Effect of dexmedetomidine on intracranial pressures during laparoscopic surgery: A randomized, placebo-controlled trial

Nishant Sahay, Umesh K. Bhadani, Subhajit Guha, Alok Himanshu, Chandni Sinha, Mamta Bara, Anubha Sahay, Alok Ranjan, Prashant Singh
Departments of Anesthesiology, ‘CFM and ‘General Surgery, AIIMS, ‘Dr. Anubha’s Imaging Centre, Patna, Bihar, India

Abstract

Background and Aims: Laparoscopic surgeries cause an increase in intracranial pressure (ICP) after creation of pneumoperitoneum. Sonographically measured, optic nerve sheath diameter (ONSD) correlates well with changes in ICP. Dexmedetomidine (Dex), an α₂ agonist is extensively used in day-care surgeries, although its effect on ICP during laparoscopy in humans has not been reported in the literature. The aim of this study was to note the effect of dexmedetomidine infusion on changes in ICPs during laparoscopic cholecystectomy.

Material and Methods: This was a prospective, randomized, placebo-controlled, double-blind study done on 60 patients scheduled for laparoscopic cholecystectomy. The study drug, dexmedetomidine hydrochloride (Dex) or placebo saline infusion, was started 10 min before induction and continued till extubation. Changes in ICP were assessed sonographically at baseline before pneumoperitoneum, 5 min after establishing pneumoperitoneum, 10 min after positioning the patient 20° head up, and 5 min after desufflation.

Results: Demographically, both groups were comparable. The ONSD showed a significant increase after pneumoperitoneum in both groups (P = 0.0001 and 0.0011). Dex group could marginally attenuate this increase (P = 0.075). After changing patient’s position to reverse Trendelenburg, ONSD increased further in both groups. Dex group could significantly attenuate the increase (P = 0.001). The ONSD did not return to baseline values till after 5 min of release of pneumoperitoneum in both groups.

Conclusion: Dexmedetomidine is effective in attenuating increase in ICP associated with laparoscopic surgeries. The benefit was marked 10 min after placing patient in the reverse Trendelenburg position during laparoscopic cholecystectomy.

Keywords: Dexmedetomidine, intracranial pressure, laparoscopy, optic nerve sheath diameter

Introduction

Laparoscopic surgeries are rapidly gaining popularity around the world. They have many documented benefits, however, one adverse effect is the increase in intracranial pressure (ICP) after pneumoperitoneum.[1-3] Mechanism of increased ICP during laparoscopy is unique because increase in intraabdominal pressure results in increased venous pressures and a stasis of intracranial blood outflow.[2,3] This results in a sudden and progressive increase in ICPs, which may be further aggravated by increase in arterial carbon dioxide (CO2) secondary to carboperitoneum and due to catecholamine surge during laparoscopy. Anesthetic drugs used intraoperatively may have a significant influence on ICPs. ICP homeostasis is critical in certain patient populations such as in trauma, emergency, and in neurosurgical patients undergoing minimally invasive surgery. Dex is extensively used in laparoscopic surgeries; however, its influence on laparoscopy that induced changes in
ICP in humans has not been reported in the literature. Optic nerve sheath diameter (ONSD) measured sonographically has been proposed as a reliable, reproducible, noninvasive monitor for ICPs. This study evaluates the influence of dexmedetomidine on laparoscopy that induced changes in ICPs using ultrasonographic measurement of the ONSD.

