Original Article

Comparison of subarachnoid block with bupivacaine and bupivacaine with fentanyl on entropy and sedation: A prospective randomized double-blind study

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Abstract

Background and Aims: We studied the state entropy to monitor the sedative effect of subarachnoid block (SAB) using bupivacaine alone or combination of bupivacaine and fentanyl. The effect of use of fentanyl via the subarachnoid route on the sedation level was also studied using the entropy scores and the decrease in the requirement of propofol used as an adjuvant sedative drug.

Materials and Methods: In this prospective randomized double-blind study, 30 patients of age 18-70 years requiring SAB were enrolled for the study. Patients with any known allergy to study drugs, contraindication for SAB, obesity, neurological or psychiatric disease on concurrent medication and refusal were excluded from the study. Patients were randomly allocated into two groups: Group C: SAB was administered with 2.5 mL (12.5 mg) of 0.5% hyperbaric bupivacaine; Group D: SAB was administered with 2.5 mL of 2 mL (10 mg) of 0.5% hyperbaric bupivacaine and 0.5 mL (25 μg) fentanyl. Propofol infusion was started if the state entropy (SE) value was ≥75, at the rate of 100 μg/kg/min till the SE value reaches in the range of 60-75 (recorded as onset time). Thereafter the infusion rate was titrated to maintain SE value between 60 and 75. The level of sedation was measured with SE and Ramsay sedation (RS) scale.

Results: The demographic profile and baseline parameters, were comparable in two groups ($P > 0.05$). After SAB, decrease in SE and response entropy was noted in both the groups and fall was significant in Group D ($P < 0.0001$). The total propfol required in thew two groups were comparable being 3.97 ± 2.14 mg/kg in Group C and 3.41 ± 2.34 mg/kg in Group D ($P = 0.342$). The change in the mean RS values was from 1.17 ± 0.38 to 1.69 ± 0.47 in Group D ($P = 0.06$), whereas in Group C it was from 1.03 ± 0.18 to 1.43 ± 0.50 ($P = 0.041$) within 20 min of SAB.

Conclusion: 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 intraoperatively. 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.

Key words: Bupivacaine, fentanyl, sedation, state entropy, subarachnoid block

Introduction

Subarachnoid block (SAB) has been conventionally used for various surgeries. The neuraxial block has been documented to have sedative effect.[1,2] The presumed underlying mechanism is that spinal anesthetic blocks ascending somatosensory drive on to reticulo-thalamocortical projection pathways, thereby reducing their excitability and hence decreasing the arousal level of brain.[1] Furthermore, muscle spindle activity regulates the excitability of brain and arousal system. Hence, after SAB, the reduced muscle spindle afferent impulse will lower the level of consciousness and awakening.[2,3] The SAB block usually includes addition of an adjuvant such as fentanyl and clonidine to improve the efficacy of the block with local anesthetic agent. However, the effect of fentanyl on sedation has not been studied earlier.

When surgeries are done under SAB, an adequate sedation level is of prime importance not only for the comfort of the patient, but also for the success of the surgery. However,

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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.[3] Various techniques like clinical assessment (Ramsay scale, Observer's Assessment of Alertness/Sedation scale [OAA/S scale]) or electroencephalogram (EEG) based monitors (Bispectral [BIS] index and entropy) have been used to titrate the intravenous (i.v) drug given for sedation. Balci *et al.*[4] used state entropy (SE) as an objective tool to titrate sedation in patients who were operated under monitored anesthesia care where they concluded that SE is a reliable indicator of sedation in nonparalyzed patients similar to BIS.

Therefore in present study, we studied the state entropy to monitor the sedative effect of SAB using bupivacaine alone or combination of bupivacaine and fentanyl.

