Effect of Prone Positioning on Intraocular Pressure in Patients With Acute Respiratory Distress Syndrome

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Objectives: To evaluate the effect of prolonged duration of prone position (with head laterally rotated) on intraocular pressure in acute respiratory distress syndrome patients.

Design: Prospective observational study.

Setting: University hospital ICU.

Patients: Twenty-five acute respiratory distress syndrome patients, age 60 years (51–67 yr), Sequential Organ Failure Assessment score 10 (10–12), Pao_2/Fio_2 ratio of 90 (65–120), and all in septic shock.

Interventions: None.

Measurements and Main Results: Intraocular pressure (in mm Hg) measured by hand-held applanation tonometer, at different time points. Before prone (in both eyes): at 30–45° head-end elevation position ($T_{HE\ pre\text{-}prone}$), in supine position just before turning prone ($T_{supine\ pre\text{-}prone}$); during prone (in nondependent eye): at 10 minutes ($T_{10\ prone}$), 30 minutes ($T_{30\ prone}$), and at just before end of prone session ($T_{end\text{-}prone}$). After end of prone session (both eyes): at 5 minutes ($T_{5\ supine\ post\text{-}prone}$), 10 minutes ($T_{10\ HE\ post\text{-}prone}$), 15 minutes ($T_{15\ HE\ post\text{-}prone}$), and 30 minutes ($T_{30\ HE\ post\text{-}prone}$). Median duration of prone position was 14 hours (12–18 hr). Median intraocular pressure increased significantly ($p \leq 0.001$) in both eyes. In dependent eye, from 15 (12–19) at $T_{HE\ pre\text{-}prone}$ to 24, 21, 19, and 16 at $T_{5\ supine\ post\text{-}prone}$, $T_{10\ HE\ post\text{-}prone}$, $T_{15\ HE\ post\text{-}prone}$, and $T_{30\ HE\ post\text{-}prone}$ respectively, whereas in nondependent eye from 14 (12–18.5) at $T_{HE\ pre\text{-}prone}$ to 23, 25, 32, 25, 22, 20, and 17 at $T_{10\ prone}$, $T_{30\ prone}$, $T_{end\text{-}prone}$, $T_{5\ supine\ post\text{-}prone}$, $T_{10\ HE\ post\text{-}prone}$, $T_{15\ HE\ post\text{-}prone}$, and $T_{30\ HE\ post\text{-}prone}$ respectively. Bland-Altman plot analysis showed significant linear relationship ($r = 0.789$; $p \leq 0.001$) with good agreement between rise in mean intraocular pressure of the both eyes (dependent eye and nondependent eye) with their paired differences after the end of different duration of prone session ($T_{5\ supine\ post\text{-}prone}$).

Conclusions: There is significant increase in intraocular pressure due to prone positioning among acute respiratory distress syndrome patients. Intraocular pressure increases as early as 10 minutes after proning, with increasing trend during prone position, which persisted even at 30 minutes after the end of post prone session although with decreasing trend. (*Crit Care Med* 2019; 47:e761–e766)

Key Words: acute respiratory distress syndrome; complication; intraocular pressure; prone position

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Presented, in part, as an abstract at the ESICM LIVES (September 27, 2017, Vienna, Austria) and ISCCM CRITICARE (March 8, 2018, Varanasi, India) meetings.

Dr. Gurjar received funding from Intramural and Extramural Research Grant (unrelated to submitted work), and he received funding from Jaypee Medical Publishers, New Delhi, India (royalties). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000003893

Acute respiratory distress syndrome (ARDS) commonly complicates acute illness in patients admitted to ICUs and is associated with high morbidity and mortality (1, 2). In the management of ARDS patients, lung-protective ventilation and prone ventilation are the key strategies which have shown survival benefits and now became the standard part of care in these patients (3). The complications associated with prone positioning includes facial edema, potential dislodgement of invasive catheters, pressure sores, hemodynamic instability, increase in intracranial pressure (ICP), and ocular complications, with overall occurrence rate of 11.9% (4–6).

