Sevoflurane sparing effect of dexmedetomidine in patients undergoing laparoscopic cholecystectomy: A randomized controlled trial

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Abstract

**Background and Aims:** Sevoflurane is an excellent but expensive anesthetic agent for laparoscopic cholecystectomy. To decrease sevoflurane consumption during surgery adjuvants like dexmedetomidine may be used. Dexmedetomidine is a recently introduced drug which alleviates the stress response of surgery, produces sedation and analgesia. We aimed to evaluate sevoflurane sparing effect of dexmedetomidine in patients undergoing laparoscopic cholecystectomy under entropy-guided general anesthesia (GA).

**Material and Methods:** In this prospective randomized control study, 100 American Society of Anesthesiologists physical status I–II adult surgical patients scheduled to undergo laparoscopic cholecystectomy were enrolled. Patients were randomly divided into two groups (n = 50). In dexmedetomidine group, patients received intravenous (IV) dexmedetomidine 0.5 µg/kg over 10 min before induction followed by 0.5 µg/kg/h infusion while in control group, patients received the same volume of normal saline.

**Results:** Sevoflurane consumption was 41% lower in dexmedetomidine group as compared to control group (7.1 [1.6] vs. 12.1 [1.9] ml, P < 0.001). A 40% reduction was observed in induction dose of propofol (83.0 [19.1] vs. 127.6 [24.8] mg, P < 0.001). Mean Riker sedation-agitation score, visual analog score for pain and Aldrete’s score were significantly lower in dexmedetomidine group as compared to control group. None of the patients experienced any significant side effects.

**Conclusion:** A 41% reduction in sevoflurane consumption was observed in patients receiving IV dexmedetomidine as an adjuvant in patients undergoing laparoscopic cholecystectomy under GA.

**Keywords:** Dexmedetomidine, laparoscopic cholecystectomy, sevoflurane

Introduction

Laparoscopic or minimal access surgeries are associated with reduced pain and hospital stay, resulting in better acceptance among patients. Due to associated adverse physiological effects of pneumoperitoneum and uncomfortable position, general anesthesia (GA) is preferred over regional anesthesia. Among inhalational agents, sevoflurane makes an excellent choice in terms of its nonpungency and rapid change in alveolar anesthetic concentration but is expensive.

To attenuate hemodynamic changes, various pharmacological agents including opioids, increased dose of inhalational agents, clonidine, beta blockers, vasodilators like nitroglycerine, and propofol have been used. Recently, dexmedetomidine has emerged as an attractive adjuvant in anesthetic practice. It is a highly selective α₂-adrenoceptor agonist reducing the adverse

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effects associated with α1 receptors. Dexmedetomidine produces a dose-dependent decrease in pathophysiologic consequences of laparoscopic surgeries which occur due to increased intra-abdominal pressure during intraoperative period.[4-8]

Both over and under dosing of anesthetic agents is not desirable for patient safety and smooth recovery. Conventionally bispectral index (BIS) scale of electroencephalography has been used to monitor the depth of anesthesia (DoA). Spectral entropy (SE), a newer technology, is more favorable as compared to BIS, as it is not affected by the use of surgical diathermy.[9] Search of the available literature revealed scant studies evaluating the effect of dexmedetomidine infusion on intraoperative sevoflurane consumption using SE guided DoA monitoring in patients undergoing laparoscopic cholecystectomy.[5,8]

So far, no study has evaluated the sparing of sevoflurane with a loading dose of 0.5 µg/kg dexmedetomidine, followed by 0.5 µg/kg/h infusion. Hence, the present study was planned. The primary outcome of the present study was to determine sevoflurane sparing effect of dexmedetomidine, used as an adjuvant under entropy-guided GA. This will help to save a costly inhalational agent like sevoflurane. Secondary outcomes studied were induction dose of propofol, hemodynamic parameters, postoperative recovery characteristics, and cost-effectiveness.

