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STUDY OF EFFECT OF DEXMEDETOMIDINE ON ENTROPY AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE IN PATIENTS UNDERGOING ELECTIVE SURGERIES UNDER CENTRAL NEURAXIAL BLOCKADE

Geeta Kanithi — Associate professor, Dept of Anesthesiology and Intensive care, Nizam's institute of medical sciences, Hyderabad: 500082,

Srikanth Inturi — Senior resident, Dept of Anesthesiology and Intensive care, Nizam's institute of medical sciences, Hyderabad: 500082,

Shibani Padhy — Assistant professor, Dept of Anesthesiology and Intensive care, Nizam's institute of medical sciences, Hyderabad: 500082,

R. Gopinath — Professor & HOD, Dept of Anesthesiology and Intensive care, Nizam's institute of medical sciences, Hyderabad: 500082, e

ABSTRACT **Background:** Sub arachnoid block, due to its inherent sedative effects, may potentially convert conscious sedation into hypnosis, with the unmonitored use of sedative drugs at standard doses,thereby increasing the probability of adverse events. Intrathecal α2-agonists like Dexmedetomidine, is now being used as a neuraxial adjuvant, provides stable hemodynamics with excellent intraoperative and postoperative analgesia with minimal side effects. The aim of our study to assess the effect of dexmedetomidine as an adjuvant to hyperbaric bupivacaine on entropy response in patients undergoing elective surgeries under central neuraxial blockade. **Material and methods:** Hundred patients of ASA class I or II scheduled for lower abdominal or lower limb surgeries under central neuraxial blockade were studied. All patients were received intrathecal 15mg of 0.5% Bupivacaine (heavy) and 0.1μ/kg of Dexmedetomidine. **Results:** Intrathecal dexmedetomidine as an adjuvant to hyperbaric bupivacaine in neuraxial blockade results in a decrease in response entropy (RE) and state entropy (SE) values. **Conclusion:** The addition of dexmedetomidine to hyperbaric bupivacaine as an adjuvant provides clinically acceptable sedation levels without any significant hemodynamic changes.

KEYWORDS : subarachnoid block, dexmedetomidine, entropy.

INTRODUCTION

For surgeries done under subarachnoid blockade(SAB) , an adequate sedation level is of prime importance for the comfort of the patient. However, due to the inherent sedative effect of SAB, an unmonitored use of sedative drugs at standard doses may potentially convert conscious sedation into hypnosis, thereby increasing the probability of adverse events.(1)

Intrathecal α2-agonists are increasing in popularity as adjuvant drugs to local anaesthetics.(2,3,4). They potentiate the effect of local anaesthetics and allow a decrease in required doses.(3,4,5).

Dexmedetomidine , as a neuraxial adjuvant provides stable hemodynamics with excellent intraoperative and postoperative analgesia with minimal side effects.(8) Dexmedetomidine has been approved by Food and Drug Administration (FDA) as a short-term sedative for mechanically ventilated intensive care unit (ICU) patients. Dexmedetomidine is an agonist of the α2 adrenoceptors that are found densely in the pontine locus ceruleus, which is an important source of sympathetic nervous system innervations of the forebrain and a vital modulator of vigilance. The sedative effects evoked by α2 agonists most likely reflect inhibition of this nucleus.(14).

Very few clinical investigations studying the sedative properties of intrathecal dexmedetomidine have been reported in the available literature so far. Thus we conducted a prospective study to assess the effect of dexmedetomidine as an adjuvant to hyperbaric bupivacaine on entropy response in patients undergoing elective surgeries under central neuraxial blockade.