Due to prone position, ocular complications (conjunctivitis, abrasion of cornea) have been reported as 0.11% (2/1,749) during surgeries in operation room (OR) (7, 8) and 1.9% (2/101) in a prospective multicenter prevalence study on prone positioning in ARDS patients (4). Effect of prone positioning on intraocular

pressure (IOP) had been studied in awake volunteers (9, 10) and in patients during surgeries (11–16), revealed IOP increases within few hours of prone positioning (normally, IOP value is between 10 and 20 mm Hg). As prone positioning is commonly being used among ARDS patients, its prolonged duration (3–4 times longer than intraoperative duration), may lead to possibly higher rise in IOP. Recently, more severe ocular complication like blindness have also been reported in ARDS patients after prone positioning due to anterior ischemic optic neuropathy (AION) and posterior ischemic optic neuropathy (PION) (17, 18). Retinal vascular occlusion due to mechanical compression of the eye, decreased arterial supply, impaired venous drainage leading to AION, PION or branch retinal arterial occlusion, cortical blindness, and acute glaucoma are the predominant reasons implicated in the pathophysiology of the blindness that can happen due to prone position (7, 8, 19). Among the risk factors for perioperative visual loss during prone position, orbital compression and duration of prone position were found predominant risk factors during surgeries (7, 8, 19–21). In ARDS patients who are already hypoxic, any acute rise in IOP may further make these patients prone to develop complications related to decreased retinal and optic nerve head (ONH) perfusion which can lead to rapid development or progression of ONH cupping in both nonglaucomatous and glaucomatous subjects, respectively. There is no study available, where changes of IOP were assessed in ARDS patients after prone positioning. For this reason, we undertook a prospective observational study to know the effect of prone positioning on IOP in moderate-to-severe ARDS patients. This work was presented at the 2017 ESICM LIVES (30th Annual Congress of European Society of Intensive Care Medicine) and 2018 CRITICARE ISCCM (24th Annual Conference of Indian Society of Critical Care Medicine) meetings.

MATERIAL AND METHODS

Study Design

This single-center prospective observational study was conducted in a 12-bed ICU of a tertiary care academic hospital in North India from May 2016 to October 2017. The primary objective of this study was to know the effect of prone positioning on IOP in patients with moderate-to-severe ARDS. The secondary outcome was to follow up the survivors for detailed ophthalmologic examination of anterior and posterior segment of both eyes at the time of ICU discharge, and at 1 and 3 months after discharge from the ICU. The study protocol was approved by institute ethical committee (code: 2016-55-DM-EXP). Informed consent from the patient's family was obtained. The study was recorded in the ClinicalTrials.gov website (ClinicalTrials.gov Identifier: NCT02711930).

Study Population

All adult (age >18 yr) patients with moderate-to-severe ARDS requiring prone ventilation were screened for inclusion in this study. Exclusion criteria are as follows: clinical conditions with suspected raised ICP, history of previous eye trauma or disease or surgery, family history of glaucoma. Also, any prone positioning of less than 6 hours duration (planned or unplanned) were excluded from the analysis.

As a part of standard treatment for ARDS, all patients were ventilated with lung-protective ventilation strategies with appropriate sedation and paralysis with relevant invasive monitoring as per ICU protocol and according to the treating physician. Ventilator settings were not changed during study period. The prone positioning (complete proning, 180°) was done with protective measures for eyes (covered with cotton pads to prevent any ocular compression), extremities, and using thoracopelvic supports, on alternating-pressure mattresses with other supportive measures as per ICU protocol in all studied patients. In prone position, the head of the patient was kept rotated about 45° to one side, either right or left, thereby making one eye in dependent position in comparison with the other. The head was kept in the same position (i.e., either to the right or to the left) during the entire prone ventilation period.

