Original Article

# Quantifying influence of epidural analgesia on entropy guided general anaesthesia using sevoflurane – A randomised controlled trial

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## ABSTRACT

**Background and Aims:** Minimum alveolar concentration (MAC) of inhalational agent denotes the requirement of it to maintain adequate plane of general anaesthesia. The precision to the maintenance of anaesthesia can be further guided by use of entropy to titrate the depth of anaesthesia. Regional anaesthesia and the concomitant deafferentation will decrease the need of general anaesthetics. We conducted a randomised double-blind trial to quantify the effect of addition of regional anaesthesia to sevoflurane based general anaesthesia technique guided by entropy to achieve satisfactory depth of anaesthesia. **Methods:** Forty patients posted for elective laparotomies were randomised to two groups. All patients received a bolus followed by an epidural infusion. Group GE (general anaesthesia + epidural bupivacaine) received 0.25% epidural bupivacaine and Group GS received epidural saline. Both groups received narcotic, relaxant and sevoflurane anaesthesia guided by entropy monitoring. The state entropy (SE) was maintained at 40–60 by titrating end tidal sevoflurane concentration ($ET_{sevo}$). Heart rate, blood pressure, $SpO_2$, end tidal carbon dioxide ($ETCO_2$) and sevoflurane were recorded. **Results:** Both groups were similar in heart rate and mean blood pressure during anaesthesia maintenance. The minimum $ET_{Sevo}$ required to maintain entropy between 40 and 60 in group GE was 0.53% compared to 0.95% in group GS the epidural saline group ($P < 0.001$). The end-tidal sevoflurane requirement to maintain adequate depth of anaesthesia dropped by 44.2% in group GE. **Conclusion:** Lower concentrations of volatile anaesthetic are required when entropy-guided general anaesthesia is combined with regional blockade.

**Key words:** End tidal, entropy, epidural, sevoflurane

## INTRODUCTION

The aim of general anaesthesia is to produce reversible unconsciousness with loss of movement to painful stimuli and lack of recall to surgical intervention. The dependence on muscle relaxants during 60s and 70s led to "lack of movement", an unreliable sign of adequate anaesthesia and complications like awareness under general anaesthesia surfaced. The concept of minimal alveolar concentration (MAC) was propagated when measurement of end tidal concentration became practical. A search for monitoring depth of anaesthesia resulted in the introduction of the Bispectral index monitor (BIS) and the Electroencephalogram (EEG) entropy monitor. While using inhalational agents, it has been shown that increasing the end tidal sevoflurane ($ET_{Sevo}$) from 1.3% to 2.5% produced a corresponding decrease



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in state entropy values and vice versa[1] as well as a correlation to movement and non-movement. The combination of regional analgesia with general anaesthesia technique for major abdominal surgeries is commonly practiced. Studies have been conducted showing a reduction in the requirement of inhalational anaesthetic agents when combined with epidural analgesia.[2-4] Some of these studies looked at a single time point ($MAC_{BIS50}$- minimum alveolar concentration of sevoflurane for maintaining bispectral index below 50) and others assessed response to different concentrations of local anaesthetics.

There are no studies quantifying the requirements of sevoflurane when general anaesthesia was combined with epidural blockade. We conducted this double blinded study to quantify the reduction in sevoflurane requirements while maintaining entropy between 40 and 60.

## METHODS

After approval from the Institutional Research and Human Ethics Committee, (MGMCRI 2013 MD/MS-02- 27/02/2103) a randomised double-blind prospective study was conducted in 40 patients between 18-65 years age, American Society of Anesthesiologists' (ASA) physical status I and II, posted for elective laparotomies. The study was conducted between March 2013 to October 2014. The study was conducted in accordance with the principles of the declaration of Helsinki. A written informed consent was taken from each patient recruited for the study. Patients with history of major back problems, difficult airway, allergy to local anaesthetics, coagulation abnormalities, morbid obesity, severe malnutrition and those on anti-convulsants or anti-depressants were excluded.

