $EtCO_2$ levels as per randomization sequence in 3 different ranges (35–37 mm Hg, 32–34 mm Hg and 29–31 mm Hg) with PEEP level at zero. After 5 minutes of stabilization of each new $EtCO_2$ range, ONSD was measured likewise (T_4, T_5 and T_6, respectively). The basic parameters like HR, NIBP, MAP and SpO_2 were recorded again with each new range of $EtCO_2$. Once all measurements were done, the surgery was allowed to commence and rest of the anaesthesia was managed as per standard protocol. The duration of surgery, duration of anaesthesia, the amount of intra-operative blood loss and the volume of administered fluid were also assessed. In the recovery room, ocular examinations were carried out to rule out any ocular injury or trauma.

Based on the data of normal ONSD by Rosenberg *et al*. as 0.45 ± 0.02 cm, with value of 0.50 ± 0.05 cm to be significant; the minimum required sample size at 5% level of significance and 95% power was obtained as 41 patients.[8] The quantitative variables were expressed as Mean ± SD and compared across between follow-ups using paired *t*-test. Qualitative variables were expressed in number and percentage. Correlation between various variables was assessed using Pearson's Correlation coefficient. A *P* value < 0.05 was considered statistically significant. The data was analysed using Statistical Package for the Social Sciences (SPSS) Version 16.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

During the study period, 54 patients of age group 18–60 years were enrolled. Of these, 4 were excluded due to: different drug protocol (n = 1), insonation non-feasibility (n = 1) and supraglottic device used (n = 2). 50 patients (25 males) belonging to ASA Class I and II completed the study protocol [Figure 2]. Demographic profile of the patients has been shown in Table 1. The overall ONSD in our study population was 0.44 ± 0.06 cm. There was no significant correlation between ONSD and age (P = 0.286), gender (P = 0.170), height (P = 0.410), weight (P = 0.896) and BMI (P = 0.3790) [Table 2].

The changes in heart rate and mean arterial pressure after applying various levels of PEEP and $EtCO_2$ were also evaluated. It was found that increase in PEEP and hyperventilation is associated with a statistically significant (P < 0.05) decrease in pulse rate but it

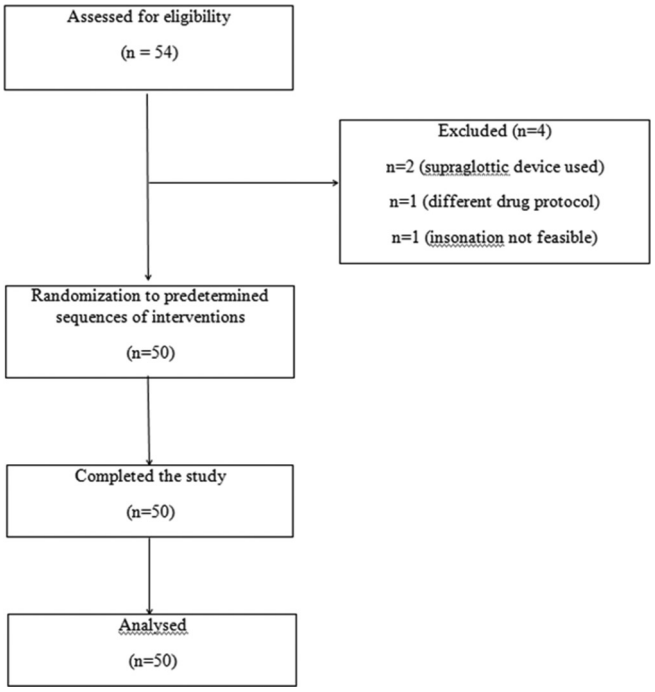

Figure 2: CONSORT diagram

Table 1: Demographic profile of patients

Parameter		Value
Age (Mean±SD)		39.425±12.69
HT cm (mean±SD)		161.86±9.64
WT kg (mean±SD)		61.92±12.15
BMI kg/m² (Mean±SD)		23.54±3.56
Gender	Male	25 (50%)
	Female	25 (50%)
Asa	I	35 (70%)
	II	15 (35%)
Type of surgery	Orthopaedic	11 (22%)
	Breast	12 (24%)
	Abdominal	25 (50%)
	Skin grafting	2 (4%)

was clinically not relevant. Furthermore, increase in PEEP is not associated with any significant change in MAP however hyperventilation is associated with a statistically significant decrease in MAP at T_5 (p 0.037) and T_6 level (p 0.004) when compared to T_4.