IOP Measurement

For our study, we used Tonopen AVIA (Reichert Technologies, Depew, NY) to measure IOP. Tonometry-guided IOP measurement is one of the commonly used modality to assess IOP which has been used in awake volunteers and patients undergoing surgeries in OR (9–16). Tonometry-guided (Tonopen AVIA; Reichert Technologies) instruments work on Imbert-Fick law (P = F/A, P: IOP, F: force exerted by tonometer to flatten a specific area of the cornea, and A: the area flattened), and Tonopen AVIA has a strain gauge incorporated, converting each applanation (flattening of a convex surface) to an electric signal displayed on liquid crystal display screen. The IOP measured is displayed with statistical confidence indicator (SCI) after eight to 10 applanations. SCI 95 means that the SD of the valid measurements is 5% or less of the number shown. If SCI is 80 or 80–, a repeat measurement is suggested. Tonopen readings displayed after 10 applanations with 95% confidence limits were recorded. This technique was validated and showed good correlation with gold standard invasive techniques and even with the most commonly used Goldmann applanation technique (22). All IOP measurements were taken by same investigator throughout the study, who was trained to monitor IOP in 10 patients under direct supervision of an experienced ophthalmologist.

Data Collection

All relevant demographic, clinical characteristics along with ICU severity scores (Sequential Organ Failure Assessment [SOFA] and Acute Physiology and Chronic Health Evaluation [APACHE] II) were recorded. IOP was measured at different time points for both eyes except during prone, where IOP was not measured in dependent eye (DE) due to inaccessibility.

$T_{HE\ pre\text{-}prone}$: 30–45° head end elevation (pre-prone, both eyes).

$T_{supine\ pre\text{-}prone}$: In supine before turning the patient prone (pre-prone, both eyes).

$T_{10\ prone}$: After prone at 10 minutes (during prone, nondependent eye [NDE]).

$T_{30\ prone}$: After prone at 30 minutes (during prone, NDE).

$T_{end\text{-}prone}$: Just before the end of prone session (during prone, NDE).

$T_{5\ supine\ post\text{-}prone}$: In supine at 5 minutes after the end of prone session (post-prone, both eyes).

$T_{10\ HE\ post\text{-}prone}$: 30–45° head end elevation at 10 minutes after the end of prone session (post-prone, both eyes).

$T_{15\ HE\ post\text{-}prone}$: 30–45° head end elevation at 15 minutes after the end of prone session (post-prone, both eyes).

$T_{30\ HE\ post\text{-}prone}$: 30–45° head end elevation at 30 minutes after the end of prone session (post-prone, both eyes).

Follow up ophthalmic examination among survivors was done at the time of ICU discharge, 1 and 3 month that included visual acuity, slit lamp examination, Goldmann applanation tonometry along with IOP measurement by Tonopen-AVIA, and fundus examination.

Statistical Analysis

Sample size was calculated at minimum two-sided 95% CI and 95% power of the study for one group in which observation was taken at least six times as repeated design. Assuming 0.28 SD of the effect size of the mean difference, calculated sample size came out to be 23. Power and sample size software version 16 (PASS-16, NCSS, LLC, Kaysville, UT) have been used to calculate sample size.

Continuous data following normal distribution were analyzed using parametric test, whereas nonnormal continuous data as well as discrete or categorical data were analyzed using nonparametric test. Data represented as mean ± SD/median (interquartile range), and Wilcoxon rank sum test applied to compare IOP at various time periods. Bland-Altman analysis was done to estimate an agreement between rise in IOP in both eyes (dependent and nondependent) at the end of prone session. To test the linear relationship between two continuous variables, Pearson correlation coefficient (r) was calculated. *p* value of less than 0.05 was considered statistically significant. Statistical analysis was done using statistical software SPSS-22 (Statistical package for social sciences, Version 22, Chicago, IL).

RESULTS

During the study period, 326 patients were admitted in the ICU, out of which 112 patients had ARDS during their stay. Fifty-six patients had prone ventilation, at least for one session. Out of these 56 patients, 26 patients were not included due to refusal for consent or unavailability of Tonopen. Among included 30 patients, five were excluded from the analysis (three patients had prone duration less than 6 hours and in the remaining two patients' data could not be recorded at appropriate time intervals). Finally, data for 25 patients were included in this study for the analysis.

