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SEVOFLURANE REQUIREMENT TO ATTENUATE STRESS RESPONSE TO PNEUMO-PERITONEUM AND POST-OPERATIVE ANALGESIA DURING LAPAROSCOPIC CHOLECYSTECTOMY: INTRATHECAL DEXMEDETOMIDINE VS. FENTANYL. A PROSPECTIVE RANDOMISED STUDY

Anaesthesiology

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ABSTRACT

Background and aims: Laparoscopic cholecystectomy is considered as the gold standard for cholelithiasis with better preservation of surgical anatomy, early recovery and post-operative analgesia but haemodynamic instability due to pneumo-peritoneum is a concern. This study was contemplated to assess the effect of intrathecal dexmedetomidine or fentanyl on end-tidal inhalation agent concentration requirement as an indirect measure of haemodynamic stress response during the creation of pneumo-peritoneum and on post-operative analgesia. **Methods:** This prospective, randomized, comparative study was conducted in 75 ASA I and II patients with three groups of 25 each. The patients in group-1 received 10µg of intrathecal dexmedetomidine, group-2 50µg fentanyl and group-3 equal volume of normal saline before administration of general anesthesia. We assessed the vital parameters and end-tidal concentration of sevoflurane requirement before and 10minutes after creation and immediately after deflation of pneumo-peritoneum. Post-operative pain scores were measured using Visual analogue scale(VAS) for 24hrs and rescue analgesia was 0.5µg/kg fentanyl in the immediate post-operative period and paracetamol 15mg/kg if the score was ≥4 in the post-operative period. **Results:** Demographic data were comparable in all the groups. Systolic blood pressure before onset of pneumo-peritoneum(P=0.03),end-tidal inhalation agent concentration to maintain stable haemodynamics post-pneumoperitoneum were significantly low(P=0.036) in group-1 as compared to group-3. Immediate bolus dose requirement of fentanyl after extubationwas significantly low, and the duration of post-operative analgesia was prolonged(P=0.009) in group-1.**Conclusion:** Intrathecal dexmedetomidine may be a safe and effective method in alleviating haemodynamic stress response during pneumo-peritoneum and provides adequate post-operative analgesia in laparoscopic cholecystectomy.

KEYWORDS

Intrathecal fentanyl, Intrathecal dexmedetomidine, Pneumoperitoneum, Laparoscopic cholecystectomy, Haemodynamic response

INTRODUCTION:

Laparoscopic cholecystectomy is considered as the gold standard surgical procedure for the treatment of cholelithiasis. The ease of doing surgery by preservation of surgical anatomy, early recovery and reduced post-operative pain are significant advantages.[1]However few concerns do exist like, exaggerated hemodynamic stress response and hypercapnia of pneumo-peritoneum, reverse trendelenburg position altering the normal physiology and post-operative nausea and vomiting. Many drugs like intravenous nitroglycerine(NTG), fentanyl, dexmedetomidine, clonidine and inhalational anesthetic agents were used to reduce the pneumo-peritoneum induced stress response with varied results.[2]Use of intravenous(IV) agents to control the stress response of pneumo-peritoneum is associated with the issue of large dose requirement along with varied response across the population. Use of inhalational agents at higher concentration has problems related to drug delivery, as the lung physiology is altered because of high abdominal pressure and steep trendelenburg position. Dexmedetomidine is a selective alfa2 agonist with sedative, analgesic, sympatholytic and anxiolytic properties. With the added benefit of no respiratory depression, it was studied extensively on its effect on pneumo-peritoneum induced stress response.[3-5] Studies have shown that IV dexmedetomidine decreases serum catecholamine levels by 90% in the post-operative period.[6]Drug requirement in the intrathecal route is considerably low as compared to intravenous route to produce similar effects with fewer complications. Dexmedetomidine has not been FDA approved drug for intrathecal use. However, it has neuroprotective effects that are similar to methylprednisolone without long-term and irreversible harmful effect.[7,8] An English literature search showed scant data on the role of intrathecal dexmedetomidine given before induction of anaesthesia in attenuating the overall opioid usage during laparoscopic cholecystectomy.[9] We hypothesized that intrathecal administration of dexmedetomidine might attenuate the pneumoperitoneum induced haemodynamic stress response during laparoscopic cholecystectomy. The end-tidal sevoflurane concentration requirement during various phases of pneumoperitoneum used as a surrogate to assess the haemodynamic stability. This study was contemplated with a primary objective to evaluate the effect of intrathecal dexmedetomidine or fentanyl on end-tidal sevoflurane requirement to maintain safe haemodynamic parameters during pneumo-peritoneum in comparison to a control group in a double-blinded manner. The secondary objectives were to assess, blood sugar response during pneumo-peritoneum, the duration of recovery and post-operative analgesia.