Materials and Methods

This prospective, randomized, double-blind study was conducted after obtaining approval by the Institute Ethics Committee (vide reference no. IESC/T-76/2011 dated 18th February 2011 at Institutional Ethics Committee) and written informed consent from the patient. Sixty patients of age 18-70 years, either sex, American Society of Anesthesiologists (ASA) physical status I and II undergoing surgery (duration of less than 2 h) under SAB or combined spinal epidural anesthesia (CSEA) were enrolled for the study. Patients with any known allergy to study drugs, contraindication for central neuraxial block, obesity (body mass index, [BMI] >35 kg/m^2), neurological or psychiatric disease on concurrent medication and refusal were excluded from the study.

Patients were randomly allocated into two groups by drawing sequential numbered, opaque sealed envelopes, containing a code based on a computer generated random number list.

Group C (*n* – 30)

Subarachnoid block was administered with 2.5 mL (12.5 mg) of 0.5% hyperbaric bupivacaine.

Group D (*n* – 30)

Subarachnoid block was administered with 2.5 mL of 2 mL (10 mg) of 0.5% hyperbaric bupivacaine and 0.5 mL (25 μg) fentanyl.

To maintain blinding, drug preparation and procedure of SAB or CSEA was performed by an independent anesthesiologist blinded to the study, while the observation was done by the attending anesthesiologist.

Anesthetic technique

Patients were shifted to the operating-room and routine monitoring like electrocardiogram, pulse oximetry (oxygen saturation [SpO_2]) and noninvasive blood pressure were established. The disposable Entropy Sensor (Entropy™ Module, Datex Ohmeda, Madison, WI) was attached to monitor state entropy (SE) and response entropy (RE) with the Datex Ohmeda S/5 Avance machine. The sensor was attached after cleaning the forehead with spirit and letting it air dry. The first part of the electrode was attached frontally in the midline, second part was attached 2 cm above the eyebrows and the lateral part of the electrode was put 2 cm laterally from the outer canthus of left eye, as recommended by the manufacturer. Baseline readings of mean blood pressure (MBP 0), heart rate (HR 0), peripheral arterial SpO_2 0, sedation score (Ramsay sedation [RS] 0, according to RS scale), and SE 0 and RE 0 values were noted. The sedation score throughout the duration of the study was assessed by an anesthesiologist blinded to the study, that is, unaware of the study drugs.

An 18G i.v cannula was secured and patients were preloaded with 500 mL of balanced salt solution. The SAB was administered under strict aseptic precautions in lateral decubitus position at L3-L4 or L4-L5 interspace using 24/25G spinal needle or 26/27G spinal needle of the CSEA set. A fixed volume of the drug was prepared, that is, 2.5 mL and was administered in the subarachnoid space as per randomized group. Sensory block level was evaluated by pin prick test every 2 min until the drug gets fixed (block remains at the same level at three consecutive readings). Motor blockade was assessed using the Modified Bromage score. 20 min after the drug has been injected into the subarachnoid space, the SE and RE scores were noted and surgery was started. Propofol infusion was started if the SE value was ≥75, at the rate of 100 μm/kg/min until the SE value reaches in the range of 60-75 (recorded as onset time). Thereafter, the infusion rate was titrated to maintain SE value between 60 and 75. When SE values either increased or decreased from the range of 60-75 for >10 s, the dose of propofol infusion was either increased or decreased by 10 μm/kg/min every 30 s respectively. The onset time and total propofol requirement for SE to reach <75 was recorded in the two groups.

The readings of MBP, HR, SpO_2 and sedation score were taken every 5 min. Though SE, RE was recorded every 5 min but was continuously monitored for the purpose of propofol dose titration.

The MBP was maintained within 20% of the baseline values. Episodes of hypotension, defined as MBP <20% of baseline or systolic blood pressure <90 mm of Hg was managed

initially with the bolus of balanced salt solution (5 mL/kg) and then i.v ephedrine 3-6 mg bolus as required. Bradycardia (HR <60 beats/min) was treated with i.v atropine 0.3 mg bolus dose and repeated if required. Episodes of desaturation was defined as SpO_2 <94% for more than 15 s was treated with increased oxygen flow and decrease in propofol infusion rate till saturation normalizes (SpO_2 >95%). Oxygen was given at the rate of 6 L/min by face mask.

