Original Article

Effect of intraoperative depth of anesthesia on postoperative pain and analgesic requirement: A randomized prospective observer blinded study

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Abstract

Background: Intraoperative depth of anesthesia may affect postoperative pain relief. This prospective, randomized, and observer-blinded study assessed the effect of intraoperative depth of anesthesia on the postoperative pain and analgesic requirements in patients undergoing laparoscopic cholecystectomy.

Materials and Methods: A total of 80 patients were randomly divided into two groups of 40 each. A standard technique for anesthesia was followed in all patients. Depth of anesthesia was monitored by bispectral index (BIS) and adjusted with 0.5 to 1.5% isoflurane in group S by addition of propofol in group B, if required, to maintain a BIS value of 45 to 40. Postoperative analgesia was provided by tramadol 1 mg/kg every 6 hours and rescue analgesia by morphine boluses. Postoperative pain was assessed by Visual analogue scale score at 0, 8, 16, and 24 hours.

Results: The demographic characteristics were comparable in both groups. The mean BIS value in Group S was 63.32 ± 11.43 and 45.06 ± 15.31 in Group B, well in the range of 40 to 60, reflecting adequate hypnotic effect for general anesthesia. The mean arterial pressure was low in group B throughout the surgery ($P<0.05$-0.001). The pain score were lower in group B at 0 and 8 hours postoperatively when compared with group S ($P<0.05$). The rescue analgesic requirement was less in group B, compared with group S ($P<0.05$).

Conclusion: Maintaining BIS to a value of 45 to 40 throughout the surgery results in better postoperative pain relief and decreased requirement of rescue analgesic without any untoward effect.

Key words: Analgesia, bispectral index, postoperative pain, surgery laparoscopic cholecystectomy

Introduction

Ineffective pain relief is a common sequel to surgery, and up to 69% of the patients experience severe pain postoperatively.[1] Postoperative pain, associated with laparoscopic cholecystectomy though less severe and of shorter duration as compared with open cholecystectomy, is still a source of marked discomfort and surgical stress.[2,3] Different groups of analgesic drugs are used for postoperative pain, but their use can be associated with side effects and complications.[4]

Better understanding of the pain mechanism has led us to use of methods aimed specifically at interrupting the mechanism responsible for the generation of pain such as preemptive analgesia, administration of intraoperative analgesics, or combination of these. Few studies have shown that adequate intraoperative depth of anesthesia is associated with less postoperative pain and decreased analgesic requirements.[5,6] The use of clinical signs may not reliably measure the hypnotic component of anesthesia, as they can be affected by factors such as blood volume, cardiac contractility, and drug effects on the cardiovascular system.[7] Bispectral index (BIS) provides a continuous age-independent monitoring of hypnotic state induced by the most widely used sedative-hypnotic agent and has been used to assess the induction quality, depth of anesthesia, intraoperative requirement of anesthetics, postoperative recovery, and to reduce the incidence of intraoperative recall awareness.[8-11] BIS value of 0 represents

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an isoelectric electroencephalogram and 100 represents an awake state, whereas 40 to 60 reflect adequate hypnotic effect for general anesthesia.

The aim of the current study was to investigate the effect of intraoperative depth of anesthesia measured by BIS on the postoperative pain response and analgesic requirements in patients undergoing laparoscopic cholecystectomy.

Materials and Methods

After obtaining approval from the Institutional Ethics Committee and written informed consent, a total of 80 women, 25 to 60 years old, of physical status ASA I and II, scheduled to undergo laparoscopic cholecystectomy were included in a prospective, observer-blinded, and randomized manner. Patients with a history of hearing loss, neurological disease, language or communication difficulties, chronic pain on analgesic medications, renal or hepatic disease, and body mass index >35 kg/m^2 were excluded from the study.

A preanesthetic checkup was done to assess the fitness for the proposed surgical procedure under general anesthesia. Visual analogue scale (VAS) 0-100 was explained to the patients (where 0 represented no pain and 100 represented the worst imaginable pain).