The median (interquartile range) age of the patients was 60 years (51–67 yr), with medical/surgical illness: 24/1, male 17, APACHE II at admission 25 (22–26); SOFA score on the day of study 10 (10–12), all in septic shock (on norepinephrine at 0.2 µg/kg/min) (**Table 1**). Pre-prone Pao_2/Fio_2 ratio was 90 (65–120) with positive end-expiratory pressure (PEEP) 12 cm H_2O (10–14 cm H_2O). The duration of prone position was 14 hours (12–18hr).

TABLE 1. Demographic and Clinical Characteristics

Clinical Characteristic (*n* = 25)	Median (IQR)
Age (yr)	60 (51–67)
Type of illness (medical/surgical), *n*	24/1
Acute Physiology and Chronic Health Evaluation II score at admission	25 (22–26)
Sequential Organ Failure Assessment score on the day of study	12 (10–13)
Type of acute respiratory distress syndrome: pulmonary/extrapulmonary, *n*	24/1
Prone duration (hr)	14 (12–18)
Pre prone Pao_2/Fio_2	90 (65–120)
Septic shock, yes/no: 25/0, µg/kg/min	Median norepinephrine 0.2 (0.1–0.32)
Patients on steroids (yes/no), *n*	16/9
Survivors/nonsurvivors, *n*	5/20

IQR = interquartile range.

Median IOP for right and left eyes was 14 (11–19) and 14 (12–19) in 30–45° head end elevation ($T_{HE\ pre\text{-}prone}$), which changed to 15 (13.5–19) (0.001) and 16 (13.5–19) (0.001) in supine position ($T_{supine\ pre\text{-}prone}$), respectively.

After prone positioning, IOP in NDE increased from 14 (12–18.5) to 23 (20–25) (64% from $T_{HE\ pre\text{-}prone}$ NDE; $p = 0.001$) at 10 minutes ($T_{10\ prone}$) with increasing trends to 25 (23–29) (78%; $p = 0.001$) at 30 minutes ($T_{30\ prone}$) and to 32 (26.5–37.5) (128%; $p = 0.001$) just before termination of prone session ($T_{end\text{-}prone}$) (**Fig. 1**; and **Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/E732).

After the end of prone session and turning the patient back to the supine position again, IOP in NDE was found to rapidly decrease to 25 (20.5–30) at 5 minutes ($T_{5\ supine\ post\text{-}prone}$). This measurement further decreased to 22 (18–28.5) at 10 minutes ($T_{10\ HE\ post\text{-}prone}$), 20 (15.5–25) at 15 minutes ($T_{15\ HE\ post\text{-}prone}$), and 17 (15–21) at 30 minutes ($T_{30\ HE\ post\text{-}prone}$) in 30–45° head end elevation. Corresponding IOP values in DE were as follows: 24 (19.5–27), 21 (16.5–24.5), 19 (15–22), and 16 (14–21). Despite decreasing trend, IOP values remained significantly higher than the baseline $T_{HE\ pre\text{-}prone}$ values until 30 minutes after turning patient supine from prone (Fig. 1) (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/E732). In our study, the IOP measurements obtained after the end of prone session had higher values; of these, 2% were above 50 mm Hg, 8% had IOP between 40 and 50 mm Hg, 18% measurements were between 30 and 40 mm Hg, and 52% had IOP between 20 and 30 mm Hg.

There was no correlation found between duration of prone position to raised values at $T_{5\ supine\ post\text{-}prone}$, both in DE ($r = 0.006$; $p = 0.97$) and NDE ($r = 0.08$; $p = 0.69$).

To know the impact of head/neck rotation and keeping one eye down (DE) in comparison with other (NDE) for prolonged