Propofol infusion was stopped at 120th min of SAB or at the end of surgery, whichever was earlier and time for SE values to reach 91 again was noted. This was the recovery time. Recovery time (in minutes) and total consumption of propofol (in milligram) was noted. In case surgery was prolonged beyond 2 h, propofol infusion was restarted until the end of surgery at the discretion of the attending anesthesiologist or on patient's choice. If the patient is clinically uncomfortable (Ramsay score of 1) despite appropriate SE values, they were planned to be sedated further and excluded from the study. Any patient requiring general anesthesia at any point in the study period was excluded from the study. At the end of the surgery, we waited for the spectral entropy (SE) value to reach 91 before shifting the patient to postanesthesia care unit.

Statistical analysis

Sample size for the study was calculated for the two groups designed required to reach the adequate sedation levels (SE <75). Assuming mean ± standard deviation (SD) of required induction dose in Group C to be 2.0 ± 0.5 mg/kg and in the Group D as 1.5 ± 0.5 mg/kg, to detect this difference with 95% confidence interval and 90% power, we required 24 evaluable patients. Therefore, we enrolled 30 patients to compensate for any dropouts or exclusion for analysis. Data were recorded on a predesigned proforma and was managed on an excel spread sheet. STATA 12 statistical software (StataCorp LP, exas, USA.) has been used for statistical analysis. All entries were checked for any possible keyboard error. Qualitative variables were summarized as frequency and Fischer exact test is used to compare the difference in proportion in the two groups. The quantitative variables (after conforming for approximate normality) were summarized by mean ± SD and student *t*-test was used to compare the two groups. Within group change in continuous parameters was seen by repeated measure ANOVA (two-way ANOVA). Between the group change was analyzed by *t*-test/Wilcoxon rank-sum as appropriate. In case of categorical variables, between the groups comparison was done by Chi-square/Fischer exact test. Correlation at each time point was seen by Carl Pearson correlation. $P < 0.05$ is taken as statistically significant.

Results

Out of 72 patients, 60 patients were recruited for the study as other patients did not meet the inclusion/exclusion criteria. Two patients were excluded from the study due to conversion to general anesthesia. Of these, one was due to failure to place a spinal block and the other was because of failed spinal effect.

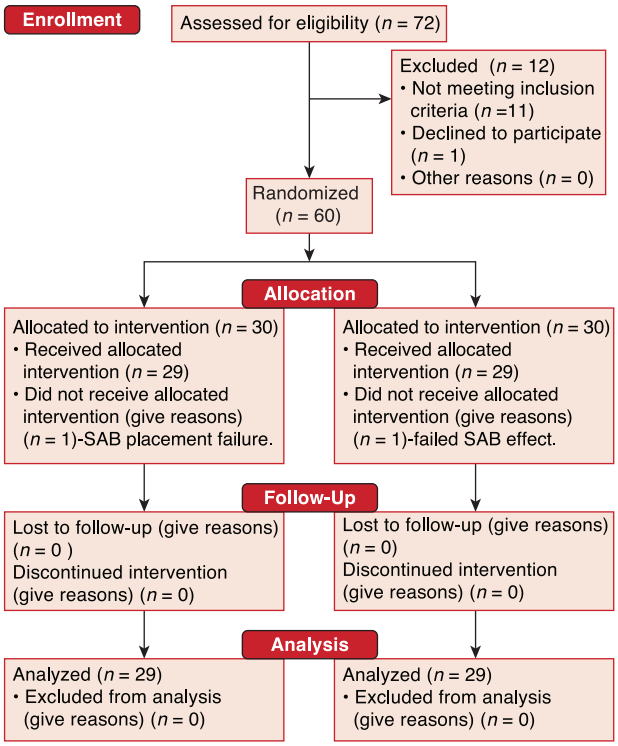
Baseline parameters

The demographic profile including age, weight, height, ASA physical status, BMI of patients, surgical procedures and duration of surgery were comparable in the two groups ($P > 0.05$) [Tables 1 and 2]. The baseline parameters including RE 0, SE 0, HR 0, MBP 0, SpO_2 0 and RS score (RS 0) were comparable ($P > 0.05$) [Table 3].