METHODS:

This prospective randomized, double-blind clinical investigation was undertaken at a tertiary care centre over a period of six months. After approval from the institutional ethics committee (EC/NIMS/1987/2017), the study was prospectively registered with Clinical trial registry of India(CTRI/2018/10/016016). Written informed consent were obtained from 75 American Society of Anesthesiologist Physical Status I and II (ASAPS-I and II) patients scheduled for elective laparoscopic cholecystectomy belonging to both the gender aged between 18 and 60 years were recruited for the study. Patients with coagulation disorder and on heart rate control drugs like beta-blockers, alpha2-agonists, calcium channel blockers were excluded from the research and instances where laparoscopic surgery was converted to open procedures were also excluded after inclusion. All the patients received premedication with oral alprazolam 0.25 mg, given in the night before surgery, and pantoprazole 40mg orally on the day of surgery. The patients were randomly assigned to three groups of 25 each according to a computer-generated random number sequence and closed envelop method. Patient allocated to group-1, group-2 and group-3 received 10µg of dexmedetomidine, 50µg of fentanyl and an

equal volume of normal saline respectively via intrathecal route. The study drug dexmedetomidine was prepared by diluting 0.5ml(50µg) of the drug with 9ml normal saline, from which 10µg (2ml) of the drug was taken for intrathecal injection. Similarly, fentanyl was prepared with 1ml (50µg) of the drug diluted with an equal volume of normal saline by an independent investigator who did not participate in the trial so that the primary investigator and the patient remained blind to the type of the drug used. Heart rate (HR),systolic, diastolic and mean arterial blood pressure (SBP, DBP, MAP), SPO2, Surgical Pleth-Index (SPI), State and response entropy (SE and RE), serum blood sugar were noted before the intervention and at different stressful time points of surgery. The patients were premedicated with IV glycopyrrolate 4µg/kg and ondansetron 4mg. Under strict aseptic precaution and the patient in sitting position subarachnoid block was given as per randomization with 25G spinal needle at L3-L4 / L2-L3 intervertebral space. Post-procedure, patients were assisted to supine, and vital signs were noted. Standard general anaesthesia was administered to all the patients. Induction of anaesthesia was done with propofol 2mg/kg, fentanyl 2µg/kg, atracurium 0.5mg/kg, and sevoflurane after pre-oxygenation for three minutes. All the patients were given ketorolac 30mg in 100 ml of normal saline, slow intravenous infusion at the time of induction. The trachea was intubated with appropriate sized endotracheal tubes and were maintained on positive pressure ventilation targeting $ETCO_2 \approx 40mmHg$. Anaesthesia was maintained with oxygen, air, and sevoflurane with intermittent doses of atracurium tailored to the need of the patientSevoflurane concentration was titrated to maintain MAP around 20% of baseline. Haemodynamic parameters, end-tidal sevoflurane concentration, entropy and blood sugar were measured after intubation, just before pneumo-peritoneum(BPN), 10 minutes after pneumo-peritoneum(APN) and immediately after deflation of pneumo-peritoneum(AD). End-tidal sevoflurane concentration requirement was used as an indicator to assess the haemodynamic stress response to pneumo-peritoneum in the post inflation stage.