Patients were randomized to Standard Practice group (Group S), where depth was adjusted according to standard practice and BIS value was recorded; or BIS Titrated group (Group B), where depth was adjusted to a BIS value of 45 to 40, with additional infusion of propofol if required. Observer was blinded to the intraoperative management and BIS values of both the groups, and decoding was done at the end of the study.

The anesthetic protocol was same in both groups. Patients were premedicated with oral alprazolam 0.25 mg night before and 60 to 90 minutes before the expected time of surgery. On the arrival in operation theatre, an intravenous line was started. For monitoring, continuous electrocardiogram, heart rate (HR), noninvasive mean arterial pressure (MAP), oxygen saturation, end-tidal carbon dioxide ($EtCO_2$), minimum alveolar concentration (MAC), and BIS were monitored. Anesthesia was induced with morphine 0.1 mg/kg and propofol 2 mg/kg. Vecuronium 0.1 mg/kg was used to facilitate endotracheal intubation. Anesthesia was maintained with 66% nitrous oxide in oxygen, supplemented by 0.5 to 1.5% isoflurane in group S and if patient required more than 1.5% isoflurane, then an infusion of propofol (8-15 ml/hr) was started to maintain BIS value of 45 to 40 in group B. Mechanical ventilation was adjusted to maintain an $EtCO_2$ of 35 to 40 mmHg. Approximately 15 minutes before weaning off anesthesia, the patients were given 1 mg/kg of tramadol[12] and ondansetron 6 mg intravenously, to reduce pain and emesis, respectively. After completion of surgery, isoflurane and propofol infusion were discontinued, and the residual neuromuscular block was reversed and extubation was done when patients were awake and respiration was regular and adequate.

The BIS, HR, MAP, and MAC values of isoflurane were recorded at 1-minute intervals during induction of anesthesia and subsequently at 5-minute intervals during the maintenance period. Total propofol requirement was also recorded at the end of surgery. Recovery time was determined at 1-minute interval from discontinuation of isoflurane and tramadol to awakening (e.g., opening eyes on verbal command) and subsequently at 1-minute interval till zero hour (conscious and responding to verbal commands) in the postanesthesia care unit (PACU). Postoperative analgesia was provided by tramadol 1 mg/kg 6 hourly and rescue pain medication by morphine 1.5 mg boluses intravenously when patient had a VAS score of more than 40 until patient became pain free.

Postoperative pain was assessed by the blinded observer by VAS score, at rest and when coughing at 0, 8, 16, and 24 hours after the completion of surgery. HR, MAP, respiratory rate, sedation, and nausea or vomiting was also assessed at same points of time.

Sedation[6] was graded as: 0 = completely alert, 1 = sleepy occasionally but rousable, 2 = asleep often but rousable, 3 = asleep and unrousable. Nausea and vomiting[6]were graded as: 0 = no nausea or vomiting, 1 = slight nausea resolving without treatment, 2 = slight nausea and/or vomiting resolves on treatment, 3 = nausea and/or vomiting not resolving on treatment.

Total analgesic consumption including tramadol and morphine was recorded at the end of 24 hours. Overall satisfaction with pain management was assessed using a 0-100 VAS (where zero represents very dissatisfied and 100 very satisfied) at 24 hours.

Prospective power analysis was based on the primary outcome, which was defined as the VAS score. We calculated that a sample size of 36 patients in each group was having 90% power at 5% significance level to detect a difference in VAS score of 10 among groups based on a pilot study. To allow the potential dropout, we decided to recruit a total of 40 patients per group. Demographic and parametric data like HR, MAP, and respiratory rate were represented in the form of mean ± standard deviation (SD) and comparison of these between

groups was done by unpaired *t*-test and within groups by one way ANOVA. Nonparametric data like VAS score were represented in the form of median and mean ± SD and comparison was done by Mann Whitney test, and Wilcoxon Sign Rank test and Chi-square test was used to compare postoperative nausea and vomiting scores, sedation scores, and additional analgesic requirement between the two groups. $P<0.05$ was considered significant.

Results

The standard practice and BIS titrated groups were comparable with respect to age, weight, and duration of surgery [Table 1].