Table 1: Demographic data in the two groups

Parameters	Group C	Group D	*P* value
Age (years)	45.53±13.71	40.53±14.01	0.1676
Sex (male and female) (%)	Male: 16 (53.33) Female: 14 (46.67)	Male: 21 (70) Female: 9 (30)	0.184
Height (cm)	160.95±8.12	163.12±9.62	0.3491
Weight (kg)	57.17±10.15	60.97±14.70	0.2488
BMI (kg/m^2)	22.23±2.95	22.41±3.99	0.8514
ASA status (ASA I and ASA II) (%)	I: 19 (63.33) II: 11 (36.67)	I: 24 (80) II: 6 (20)	0.152

The parameters are mean ± SD ASA status and sex is represented as n (%), SD=Standard deviation, BMI = Body mass index, ASA = American Society of Anesthesiologists



CONSORT Flow Diagram

Block height and time taken

The maximum block height reached was comparable in both groups (thoracic dermatomal level of median 8 [range: 4-11] in group C and median 8 [range: 2-11] in Group D) ($P = 0.95$). Time taken to reach the maximum height was 11.4 ± 4.9 min in Group D when compared to 10.8 ± 4.3 min in Group C ($P = 0.58$).

State entropy and response entropy

After placement of SAB, decrease in SE and RE was noted in both the groups [Figures 1 and 2]. The mean fall in SE value from a baseline of 88.7 ± 1.6-87.9 ± 3.1 in Group C ($P = 0.103$) whereas 88.4 ± 3.7-85.8 ± 6.2 ($P = 0.007$) in Group D within 20 min of SAB when the block height was fixed [Figure 1]. The fall of RE values in Group C was from a mean value of 97.7 ± 1.21-95.43 ± 5.77 ($P < 0.0001$) and that in Group D was from a mean value of 97.43 ± 2.69-94.83 ± 5.81 ($P < 0.0001$) within 20 min of SAB [Figure 2]. The fall in RE is statistically significant in both groups but the fall does not reach clinically significant levels. The fall in RE values is faster in the Group D and there is statistically significant difference between the two groups after the 25 min time point till 55th min.

Propofol requirement

Of the 58 patients analyzed, 2 patients in the Group C and 3 patients in the Group D had SE values <75 and hence did not need propofol at all. So apart from these 5 patients, propofol infusion had to be started in all patients for SE to reach a clinical target level of <75. After starting propofol infusion, there is a gradual decrease in SE value in both the groups. The mean ± SD onset time that is, time taken for decrease in SE values to <75 in Group C was 15.9 ± 7.1 min and that in Group D was 13.3 ± 8.7 min ($P = 0.19$). The dose of propofol required to achieve the SE value of <75 was 1.93 ± 1.47 mg/kg in Group C and that in Group D was 1.28 ± 0.87 mg/kg ($P = 0.042$). The mean maintenance dose of propofol required to keep SE in the range of 60-75 required in Group C was 2.04 ± 1.85 mg/kg and that in Group D was 2.13 ± 1.83 mg/kg ($P = 0.843$). The total propfol required in the two groups were comparable being 3.97 ± 2.14 mg/kg in Group C and 3.41 ± 2.34 mg/kg in Group D ($P = 0.342$). The time adjusted propofol requirement 4.04 ± 1.77 mg/min in Group C and 3.44 ± 2.37 mg/min in Group D ($P = 0.275$). The decrease in SE value to the desired value without the propofol requirement, the difference in proportion and its 95% confidence interval was 3.4% (−17.8-11.0%) ($P = 0.548$).