MATERIALS and METHODS

This prospective observational study was conducted after Institutional Ethics Committee approval .between AUGUST 2015 and SEPTEMBER 2015.Informed written consent was obtained from all patients preoperatively 100 ASA 1 and 2 , patients, of either sex, between the age of 18 to 60 years,presenting for elective lower limb and lower abdominal surgeries under central neuraxial blockade were recruited for the current study. Exclusion criteria included,ASA 3 & 4 patientsPatients with contraindication to central neuraxial blockadePatients with significant coexisting diseases like ischemic heart disease, hypertension ,impaired renal function and severe liver disease and patients on alpha blockers.. Patients were pre medicated with per oral Tab. Alprazolam 0.5 mg and Tab. Ranitidine 150 mg the night before surgery After shifting patient to operation theatre, intravenous cannulation was established and standard monitoring was done including pulse oximetry, electrocardiography and non invasive arterial blood pressure recordings every 5 min. The entropy sensor was connected to all patients with disposable leads placed on forehead which were in turn connected to the entropy cable. Apart from the baseline vitals, the baseline response entropy(RE) and state entropy(SE) were recorded(using Datex- ohmeda work statoin,GE healthcare Helsinki, Finland)

All patients received combined spinal and epidural anaesthesia at L2-L3 or L3-L4 level with the aid of a Combined Spinal and Epidural Anaesthesia set consisting of an 18 gauze epidural needle, a 20 gauze epidural catheter and a 26 gauze spinal needle. 15 mg of 0.5% Bupivacaine (heavy) and 0.1 microgram/kg of Dexmedetomidine was given for subarachnoid blockade. Epidural catheters were fixed after advancing 5 centimetres into the epidural space. A minimum sensory blockade till T8-T10 was ensured before commencement of surgery.

All hemodynamic variables including heart rate(HR), systolic blood pressure(SBP), diastolic blood pressure(DBP) and mean arterial pressure(MAP) were recorded throughout the procedure . Response entropy (RE) and state entropy(SE) were recorded after establishing adequate block i.e. T8-T10 for every 30 min up to duration of 3 hours. All hemodynamic variables also have been recorded after establishing adequate block for every 30 min up to duration of 3 hours.

Statistical analysis:

Statistical analysis was carried out using NCSS 9 version 9.0.8 statistical software. Continuous data were represented as mean (SD), both categorical data and ordinal data as percentages. The normality distribution of data was assessed graphically and by Anderson-Darling test. Repeated measure of ANOVA test within the group for continuous data, followed by Tukey-Kramer multiple comparison analysis. P value < 0.05 was considered as statistically significant.

RESULTS

Demographics:

The demographical data of study population is tabulated.

Table 1.Demographic data

Parameter	Mean(SD)
Age(years)	37.5(12.98)
Height(metre)	1.57(0.048)
Weight(kg)	63.91(6.367)
BMI (Kg/m2	31.05(3.21)

Table 2.. Demographic data

Parameter	Ratio
GENDER(MALE:FEMALE)	84 : 16
ASA(1:2)	90 :10
INTERVERTEBRAL SPACE(L2-L3 : L3-L4)	67 : 33
LEVEL OF BLOCK T8:T10	98 : 2

Entropy :
Analysis of Response Entropy(RE) and State Entropy(SE) using Repeated measures of ANOVA was done and tabulated.

Table 3. Results of repeated measures of ANOVA of RE and SE

Parameter	Degree of freedom	Sum of squares	Mean Square	F Value	P Value
RE	6	18322.28	3053.713	39	0.0000
SE	6	18408.5	3068.083	36.27	0.0000

RE and SE at various time intervals were compared using repeated measures of ANOVA. It was found to be statistically significant ($p < 0.05$).