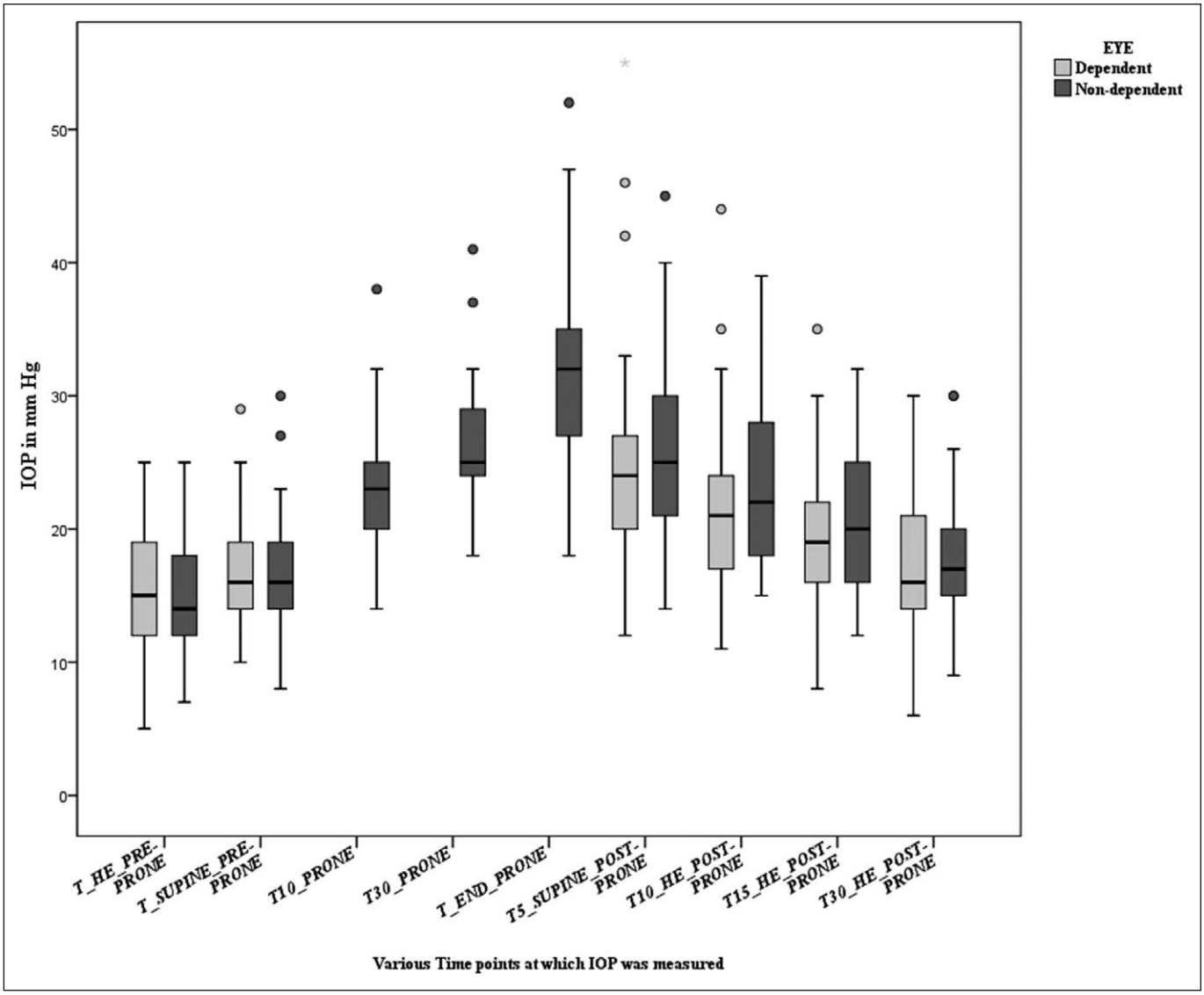

Figure 1. Intraocular pressure (IOP) trend during various time periods in dependent eye and non-dependent eye. °represents outlier value and *represents extreme outlier value, $T_{HE\ pre\text{-}prone}$ = 30–45° head end elevation (pre-prone, both eyes), $T_{supine\ pre\text{-}prone}$ = in supine before turning the patient prone (pre-prone, both eyes), $T_{10\ prone}$ = after prone at 10 min (during prone, nondependent eye), $T_{30\ prone}$ = after prone at 30 min (during prone, nondependent eye), $T_{end\text{-}prone}$ = just before the end of prone session (during prone, nondependent eye), $T_{5\ supine\ post\text{-}prone}$ = in supine at 5 min after the end of prone session (post-prone, both eyes), $T_{10\ HE\ post\text{-}prone}$ = 30–45° head end elevation at 10 min after the end of prone session (post-prone, both eyes), $T_{15\ HE\ post\text{-}prone}$ = 30–45° head end elevation at 15 min after the end of prone session (post-prone, both eyes), $T_{30\ HE\ post\text{-}prone}$ = 30–45° head end elevation at 30 min after the end of prone session (post-prone, both eyes).