Material and Methods

This prospective randomized controlled study was conducted during May 2014–August 2015, after approval of protocol by Institutional Ethics Committee (GMCH/TA-I-(19)/2014/09559). The study was registered with Clinical Trial Registry India (CTRI/2014/06/004687). After written informed consent, 100 patients of the American Society of Anesthesiologists physical status (PS) I and II of either sex, aged between 18 and 60 years, scheduled for laparoscopic cholecystectomy under GA were enrolled (enrolled by PS). Patients with significant cardiorespiratory, hepatic or renal insufficiency, patients on beta blockers, anticonvulsants, or any other centrally acting medications, anticipated difficult airway, pregnancy, lactation, alcohol or substance abuse or patients not willing for the study were excluded from this study.

The patients were kept fasting 8 h before surgery and were premedicated with tablet alprazolam 0.25 mg and ranitidine 150 mg night before and 2 h before surgery. On arrival in the operation room, an intravenous (IV) access was secured. A standard monitoring was done which included heart rate (HR), electrocardiogram (ECG), noninvasive blood pressure (NIBP), arterial oxygen saturation (SpO2), and entropy (response entropy [RE] and state entropy [SE]) (GE Healthcare, Helsinki, Finland). Computer generated random number table was generated by an anesthesiologist who did not participate in the conduct or data analysis of the study. The patients were randomly allocated to one of the following two groups of fifty patients each by an anesthesia resident (who did not participate in the management of the patients).

- Group I: dexmedetomidine group; patients received IV dexmedetomidine (dextomid 200 µg/ml Neon Laboratories Limited, Mumbai, India) 0.5 µg/kg bolus over 10 min, followed by infusion at the rate 0.5 µg/kg/h
- Group II: control group: received same volume of normal saline as bolus IV followed by infusion.

Group allocation was concealed with use of coded sealed opaque envelopes and decoding was done at the end of the study. Both patient and the assessor were blinded to the study group. The study drug was prepared in identical looking 20 ml syringes, diluted to a total volume of 20 ml (concentration 5 µg/ml dexmedetomidine) by an anesthesiologist not involved in the collection and analysis of data. To ensure blindness, the calculated dose of the drug was according to body weight and was administered by an anesthesiologist (who was unaware of the study group) using a syringe infusion pump (Simtek Infutek 405 Infusion Pump, Simtek Medico Systems Pvt. Ltd, Mumbai, India) over 10 min, followed by infusion of same volume of the drug per hour. A similar volume of normal saline was infused in the control group through the syringe infusion pump. Five minutes after completion of bolus, GA was induced.

A standard anesthetic technique for conduct of anesthesia was used for all the patients. After preoxygenation for 3 min, anesthesia was induced with IV fentanyl 2 µg/kg followed by IV propofol (Nirfol 1% Nirma Limited, Gujarat, India) 2–2.5 mg/kg till the entropy value reached 40–60. After checking for the ability to adequately mask ventilate the patients, IV vecuronium 0.1 mg/kg was given to facilitate endotracheal intubation. Anesthesia was maintained with 39% oxygen in 60% nitrous oxide with sevoflurane (Sevoflurane, Piramal Healthcare Limited, Andhra Pradesh, India) (inspired concentration 0.4%–3%) was carried out using circle absorber with total fresh gas flow (FGF) rate of 2 L/min and volume controlled ventilation. NIBP were maintained within 20% of preinduction values, and hypotension (systolic blood pressure [SBP] <20% of baseline value) was corrected with IV fluids and if required, small dose of IV mephalermine 3 mg was administered. Bradycardia, (HR <20% of baseline value), was corrected with IV atropine 0.6 mg. SE values were maintained between 40 and 60, by adjusting inspired
sevoflurane concentration to a maximum of 3.0%, with an increment or decrement by 0.5%. After skin closure, all anesthetics (sevoflurane, N₂O and study drug) were turned off. Residual neuromuscular block was antagonized using IV glycopyrrolate 10 µg/kg and IV neostigmine 0.05 mg/ kg. Extubation was done when the following criteria were fulfilled; adequate spontaneous ventilation, SE of >90, and patient responding to verbal commands. All the patients received IV paracetamol 1 g very six hourly for postoperative analgesia.