Propofol used at induction and MAC isoflurane was comparable in both the groups. However, additional propofol used in group B (to maintain BIS value of 45 to 40) was a mean of 77.12 ± 34.33 mg. The mean BIS value in group S and B were 63.32 ± 11.43 and 45.06 ± 15.31, respectively, and were well within the range of surgical anesthesia. The mean intraoperative HR was comparable in both the groups at 1-minute interval during induction of anesthesia and subsequently at 5-minute intervals ($P>0.05$). However, the MAP was lower in group B compared with group S during induction and subsequently at 5-minute intervals ($P<0.05$) [Table 1] [Figure 1].

Postoperatively, time to eye opening after discontinuation of anesthetics and subsequently zero hour was more in group B in comparison with Group S with an average of 4.6 minutes. Group S patients had a significantly faster time to achieve zero hour in PACU ($P<0.001$) [Table 2].

Tramadol use for pain was comparable in both the groups. The mean pain scores at rest and on coughing at 0 hour were 41.75 ± 21.5 and 55.25 ± 24.59, respectively, in group S and 31.50 ± 18.33 and 43.25 ± 20.92 at rest and on coughing, respectively, in the group B patients. At 8 hours, the mean VAS pain scores at rest and on coughing were 41.50 ± 18.88 and 54.25 ± 21.35, respectively, in the group S and 30.00 ± 13.96 and 41.75 ± 16.77, respectively, in group B. The VAS scores were higher on coughing in comparison with at rest in both the groups. The group S patients had higher VAS pain score at rest and on coughing postoperatively, which were statistically significant at 0 and 8 hours in comparison with group B ($P< 0.05$) [Figure 2]. The VAS pain scores at 16 and 24 hours were more in group S in comparison with group B, but statistically insignificant. The rescue analgesic consumption (morphine) was more in group S patients as compared with patients in Group B ($P<0.05$).

HR, MAP, respiratory rate, and sedation score did not differ between the two groups at 0, 8, 16, and 24 hours postoperatively [Table 3]. However, less number of patients complained of nausea and vomiting in Group B at 0 hour as compared with Group S (12.5% *vs* 52%) ($P<0.001$)

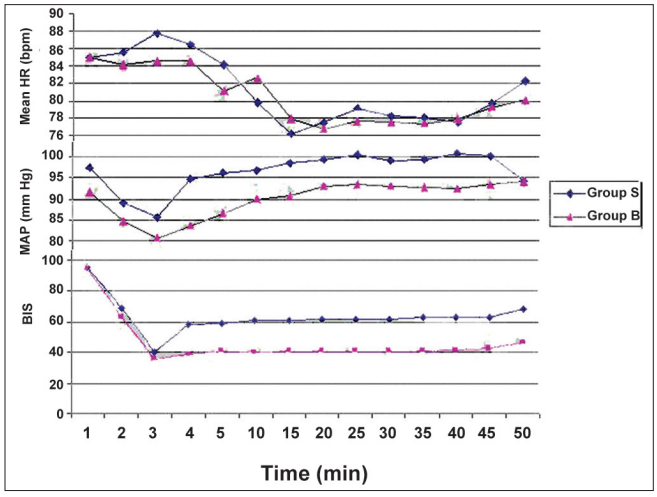

Figure 1: Intraoperative mean heart rate, mean arterial pressure, and bispectral index

Table 1: Demographic and intraoperative parameters (mean ± SD)

	Group S (n=40)	Group B (n=40)	*P* value
Age (years)	38.38 ± 11.73	39.45 ± 10.16	0.663†
Weight (kg)	62.43 ± 7.54	58.95 ± 8.31	0.054†
ASA I/II	31/9	30/10	0.793†
Duration of surgery (min)	58.95 ± 8.31	48.33 ± 7.56	0.140†
<Propofol (mg) Additional	125.75 ± 16.31 -	136.54 ±15.99 77.12 ±34.33	0.087†
MAC of Isoflurane	0.90 ± 0.07	0.93±0.07	0.70†
BIS value	63.32 ±11.43	45.06 ±15.31	0.001**
Heart rate (bpm)	81.46 ±10.51	80.16 ±11.59	0.980†
MAP (mm Hg)	96.72 ±9.73	89.69±8.85	0.014*