The patients were kept nil per oral (NPO) for 8 hours and pre-medicated with oral ranitidine 150 mg, diazepam 10 mg and metoclopramide 10 mg the previous night and on the morning of surgery. Patients were preloaded with 10 mL/kg of Ringer's lactate solution in the pre-operative holding area. Injection Morphine 0.15 mg/kg was given intramuscularly 45 minutes before the start of surgery. MACBAR for sevoflurane is 3.3 times the MAC. Addition of narcotic brings it down to 1.3. Hence narcotic was added. The patients were shifted into the operating theatre (OT) and routine monitoring of electrocardiogram (ECG), non-invasive blood pressure (NIBP) and pulse oximetry ($SpO_2$) was done using GE Carescape B850 patient monitor. The disposable entropy sensor was attached to the patient's forehead after degreasing the skin, according to the manufacturer's instructions. Datex–Ohmeda S/5™ M entropy module was used to monitor the State Entropy (SE) and Response Entropy (RE). The anaesthetic gas module E-CAiO (Datex-Ohmeda) incorporated into the AISYS anaesthesia machine was used to analyse the anaesthetic agent concentration and the $ETCO_2$. In end tidal (Et control) control mode, the same module gave feedback to the anaesthesia machine for achieving the targets. In all patients, epidural catheter was placed in the $T_{12}$-$L_1$ inter space and introduced 4 cm from the level of insertion. As a test dose, 3 mL of saline with 1:200,000 adrenaline was given to exclude intravascular placement. Fentanyl 2 μg/kg and midazolam 0.03 mg/kg was given intravenously as premedication on table. The AISYS anaesthesia machine with end tidal control software loaded was used in all cases. After pre-oxygenation, patients were induced with thiopentone 5 mg/kg IV. Vecuronium 0.1 mg/kg IV was given after they were unconscious and ventilated in Et control mode with a target sevoflurane concentration of 1.5% and target oxygen of 30%. The second carrier gas was chosen as nitrous oxide. A flow rate of 4 L/minute was used in the beginning. After 4 minutes, patients were intubated with appropriate sized endotracheal tube. Ventilation was started in volume control mode, with a tidal volume of 10 mL/kg and a respiratory rate of 12/minute. Ventilatory parameters were adjusted to maintain an $ETCO_2$ between 32-36 mm Hg. After stabilising the patient, gas flow was set to minimum (500 mL) with the target $ET_{Sevo}$ of 1.5% and target $ETO_2$ of 30%. Before the surgical incision, patients were allocated by a sealed envelope technique into one of the groups – group GE received GA with epidural 0.25% bupivacaine while group GS received GA with epidural saline. The primary investigator was blinded to the group allocation. An independent investigator, who was not involved in the study, prepared the study drug. A bolus of 15 mL from the loaded 50 mL syringe was injected through the epidural catheter and the remaining solution was set up with a syringe infusion pump (Perfusor Compact Syringe Pump) to deliver 10 mL/h. HR, SBP, DBP, $SpO_2$, Temperature, $ETCO_2$, $ET_{Sevo}$ and entropy were recorded every five minutes for the entire duration of the surgery. S5 Collect™ software was used to collect real time data from the Carescape™ B850 monitor integrated to the anaesthesia machine for offline analysis. The target

end tidal Sevoflurane ($ET_{Sevo}$) concentration was reduced in steps of 0.2% every 10 minutes as long as entropy remained between 40 and 60. If the entropy value went above 60, $ET_{Sevo}$ was increased by 0.2%. Anaesthesia was continued with the lowest $ET_{Sevo}$ concentration required to maintain entropy between 40 and 60. Fentanyl 0.5 μg/kg IV was repeated every hour during the intraoperative period irrespective of the entropy value. Hypotension occurring due to the technique was corrected with IV fluids and bolus doses of ephedrine 5 mg IV. Hypotension occurring due to blood loss was managed with IV fluids and blood transfusion as and when required. If the heart rate went below 50/minute, it was managed with glycopyrrolate 0.2 mg IV. The epidural infusion was stopped 15 minutes before the end of surgery and an epidural bolus of 8 mL of 0.125% bupivacaine with 3 mg morphine was administered for postoperative pain relief. At the end of surgery, neuromuscular blockade was reversed with neostigmine 50 μg/kg IV and glycopyrrolate 0.01 mg/kg IV. All patients were assessed 24 hours postoperatively for awareness using a modified Brice questionnaire. Post-operative pain management was done as described prior.