Continuous monitoring of HR, ECG, NIBP (systolic and diastolic), SpO₂, end-tidal carbon dioxide (EtCO₂), RE and SE was done at baseline, before induction, before intubation, 1 min after intubation, after insertion of surgical trocar, initiation of pneumoperitoneum, every 5 min during surgery, end of surgery, and after extubation. Sevoflurane consumption was calculated from the observed vaporizer dial setting. Sevoflurane consumption per minute was calculated using following formula: The density of sevoflurane is 1.5; hence, 1 ml of sevoflurane will weigh 1.5 g. Molecular weight of sevoflurane = 200 g (weight of 1 M of sevoflurane). Hence, 1.5 g of sevoflurane has 1.5/200 = 0.0075 M. According to the universal gas equation, 1 M of an ideal gas will liberate 22.4 L of vapor at standard temperature and pressure. Hence, 1 ml of sevoflurane (which has 0.0075 M) will convert to 22.4 × 0.0075 = 0.168 L = 168 ml of sevoflurane vapor. If sevoflurane dial setting is 1% = 1 ml vapor/100 ml FGF. When 2 L (2000 ml) FGF is allowed, then 1% dial setting will give 20 ml of sevoflurane vapor per minute, which will translate to 0.12 ml of liquid sevoflurane per minute.

Hence, at 2 L/min FGF, with 1% inspired sevoflurane: consumption of sevoflurane will be 0.12 ml/min or 7.2 ml/h.

Inhaled and end-tidal sevoflurane concentration was recorded every 1 min from induction to the end of anesthesia. After extubating, within 2 min, Riker sedation-agitation scale[10] was applied to assess sedation and agitation. Postoperative recovery was assessed using modified Aldrete score[11] and a score of >9 was considered as a time to shift the patient to ward. Visual analog score (VAS) was measured at 30 min postoperatively.

**Statistical analysis**

We conducted a pilot trial in ten patients where the mean sevoflurane consumption was found to be 9.1 ml/h with a standard deviation (SD) of 3.8. Assuming sevoflurane consumption as the primary outcome measure, the sample size was calculated to detect a 25% change from placebo group. To achieve a power of 80%, α error of 0.05 and confidence interval of 95%, sample size was estimated to be 43 patients per group. To compensate for possible dropouts, it was decided to include fifty patients per group. The data were analyzed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used for normality of distribution. Parametric data were compared using an unpaired t-test. Nonparametric data were compared with Fisher’s exact test or Chi-square test. Data were presented as mean (SD) with $P < 0.05$ considered statistically significant.

**Results**

A total of 120 patients were screened, out of which 20 patients were excluded for not meeting inclusion criteria, and so 100 patients were enrolled for the study. The demographic characteristics of patients and duration of surgery were comparable in both groups, as shown in Table 1. Mean sevoflurane consumption in control group was significantly higher than in dexmedetomidine group [Table 2]. The difference in the mean exhaled sevoflurane concentration between the two groups at every minute till end of surgery was statistically significant as shown in Figures 1.

Mean induction dose of propofol was significantly higher in control group as compared to dexmedetomidine group [Table 2]. In dexmedetomidine group, hemodynamic parameters were significantly lower at all time points than control group [Figures 2 and 3]. The difference in the mean EtCO₂ and SpO₂ between two groups at any time during surgery was not statistically significant. Mean SE and RE values were lower in patients receiving dexmedetomidine as compared to control group till 20 min of surgery, which remained within desired range of 40–60 during the entire study period.

Mean RAS score in control group was significantly higher than in dexmedetomidine group. Mean VAS for pain at 30 min postoperatively in control group was significantly higher than in dexmedetomidine group. Mean time to shift the patient from postanesthesia care unit (PACU) to ward in control group was significantly shorter than in dexmedetomidine group.