Material and Methods

This was a prospective, randomized, placebo-controlled, double-blind study conducted at a tertiary level hospital after obtaining approval from Institutional Ethics Committee and registry of trial. Written and informed consent has been taken from all patients before enrollment. Sample size for this study was calculated on the basis of a pilot project on 20 patients. At 5% level of significance and 90% power to detect a 10% change in ONSD after pneumoperitoneum, sample size estimated was 50 subjects. Considering dropouts and other factors leading to exclusion from the process, we included 30 subjects in each group. Patients belonging to American Society of Anesthesiologist (ASA) I and II physical status, aged between 18 and 50 years, and admitted to the hospital for elective laparoscopic cholecystectomy were included. History of any intracranial pathology, any cardiac pathology, any intraocular/ophtalmic pathology, patients with history of uncontrolled hypertension or diabetes, patients with renal and hepatic derangements, beta blocking drugs, calcium channel blockers, monoamine oxidase inhibitors, pregnant and lactating women, or patients with history of allergy to α₂-agonist were excluded from this study. Institutional fasting protocols were followed. Two intravenous (i.v.) lines were established on the morning of surgery: one for maintenance crystalloid infusion and the other for dexmedetomidine or normal saline infusion (placebo) in intraoperative period. Patients were allocated randomly to two groups as per computer-generated sequence to receive either dexmedetomidine infusion or saline infusion was started as per randomization. All patients were premedicated with fentanyl 1 μg/kg intravenously. After 3 min of preoxygenation, they were induced with propofol titrated to loss of verbal response. Muscle relaxation was facilitated using i.v. vecuronium 0.1 mg/kg body weight and airway was managed using a supraglottic device IGel in all patients. Anesthesia was maintained with 50% oxygen in nitrous oxide, sevoflurane, and vecuronium bromide. The end-tidal carbon dioxide was maintained between 35 and 45 mm Hg. Intraabdominal pressure was not allowed to exceed 12 mm Hg throughout the surgical procedure. Systolic blood pressure, diastolic blood pressure, mean arterial pressure (MAP), heart rate (HR), SpO₂, EtCO₂, ECG with ST segment analysis were monitored. About 5 min after induction, when stabilization of cardiovascular status had been achieved, baseline ONSD was measured in the supine position by ultrasonographic measurement. To measure the ONSD after application of a thick gel layer to the closed upper eyelids of patients, a linear 13-6 MHz probe (M-Turbo; Fujifilm Sonosite Inc., Tokyo, Japan) was carefully placed on the gel. Adjustments were made, gently maneuvering the probe to ensure a good image of optic nerve exiting the globe opposite optic lens. Optimal contrast between the retrobulbar echogenic fat tissue and the optic nerve appearing as a vertical hypoechoic band ensures accurate measurement of the ONSD. ONSD was measured 3 mm behind the optic disc using an electronic caliper keeping probe in a transverse plane. Values from both eyes were noted and the average ONSD value was used for calculations.

After measurement of baseline ONSD, artificial pneumoperitoneum was made by the surgeon. The insufflation pressure during the procedure was limited to 12 mm Hg. Five minutes after pneumoperitoneum creation, ONSD was measured in the manner described earlier. ONSD was next measured 10 min after assumption of the reverse Trendelenburg position during laparoscopic cholecystectomy. An electronic inclinometer was used to keep the operating table inclination at 20°. Whenever ONSD was measured, ETCo₂ and MAP were also noted simultaneously. Measurements were thus performed at four timepoints: T0 (baseline): 5 min after intubation but before pneumoperitoneum; T1: 5 min after introducing pneumoperitoneum; T2: 10 min after introducing pneumoperitoneum and change of position; and T3: 5 min after desufflation once patient had become supine.

It was decided that intraoperative mean arterial blood pressures would be kept within 20% of baseline values. If the mean BP was found to increase, sevoflurane concentrations would be increased maximum to 1.5 MAC and then inj. nitroglycerine would be used to normalize the mean BP. If the BP fell below 20% baseline value, i.v. crystalloid (ringer lactate or normal saline) boluses would be given to normalize it. Intraoperative bradycardia would be treated by i.v. atropine.
0.6 mg (20% below preoperative level). At the end of surgery, residual neuromuscular block was reversed by neostigmine 0.04 mg/kg body weight and glycopyrrolate 0.01 mg/kg body weight intravenously. Final ONSD measurement was made after desufflation once patient had remained supine for 5 min. The results obtained were statistically analyzed, and P value <0.05 has been considered as significant.