*†P>0.05, *P<0.05, **P<0.001, ASA = American society of anesthesiologists, MAC = Minimum alveolar concentration, BIS = Bispectral index, MAP = Mean arterial pressure*

Table 2: Postoperative parameters, nausea, analgesic consumption, and overall satisfaction with pain management (mean ± SD)

Parameters	Group S (n=40)	Group B (n=40)	*P* value
Time to eye opening (min)[a]	7.38 ± 2.35	10.23 ± 3.81	<0.001
Zero hour (min)*	2.90 ± 1.35	4.68 ± 1.60	<0.001
Nausea vomiting	21 (52%)	5 (12.5%)	<0.001
Tramadol (mg)	253.53 ± 43.29	236 ± 6.0	0.053†
Rescue morphine (mg)	2.4 ± 1.16	1.69 ± 0.51	<0.05
Overall satisfaction (VAS)	69.75 ± 1.40	76.0 ± 7.0	<0.001

*[a]Time to eye-opening discontinuation of anesthetics to awakening. *Zero-hour eye opening to conscious and responding to verbal commands in PACU. †P>0.05, VAS = Visual analogue scale*

Table 3: Postoperative pulse rate, mean arterial pressure, and respiratory rate (mean ± SD)

Parameters	0 hours	8 hours	16 hours	24 hours
Pulserate (beatspm)				
Group S	83.85 ± 13.07	80.25 ± 8.66	77.40 ± 5.99	100.3 ± 20.36
Group B	78.88 ± 11.85	76.55 ± 8.22	73.90 ± 9.96	75.00 ± 7.48
MAP (mm Hg)				
Group S	97.50 ± 18.41	90.98 ± 6.47	90.98 ± 6.47	90.80 ± 8.90
Group B	93.90 ± 11.36	91.93 ± 8.00	87.95 ± 7.52	88.18 ± 7.21
RR (breaths)				
Group S	17.43 ± 2.69	17.89 ± 1.44	18.80 ± 1.87	18.80 ± 1.68
Group B	17.93 ± 2.47	18.01 ± 2.00	18.40 ± 1.54	18.70 ± 1.47

MAP = Mean arterial pressure, RR = Respiratory rate

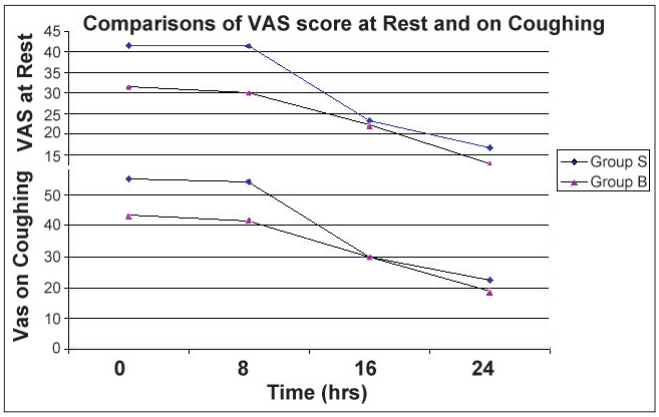

Figure 2: Comparison of VAS score at rest and on coughing

[Table 2]. At 8 hours postoperatively, three patients in each group had nausea and/or vomiting resolved with treatment. Patients in both groups were free of postoperative nausea and vomiting (PONV) at 16 and 24 hours.

Group B patients were more satisfied with overall pain management compared with group S assessed by VAS at 24 hours ($P<0.001$) [Table 2].

Discussion

Our results suggest that pain relief was better in patients in whom depth of anesthesia was adjusted according to BIS (BIS, 45-40). This group of patients experienced lower pain intensity, reduced analgesic consumption and were more satisfied with the overall pain management compared with the patients in whom anesthesia was maintained according to the standard practice.

The results of the present study are comparable with those of Gurman *et al.* who used spectral edge frequency (SEF) as a depth of anesthesia monitor, shows that keeping SEF range between 8 and 12 Hz for more than 80% of surgical and anesthesia time for laparoscopic gastric binding for morbid obesity, both the immediate postoperative pain intensity and morphine requirement was significantly reduced.[6] Furthermore, Henneberg *et al.*, who assessed the influence of the depth of anesthesia using middle latency auditory, evoked potentials on postoperative pain and opioid requirement. The result of their study shows that patients maintained in the lighter plane of anesthesia intraoperatively activated the patient controlled anesthesia (PCA) pump more frequently than those maintained in deeper plane during the first 24 postoperative hours.[5] In these studies, authors speculated that intraoperative deeper plane of anesthesia may have partially aborted the noxious stimuli, influencing the postoperative pain intensity and analgesic requirement.

