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A randomised trial to compare the increase in intracranial pressure as correlated with the optic nerve sheath diameter during propofol versus sevoflurane-maintained anesthesia in robot-assisted laparoscopic pelvic surgery

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Abstract
Robot-assisted surgery can cause raised intracranial pressures (ICP) due to steep trendelenburg position and pneumoperitoneum. The choice of anesthetic agents can influence the ICP, which can be measured indirectly by correlating it with the sonographically measured optic nerve sheath diameter (ONSD). In this study, our primary aim was to compare the change from baseline of the ONSD during propofol versus sevoflurane-maintained anesthesia in patients undergoing robotic pelvic surgery. In this prospective, interventional, double-blinded study, we randomised 50 patients into two groups P and S. Subjects in group P received intravenous propofol infusion while those in group S received inhalation sevoflurane for maintenance of anesthesia. The ONSD at fixed intervals was noted as the mean of four values measured using ultrasound in both eyes by two independent anesthesiologists who were blinded to the group allocation. The patient demographics and baseline parameters were similar. The mean maximum rise in ONSD from baseline was 0.01 ± 0.01 cm in group P while it was 0.03 ± 0.01 cm in group S ($p = 0.001$). Percentage change from baseline in group P was $3.41 \pm 1.81\%$ and $8.00 \pm 2.95\%$ in group S ($p = 0.001$). We found a positive correlation between the duration of surgery and the maximum rise in ONSD in group S ($p = 0.003$), but not in group P. Propofol-based total intravenous anesthesia is more effective than inhalation sevoflurane in attenuating the increase in ICP as correlated with the ONSD during robotic pelvic surgery.
Clinical trial registration: Yes; Principal investigator: Nambiath Sujata; Trial number: REF/2016/11/012713 (registered); Trial registry: CTRI—http://ctri.nic.in.

Introduction

Robotic-assisted pelvic surgery has unique requirements like a very steep trendelenburg position of 30°–45° along with CO_2 pneumoperitoneum for a longer duration of time which creates specific anesthesia challenges. These include a raised airway, abdominal and ICP [1, 2]. Cerebral blood flow rises by 1.8 mL/100 g/min for each 1 mmHg rise in the partial pressure of CO_2 [3]. Additionally, retroperitoneal dissection increases the CO_2 absorption. A raised ICP can cause a fall in the cerebral perfusion pressure (CPP) leading to ischemia of the brain parenchyma and delayed recovery from anesthesia.

Sonographically measured optic nerve sheath diameter (ONSD) is a simple bedside tool that shows a good degree of correlation with the ICP with high a sensitivity and specificity. It is non-invasive and reliable with good reproducibility [4]. Hence ONSD can be used as a surrogate for direct measurement of ICP.

The anesthesia technique and the pharmacology of the maintenance agents can influence the intracranial pressure. Both propofol and volatile anesthetics are used for maintenance of anesthesia in patients undergoing robot-assisted laparoscopic surgery in steep trendelenburg position.

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Propofol reduces the cerebral blood flow, cerebral metabolic rate and ICP [5]. For this reason, it is preferred over inhalational agents in craniotomies [6].

In this study, our primary aim was to compare the effect of intravenous propofol versus inhalational sevoflurane on sonographically measured diameter of the optic nerve sheath in patients undergoing robotic pelvic surgery. The secondary objectives were to find out any correlation between the change in ONSD from the baseline and the total dose of propofol used (group P) or the duration of surgery.

Methods

This prospective, randomized double-blinded study was approved by Max Healthcare Ethics Committee (TS/MSSHSKT/MHIL/ANES/MHES/16–16; dated 10th October 2016). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

The trial was registered prior to patient enrollment at http://ctri.nic.in (REF/2016/11/012713, Principal investigator: Nambiath Sujata, Date of registration: 12th October 2017).The study was conducted at Max Super Speciality Hospital, New Delhi, India from October 2016 to May 2017. This manuscript adheres to the applicable CONSORT guidelines.