Results

A total of 52 subjects were analyzed. Eight patients dropped out of this study because in five patients, the ONSD sonographic images were unsatisfactory and in three patients laparoscopy was converted into an open procedure. Both the groups were comparable with respect to age, weight, height, and body mass index [Table 1]. Mean ONSDs measured at different time points with the standard deviations has been depicted in Table 2. ONSD measured at baseline is comparable in both groups.

After pneumoperitoneum both groups showed a statistically significant increase in ONSD, which may be seen in Table 3. Patients given dexmedetomidine showed a lesser increase in the mean ONSD as compared with the placebo NS group; however, this was not statistically significant (P = 0.075) [Table 4].

Although ONSD was comparable in both groups, 5 min after release of pneumoperitoneum, ONSD did not return to the original baseline pre-pneumoperitoneum values in either group. Table 5 shows that there was a significant residual increase in ONSD as compared to baseline values in both groups till 5 min after desufflation.

Discussion

Increase in ICPs during laparoscopy has been reported in recent literature and may be of concern in vulnerable patients. ICPs are raised after pneumoperitoneum because of an increase in the intraabdominal pressure, which raises the central venous pressures and hinders intracranial venous outflow. This is independent of the hypercarbia of pneumoperitoneum, which causes intracranial vasodilation, increases cerebral blood flow, and increases ICPs. Authors also believe that catecholamines released during laparoscopy contribute in increasing ICPs.

Intracranial hypertension is deleterious, especially in patients with existing intracranial tumors or in a polytrauma patient with traumatic brain injury undergoing diagnostic or therapeutic laparoscopy for coexisting abdominal injuries. Pneumoperitoneum increases intraabdominal pressure and positive pressure ventilation increases intrathoracic pressures in a patient where effect on the ICP is uncertain. Elevated ICP

![Figure 1: Trends of ONSD as a measure of the intracranial pressure at various time points. Note the increase in ONSDs after pneumoperitoneum. After patient positioning, dexmedetomidine attenuated the increase in intracranial pressure significantly](image-url)
promotes cerebral blood flow (CBF) deterioration, potentially leading to global or regional cerebral ischemia.

Of late, ultrasonographic measurement of ONSD has proved to have a high specificity for detecting increased ICP.\textsuperscript{[4,5]} ONSD increases instantaneously with ICP with good interobserver correlation.\textsuperscript{[6,7]} Although gold standard for measurement of ICP is an invasive monitor,\textsuperscript{[8,9]} ONSD has some significant advantages as it is an easily learnt noninvasive modality and is readily available in operation theatre.

Various drugs used intraoperatively in a laparoscopic surgery have direct influence on the ICPs. Dexmedetomidine (Dex) is a selective $\alpha_2$-agonist drug that is used to decrease the requirement of anesthetics and opioids. It attenuates the sympathoadrenal response to stress and provides a good recovery profile after laparoscopic surgeries.\textsuperscript{[10]} Dex has been found to possess neuroprotective properties and it reduces CBF.\textsuperscript{[11]} Effect of Dex on laparoscopy induced intracranial changes; however, it has not been reported in the literature yet.

Dex has a marked influence on HR and BP.\textsuperscript{[12]} It also reduces CBF. This reduction in CBF cannot be explained just by the modest reduction in HR and BP, but it causes by acting on the systemic vasculature.\textsuperscript{[12]} Authors have documented a reduction in CBF by about (40–45%) in halothane and isoflurane-anaesthetized dogs with the use of Dex, and this was not accompanied by a proportional decrease in cerebral metabolic rate (CMRO2).\textsuperscript{[13,14]} CBF reduction by Dex is through direct cerebral vasoconstriction mediated by $\alpha_2$ receptor activation.\textsuperscript{[10]} This could also be the probable mechanism for its role in pneumoperitoneum-induced ICP changes. CBF reduction may be detrimental in conditions where patients depend on CBF for cerebral perfusion, e.g., acute stroke; however, it is an advantage when ICP rises due to vasogenic conditions as in laparoscopy. Catecholamine pathways play an important role in the neuroprotective property of Dex, possibly by modulating neurotransmitter release in the central and peripheral sympathetic nervous system.\textsuperscript{[8]} Studying intracranial hypertension in dogs, McCormick \textit{et al.} found a significant dose-dependent decrease in ICP after treatment with the $\alpha_2$-agonist xylazine.\textsuperscript{[15]} $\alpha_2$-agonists are more potent vasoconstrictors than arteriolar vasoconstrictors of the cerebral vasculature.\textsuperscript{[16]} Venous compartment comprises most of the cerebral blood volume, thus $\alpha_2$-agonists could decrease ICP without greatly increasing arteriolar cerebrovascular resistance. Dose-dependent decrease in CBF was reported by Zornow \textit{et al.} at four steady-state concentrations of Dex.\textsuperscript{[10]}