The effect of various levels of PEEP and $EtCO_2$ has been shown in Table 3. The mean ONSD value at PEEP of zero (ZEEP) (T_0) was 0.44 ± 0.06 cm. It significantly increases ($P < 0.001$) to 0.45 ± 0.07 cm after application of 8 cm H_2O PEEP (T_1). It further increased significantly to 0.47 ± 0.07 cm and 0.49 ± 0.07 cm after application of 12 and 15 cm H_2O PEEP (T_2 and T_3), respectively. The increase is significant when compared to T_0 ($P < 0.001$), T_1 ($P < 0.001$) and T_2 ($P < 0.001$). The mean ONSD value at $EtCO_2$ range 38-42 mm Hg (T_0) with ZEEP was 0.44 ± 0.06 cm. It significantly ($P < 0.001$) decreased to 0.42 ± 0.06 cm after hyperventilation to $EtCO_2$ range 35-37 mm Hg (T_4). It further decreased significantly ($P < 0.005$) to 0.41 ± 0.06 cm after hyperventilation to $EtCO_2$ range 32–34 mm Hg (T_5) and to 0.40 ± 0.06 cm after hyperventilation to $EtCO_2$ range 29–31 mm Hg (T_6). The decrease is significant when compared to T_0 ($P < 0.001$), T_4 ($P < 0.005$) and T_5 ($P < 0.001$). ONSD has significant correlation with $EtCO_2$ at T_5 and not at any other time-points [Figure 3].

Table 2: Correlation of baseline ONSD with age, height, weight and BMI

ONSD (T_0) vs.	Correlation	*P*
Age (yrs)	–0.154	0.286
Height (cm)	0.119	0.410
Weight (kg)	–0.019	0.896
BMI (kg/m^2)	–0.127	0.379

Table 3: Effect of various levels of PEEP and EtCO2 on ONSD

ONSD	T_0	T_1	T_2	T_3	T_4	T_5	T_6
Mean	0.44	0.45	0.47	0.49	0.42	0.41	0.40
± SD	± 0.06	± 0.07	± 0.07	± 0.07	± 0.06	± 0.06	± 0.06
95% CI	0.4234, 0.4566	0.4306, 0.4694	0.4506, 0.4894	0.4706, 0.5094	0.4034, 0.4366	0.3934, 0.4266	0.383, 0.417
P (vs T0)	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
P (vs T1)	-	-	<0.001	<0.001	<0.001	<0.001	<0.001
P (vs T2)	-	-	-	<0.001	<0.001	<0.001	<0.001
P (vs T3)	-	-	-	-	<0.001	<0.001	<0.001
P (vs T4)	-	-	-	-	-	0.005	<0.001
P (vs T5)	-	-	-	-	-	-	<0.001

PEEP – Positive end-expiratory pressure; $EtCO_2$ – End-tidal carbon dioxide; T_0 – Baseline values at PEEP zero and $EtCO_2$ (38-42 mm Hg); T_1 – Values at PEEP (8 cm H_2O) and $EtCO_2$ (38-42 mm Hg); T_2 – Values at PEEP (12 cm H_2O) and $EtCO_2$ (38-42 mm Hg); T_3 – Values at PEEP (15 cm H_2O) and $EtCO_2$ (38-42 mm Hg); T_4 – Values at PEEP zero and $EtCO_2$ (35-37 mm Hg); T_5 – Values at PEEP zero and $EtCO_2$ (32-34 mm Hg); T_6 – Values at PEEP zero and $EtCO_2$ (29-31 mm Hg)