Table 4. Mean(SD) values of RE and SE at various time intervals

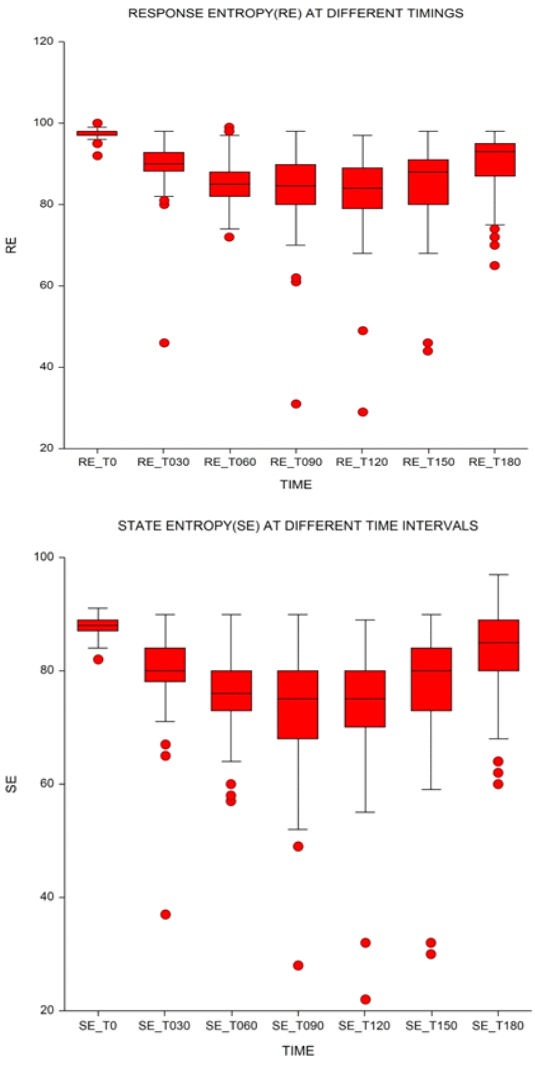
TIME INTERVAL	Mean RE(SD)	Mean SE(SD)
T0-base line	97.42(1.173)	87.91(1.63)
T30-30 minutes after establishing adequate block	89.59(7.123)	79.4(7.655)
T60 - 60 minutes after establishing adequate block	85.17(5.38)	75.86(6.514)
T90-90 minutes after establishing adequate block	82.36(12.33)	72.66(12.122)
T120-120 minutes after establishing adequate block	81.98(12.02)	73.16(12.422)
T150-150 minutes after establishing adequate block	84.23(10.28)	77.12(11.173)
T180-180 minutes after eestablishing adequate block	90.1(8.02)	83.38(7.896)
T180-180 minutes after eestablishing adequate block	90.1(8.02)	83.38(7.896)

HAEMODYNAMIC PARAMETERS: Within Group Analysis using Repeated Measures ANOVA.

Table 11 . Results of repeated measures of ANOVA for HR ,SBP, DBP and MAP

Parameters	Degree of freedom	Sum of Squares	Mean Square	F value	P value
HR	6	17960.67	2993.446	45.03	0.0000
SBP	6	34469.88	5744.979	66.24	0.0000
DBP	6	12883.65	2147.276	37.85	0.0000
MAP	6	20565.57	3427.595	68.58	0.0000

Fig 7. Graph showing comparison of baseline RE to RE at different time intervals



Graph showing comparison of base line SE to SE at different time intervals

All parameters such as HR, SBP, DBP and MAP at various time intervals were compared using repeated measures of ANOVA. It was found to be statistically significant ($p < 0.05$). Later, Tukey Kramer multiple comparison test was done within the group to compare base line values to values at different time intervals.

DISCUSSION

Our study shows that dexmedetomidine as adjuvant to hyperbaric bupivacaine in neuraxial blockade results in a decrease in response entropy (RE) and state entropy (SE) values. .The physiological mechanism of sedation in spinal anaesthesia is that it blocks ascending somatosensory driven onto reticular-thalamus-cortical projection pathways, reducing their excitability and decreasing the arousal level of the brain .(16,52)

Ben-David et al and Gentili et al concluded that high spinal anaesthesia increases the sensitivity to sedative effects of midazolam and that sedation increases as a function of block height.(32,53)In our study , none of patients attained level of block more than T8 and we have not used any sedatives to supplement.