In our study we noted that Dex only marginally attenuated increase in ONSD after pneumoperitoneum. Mean ONSD increased by 11.76% after pneumoperitoneum in NS group from mean ONSD 4.369 mm to 4.883 mm. In the Dex group, increase in ONSD was 7.11% from baseline. About 10 min after position change to reverse Trendelenburg..

### Table 3: Change in ONSD brought about by pneumoperitoneum

| Group                  | ONSD baseline | ONSD after pneumoperitoneum | Paired differences | Two-tailed |
|------------------------|---------------|----------------------------|--------------------|------------|
|                        | Mean (cm)     | SD                         | SEM                | 95% CI     | Significant (two-tailed) |
| DEX                    | −0.03121      | 0.01999                    | 0.00392            | Lower: −0.0392 Upper: −0.02314 | <0.0001 |
| NS                     | −0.05135      | 0.02931                    | 0.00575            | Lower: −0.06318 Upper: −1.03951 | <0.0001 |

ONSD rises significantly after pneumoperitoneum in both groups. ONSD=Optic nerve sheath diameter, SD=Standard deviation, CI=Confidence interval, SEM=Standard error of mean, Dex=Dexmedetomidine

### Table 4: ONSD between two groups compared after pneumoperitoneum and after position change

| Dex versus placebo | Difference in mean between groups | SEM | 95% CI of the difference | Significant (two-tailed) |
|--------------------|----------------------------------|-----|--------------------------|--------------------------|
| ONSD after pneumoperitoneum | −0.0171 | 0.0094 | Lower: −0.03603 Upper: 0.00180 | 0.075 |
| ONSD after position change (head up) | −0.0413 | 0.0114 | Lower: −0.06443 Upper: −0.01826 | 0.001 |

ONSDs, were not found to be significantly different between the two groups till five minutes after pneumoperitoneum ($P = 0.075$). However, 10 minutes after change in position to reverse Trendelenburg, ONSD was significantly lesser in Dex group compared with placebo ($P = 0.001$). ONSD=Optic nerve sheath diameter, SD=Standard deviation, CI=Confidence interval, SEM=Standard error of mean, Dex=Dexmedetomidine

### Table 5: Effect of Dex on ONSD after desufflation

| Groups | ONSD measure timing | Mean | SD | SEM | Significant (two-tailed) |
|--------|---------------------|------|----|-----|--------------------------|
| DEX    | ONSD baseline       | 0.4399 | 0.0365 | 0.0071 | 0.0001 |
|        | after desufflation  | 0.4627 | 0.0465 | 0.0079 |              |
| NS     | ONSD baseline       | 0.4369 | 0.0333 | 0.0065 | 0.0001 |
|        | after desufflation  | 0.4721 | 0.0413 | 0.0081 |              |

ONSD compared after desufflation to assess whether baseline values were reached. Note the significant residual enlargement till 5 min after release of pneumoperitoneum. ONSD=Optic nerve sheath diameter, SD=Standard deviation, SEM=Standard error of mean, Dex=Dexmedetomidine
position, difference in ONSD between Dex and placebo was significant [Table 4]. ONSD had risen 17.83% from baseline in NS group, whereas ONSD had risen only by 7.36% from baseline in Dex group. We believe this could be because plasma concentration of Dex required to attenuate increase in ICP due to pneumoperitoneum may have been inadequate or suboptimal at the time of pneumoperitoneum. Once plasma concentration of Dex had reached therapeutic levels, it was able to attenuate increases in ICP. Further studies with an initial bolus dose or a higher infusion rate of Dex with plasma drug level monitoring will be needed to confirm this hypothesis.