Demographic profile, haemodynamic variation, changes in end tidal $N_2O$, changes in entropy and changes in MAC were compared by the unpaired *t*-test (IBM SPSS 2015). The sample size was determined by a power analysis based on the variability observed in our pilot study (SD 0.2%) and the ability to detect a difference in end tidal Sevoflurane of 0.2% with power set at 0.8 and alpha value of 0.05. A minimum sample size of 16 per limb was calculated. We selected 40 patients for our study considering the dropouts.

## RESULTS

Forty patients admitted to the surgical wards and posted for elective laparotomy successfully completed the study. The demographic profile was comparable between the two groups [Table 1]. Mean heart rate and mean arterial pressure (MAP) from baseline to 120 minutes are depicted in Figure 1. In GE Group, there was a significant fall in MAP after epidural bolus ($P = 0.038$) when compared to baseline and pre-induction. In GS Group, there was a significant fall in MAP at intubation ($P = 0.01$), after epidural bolus ($P = 0.007$) and at 5 minutes ($P = 0.00$) when compared to pre-induction. This effect on haemodynamics may look contradicting. It's not a must that epidural should produce a fall of blood pressure. The epidural was given after the induction of GA. The anaesthesiologist was blinded to the infusion. We can infer that a possible fall of blood pressure following GA overshadowed the effect of epidural.

**Table 1: Demographic profile**

| Category | Group GE (*n*=20) | Group GS (*n*=20) | *P* |
|---|---|---|---|
| Age Median (Years) (Range) | 46 (19-65) | 43 (25-55) | 0.816 |
| Gender (M/F) | 12/8 | 8/12 | 0.343 |
| Weight Median (Kgs) (Range) | 57 (42-85) | 57 (38-76) | 0.823 |
| ASA (1/2) | 17/3 | 14/6 | 0.451 |

Nitrous oxide remained constant at 60% in all cases throughout maintenance phase of anaesthesia. Statistically there was no significant difference between the two groups. Changes of entropy over time [Figure 2]: The induction of anaesthesia with thiopentone brought down the entropy between 20 and 30. During maintenance of anaesthesia, the entropy values were maintained in the range of 40 and 60 [Figure 3]. When both groups were compared with each other, there was no statistically significant difference.

Lowest intraoperative $ET_{Sevo}$: In GE Group, the mean lowest value of $ET_{Sevo}$ obtained was 0.53 (95% Confidence Interval 0.37.0.68) while it was 0.95 (95% Confidence Interval 0.83, 1.07) in Group GS [Figure 4]. This difference was found to be statistically significant ($P < 0.05$). The lowest MAC was noted in all cases and controls. The mean of the lowest MAC was calculated and plotted from lowest value to highest value [Figure 5]. In Group GE, the mean lowest MAC was 0.86 (95% Confidence Interval 0.78, 0.93) while it was 1.06 (Confidence Interval 1.00, 1.12) for the epidural saline group. This difference in MAC was statistically significant ($P = 0.018$). There were no reports of intra-operative awareness in the patients who participated in the study.