In the present study, five out of fifty patients who received dexmedetomidine developed bradycardia (occurred intraoperatively) which promptly responded to injection atropine 0.6 mg intravenously. In the control group, eight out of fifty patients required esmolol to keep SBP and diastolic blood pressure within 20% of baseline during intubation and extubation. No other significant adverse effects were observed during the study period in patients of both groups.

The cost evaluation was done considering the following cost available at our institute. A 250 ml of liquid sevoflurane...
bottle costs Rs. 4870 to our institution, i.e., Rs 19.5/ml. Dexmedetomidine 2 ml ampoule (200 μg) costs Rs. 180, while propofol 1% w/v 20 ml vial (Neorof, Neon) costs Rs. 120 to our institution. According to mean weight of our patients, 64 kg and mean duration of surgery, 40.5 min, under strict aseptic precautions one ampoule of 200 μg dexmedetomidine will serve three patients, that is, it will cost Rs. 60 for each patient. Laparoscopic cholecystectomy being generally <1 h procedure (mean duration 30–45 min), and approximately 4–6 cases are easily performed per day in

Figure 1: Intraoperative exhaled sevoflurane concentration in dexmedetomidine versus control group. Data are represented as mean with error bars (standard deviation), *P < 0.05

Figure 2: Intraoperative heart rate during general anesthesia in dexmedetomidine versus control group. Data are represented as mean with error bars (standard deviation), *P < 0.05

Figure 3: Intraoperative systolic blood pressure during general anesthesia in dexmedetomidine versus control group. Data are represented as mean with error bars (standard deviation), *P < 0.05
our institute. We observed mean sevoflurane consumption of 12.2 ml in control group and 7.1 ml in dexmedetomidine group and mean induction dose of propofol requirement of 127.6 mg in control versus 83 mg in dexmedetomidine group. On an average, our institution conducts 1200 laparoscopic cholecystectomies per year.

**Discussion**

A 41% reduction of sevoflurane consumption per hour was observed in dexmedetomidine group as compared to control group while maintaining adequate DoA using SE and RE in patients undergoing laparoscopic cholecystectomy under GA. The patients in control group required higher dial setting of sevoflurane at all time point intraoperatively for maintaining DoA (SE 40–60) as compared to dexmedetomidine group.

Harsoor et al. reported a 28% reduction in sevoflurane consumption during 1st h in various abdominal surgeries, both open and laparoscopic surgeries. The authors used dexmedetomidine IV 1 µg/kg followed by 0.5 µg/kg/h, under entropy-guided DoA and reported a lower reduction in sevoflurane consumption as compared to the present study. This difference was possibly due to the nonstandardization of the type and duration of surgery while, in the present study only laparoscopic cholecystectomy surgeries lasting up to 1 h were included. Magalhães et al. reported 33.1% decrease in end-tidal sevoflurane concentration while using IV dexmedetomidine 1 µg/kg followed by 0.2–0.7 µg/kg/h in various surgeries. However, the authors did not calculate the actual total sevoflurane consumption in their patients. A 21% reduction in sevoflurane consumption was noted in patients receiving IV dexmedetomidine 1 µg/kg over 10 min before induction followed by 0.5 µg/kg/h as compared to fentanyl 2 µg/kg in control group. The authors did not use opioids along with dexmedetomidine as they hypothesized that it may be a confounding factor regarding the evaluation of sparing effect of dexmedetomidine on the requirement of inhalation agent and diclofenac 1 mg/kg was used intraoperatively for analgesia in patients of both groups. In the present study, a greater reduction in total sevoflurane consumption was observed because, with dexmedetomidine, IV fentanyl was used intraoperatively. Moreover, 41% sevoflurane sparing effect with IV dexmedetomidine was due to hypnotic and supraspinal analgesic effects of dexmedetomidine occurring due to suppression of neuronal firing in the locus coeruleus and inhibition of norepinephrine release. The analgesic effect occurs at spinal level as a result of direct suppression of pain transmission by reducing the release of pronociceptive transmitters, substance P and glutamate. Furthermore, the activation of α2-adrenoceptors located at nerve endings has a possible role in the analgesic mechanisms by preventing norepinephrine release.