Table 2: Type of surgery in the two groups

Type of surgery	Group C	Group D
Orthopedic surgery (*n*)	7	8
Gynecological surgery (*n*)	10	9
Urological surgeries (*n*)	11	10
General surgery (*n*)	2	3
Surgery time (mean±SD)	59.83±24.3	61.33±24.28

n = Number of patients, SD = Standard deviation

Table 3: Baseline study parameters in the two groups

Parameter	Group C	Group D	*P* value
SE 0	88.7±1.62	88.43±3.73	0.7208
RE 0	97.7±1.21	97.43±2.69	0.6219
RS 0	1.03±.183	1.17±0.39	0.0879
MBP 0 (mm Hg)	96.7±10.57	95.23±11.29	0.6055
HR 0 (per min)	87.9±16.36	86.77±14.08	0.7747
SpO_2 0 (percentage)	98.87±1.25	99±1.51	0.7109

The parameters are mean ± SD, SD = Standard deviation, SE = State entropy, RE = Response entropy, RS = Ramsay sedation, MBP = Mean blood pressure, HR=Heart rate, SpO_2 = Oxygen saturation

Sedation score

With the administration of SAB, the RS score show a gradual and progressive increase in both the groups [Figure 3]. The change in the mean RS values was from 1.17 ± 0.38 to 1.69 ± 0.47 in Group D ($P = 0.06$), whereas in Group C it was from 1.03 ± 0.18 to 1.43 ± 0.50 ($P = 0.041$) within 20 min of SAB. When compared between the groups the RS score was statistically significant at 20 min ($P = 0.04$). The decrease in respective groups although statistically significant did not reach

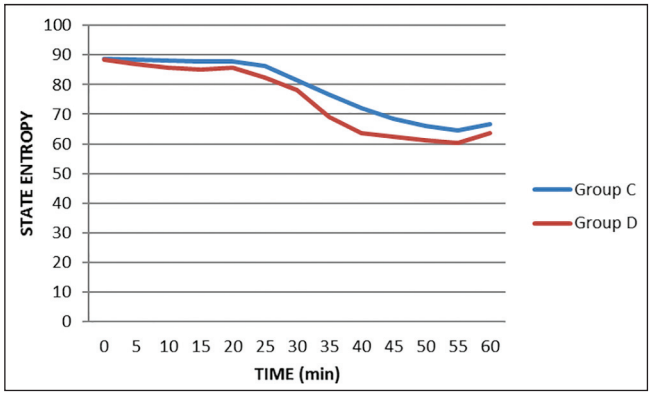


Figure 1: Trend of state entropy in the two groups

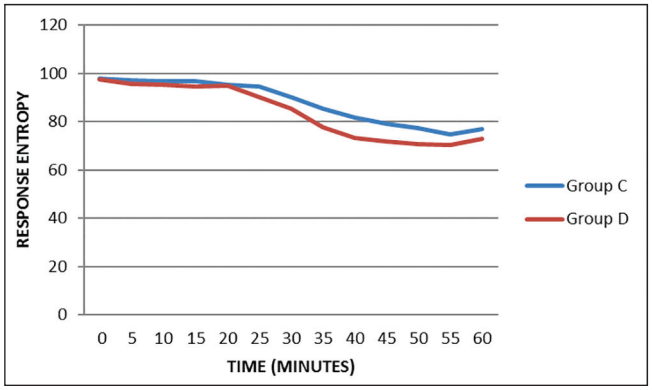


Figure 2: Trend of response entropy in the two groups

clinically relevant target (2-3) and thus required propofol infusion sedation. The target sedation of RS score of 2-3 was achieved earlier with propofol infusion in Group D when compared to Group C being 15 min in the Group C while it was 5 min in Group D after the start of the propofol infusion. The time at which the mean SE value reached the sedation range (60-75), the corresponding RS value was noted. In Group C the mean RS score was 2.83 (SE - 72.07), while in Group D the RS score was 2.69 (SE - 69.14) was found to have good correlation.

Hemodynamic parameters

The MBP within the two group show a gradual decrease ($P = 0.001$ in both the groups). The MBP between the two groups was statistically insignificant ($P > 0.05$). There is a decreasing trend of HR in each group ($P = 0.056$ in Group C and 0.072 in Group D). When between the two groups analysis was done, the decrease was comparable at all-time points ($P > 0.05$). There was no significant change in the SpO_2 either within the two groups or between the two groups ($P > 0.05$).