duration during prone, Bland Altman plot was drawn to test the agreement between mean and corresponding difference of the DE and NDE. There was significant agreement between IOP values in both eyes (DE and NDE) at the end of the prone session as most of the values of the differences were between mean ± 1.96 SD. Good correlation was observed between the IOP measurements in both eyes ($r = 0.78$; $p < 0.001$). Similar result was evident as statistically nonsignificant paired differences were detected in the dependent and NDE of the IOP values (mean, –1.92; 95% CI, –4.46 to 0.62).

In the follow up of the seven survivors, three were lost to follow-up, and rest of the four patients had no significant ocular problems at ICU discharge, 1 and 3 months for visual acuity, slit lamp, and fundus examination respectively. Their IOP values were within normal ranges (10–12 mm Hg) as measured by both applanation tonometry techniques.

DISCUSSION

This is the first study which assessed the effect of prolonged duration (median of 14 hr) of prone position on IOP in critically ill patients. The underlying mechanism which leads to increase in IOP is unclear, various factors like improper positioning and/or external compression of the eye may lead to impaired outflow drainage of aqueous humor at any point in its pathway (IOP = [rate of aqueous humor production/facility of outflow] + episcleral venous pressure). Aqueous humor is produced in the posterior chamber by ciliary process of ciliary body and flows through the pupil into anterior chamber. From

here, aqueous humor sequentially drains from trabecular meshwork to Schlemm's canal and then to collector vessels to episcleral veins, which subsequently drain into cavernous sinus via anterior ciliary and superior ophthalmic veins. Ultimately it drains into the internal jugular veins (23).

Normally, blood flow to the retina and ONH is efficiently autoregulated; moderate increments in IOP would have no or little effect on blood flow through these tissues. The situation may be different in the presence of deficient autoregulation, and ocular blood flow would then be compromised even by small increments in IOP, vis-a-vis any sudden and acute rise in IOP can alter autoregulation mechanism, which may leads to decrease in blood flow to the retina and ONH (24–26). This reason necessitate clinicians to be cautious about avoiding any external compression on the eye, keeping the head in neutral forward position (i.e., without significant neck flexion or extension, lateral flexion or rotation), keeping head level with or higher than the heart (7, 8). Unfortunately, these practice advisory by ASA Task Force on Perioperative Visual Loss, the North American Neuro-Ophthalmology Society, and the Society for Neuroscience in Anesthesiology and Critical Care (2019) to be used during spine surgery in OR are difficult to follow in critically ill patients undergoing prone ventilation in standard ICU beds (8).

Deniz et al (13) reported 12.43 ± 4.52 mm Hg IOP values in anesthetized patients in supine position. In study by Cheng et al (11) found that there was 31% reduction from 19 ± 1 mm Hg before anesthetizing to 13 ± 1 mm Hg measured 10 minutes after intubaton under anesthesia in supine position. In the study by Park et al (14) IOP measured 5 minutes after intubation under anesthesia in supine was 9.8 ± 2.5 in desflurane group and 10.1 ± 2.1 mm Hg in sevoflurane group reducing from 15 ± 3.6 in the former and 16 ± 2.5 in the latter groups, respectively. In our study sedated patients had higher IOP values 15–16 mm Hg (13.5–19 mm Hg) in supine position; this may be because of various reasons, including presence of hypoxemia and requiring high dose vasopressor and not using inhalational agent (which may reduce IOP) (14, 15).