There is no single consensus overdose to be used as an adjuvant to GA but higher dosage may cause significant bradycardia. An earlier study used a similar loading dose of dexmedetomidine to effectively attenuate the pressor response to laryngoscopy and intubation without any adverse effects. We chose dexmedetomidine IV 0.5 µg/kg for induction and 0.5 µg/kg/h for maintenance in patients undergoing laparoscopic cholecystectomy GA (sevoflurane) which has not been reported.

In this study, there was a 40% reduction in induction dose of propofol during GA. This finding is supported by Anjum et al. and Ghodki et al. These authors used different agents for maintenance of anesthesia as contrast to sevoflurane in the present study.

**Table 1: Patient baseline characteristics and duration of surgery**

| Variable               | Dexmedetomidine group (n=50) | Control group (n=50) |
|------------------------|-----------------------------|----------------------|
| Age (years)            | 43.5 (11.8)                 | 44.3 (12.5)          |
| Sex (n), male/female   | 8/42                        | 13/37                |
| Weight (kg)            | 65.0 (11.2)                 | 62.9 (8.8)           |
| ASA status (n), 1/2    | 33/17                       | 39/11                |
| Duration of surgery (min) | 39.1 (9.7)               | 41.8 (9.8)          |

Values are reported as number of patients or mean (SD). ASA = American Society of Anesthesiologists, SD = Standard deviation

**Table 2: Induction dose of propofol, Riker sedation-agitation score, visual analogue score, shifting time from postanesthesia care unit to ward, sevoflurane consumption in both groups**

| Variable               | Dexmedetomidine group (n=50) | Control group (n=50) | P       |
|------------------------|-----------------------------|----------------------|---------|
| Induction dose of propofol (mg) | 83.0 (19.1)                 | 127.6 (24.8)         | 0.001   |
| RSAS                   | 3.2 (0.6)                   | 3.9 (0.9)            | 0.001   |
| VAS                    | 2.3 (1.0)                   | 5.8 (1.3)            | 0.001   |
| PACU to ward time (min) | 69.7 (14.1)                 | 61.4 (5.7)           | 0.001   |
| Sevoflurane consumption (ml/h) | 7.1 (1.6)                   | 12.1 (1.9)           | 0.001   |

Values are reported as mean (SD). RSAS = Riker sedation-agitation score, VAS = Visual analogue score, PACU = Postanesthesia care unit, SD = Standard deviation
There is conflicting evidence in literature regarding use of BIS and SE for monitoring DoA with dexmedetomidine during induction in GA. Recently, Chen et al. mentioned that use of dexmedetomidine with propofol during induction in GA may not reliably indicate BIS and may rather lead to loss of consciousness at higher BIS value. Use of SE is highly accurate in discriminating dexmedetomidine-induced sleep from the awake state but there is extensive interindividual variability suggesting poor performance of BIS and entropy in differentiating consciousness from unconsciousness. In the present study, attainment of SE value of 40–60 was considered as the propofol induction dose because a pharmacological agent may obtund a patient’s willingness to obey commands and initiate movement due to drug-induced suppression of motor regions in the brain. Moreover, clinical unresponsiveness does not unequivocally mean unconsciousness. BIS and SE are designed to measure hypnosis during surgical anesthesia with background noxious stimuli and quite perform quite well in deep, steady state anesthesia but may not detect the transition from consciousness to unconsciousness. But currently, BIS and SE still remains a readily available method for monitoring DoA during GA.

Intraoperative bradycardia has higher risk of development with higher doses of dexmedetomidine. Harsoor et al. reported significant bradycardia in three out of twenty patients receiving dexmedetomidine in a dose of 1 µg/kg bolus followed by 0.5 µg/kg/h infusion. The incidence of bradycardia was less in our study probably due to lower dose of dexmedetomidine as compared to Harsoor et al. None of the patients in dexmedetomidine group required any treatment for hypotension.