Entropy is an EEG based monitor to assess the depth of anaesthesia and also as a tool to titrate sedation.It calculates two numerical parameters: State entropy(SE, range: 0-91) and RE (range: 0-100).

We believe that fall in SE value was due to blockade of the afferent sensory pathway. There was a progressive fall in SE values after the drug was administered in the subarachnoid space up to the time of fixation of drug. There was a fall in SE values for up to 120min of intrathecal drug administration after which there was no further fall in levels of SE values, instead we have found that there was an increase in SE values.

Luis et al., conducted a prospective study on monitoring of sedation during neuraxial blockade using 0.5% hyperbaric bupivacaine in 40 patients of ASA1-3 status ,over 60 years of age orthopaedic patients, comparing Observer's Assessment of Alertness/Sedation OAA/S, response (RE) and state entropy (SE) and BIS ,which showed RE and BIS showed a better correlation with the OAA/S scale values than SE . The OAA/S, RE and SE showed significant differences from basal values after 30 min of neuraxial anaesthesia (ANOVA $p<0.05$). BIS showed differences after 40 min (ANOVA $p<0.05$). There were no differences between BIS and RE values along the study (ANOVA $p>0.05$).They concluded that The spinal anaesthesia decreased the cortical activity and these were founded by OAA/S scale and depth anaesthetics monitors. OAA/S was a more sensitive value of this induced sedation. BIS and RE showed a better correlation with OAA/S scale than SE.(50)The cause of sedation in this study which included orthopaedic old age patients, may be due to decrease in pain after giving spinal anaesthesia.

Varma et al , conducted a prospective randomized double-blind study, 30 patients of age 18-70 years requiring SAB ,to monitor the sedative effect of sub arachnoid blockade using hyperbaric bupivacaine and fentanyl with hyperbaric bupivacaine alone as control group by entropy and they have also used propofol infusion to titrate the levels of SE to <75. The level of sedation was measured with SE and Ramsay sedation (RS) scale . After SAB, decrease in SE and response entropy was noted in both the groups and fall was significant in bupivacaine and fentanyl group . The change in the mean RS values was from 1.17 ± 0.38 to 1.69 ± 0.47 in bupivacaine and fentanyl group , whereas in bupivacaine alone it was from 1.03 ± 0.18 to 1.43 ± 0.50 within 20 min of SAB. The total propfol required in the two groups were comparable being 3.97 ± 2.14 mg/kg in bupivacaine alone group and 3.41 ± 2.34 mg/kg in bupivacaine and fentanyl group. They have concluded that Subarachnoid block causes sedation per se, but the level of sedation is not clinically significant and the sedation caused is not enough to avoid sedative agents for allaying anxiety in patients intra operatively. The sedative effect of SAB was enhanced by adding intrathecal fentanyl probably because of better quality of SAB. SE showed good correlation with RS scaling system. Therefore, SE may be used as reliable tool to titrate sedation in patients undergoing surgery under SAB.(51)

Some authors believe that sedative effect of SAB was not only due to afferent pathway blockade alone, but other factors also play a role. One of the factors that is being proposed is hypotension.It is proposed that hypotension leads to decrease in cerebral blood flow with resultant somnolence. However, in the present study, hypotension as a cause of sedation is very unlikely because the fall in MAP levels is not clinically significant.

Another theory postulated in literature as a cause of sedation following SAB is rostral spread of local anaesthetic with direct action on the brain and systemic general anaesthetic effect of absorbed local anaesthetic.(18,56) However in the present study, we cannot comment conclusively on such mechanisms as neither the measurements of systemic levels of local anaesthetic nor the concentration of local anaesthetic at higher spinal levels were checked in the present study.We observed that sedation is not clinically significant as measured by entropy.

Conclusion: We conclude that the addition of dexmedetomidine to hyperbaric bupivacaine as an adjuvant provides clinically acceptable sedation levels without any significant hemodynamic changes.

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