Fifty ASA I to III patients in the age group 18–80 years scheduled to undergo any robot-assisted laparoscopic pelvic surgery were recruited for the study. Patients with preexisting glaucoma, chronic obstructive pulmonary disease, raised intracranial pressure or surgery with an expected console time of more than 5 h were excluded from the study. A written informed consent was taken from all subjects. After study inclusion, the subjects were randomized by the sealed envelope method into two groups of 25 each—Group P (propofol) and Group S (sevoflurane).

The baseline ONSD was measured in all patients in both eyes by ultrasound (sonosite M Turbo Fujifilm Bothell, Washington, United states) in the preoperative area (D_B). A 13-6 MHZ hockey-stick ultrasound probe was placed transversely over the closed eyelid with the patient in supine position. Distilled water was used as a conducting medium. 2D mode was selected and the field depth adjusted to 4 cm. The diameter of the optic nerve was measured at a point 3 mm behind the retina.

In the operation theatre, a standard protocol for anesthesia induction and maintenance was followed. Standard monitors (PHILIPS Intellivue MP 20 G5-M1019A) were applied including arterial blood pressure, electrocardiography, pulse oximetry and bispectral index (BIS). All subjects were premedicated with 1 mg of intravenous midazolam, 0.2 mg of glycopyrrolate, 4 mg of ondansetron and 2 mcg per kg weight of fentanyl. After preoxygenation, anesthesia was induced with 2 mg/kg of propofol and 0.5 mg/kg of atracurium. Following intubation with appropriate sized cuffed endotracheal tube, the radial artery was cannulated for invasive arterial blood pressure monitoring. After induction of anesthesia, a nasogastric tube, esophageal temperature probe and foley's catheter was also inserted. Both eyes were covered with transparent dressing. A sequential compression device was applied on both lower limbs for deep venous thrombosis prophylaxis. To maintain body temperature, a forced-air warming blanket was used. In both groups, a continuous intravenous infusion of fentanyl at 40 mcg/h and atracurium at 20 mg/h was started after intubation. A single dose of 1 g of intravenous paracetamol was administered before skin incision.

Subjects in group P received a continuous intravenous infusion of propofol (Profol Claris Injectables Limited, Chacharwadi-Vasana, Ahmedabad, India) through an infusion pump (B.Braun-strabe 1 Melsungen Germany). The rate of infusion was initially set at 8 mg/kg/h, and then titrated to achieve a BIS score of 40–60. In group S, anesthesia was maintained with sevoflurane (Aesica Queenborough Ltd United Kingdom). The inspired concentration of sevoflurane was adjusted to maintain a BIS score of 40–60. An infusion pump containing propofol or normal saline as per group allocation was connected to all subjects. The pump and the vaporiser was covered with a sterile cloth for purposes of blinding. All patients were ventilated (Drager Primus-Deckentragsystem, Drager Medical AG & Co. KgaALubeck, Germany) using an air:oxygen mixture of 0.5 FiO_2 and tidal volumes of 6–8 ml/kg with a maximal airway pressure of 35 cm H_2O, adjusted to maintain the end-expired CO_2 partial pressure between 30 and 45 mmHg. After the laparoscopic ports were in, the operating table was tilted to a trendelenburg of 40°–45°. The da Vinci Xi ® robotic system (Intuitive Surgical, Sunnyvale, California, USA) was then docked and robot-assisted surgery was started. A total of 1500 ml of intravenous fluids was given during the surgery. In cases of excessive blood loss, it was planned to exclude the subject from the study. Boluses of 30 mcg of fentanyl or 100 mcg of phenylephrine was administered as required, in case of hypertension or hypotension respectively, to maintain the blood pressure within 30% of the baseline.

The ONSD of both eyes were measured separately at fixed time points (Table 1) during the surgery using ultrasound by two independent anesthesiologists who were experienced in ocular scans and blinded to the group allocation. These observers were not involved in patient recruitment, randomisation, group allocation or data analysis.