RSA was lower in dexmedetomidine group because of centrally mediated action of dexmedetomidine on alpha receptors. A study in elderly patients undergoing orthopedic surgery suggested that dexmedetomidine (0.4 µg/kg/h) can be used as an effective adjuvant drug intraoperatively to ensure a smooth recovery.

We observed a 60% decrease in average VASs in patients who received dexmedetomidine as compared to control group. Dexmedetomidine produces analgesic effects through α2-adrenergic receptors in the dorsal horn of the spinal cord, which modulates release of substance P. Lower rescue analgesics were required in patients undergoing spine surgeries who received dexmedetomidine in dose. Use of dexmedetomidine infusion decreased the requirement of fentanyl by 40%.

Modified Aldrete’s score was 12% lower in patients receiving dexmedetomidine as compared to control. Sedation was the most common reason for longer PACU stay and delayed shifting to the ward. Our results are consistent with Godhki et al. and Manne et al., who reported significantly higher sedation scores in patients who received dexmedetomidine as compared to control.

There are certain limitations of the present study; low flow anesthesia was not used due to the fact that first, compound A, a nephrototoxic vinyl ether is formed when high inspired concentration of sevoflurane with a low FGF (<1 L/min) is used for long periods and second, a quick increase or decrease in inspired concentration of inhalational agent cannot be achieved with low flow anesthesia as required in stressful surgeries like laparoscopic cholecystectomy. Third, no further subanalysis of hemodynamic characteristics of hypertensive and nonhypertensive patients was done. Fourth, we did not measure the time from stopping of dexmedetomidine to consciousness of the patient. Further randomized controlled trials are required in larger sample size, including patients with cardiovascular comorbidities and in longer duration surgeries to analyze sevoflurane sparing effect.

Conclusion

A 41% reduction in sevoflurane consumption was found in patients receiving IV dexmedetomidine as an adjuvant in patients scheduled for laparoscopic cholecystectomy under GA with significant cost reduction.

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Conflicts of interest

There are no conflicts of interest.

References

1. Grace PA, Qureshi A, Coleman J, Keane R, McEntee G, Broe P et al. Reduced postoperative hospitalization after laparoscopic cholecystectomy. Br J Surg 1991;78:160-2.
2. Martin JL. Inhaled anesthetics: Metabolism and toxicity. In: Miller RD, editor. Miller’s Anaesthesia. 7th ed. New York: Churchill Livingstone Elsevier; 2009. p. 1409-11.
3. Joris JL. Anaesthesia for laparoscopic surgery. In: Miller RD, editor. Miller’s Anaesthesia. 7th ed. New York: Churchill Livingstone Elsevier; 2009. p. 4689-90.
4. Aantaa R, Jaakola ML, Kallio A, Kanto J. Reduction of the minimum alveolar concentration of isoflurane by dexmedetomidine. Anesthesiology 1997;86:1055-60.
5. Patel CR, Engineer SR, Shah BJ, Madhu S. The effect of dexmedetomidine continuous infusion as an adjuvant to general anesthesia on sevoflurane requirements: A study based on entropy analysis. J Anaesthesiol Clin Pharmacol 2013;29:318-22.

6. Ibáñez ME, Muñoz HR, Brandes V, Morales AL. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. Anesth Analg 2004;98:60-3.

7. Keniya VM, Ladi S, Naphade R. Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. Indian J Anaesth 2011;55:352-7.

8. Hansoo SR, Rani DD, Lathashree S, Nethra SS, Sudheesha K. Effect of intraoperative Dexmedetomidine infusion on Sevoflurane requirement and blood glucose levels during entropy-guided general anesthesia. J Anaesthesiol Clin Pharmacol 2014;30:25-30.

9. Soto R, Nguyen TC, Smith RA. A comparison of bispectral index and entropy, or how to misinterpret both. Anesth Analg 2005;100:1059-61.

10. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med 1999;27:1325-9.

11. Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth 1995;7:89-91.

12. Magalhães E, Govêia CS, Ladeira LC, Espíndola BV. Relationship between dexmedetomidine continuous infusion and end-tidal sevoflurane concentration, monitored by bispectral analysis. Rev Bras Anestesiol 2004;54:303-10.