## DISCUSSION

The development of new techniques of monitoring and adequacy or depth of anaesthesia has led to the use of various monitors like BIS™, Entropy$^S$, Narcotrend $^R$ etc., which have helped to adjust the usage of volatile anaesthetics[5] and has brought down the incidence of awareness in modern day clinical practice.[6] The addition of a regional anaesthetic technique reduces the requirement of general anaesthetic drugs and volatile agents.[2,7-9] We studied the effect of using epidural analgesia combined with

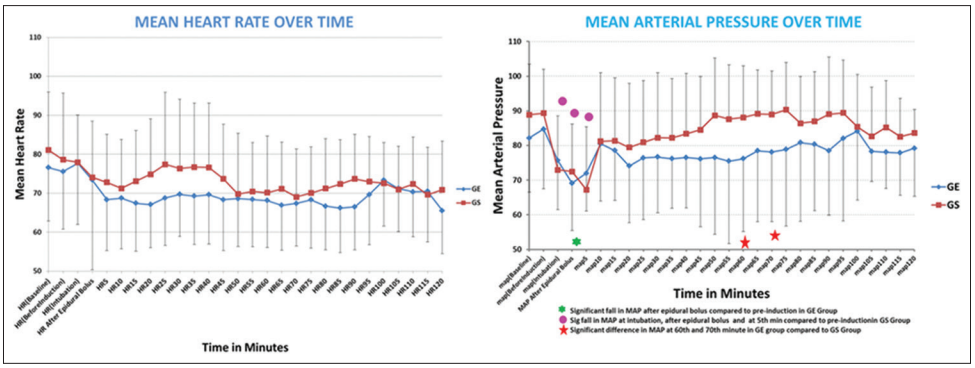


**Figure 1:** Changes in Mean Arterial Pressure and Heart rate in the two groups (The dots represent mean values and error bars represent SD which have been indicated on one side for clarity)

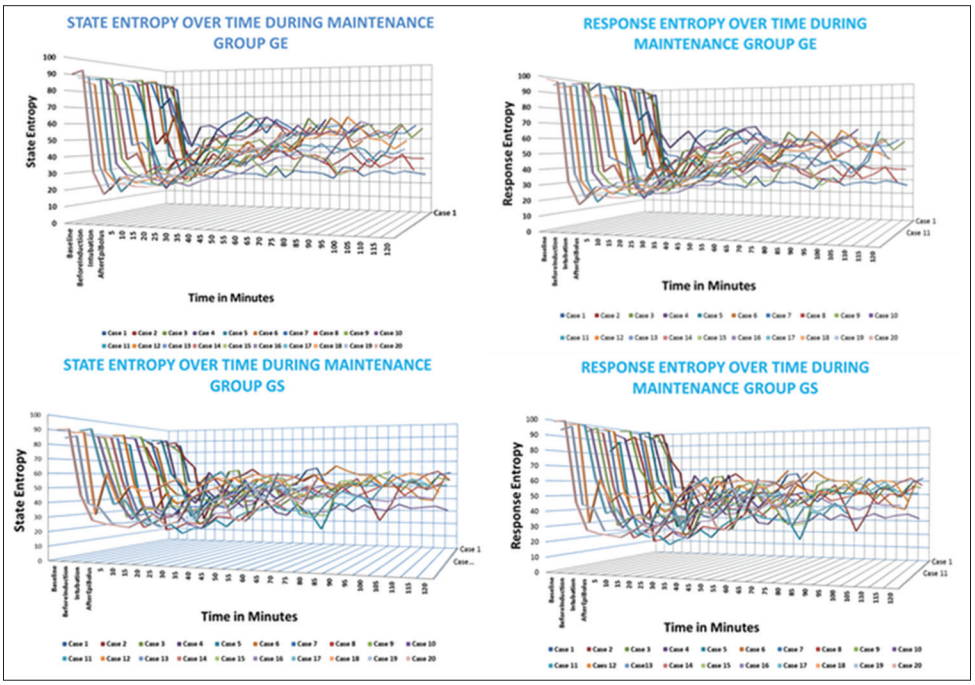


**Figure 2:** Changes in State and Response Entropy over time in both groups

general anaesthesia guided by entropy monitoring on reduction of volatile agent requirement.