DISCUSSION

In present study, we found that ONSD increased with PEEP of 8 cm H_2O when it was compared with the baseline PEEP of zero. It further increased with PEEP of 12 and 15 cm H_2O. The changes were slight and persistent, may be clinically irrelevant but statistically significant. Our results are in accordance with those by Robba *et al*. who also reported an increase in ONSD with PEEP of 8 cm H_2O in patients undergoing spine surgery/in supine position.[3] Similar results were also reported by Chin *et al*. with application of PEEP of 8 cm H_2O in patients undergoing laparoscopic surgeries. They reported a significant increase in ONSD with PEEP of 8 cm H_2O in supine position. But they noticed that PEEP of 8 cm H_2O following steep Trendelenburg position and pneumoperitoneum did not increase ONSD. The authors contributed it to decreased lung compliance caused by steep Trendelenburg position and pneumoperitoneum, or PEEP might not exceed the already increased ICP resulting in failure of transmission of PEEP to intracranial compartment.[9] In both the above mentioned studies the increase in ONSD was slightly more than that in our study. It could be due to different ethnicity of the study population, difference in anaesthetic agents used, presence of surgical stimulus or could be an incidental finding. Some other studies also found similar results with

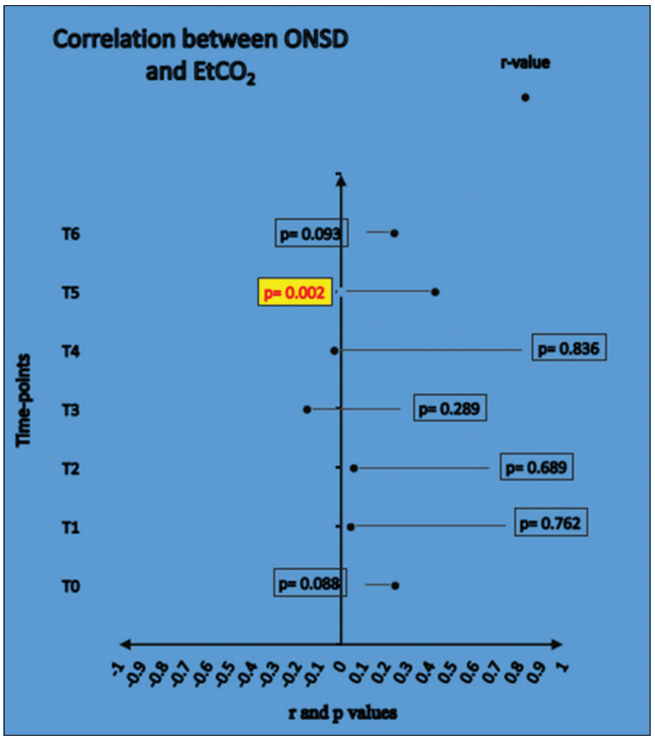

Figure 3: Correlation between ONSD and $EtCO_2$

PEEP application in neurological or neurosurgical patients in which ICP was measured using invasive methods.[10-13] Steep trendelenburg position can also lead to complications at extubation. Sujata N *et al*. have described the use of ONSD to guide the timing of extubation.[14] In contrast, Muench found that PEEP of up to 5 to 20 cm H_2O had no significant ($P > 0.05$) effect on ICP in patients of subarachnoid haemorrhage without vasospasm. However, they noticed an increase in the ICP on seventh day of SAH.[4] Similar results were also found by Caricato *et al*. who reported no change in ICP with PEEP of up to 12 cm H_2O in 21 comatose patients of severe brain injury with either normal or low respiratory system compliance.[6] Georgiadis *et al*. also reported no significant change in ICP with PEEP of 4 to 12 cm H_2O in patients of acute stroke.[5]