The mean BIS value in group S and B were 63.32 ± 11.43 and 45.06 ± 15.31, respectively, and were well within the range of surgical anesthesia, verifying that the two groups were managed differently with regard to depth of anesthesia. The deeper level of anesthesia maintained in BIS titrated group to a value of BIS 45-40 could be responsible for lower pain intensity and reduced analgesic consumption postoperatively. We used the BIS to monitor the depth of anesthesia which provides a continuous age-independent monitoring of hypnotic state induced by the most widely used sedative-hypnotic agent and has been used to assess the induction quality, depth of anesthesia, intraoperative requirement of anesthetics, and to reduce the incidence of intraoperative recall and awareness.[8-11] Doi *et al.* studied the relationship between calculated blood concentration of propofol and electrophysiological variables (BIS, 95% SEF, median frequency, and auditory evoked potential index) during emergence from anesthesia and concluded that blood concentration of propofol best correlates with BIS value.[13] We used Propofol as induction agent for this reason.

However, Avidan *et al.* compared BIS-guided and end-tidal anesthetic agent-guided anesthesiaand concluded that maintenance of anesthetic depth according to BIS, when inhalational agents are used to maintain anesthesia, is not superior to that with measurement of end-tidal anesthetic agent concentration to maintain anesthetic depth.[14] In

our study, we used BIS to monitor depth of anesthesia and concentration of isoflurane used was more than 0.7 MAC, which was also the lower cut down limit for alarm in the study by Avidan *et al*. Moreover, they compared awareness in both the groups while we assessed analgesia and analgesic requirement. In their study, as in all studies of anesthesia awareness, the diagnosis of anesthesia awareness was subjective. The awareness interview may be invalid because repeated questioning may induce false memories, and it may be difficult to distinguish between memories of events in the operating room and events in the intensive care unit.

Postoperative recovery from discontinuation of anesthetics to eye opening and subsequently, till zero hour were slightly prolonged in group B with an average of 4.6 minutes. Standard practice group patients had a significantly faster time to achieve zero hour in PACU. Titration of anesthetics and monitoring depth of anesthesia by BIS was associated with reduced anesthetic drug consumption and better recovery profile.[15,16] Song *et al.* titrated volatile anesthetics using BIS and assessed its influence on recovery. The time to awakening and extubation were significantly shorter in patients maintained at BIS value in the range of 60 to 62 as compared with those maintained at BIS of 40 to 45.[9] Farag *et al.* assessed the postoperative recovery using BIS for monitoring the depth of anesthesia and observed faster time to recovery in high BIS group (50.7) compared with low BIS group (38.9).[16]

PONV was seen in both the groups, but lesser number of patients in group B experienced PONV at 0 and 8 hours postoperatively. This difference could be due to the reduction in the cumulative amount of morphine used as rescue analgesic in patients of group B, which lessened the opioid-induced PONV. Rorarius *et al.* studied the effect of gabapentin for prevention of postoperative pain after vaginal hysterectomy and reported a significantly lower cumulative incidence of PONV in patients who required lesser amount of opioid postoperatively.[17] The additional propofol used as infusion in group B patients could have decreased the severity and incidence of PONV in this group.[18]

The patients, for whom anesthesia was adjusted according to BIS value, were more satisfied with the overall pain management than the patients for whom depth was adjusted according to the standard practice, which can be explained in view of lower pain intensity, lesser amount of rescue analgesic required, and lesser incidence of nausea and vomiting postoperatively in this group.

The present study shows that maintaining BIS to a value of 45 to 40 throughout the surgery results in lower intensity of postoperative pain and decreased requirement of rescue analgesic without any untoward effect. However, the time taken to achieve zero hour was slightly more in patients kept at lower BIS value.

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