Towards the end of surgery, any residual neuromuscular blockade was reversed with 50 mcg/kg of neostigmine

Table 1 Time points for serial ONSD measurement

D_{PI}	ONSD 10 min post-induction
$D_{PD1/2}$	ONSD 30 min post-docking
D_{PD1}	ONSD 1 h post-docking
D_{PD2}	ONSD 2 h post-docking
D_{PD3}	ONSD 3 h post-docking
D_{PD4}	ONSD 4 h post-docking
D_{PD5}	ONSD 5 h post-docking
$D_{UD1/2}$	ONSD 30 min post-undocking
D_{PE}	ONSD 10 min post-extubation

and 20 mcg/kg of glycopyrrolate. After extubation, all subjects were shifted to the post-anesthesia care unit.

The parameters noted were demographic variables like age, weight, gender, baseline mean arterial pressure and the type of surgery. The total dose of propofol (group P), fentanyl and phenylephrine used and the duration of surgery from intubation to extubation was also noted.

Statistical methods and analysis

The sample size was determined based on the expected change from baseline of the sonographically measured ONSD during propofol versus sevoflurane-maintained anesthesia. With reference to previous study by Chui JH et al. [7] it was found that the ONSD increased from 4.5 mm (baseline) to a maximum value of 5.1 mm (13.33% increase from baseline) during sevoflurane-maintained anesthesia in the trendelenburg position. Thus we calculated a sample size of 25 patients in each group, with a power of 80% at an alpha 0.05 to detect a 10% difference in change from baseline of the sonographically measured ONSD between two groups where the standard deviation of the two groups was 12%.

Statistical testing was done with the statistical package for the social science system version SPSS 17.0. Continuous variables are presented as mean (SD) or median (IQR) for non-normally distributed data. Categorical variables are expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using Mann Whitney U test. The spearman's correlation test was used to detect correlation between variables. For all statistical tests, a p value less than 0.01 was taken to indicate a significant difference.

Results

The primary objective of our study was to compare the change from baseline of the sonographically measured ONSD during propofol versus sevoflurane-maintained anesthesia in patients undergoing robot-assisted laparoscopic pelvic surgery.

Fifty subjects were enrolled in the study. One subject in group S was excluded from analysis because the robotic system had to be undocked during surgery due to technical reasons (Fig. 1). The patient demographics in the two groups were similar with no statistical difference in age or weight. The baseline mean arterial blood pressure and baseline ONSD were also comparable between the two groups (Table 2). Twenty-two subjects in each group had undergone robot-assisted laparoscopic prostatectomy with extended pelvic lymph node dissection. Other surgeries were robot-assisted radical cystectomy with intra-corporeal ileal conduit urinary diversion with extended pelvic lymph node dissection (one in group P and two in group S) and robot-assisted radical hysterectomy and robotic pelvic and retroperitoneal lymph node dissection (one each in group P).

We analysed the mean and standard deviation values of the ONSD of both eyes noted by two independent observers at all the measured time points (Table 1). The degree of trendelenburg, end-tidal CO_2 and hemodynamics were kept constant throughout. The mean value of the highest recorded ONSD in a subject was significantly lower in group P (0.38 ± 0.04 cm) compared to group S (0.41 ± 0.04 cm) ($p = 0.007$). The mean maximum rise in ONSD from baseline was 0.01 ± 0.01 cm in group P while it was 0.03 ± 0.01 cm in group S ($p = 0.001$). Percentage change from baseline in group P was $3.41 \pm 1.8\%$ and $8.00 \pm 2.95\%$ in group S ($p = 0.001$). The variation in ONSD over time is shown in Fig. 2. The ONSD rose to a clinically significant value of more than 0.5 cm in one subject in group S (Table 3).