The MAC, End tidal agent concentrations of inhalational agents gives a guide to titrate the depth of anaesthesia along with BIS™ and entropy. There are various factors like age, obesity and ASA physical status, disease condition which are important in altering MAC requirements during general anaesthesia. Extremes of age affect MAC value of inhalational agents. To avoid the effect of extremes of age on MAC, patients less than 18 years of age and more than 65 years were excluded from our study.[10] Morbid obesity alters the sevoflurane uptake characteristics. Hence, no morbidly obese or severely malnourished patients were included. Our study involved patients with ASA physical status 1 and 2. This group of patients was chosen so as to avoid interference from other systemic illnesses.

Patients posted for elective laparotomies were chosen so as to ensure uniformity in surgical stimulus in the area blocked by the epidural. A changing intensity of surgical stimulus makes a difference in the requirement of anaesthetics. Aime *et al.*[1] included patients who underwent different surgical procedures and thereby induced variable surgical stimuli. The interpretation of MAC reduction may not be appropriate in such cases.

The changes in haemodynamic parameters during general anaesthesia with regional block are attributed to various factors. A fall in MAP was observed immediately after induction in patients in both

groups. This could be attributed to thiopentone. The effect of the epidural bupivacaine was masked by the use of vasopressors during the maintenance of general anaesthesia. In case of hypotension there is a reduction in the cardiac output and an increase in alveolar agent concentration. But as the cardiac output is reduced, the cerebral perfusion is decreased and the effect site concentration of the drug is in turn increased. This would in turn lead to a lower entropy value. Vasopressors were used to nullify the effect of decreased cardiac output on the brain in our study. Frequently, episodes of hypotension prompt the anesthesiologist to taper the concentration of volatile anaesthetic. This can lead to a critically low concentration of agent and probable awareness. The addition of a regional block to general anaesthesia is not routinely performed or advocated for fear of unstable haemodynamics and cardiovascular depression. Numerous studies have been done to describe the benefits and effects of a combined epidural-general anaesthetic technique[2,3,7,9] Narcotics are known to cause a reduction in anaesthetic agent requirement[11] with no significant change in entropy values (Amie *et al.*). We considered it necessary to ensure analgesia for the epidural saline group as well thereby necessitating the use of intermittent doses of fentanyl.

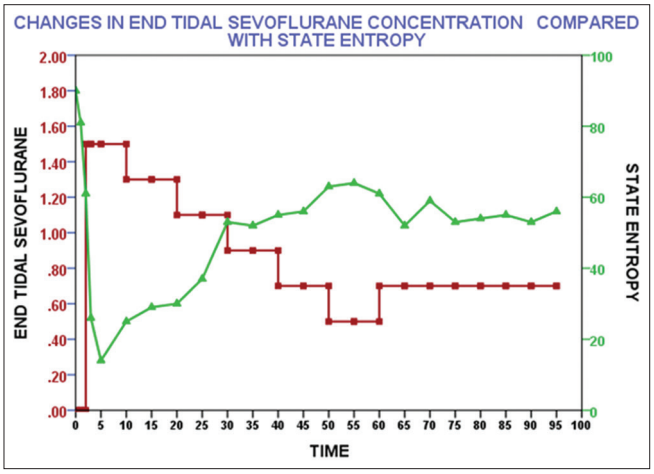


**Figure 3:** Changes in End Tidal Sevoflurane Concentration compared with State Entropy over time in a single case

The use of nitrous oxide in clinical practice has aided to reduce the requirement of inhalational anaesthetics. In our study, the concentration of nitrous oxide was kept constant during the maintenance phase of general anaesthesia. Therefore, we presume that nitrous oxide did not have an effect on the alterations seen in entropy.