Adverse effects

Significant hypotension requiring rescue ephedrine is seen in 12 out of 28 patients in each group. The inter-group analysis shows no significant difference between the two groups. No incidence of arrhythmia, post dural puncture headache, postoperative nausea and vomiting, and hypersensitivity occurred in the two groups ($P > 0.05$) [Table 4].

Discussion

We observed from out study that SAB using bupivacaine alone or combination of bupivacaine and fentanyl causes sedation.

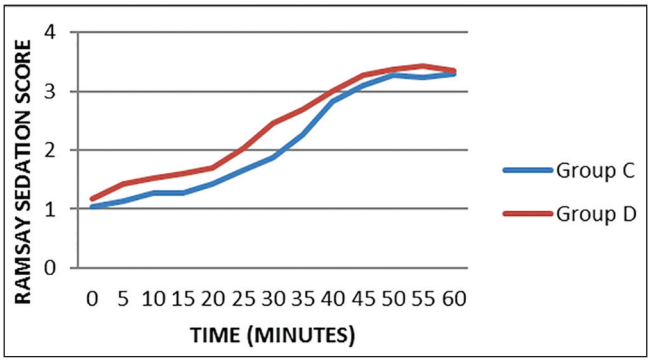


Figure 3: Trend of Ramsay sedation score in the two groups

Table 4: Adverse effects in the two groups

Adverse effects	Group C (%)	Group D (%)	*P* value
Hypotension	12 (40)	12 (40)	1.000
Bradycardia	5 (16.67)	3 (10)	0.448
Arrhythmia	0	0	—
Nausea and vomiting	1 (3.33)	0	0.313

The sedative effect of SAB is enhanced by adding intrathecal fentanyl probably because of better quality of SAB. We also observed that sedation was not to the acceptable clinical levels and thus requiring supplement sedation using propofol infusion. SE showed good correlation with RS scaling system and may be used for monitoring sedation levels.

Entropy is an EEG based monitor to assess the depth of anesthesia and also as an tool to titrate sedation.[4,5] It calculates two numerical parameters: State entropy (SE, range: 0-91) and RE (range: 0-100). The recommended level of SE values for sedation has been described as between 60 and 75.

Sedation following administration of SAB is well known.[6] The cause of sedation following SAB alone is not clear. Many believe that sedation is due to blockade of afferent pathway to RAS.[7-9] Based on the present study results, we also believe that sedation or fall in SE value following SAB 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. After this fall in SE values, no further statistically significant fall of SE value was noted before starting the propofol infusion. However, there are others who believed 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. As per this theory, 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 as the fall in the SE value did not correlate with the fall in MBP. Furthermore in the first 20 min of the present study, when there was progressive fall in SE values, there was no clinically significant hypotension probably because of adequate preloading and timely use of rescue ephedrine. The MBP was never allowed to fall below 70 mm Hg in both groups at any time point in the study. Therefore, hypotension induced somnolence as a mechanism for sedation after SAB cannot be contributory in the above effect on SE value in the present study. Another theory postulated in literature as a cause of sedation following SAB is rostral spread of local anesthetic with direct action on the brain and systemic general anesthetic effect of absorbed local anesthetic.[9,10] However in the present study, we cannot comment conclusively on such mechanisms as neither the measurements of systemic levels of local anesthetic nor the concentration of local anesthetic at higher spinal levels were checked in the present study.

The results of the present study showed decrease in state entropy values indicating sedative effect after administration of

SAB in both the groups. In the first 20 min of the study, the fall in SE values were statistically significant in Group D, but not in Group C. This may be possibly be related to additional effect of intrathecal fentanyl. These results are comparable with study of Morley *et al*.[11] where authors reported the sedative effect after administration of SAB and epidural block. In our study and the study by Morley *et al*.,[11] the fall in sedation scoring systems were not clinically significant as seen in the study by Pollock *et al*.[6] This difference in results could be because the patients in the present study as well as in the study by Morley *et al*.[11] were studied in well-lit anesthetic room and in order to determine their sedation scores, it was necessary to speak to them, which may have helped offset any mild sedative effects of regional anesthesia. This difference can also be implicated to the fact that the study subjects in the study by Pollock *et al*.[6] were volunteers who were investigated in darkened room with soft music in contrast to our unpremedicated patients, posted for surgery in a well-lit operating-rooms.