A single ONSD value that correlates with significantly high levels of ICP (>20 mm Hg) requiring possible intervention is still a matter of debate. Authors have suggested ONSD values corresponding to 20 mm Hg ICP, but these values vary between 4.8 and 5.8 mm of ONSD. Ethnic differences may influence these measurements of OSND. We considered 5.0 mm ONSD to correspond to an ICP of 20 mm Hg based on a study by Tayal et al., who invasively monitored ICP and the corresponding ONSD during a laparoscopic procedure and another similar study by Kim et al. In our study, mean ONSD after reverse Trendelenburg (head up) position in NS group was 5.148 mm, whereas patients of Dex group had a mean ONSD 4.735. In eight patients of Dex group and 17 patients of NS group, ONSD value was >5.0 mm sometimes during laparoscopic procedure. We believe, however, that a single ONSD cut-off figure to recommend intervention may be premature at this stage. Further studies may be required to ascertain a cut-off ONSD level to recommend treatment. Dex use during laparoscopy may provide some protection against raise in ICP.

Studies on Dex and cerebrovascular homeostasis encourage its use in laparoscopy. In one study, Dex at low doses was found to transiently decrease ICP by 30% in normocapnic rabbits without any intracranial pathology. Some authors noted that despite a significant increase in arterial blood pressure, ICP remained unchanged in patients who had received high doses of Dex, indicating its possible beneficial role in vasogenic causes of raised ICP. Talke et al. found that Dex administration to patients after trans-sphenoidal hypophysectomy had no effect on lumbar cerebrospinal fluid pressures. Other authors reported a significant decrease in middle cerebral artery blood flow velocity measured after administration of clonidine by transcranial Doppler sonography in healthy volunteers. Reductions in middle cerebral artery blood flow velocity with preservation of CO2 reactivity and cerebral autoregulation in healthy volunteers was demonstrated by Lam et al. It was also found that the patient pretreated with Dex shows less cerebrovascular dilation induced by either isoflurane or sevoflurane. These results indicate a pharmacodynamics response of the drug, which may be utilized during laparoscopy. However, the use of Dex for laparoscopic surgeries has some significant concerns. The foremost is bradycardia, which is a side effect of Dex and is aggravated after pneumoperitoneum. Peritoneal stretching induces a reflex vagal response causing bradycardia and cardiac arrests have also been reported after pneumoperitoneum. Increase in ICP after pneumoperitoneum may aggravate this bradycardia. Use of drugs such as morphine, propofol, vecuronium, etc., which have no vagolytic effect, may also contribute in some patients. Sinus arrest in such a situation may be expected. In our study, we needed to use atropine in 9 out of 60 patients studied. There was significant slowing of HR in patients receiving Dex. Another concern is hypotension, which is associated with bradycardia. During a laparoscopic surgery, however, this property of Dex to cause hypotension may be harvested to attenuate the hypertensive sympathetic response to laryngoscopy or the initial sympathetic response to pneumoperitoneum. Use of Dex thus results in providing stable hemodynamics during laparoscopic surgeries.

**Conclusion**

Dexmedetomidine has a protective influence on increase in ICPs associated with laparoscopy. The benefit was more marked, after more than 10 min of change from supine to reverse Trendelenburg position during laparoscopic cholecystectomy. Limitations of this study are: this was a single-center study; dexmedetomidine serum concentrations were not noted; arterial carbon dioxide and thoracic pressure monitoring would have been useful.

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**Conflicts of interest**
There are no conflicts of interest.

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