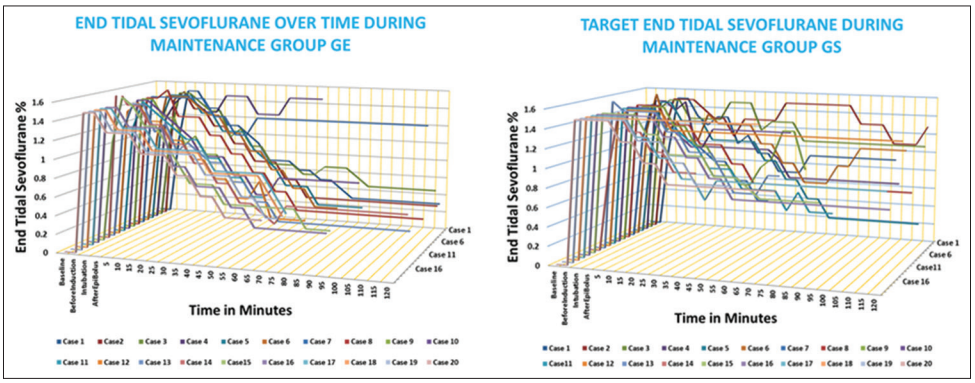


**Figure 4:** Step-wise titration of end tidal sevoflurane during maintenance

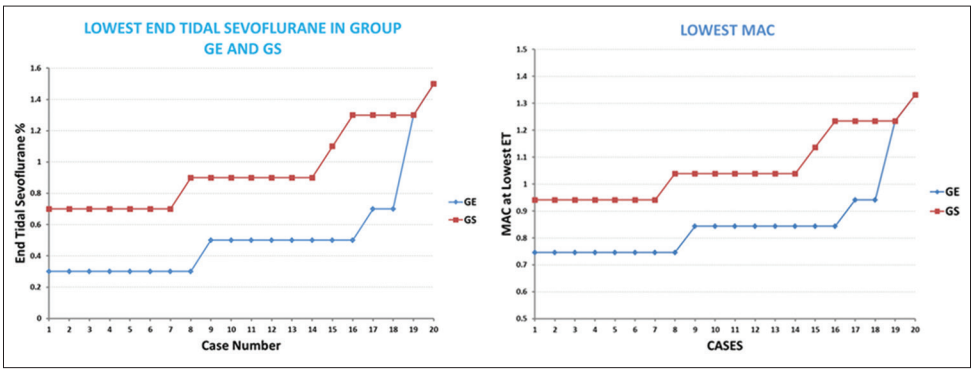


**Figure 5:** Lowest end tidal Sevoflurane and Lowest MAC in both groups (Each point represents one patient. MAC is plotted from lowest to highest value for clarity)

Ozcan *et al*.[12] studied the effect of nitrous oxide on BIS™ and concluded that there was an insignificant reduction in entropy and BIS™ values when nitrous oxide was added to Sevoflurane. Prabhakar *et al*.[13] studied the change in entropy for different anaesthetic agents with and without the use of nitrous oxide. They observed an insignificant reduction in entropy values at 1.5 MAC with the addition of nitrous oxide. But with lower concentration of the inhalational anaesthetic, nitrous oxide causes a reduction in entropy values.

Entropy is an alternate accurate monitor of depth of anaesthesia as BIS™[1,14,15] Standard anaesthetic practice was used in our study. After induction, a drop in both state and response entropy was noted. This may have been due to the effect of midazolam sedation and thiopentone induction. Once the drug undergoes redistribution, a slight increase in the entropy values is observed. Changes observed in entropy during the maintenance phase of anaesthesia were solely due to the changes made in $ET_{Sevo}$ concentration. By the end of anaesthesia, the entropy values rose to the original range of 90–100. Patients were conscious and followed verbal commands. No problems were noted with sensor contact in any of the cases.