The onset time of sedation due to SAB has been assessed earlier by Guerrero *et al*.[12] using BIS and the entropy monitor during spinal anesthesia. They observed that neuraxial blockade decreased the cortical activity after 30 min, as measured by OAA/S (Observer's Assessment of Alertness and Sedation Score) and depth anesthetics monitors. BIS and RE also showed a good correlation with OAA/S scale. The authors also raised the possibility that sedation state is detected earlier with RE, because it is faster than BIS.

In the present study, RS score was also studied to evaluate whether there is any correlation of the score with SE values. RS score is a very popular objective scoring system to titrate sedation as it is very easy, reliable, and does not require extra equipment's for its measurement. Carrasco *et al*.[13] in his study on critically ill-patients concluded that RS score can be reliably used to assess sedation. The disadvantage of these sedation scores is the repeated verbal and tactile stimulation of the patient that is required to administer the drugs.

In the present study, we found good clinical correlation between the SE values and the RS scores. The RS value was noted at the time when the mean SE value reached the sedation range (60-75). In Group C, the mean RS score was 2.83 (SE-72.07), while in Group D the RS score was 2.69 (SE-69.14). Although no significant correlation could be found at each time point of study, once the SE values reached to <75 the RS values were always ≥ 2. This indicates that SE is correlating with RS in the sedation range and therefore, SE can probably be reliably used to titrate sedation in patients undergoing surgery under SAB.

Our preference to choose propofol as the drug for titrating sedation has been based on its pharmacokinetic profile, which leads to fast onset of action, early recovery and therefore easy titration.[14] The rate of infusion of propofol for induction as well as maintenance of sedation was selected as 100 μg/kg/min on the basis of a study done by Ozkan-Seyhan *et al*.[15] After starting propofol a significant difference was seen in the values of RE between the two groups from 25 to 50 min of the study period (i.e., from immediately after starting propofol). The RE values in the two groups were comparable in the first 20 min of the study, but later these values were significantly lower in Group D as compared to Group C once the propofol infusion was started. This could be due to some additive effect of intrathecal fentanyl in Group D as compared to Group C. The onset time was lesser in Group D than in Group C although the difference was not statistically significant between the two groups. This can be explained on the basis of better quality of block after addition of intrathecal fentanyl, in spite of lesser bupivacaine dose. The result of the present study was similar to that seen in the study by Kim *et al*.,[16] but the onset time in this study was significantly longer in the group without intrathecal fentanyl as compared to the group with intrathecal fentanyl.

Another reason for no clinically significant levels of sedation seen in the present study may also be due to lower block height levels in the two groups. Ben-David *et al*.[17] and Gentili *et al*.[18] concluded that high spinal anesthesia increases the sensitivity to sedative effects of midazolam and that sedation increases as a function of block height.

The total propofol consumption between the two groups was comparable. In a study by Ozkan-Seyhan *et al*.[15] the authors concluded that difference in the propofol requirement was statistically significant between the two groups to maintain BIS values in the target range for sedation. They have explained it on the basis of difference in the block height in the two groups. They have shown result similar to a study by Gentili *et al*.[18] where higher spinal block was associated with increased sedation. However, in a study by Toprak *et al*.[19] in 2005 compared patients undergoing surgery with and without spinal anesthesia and concluded significant decrease in the midazolam requirement. However, no correlation between dose reduction and height of the block was reported.

Our study may be limited by the facts that frequent and repeated adjustments in the propofol infusion rate were required in these patients. Rapid modifications could have been better controlled with the use of target-controlled infusion, where the administration is driven by microprocessor-controlled algorithms based on pharmacokinetic models.[20,21]

Conclusion

To conclude, 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 intraoperatively. 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.

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