After completion of the surgery, port sites were infiltrated with 0.25% bupivacaine. Residual neuromuscular block reversal was done with IV neostigmine 50µg/kg and glycopyrrolate 10µg/kg. Extubation time was defined as the period from the cessation of the inhalational agent to tracheal extubation. The immediate need of fentanyl after extubation was assessed by the pain scores using Visual Analogue scale(VAS) by an independent observer not involved in the study and 25µg fentanyl IV was given if the score was ≥ 4. The patients were shifted to post-anaesthesia care units and monitored for 24 hours. Post operatively the pain severity was assessed every 4thhrly using VAS score by a trained nurse up to 24 hours and any score ≥ 4 was treated with rescue analgesia of IV paracetamol 15mg/kg taking care not to exceed 4gm in 24 hours and the request for the first demand to analgesia was the noted as the duration of analgesia. Post-operative complications like the incidence of nausea and vomiting (PONV) and post-dural puncture headache(PDPH) were recorded. PONV was treated with 4mg ondansetron IV and PDPH with IV fluids, supine position, paracetamol and caffeine.

Statistical analysis was done using the Statistical Package for Social Science (SPSS17.0 Evaluation version). Qualitative data were compared with the chi-square test, and quantitative data were compared within the group against baseline values using the paired t-test. ANOVA test was used for three group comparisons of continuous variables. Tuckey post hoc test was used if ANOVA was significant, and the results were expressed as mean ± standard deviation. P >0.05 was considered insignificant, <0.05 as significant and highly significant if <0.001. Sample size calculation was done assuming that intrathecal dexmedetomidine or fentanyl administration will reduce the sevoflurane requirement by 25% as compared to the control group. G*Power (3.1.9.4) software used for calculation of sample size.[10] With an alpha error of 5%, power of 80%, and assuming required end-tidal sevoflurane concentration 1.2% in the control group and 0.90% in dexmedetomidine and fentanyl group with a standard deviation of 0.40, a sample size of 23 was required in each group. Hence, we recruited 25 patients in each group to account for possible exclusion.

RESULTS:

Out of 75 patients, three patients were excluded from the study (Figure-1) as the laparoscopy procedure was converted to open procedure due to issues related to surgery. The demographic data of all the groups were comparable (Table1).

Legends for figures:

Figure-1 : Consorted Flow Diagram

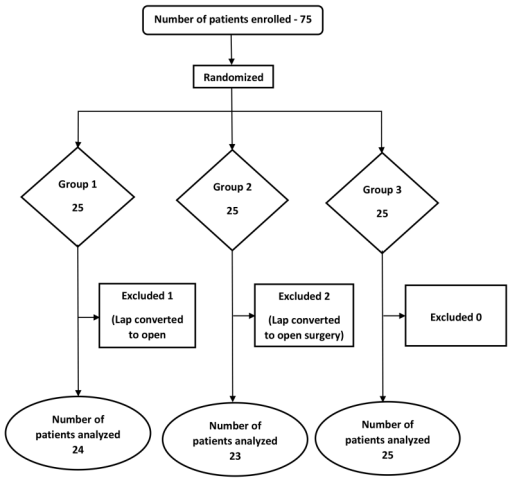


Table 1: Demographic data

	Group 1	Group 2	Group 3	P value
Age	35.88±11.07	36.88± 8.9	38.20±12.27	0.751
Gender (M: F)	16:9	16:9	17:8	0.699
Height (cm)	157.48 ±9.27	155±9.46	153.12±10.20	0.284
Weight (kg)	58.96±8.11	65.12±13.17	60.80±13.30	0.118
Duration of surgery (mins)	114.6±49.5	111.6±38.3	92.60 ±37.7	0.160
BLHR	89.2±17.5	88.1±15.6	89.1±17.9	0.967
BLSBP	134.5±23.6	135.3±20.1	136.2±21.9	0.996
BL DBP	82.0±12.9	83.2±13.4	82.1±8.6	0.931
BL MAP	103.7±16.70	103.9±16.0	104.3±14.5	0.990

BL- Baseline, HR-heart rate, SBP- Systolic blood pressure, DBP-Diastolic blood pressure, MAP- Mean arterial pressure

Heart rate in pre-pneumo phase was significantly low as compared to baseline in group-1 (P=0.035) and group-2 (P <0.001) but not so in group-3 (P=0.151). End-tidal sevoflurane concentration and entropy were comparable in all three groups in pre-pneumo phase (Table-2).