The end tidal control mode of the Aisys anaesthesia workstation was used for all the cases during the study. The machine has a closed loop feedback end tidal control which continuously measures the agent and oxygen concentrations and gives a feedback to the electronic control to maintain the end tidal concentration.[16] This helped to ensure that the set target end tidal was achieved as soon as possible. The machine temporarily increases the fresh gas flow to achieve the set target end tidal concentration. When the target ET is achieved, it automatically returns to minimal or set flow. The anaesthesia machine itself takes around 10-15 breaths (*i.e.,* approx. 1 minute) to achieve the target end tidal concentration. Once a change was made in the target $ET_{Sevo}$, it was allowed to equilibrate for ten minutes before making the next change. The time taken for the brain-alveolar concentration to equilibrate is around 6 minutes. We allowed another three minutes to obtain a steady state before any further changes were made to the target $ET_{Sevo}$.

All changes in $ET_{Sevo}$ concentration was done based on entropy values alone. The depth of anaesthesia was assessed only based on entropy. Traditionally, MAC has been used as the standard for measuring volatile agent potency. Some studies suggest that BIS™ does not adequately reflect the degree of hypnosis with increasing MAC.[17] In our study, the MAC was calculated for the lowest maintained $ET_{Sevo}$ concentration. Hodgson *et al*.[3] used BIS™ as an end point for titrating anaesthetic agent looked only at a single point of $MAC_{BIS50}$. They recorded the MAC required to achieve a BIS™ of 50 and made changes in the subsequent patient. They looked only at a single point MAC to determine a reduction. Zhang *et al*.[4] looked for patient movement to surgical incision and found the $ET_{Sevo}$ at which 50% of patients did not move. Casati *et al*.[2] looked at the mean end tidal concentration throughout the entire duration of anaesthesia including induction and recovery to determine the lowest percentage MAC. This is not reflective of the maintenance phase of anaesthesia. Our study does not have any of these methodological flaws. The lowest maintained $ET_{Sevo}$ was noted and the MAC for that $ET_{Sevo}$ was calculated. The mean MAC was then calculated to show a reduction during the maintenance phase of anaesthesia. This study looks at the entire duration of the maintenance phase and not just a single point to obtain MAC values. MAC varies according to age of the patient. Nickalls *et al*.[18] developed an age related iso-MAC chart for all the inhalational anaesthetic agents as a guide to decide the end expired agent concentration for a particular age and agent. In the epidural bupivacaine group of our study, two cases had MAC values of 1.2 and 1.3. Both these patients were young females and required a higher end tidal concentration to maintain adequate depth.

The epidural bupivacaine group showed a reduction of 44.2% in $ET_{Sevo}$ as compared to the saline group. The mean MAC calculated at the lowest end tidal in the epidural bupivacaine group was 0.86 and in the epidural saline group it was 1.06. This reduction in the end tidal concentration and MAC may be attributed to the deafferentation theory. As the noxious stimulus was applied to an area that was blocked by the epidural anaesthetic, the brain receives no afferent input from that site. Once the afferent limb is cut off, the response from the efferent limb is also suppressed or decreased. This leads to a less requirement of volatile agent to maintain unconsciousness. This theory has been suggested by several authors previously.[8,19,20] Forbes *et al*.[7] studied the effect of muscle relaxation on MAC. They observed that when the muscle spindle activity is abolished, the brain does not perceive input from the muscle. Similar to the deafferentation theory, when the input is cut off, the MAC is reduced. The abolition of

afferentation, suppression of reticulo-thalamo-cortical arousal and blockade of muscle-spindle activity all contribute to the reduction in MAC.

Ekman *et al*.[6] observed that BIS™ values more than 60 were associated with explicit recall in patients. None of the patients in our study reported awareness during surgery. This can be attributed to the fact that, during maintenance phase, no patient was allowed to have an entropy value more than 60 for a prolonged duration of time. The possible scope of this work may be that even if the blockade of afferent pain input to the CNS reduced the requirements of the inhalational agent, still the patients may need twice MAC awake to maintain anaesthetic requirements.