Though phenylephrine was required in three patients in group S, there was no statistical difference in the median use of phenylephrine or mean total dose of fentanyl between the groups. Using the Spearman's rho test, we found out that there was no correlation between the dose of propofol used in group P and the maximum rise in ONSD ($p = 0.90$). The duration of surgery defined as the time from intubation to extubation was also comparable between the two groups (Table 3). Applying the Spearman correlation test, we found that the increase in ONSD correlated with the duration of surgery (Fig. 3) in group S ($p = 0.003$) but not in group P ($p = 0.3$). Estimated blood loss was acceptable in all patients. No patient in either group had a delayed recovery from anesthesia.
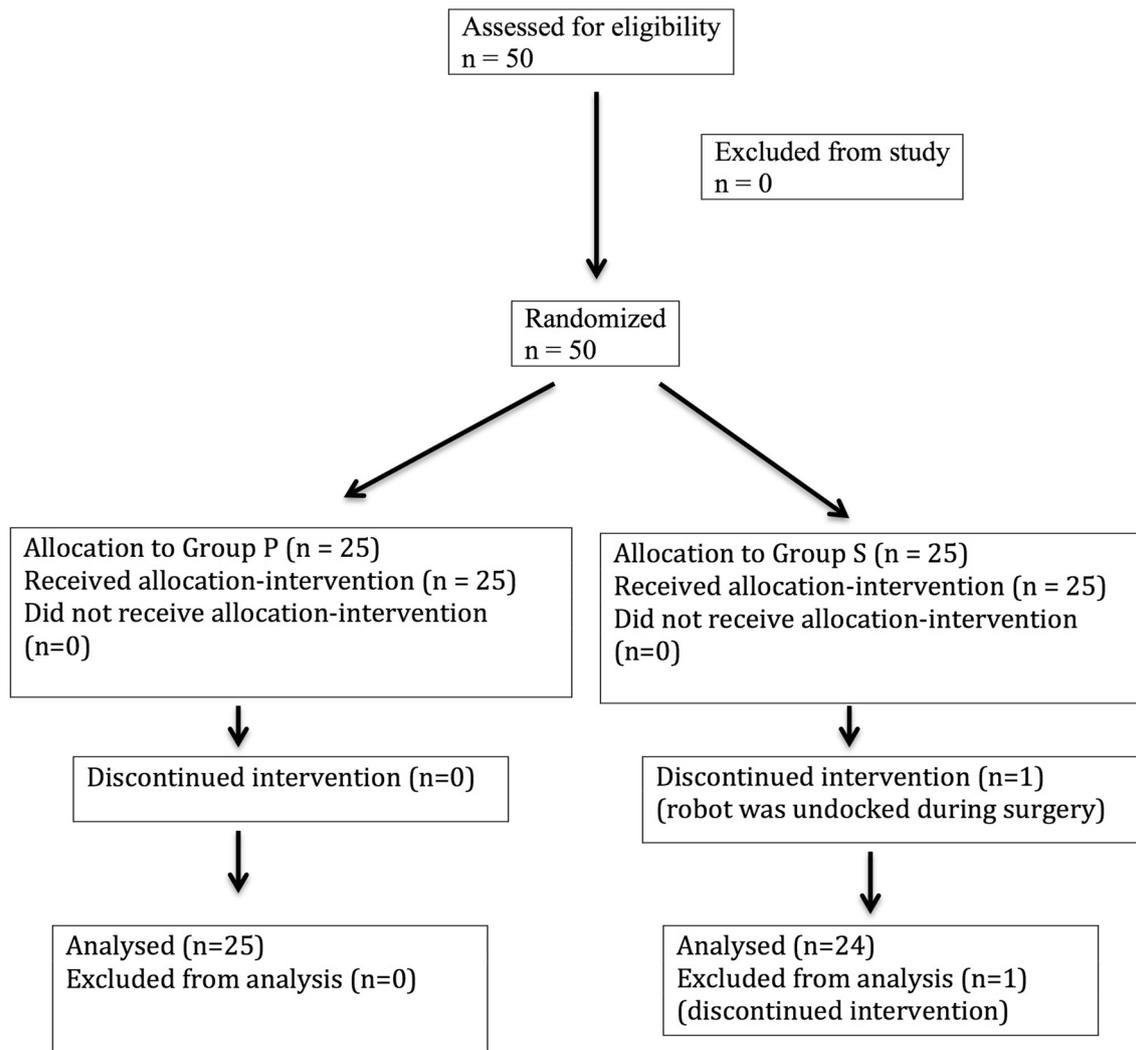
Fig. 1 Consort diagram