In the present study, we found a gradual decrease in baseline ONSD values with hyperventilation. There was 10% decrease in ONSD (0.02 cm) when $EtCO_2$ was lowered from 39.74 ± 1.23 to 35.98 ± 1.29 mm Hg. The decrease was 17% (0.03 cm) and 25% (0.04 cm) at $EtCO_2$ 33.02 ± 0.74 mm Hg and 29.29 ± 1.18 mm Hg respectively. Seo *et al*. also found a decrease in ONSD with decrease in CO_2 levels in blood. They found 0.01 cm decrease in ONSD while we report approximate 0.03 cm decrease for the similar changes in CO_2 levels. This difference might be due to the fact that they measured $PaCO_2$ prior to induction in liver failure while we measured $EtCO_2$ in ASA I and ASA II patients after induction of anaesthesia. Different demographic profile can also contribute to these differences.[15] Kim *et al*. found a 0.1 cm decrease in ONSD while we found a 0.04 cm decrease in ONSD for a similar change in $EtCO_2$ levels. In both the studies significant decrease in ONSD was appreciated with decrease in $EtCO_2$ levels, but the difference in exact values could be due to different demographic profile of the patients or the different anaesthetic agents used. The authors used propofol, remifentanyl and rocuronium bromide while we used thiopentone sodium, fentanyl and vecuronium bromide.[16] In a recent study, Dinsmore *et al*. found an increase in ONSD with hypercapnia and a decrease in ONSD with hypocapnia. The alterations were sustained throughout the measurement which was continued for 10 minutes.[17] We did not assess effects of hypercapnia; but hypocapnia lead to decrease of 0.04 cm in our study as compared to 0.15 cm decreases in Dinsmore study. The difference of exact values of ONSD at various $EtCO_2$ levels could be due to different demographic profile or administration of anaesthetic agents in our study. Since increase in cerebral blood flow by increasing CO_2 levels are easily compensated in patients who have intact cerebral auto-regulatory mechanism. It is not expected to cause increase in ICP.

There was a non-significant increase in MAP ($P = 0.419$) after application of PEEP of 8 cm H_2O. But, thereafter, it decreased non-significantly ($P > 0.05$) at PEEP of 12 and 15 cm H_2O. Similar results were reported by Chin *et al*. who found a non-significant increase in MAP with application of PEEP of 8 cm H_2O in their study.[9] Similar results were also reported by Muench *et al*. in their experimental study in healthy animals with application of PEEP of up to 25 cm H_2O and also in patients of subarachnoid haemorrhage with or without vasospasm with application of PEEP of up to 15 cm H_2O. But they noticed a significant decrease in MAP with PEEP of 20 cm H_2O in both patients with or without vasospasm.[4] However, we did not use PEEP of such high level (20 cm H_2O) in our study. Our results are not in agreement with those by Caricato *et al*. who reported a significant decrease in MAP ($P < 0.01$) with PEEP of up to 12 cm H_2O in 21 comatose patients of severe brain injury with either normal or low respiratory system compliance.[6] Georgiadis also noticed a significant decrease in MAP ($P < 0.0001$) with application of PEEP of 8 to 12 in patients of acute stroke.[11] Application of PEEP leads to increased intrathoracic pressure causing decreased venous return, thus fall in blood pressure by reducing cardiac output. We did not notice greater fall in blood pressure as we maintained euvolemia in our patients by administering adequate fluids prior to interventions. Our results are in agreement to those by Wang who also found no correlation between MAP and ONSD.[18] This is attributed to intact cerebral autoregulation which maintained cerebral perfusion over a wide range of MAP (50–150 mm Hg). We feel that the cerebral blood flow and volume remained constant, hence slight change in vitals had no effect on ONSD.

SBP had a significant positive correlation (<0.05) with ONSD at the time of PEEP application. We however attributed this increase in ONSD to PEEP application. Multivariate analysis could have been done to correctly identify the cause. We could not find any significant correlation between ONSD and other vital parameters. Another conspicuous finding of our study was quick and reversible changes in ONSD in presence of factors which are known to decrease (hyperventilation) or increase (presence of PEEP) intracranial pressure. Previously, it was

believed that ocular sonography is a sensitive but less specific marker of intracranial hypertension when ICP fluctuates acutely. The explanation provided was that there is delayed reversibility of optic nerve sheath distension.[19] Our results are in contrast to above hypothesis. Dinsmore too observed dynamic changes in ONSD with corresponding changes in carbon dioxide and their reversibility with normocapnia. Their study population comprised of healthy volunteers.[17] Similar results were earlier reported in head injury patients admitted in ICU. Banerjee A *et al*. reported that not only a new cerebral insult but also the response to the therapeutic intervention done could be detected by repeated measurement of ONSD.[20] Tracheal suctioning caused immediate rise in ONSD which corresponded to rise in invasive ICP. This rise subsided once the stimulus (tracheal suctioning) was over.[21] An alternative mechanism might be responsible for rapid rise and fall in ONSD which needs to be identified.