13. Vuyk J, Sisten E, Reekers M. Intravenous anesthetics. In: Miller RD, ed. Miller’s Anesthesia. 8th ed. New York: Churchill Livingstone Elsevier; 2015. p. 855-9.

14. Kaskinoro K, Maksimow A, Långsjö J, Aantaa R, Jääskeläinen S, Kaisti K, et al. Wide inter-individual variability of bispectral index and spectral entropy at loss of consciousness during increasing concentrations of dexmedetomidine, propofol, and sevoflurane. Br J Anaesth 2011;107:573-80.

15. Kumari K, Gombar S, Kapoor D, Sandhu HS. Clinical study to evaluate the role of preoperative dexmedetomidine in attenuation of hemodynamic response to direct laryngoscopy and tracheal intubation. Acta Anaesthesiol Taiwan 2015;53:123-30.

16. Anjum N, Tabish H, Debdas S, Bani HR, Rajat C, Anjana Basu GD. Effects of dexmedetomidine and clonidine as propofol adjuvants on intra-operative hemodynamics and recovery profiles in patients undergoing laparoscopic cholecystectomy: A prospective randomized comparative study. Avicenna J Med 2015;5:67-73.

17. Ghodki PS, Thombre SK, Sardesai SP, Harnagle KD. Dexmedetomidine as an anaesthetic adjuvant in laparoscopic surgery: An observational study using entropy monitoring. J Anaesthesiol Clin Pharmacol 2012;28:334-8.

18. Chen Z, Shao DH, Hang LH. Effects of dexmedetomidine on performance of bispectral index as an indicator of loss of consciousness during propofol administration. Swiss Med Wkly 2013;143:w13762.

19. Maksimow A, Snapir A, Särkelä M, Kentala E, Koskenvuo J, Posti J, et al. Assessing the depth of dexmedetomidine-induced sedation with electroencephalogram (EEG)-based spectral entropy. Acta Anaesthesiol Scand 2007;51:22-30.

20. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. Br J Anaesth 2002;88:669-75.

21. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. Science 2008;322:876-80.

22. Srivastava VK, Nagle V, Agrawal S, Kumar D, Verma A, Kedia S. Comparative evaluation of dexmedetomidine and esmolol on hemodynamic responses during laparoscopic cholecystectomy. J Clin Diagn Res 2015;9:UC01-5.

23. Gulbani M, Gurha P, Dass P. Kulkshreshtha N. Comparative analysis of efficacy of lignocaine 1.5 mg/kg and two different doses of dexmedetomidine (0.5 µg/kg and 1 µg/kg) in attenuating the hemodynamic pressure response to laryngoscopy and intubation. Anesth Essays Res 2015;9:5-14.

24. Piao G, Wu J. Systematic assessment of dexmedetomidine as an anesthetic agent: A meta-analysis of randomized controlled trials. Arch Med Sci 2014;10:19-24.

25. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-94.

26. Kim DJ, Kim SH, So KY, Jung KT. Effects of dexmedetomidine on smooth emergence from anaesthesia in elderly patients undergoing orthopaedic surgery. BMC Anesthesiol 2015;15:139.

27. Garg N, Panda NB, Gandhi KA, Bhagat H, Batra YK, Grover VK, et al. Comparison of small dose ketamine and dexmedetomidine infusion for postoperative analgesia in spine surgery – A prospective randomized double-blind placebo controlled study. J Neurosurg Anesthesiol 2016;28:27-31.

28. Manne GR, Upadhyay MR, Swadia V. Effects of low dose dexmedetomidine infusion on haemodynamic stress response, sedation and post-operative analgesia requirement in patients undergoing laparoscopic cholecystectomy. Indian J Anaesth 2014;58:726-31.

29. Li Y, Li YC, Zhang YN, Liu SJ, Zhou YM, Wang CS, et al. Degradation products of different water content sevoflurane in carbon dioxide absorbents by gas chromatography-mass spectrometry analysis. Chin Med J (Engl) 2011;124:1050-4.