Table 2 Demographic data

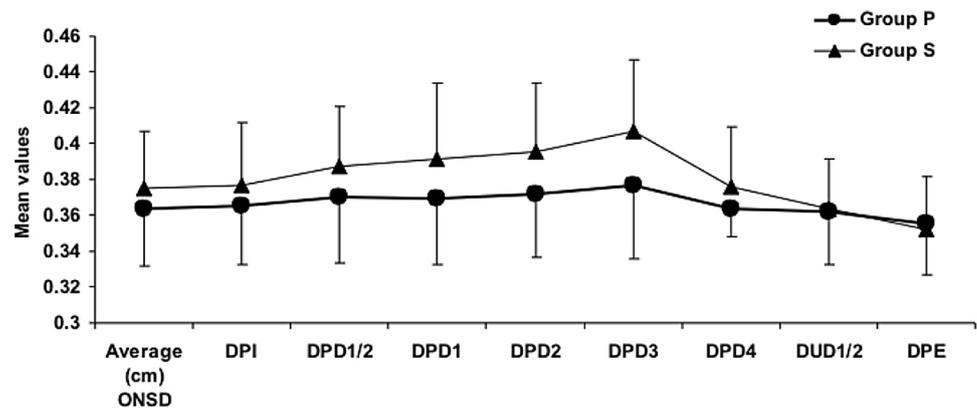| Patient data	Group P ($n=25$)	Group S ($n=24$)	p
Age[a] (years)	62.88 ± 8.14	65.33 ± 8.51	0.308
Sex[a] (Male:Female)[b]	24:1	23:1	1.000
Weight[a] (kg)	72.56 ± 9.78	78.54 ± 14.84	0.101
Mean arterial pressure—Baseline[a] (mmHg)	99.48 ± 8.71	98.42 ± 9.77	0.689

Values are mean $\pm$ SD[a] (student's t test) or ratio[b] (Fisher's exact test)

Discussion

The intracranial pressure is increased during robot-assisted laparoscopic surgeries performed in a steep trendelenburg position. Normal ICP varies between 7 and 15 mmHg in a supine adult. Pressure above 15 mmHg is considered abnormal and over 20 mmHg pathological [8]. Greater fluctuations in ICP occurs during laryngoscopy, pneumo-peritoneum, steep trendelenburg position, light planes of anesthesia and extubation. The cerebral perfusion pressure is the difference between the mean arterial pressure and ICP. Hence a raised ICP can reduce the cerebral perfusion pressure and cause cerebral ischemia. It can also delay awakening from anesthesia necessitating prolonged post-operative ventilation.

A study by Mehrpaur et al. [4] demonstrated that optic nerve ultrasound with measurement of ONSD is an accurate non-invasive technique for detection of intracranial hypertension. Rajajee et al. [9], by assessing ONSD in 536 patients with head trauma, ischemic stroke, and cranial tumor, found that increases in ICP correlates with

Fig. 2 Variation in optic nerve sheath diameter over time

Table 3 Intraoperative data

	Group P (n = 25)	Group S (n = 24)	p
ONSD—Baseline (cm)[a]	0.36 ± 0.30	0.35 ± 0.03	0.433
ONSD—maximum value (cm)[a]	0.38 ± 0.04	0.41 ± 0.04	0.007
ONSD—maximum increase from baseline[a] (cm)	0.01 ± 0.01	0.03 ± 0.01	0.001
ONSD—maximum increase from baseline[a] (%)	3.41 ± 1.81	8.00 ± 2.95	0.001
ONSD > 0.5 cm at any time point[b]	0 (0%)	1 (4%)	1.000
Duration from intubation to extubation[a] (min)	297.20 ± 73.66	337.71 ± 62.07	0.043
Total dose of fentanyl[a] (µg)	322.00 ± 65.77	328.33 ± 69.15	0.744
Total dose of phenylephrine[c] (µg)	0 (0–0)	0 (0–300)	0.071

Values are mean ± SD[a] (Student's t test), number[b] (%) (Fiher's exact test) or median[c] (min–max) (Mann Whitney U test)

*ONSD* Optic Nerve Sheath Diameter

corresponding changes in ONSD in optic nerve ultrasound. They demonstrated that the optimal cut-off for ICP > 20 cm Hg is 4.8 cm for both eyes with 96% sensitivity and 94% specificity. Hamilton et al. [10] found that ONSD increases by 0.0034 ± 0.0003 mm per mmHg rise of ICP.