Our study had the following limitations. First, we used ONSD as indirect measurement of ICP and did not compare it with gold standard which is invasive monitoring. Our study was based on fact that ONSD is surrogate measure of ICP.[22] Moreover; it is impractical and unethical to put an intraventricular catheter in patients who are neurologically sound. Second, we conducted the study in ASA I and II patients who had no neurological problems. The results might be different in these patients. Third, the measurements were conducted at 5 minutes after stabilization of each intervention. This time was based on previous results. However, it may not coincide with peak rise and fall of ICP. Fourth, $PaCO_2$ levels could have been measured. Since it precisely depict level of CO_2. Fifth "Carry-over" effect of previous intervention can be marked in patients when subsequent intervention is applied. Since it has been found that distension of optic nerve sheath occurs quickly but there is delay in reversibility of its distension when ICP decreases. Clinically speaking, the changes observed in the present study were minor, and the patients were neurologically intact. It is difficult to comment if our results can be translated to patients who have intracranial pathology. Further studies in heterogenous group of population are required to validate our findings unambiguously.

CONCLUSION

In conclusion, our study demonstrates that there are acute and dynamic alterations in ONSD in response to hyperventilation and presence of PEEP in anaesthetised patients and may be used as a reliable indicator of acute variations in ICP.

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Nil.

Conflicts of interes

There are no conflicts of interest.

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Announcement

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30 June 2019	Rukmini Pandit Award	Hon. Secretary, ISA (by log in & E Mail)
30 June 2019	Dr. Y. G. Bhoj Raj Award	Hon. Secretary, ISA (by log in & E Mail)
30 June 2019	Mrs. Shashi & Dr. P Chandra Award	Hon. Secretary, ISA (by log in & E Mail)
30 Sept 2019	Kop's Award	Chairperson, Scientific Committee ISACON 2019 copy to Hon. Secretary, ISA (by log in & E Mail)
30 Sept 2019	ISACON Jaipur Award	Chairperson, Scientific Committee ISACON 2019 copy to Hon. Secretary, ISA (by log in & E Mail)
30 Sept 2019	Prof. Dr. Venkata Rao Oration 2019	Hon. Secretary, ISA (by log in & E Mail)
30 Sept 2019	Ish Narani Best poster Award	Chairperson, Scientific Committee ISACON 2019
30 Sept 2019	ISA Goldcon Quiz	Chairperson, Scientific Committee ISACON 2019
10 Nov 2019	Late Dr. T. N. Jha Memorial Award & Dr. K. P. Chansoriya Travel Grant	Hon. Secretary, ISA, (by log in & E Mail) copy to Chairperson Scientific Committee ISACON 2019
20 Oct 2019	Bidding Application for ISACON 2021	Hon.Secretary, ISA by log in, E Mail & hard copy
20 Oct 2019	Awards (01 Oct 2018 to 30 Sept 2019)	Hon. Secretary, ISA (by log in & E Mail)

(Report your monthly activity online every month after logging in using Branch Secretary's log in ID)

1. Best City Branch
2. Best Metro Branch
3. Best State Chapter
4. Public Awareness – Individual
5. Public Awareness – City / Metro
6. Public Awareness - State
7. Ether Day (WAD) 2019 City & State
8. Membership drive
9. Proficiency Awards

Send hard copy (only for ISACON 2021 bidding) to
Dr. Naveen Malhotra
Hon Secretary, ISA National
Naveen Niketan, 128/19, Doctors Lane,
Civil Hospital Road, Rohtak-124001, Haryana, India
Email: drnaveenmalhotra@yahoo.co.in
secretaryisanhq@gmail.com
Mobile: +91-9812091051