In anesthetized patients, prone positioning leads to increase in IOP from 19 ± 1 to 27 ± 2 (42%) as per the study (n = 20) done by Cheng et al (11) whereas in our study IOP in NDE increased by 64% (14 mm Hg [12–18.5 mm Hg] to 23 mm Hg [20–25 mm Hg]) at 10 minutes ($T_{10\ prone}$). In the same study done by Cheng et al (11) reported that after a mean prone duration of 5–6 hours, IOP increased up to 110 % (40 ± 2 mm Hg), whereas it has increased by 128% after 14 hours of prone session in our study. Cheng et al (11) also found that IOP measured after turning the patient supine was 31 ± 2 mm Hg, a 22.5% reduction (from 40 ± 2 mm Hg) from the values measured at the end of prone position. In another study by Szmuk et al (12) in pediatric patients (n = 30), IOP reduced from 32 to 22 mm Hg (31% reduction) after turning the patient supine from prone position, where the duration of prone was 4.3 hours. In our study, there was 21% reduction in IOP in NDE from 32 mm Hg (26.5–37.5 mm Hg) measured at the end of prone position to 25 mm Hg (20.5–30 mm Hg) measured at 5 minutes after turning the patients supine.

In a study done by Deniz et al (13) with mean duration of prone position 1.6–2 hours revealed that IOP increase by 65% in DE (12.36 ± 3.3 to 20.4 ± 5.15), when compared with 21% in NDE (12.31 ± 3.3 to 14.95 ± 4.64), when the head was rotated by 45° in prone position. These values were measured immediately after turning the patient supine (11). In our study with 14 hours of median duration of prone session, the IOP values measured after 5 minutes of turning the patient supine in DE were 60% higher than baseline (15–24 mm Hg; Δ9 mm Hg), and these were 78% higher than baseline (14 to 25 mm Hg; Δ11 mm Hg) in NDE. Although clinical implication of this difference is questionable, plausible explanation could be because of decrease in venous flow due to stretching of internal jugular vein at nondependent side secondary to neck rotation during prone position. Another possibility for lower IOP values in DE in comparison with NDE may be due to release of possible prolonged compression of DE in prone position, after turning supine at the end of prone session (19, 27).

Carey et al (16) studied the effect of three different table positions on IOP in prone position and found that in the neutral (horizontal) group four of seven patients had IOP increased to above 30 mm Hg among which one measurement was above 40 mm Hg, whereas no patients in 5° or 10° reverse Trendelenburg (head up) position had any value above 30 mm Hg measured every 30 minutes during prone position (up to 120 min). Even the trend of IOP increment is lesser in 10° head up followed by 5° head up and neutral positions. We had not studied the effect of head up position on the IOP in our study. Also in our study, there was no change in ventilator settings during study period, including PEEP which had shown conflicting effects on IOP in previous studies (28, 29).

One of the limitations of our study is being relying on tonometry as gold standard as it is the feasible method for measuring IOP in critically ill patients. Also, we did not measure IOP after 30 minutes of the end of prone session to know after what time the IOP returns to baseline. The most obvious limitation of our study is lack of long-term clinical significance of raised IOP due to prone position, as ophthalmologic follow-up could be done for four survivors only. But expecting very low incidence of complication like visual loss, maintaining a registry could be considered by the international societies.

On the other side, strength of our study is measuring IOP at frequent time intervals in critically ill ARDS patients, which was not studied earlier. Our study paves the way for future research in such population to target specific ocular perfusion pressure (mean arterial pressure – IOP) in order to prevent ocular complications due to prone positioning. Also, findings in our study warrant further studies to know the effect of head position in comparison with heart and effect of periodic turning of head on IOP values among ARDS patients during prolonged prone positioning. At present we cannot recommend periodical turning of the head in such patients because of possibility of accidental dislodgement of invasive catheters.

CONCLUSIONS

There is significant increase in IOP due to prone positioning among moderate-to-severe ARDS patients, which continues to increase toward higher values just before termination of prone position. After the end of prone session, increased IOP values reduce rapidly but remain significantly higher than baseline values until 30 minutes. This study may lead to future research to find out risk factors associated with higher IOP values in prone position and their effect on ocular health which are associated with higher IOP values and may find out measures to reduce it.

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