An anesthetic agent which can maintain an adequate cerebral perfusion pressure while minimising any fluctuations in ICP, cerebral blood flow and cerebral oxygen requirement should be selected for procedures performed in steep trendelenburg position. Our study compared the effects of propofol with those of sevoflurane on the ONSD and indirectly the ICP, in patients undergoing robot-assisted laparoscopic pelvic surgery in a 45° trendelenberg position. In several previous studies, propofol-based total intravenous anesthesia has been reported to be superior to inhalation anesthesia for lowering ICP [6]. Strebel et al. [11] compared the effects of propofol and volatile anesthetics and concluded that propofol decreased the cerebral blood flow to a greater extent than inhaled agents while still preserving cerebral autoregulation. Propofol is cerebroprotective and is known to decrease ICP without causing hemodynamic instability [12, 13]. Our findings regarding the effect of propofol on the ONSD and hence the ICP is similar to the findings of Chui et al. [6] who demonstrated in craniotomies that propofol-maintained

and volatile-maintained anesthesia were associated with similar brain relaxation scores, although mean ICP values were lower and CPP values higher with propofol-maintained anesthesia.

Volatile anesthetics have intrinsic cerebral vasodilatory activity, resulting from direct effects on vascular smooth muscle [14]. Because this vasodilatory activity predominates under anesthesia beyond 1.0 MAC, cerebral blood flow increases significantly during general anesthesia and consequently, an increase in ICP can occur [15]. In our study, we found that the ONSD measured after induction and before pneumoperitoneum and trendelenburg positioning increased slightly from the baseline value with the use of sevoflurane, but not with propofol. This can be attributed to the vasodilatory properties of sevoflurane as well as the effects of endotracheal intubation. In the sevoflurane group, the ONSD values measured during pneumoperitoneum and trendelenburg positioning were significantly increased compared with those measured after anesthesia induction. Our findings in this group are similar to those of Kim et al. [16] who found that the mean values of ONSD at all time points after general anesthesia and during pneumoperitoneum with steep trendelenburg was significantly increased compared with that before general anesthesia. We found that the maximum