## CONCLUSION

The requirement of sevoflurane is reduced when epidural analgesia is combined with entropy-guided general anaesthesia.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Takamatsu I, Ozaki M, Kazama T. Entropy indices vs the bispectralindex™ for estimating nociception during sevoflurane anaesthesia. Br J Anaesth 2006;96:620-6.
2. Casati L, Fernández-Galinski S, Barrera E, Pol O, Puig MM. Isoflurane requirements during combined general/epidural anesthesia for major abdominal surgery. Anesth Analg 2002;94:1331-7.
3. Hodgson PS, Liu SS. Epidural lidocaine decreases sevoflurane requirement for adequate depth of anesthesia as measured by the Bispectral Index monitor. Anesthesiology 2001;94:799-803.
4. Zhang J, Zhang W, Li B. The effect of epidural anesthesia with different concentrations of ropivacaine on sevoflurane requirements. Anesth Analg 2007;104:984-6.
5. Choi SR, Lim YH, Lee SC, Lee JH, Chung CJ. Spectral entropy monitoring allowed lower sevoflurane concentration and faster recovery in children. Acta Anaesthesiol Scand 2010;54:859-62.
6. Ekman A, Lindholm ML, Lennmarken C, Sandin R. Reduction in the incidence of awareness using BIS monitoring. Acta Anaesthesiol Scand 2004;48:20-6.
7. Forbes AR, Cohen NH, Eger EI. Pancuronium reduces halothane requirement in man. Anesth Analg 1979;58:497-9.
8. Hodgson PS, Liu SS, Gras TW. Does epidural anesthesia have general anesthetic effects? A prospective, randomized, double-blind, placebo-controlled trial. Anesthesiology 1999;91:1687-92.
9. Shono A, Sakura S, Saito Y, Doi K, Nakatani T. Comparison of 1% and 2% lidocaine epidural anaesthesia combined with sevoflurane general anaesthesia utilizing a constant bispectral index. Br J Anaesth 2003;91:825-9.
10. Mapleson WW. Effect of age on MAC in humans: A meta-analysis. Br J Anaesth 1996;76:179-85.
11. Aime I, Verroust N, Masson-Lefoll C, Taylor G, Laloë PA, Liu N, *et al.* Does monitoring bispectral index or spectral entropy reduce sevoflurane use? Anesth Analg 2006;103:1469-77.
12. Ozcan MS, Ozcan MD, Khan QS, Thompson DM, Chetty PK. Does nitrous oxide affect bispectral index and state entropy when added to a propofol versus sevoflurane anesthetic? J Neurosurg Anesthesiol 2010;22:309-15.
13. Prabhakar H, Ali Z, Bithal PK, Singh GP, Laithangbam PK, Dash HH. EEG entropy values during isoflurane, sevoflurane and halothane anesthesia with and without nitrous oxide. J Neurosurg Anesthesiol 2009;21:108-11.
14. BalclcsiolH, Ali Z, Bithal PK, Singh GP, Laithangbam PK, Dash HH. EEG entropy values during isoflurane, sevoflurane and halothane anesthesia with an 2010;6:370-4.
15. Ellerkmann RK, Liermann V-M, Alves TM, Wenningmann I, Kreuer S, Wilhelm W, *et al.* Spectral entropy and bispectral index as measures of the electroencephalographic effects of sevoflurane. Anesthesiology 2004;101:1275-82.
16. Singaravelu S, Barclay P. Automated control of end-tidal inhalation anaesthetic concentration using the GE Aisys Carestation™. Br J Anaesth 2013;110:561-6.
17. Umamaheswara Rao GS, Ali Z, Ramamoorthy M, Patil J. Equi-MAC concentrations of halothane and isoflurane do not produce similar bispectral index values. J Neurosurg Anesthesiol 2007;19:93-6.
18. Nickalls RWD, Mapleson WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. Br J Anaesth 2003;91:170-4.
19. Antognini JF, Jinks SL, Atherley R, Clayton C, Carstens E. Spinal anaesthesia indirectly depresses cortical activity associated with electrical stimulation of the reticular formation. Br J Anaesth 2003;91:233-8.
20. Gillies ID, Morgan M. Accidental total spinal analgesia with bupivacaine. Anaesthesia 1973;28:441-5.