Fig. 3 Correlation between change in ONSD from the baseline and duration of surgery
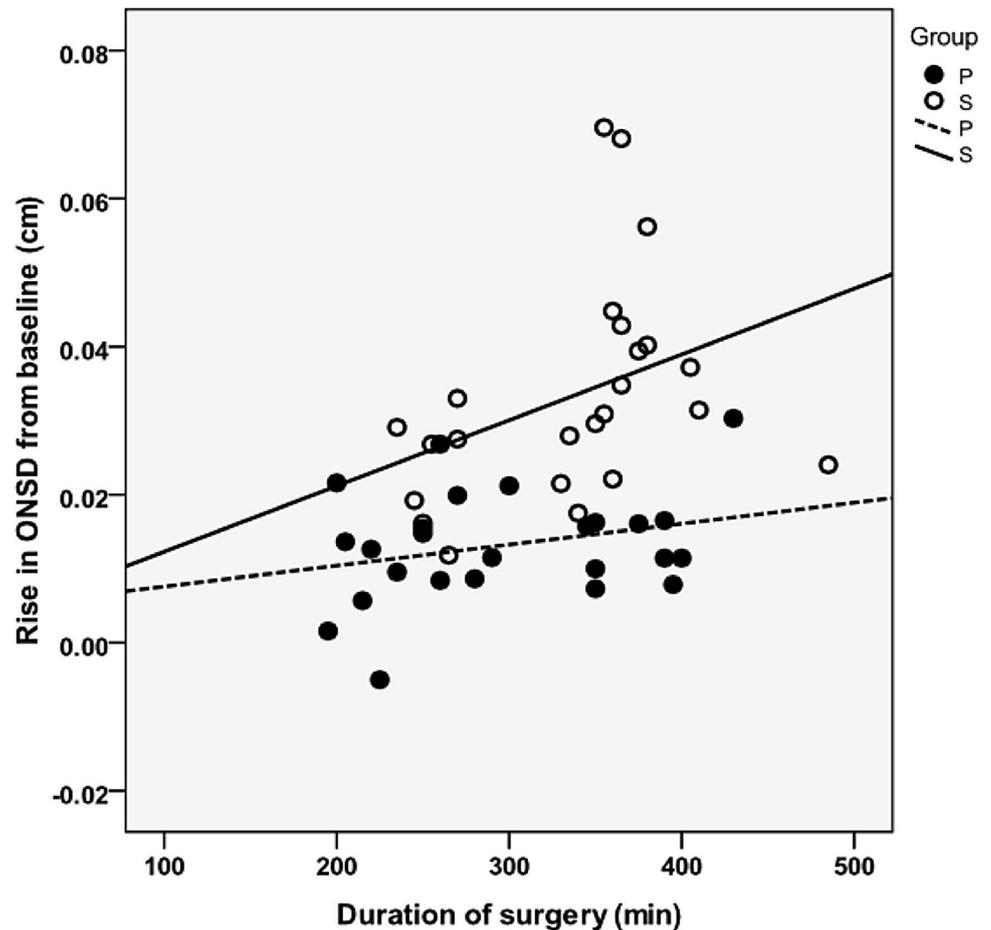
increase in ONSD occurred 3 h after docking in both groups, although the rise from baseline was significant only in the sevoflurane group. The subsequent plateauing of the ONSD and the ICP may be explained by the fact that the increased cerebral blood flow might have been partially compensated for by a translocation of the cerebrospinal fluid to the vascular component. We also found a positive correlation in the sevoflurane group between the maximum rise in ONSD and the duration of surgery. In these patients, surgery might have been prolonged because of extended pelvic lymph node excision. Retroperitoneal dissection might have caused more CO_2 absorption, leading to a further rise in ONSD. This correlation was not found in the propofol group. Though the maximum rise in ONSD was significantly lower in the propofol group, the degree of change did not correlate with the quantity of propofol used.

Only one subject in our study (group S) had an ONSD more than 0.5 cm at any point of time. Even though the ONSD increased significantly in the sevoflurane group as compared to the propofol group, the rise was not clinically significant. It might explain the absence of delayed recovery in any of our patients. This is in contrast to the study by Kim et al. [15] who observed that 15% of their enrolled patients

had ONSD values equivalent to an ICP above 20 mmHg without a reduction in cerebral oxygenation or abnormal neurologic signs. Increased CO_2 levels may have contributed to the rise in ICP in their study. However, in our study, the ventilatory settings were adjusted in all subjects to maintain an end-tidal CO_2 level between 30 and 45 mmHg. This may have been the reason why the raised ONSD values in group S were never high enough to indicate an ICP of more than 20 cm.

Our study has some limitations. The lack of experience with ocular ultrasonography may be a possible limitation. Tayal et al. [17] showed that for physicians without previous experience in ocular ultrasonography, 25 scans are needed to get an adequate image of ONSD. Experienced anesthesiologists who had already performed more than 25 scans took the measurements in our study. Inter-observer variability in ONSD values measured by ultrasonography should also be considered. As reported by Ballantyne and associates [18] ultrasonographic measurement of ONSD is an easily learned and reproducible modality and its observer variation is similar to the innate variability of the ultrasound machine. To further reduce this error, two blinded observers independently measured the ONSD in both eyes at all time points.

The mean of these four values was then taken for analysis. We studied a fixed degree of incline when establishing the trendelenburg position. But there may be a graded association between the degree of incline and the change in the ONSD. Further studies using different degrees of trendelenburg is required.

Conclusion

Total intravenous anesthesia with propofol and fentanyl maintains the ONSD and hence the ICP better than inhalational sevoflurane in robotic surgery requiring CO_2 pneumoperitoneum in the steep trendelenburg position. It may be a safer practice than inhalational anesthesia especially in very prolonged robotic surgeries.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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