Table: 2 Pre-Pneumoperitoneum parameters

Pre-pneumo value	GROUP 1	GROUP 2	GROUP 3	P VALUE
End-tidal Sevo	0.76±0.20	0.768±0.20	0.860±0.19	0.158
HR	82.6±13.2	74.7±14.7	83.7±15.5	0.084
SBP	100.3±16.8*	103.6±16.3#	112.4±16.5*#	0.033
DBP	66.3±14.6	67.8±13.8	72.2±12.1	0.290
MAP	80.8±15.7	83.0±13.6	88.6±13.1	0.144
SE	71.1±13.1	75.9±10.3	64.1±24.3	0.06
RE	67.6±13.0$	69.8±12.1^	58.1±20.3^$	0.023

SE- State entropy, RE- Response entropy
*SBP was significantly lower with comparable end tidal sevoflurane concentration (P =0.031)
^ RE significantly low between the groups (P =0.26)
# SBP was not significant in between the groups (P= 0.151)
$ RE comparable between the groups (P= 0.088)

Significantly higher end-tidal sevoflurane concentration (P=0.036) was noted in group-3 during post-pneumo-creation phase (Table-3)).

Table 3: Post-Pneumoperitoneum parameters

Post-pneumo value	GROUP 1	GROUP 2	GROUP 3	P VALUE
MAC	0.928±0.25*	0.971±0.24#	1.112±0.27*#	0.036
HR	85.0±14.9	77.8±13.8	85.9±16.5	0.121
SBP	124.1±16.2	127.1±15.9	133.0±18.2	0.177
DBP	83.3±11.0	83.3±11.7	83.6±9.8	0.993
MAP	99.3±11.3	101.9±13.9	103.0±13.5	0.585
SE	56.1±21.2	58.3±16.4	48.4±21.8	0.197
RE	51.8±17.9	55.1±17.4	43.2±20.8	0.078

*Significant higher anesthetic requirement in group I as compared to Group3 (P-value 0.037)

No Significant relation between groups (P-value 0.142)

Table 4 : Recovery and analgesia.

	Group1	Group2	Group3	P-value
Recovery time (min)	15.5±6.3	14.9±5.7	15.9±6.1	0.837
Duration of Analgesia	17.7±9.6	10.48±8.4	9.98±10.3	0.009
Immedeate Fentanyl Use	0/24	2/23	7/25	0.007
No of Rescue Analgesia doses	6/24	15/23	17/25	0.007

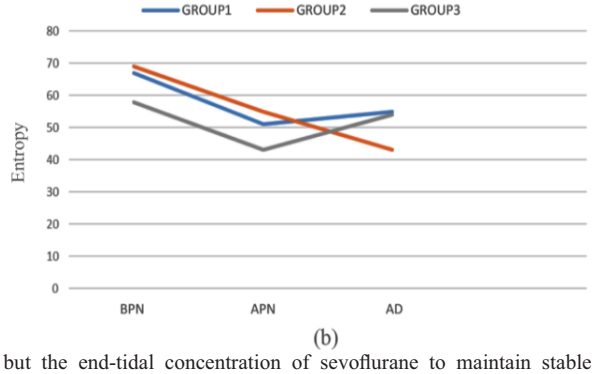
Recovery time: From cessation of inhalation agents to extubation time
* No difference in recovery time in between the three groups.
* Duration of analgesia is significantly more in Group I
* Requirement of rescue analgesia was significantly lower in Group I as compared to Group2 and Group3

Blood sugar levels were increased in all the groups. There was no difference in recovery time in the groups. None of the patients in group-1 required immediate fentanyl bolus dose, whereas two patients in group-2 and seven patients in group-3 required (P=0.007).

The duration of analgesia was prolonged significantly (17.7±9.6 hr (P= 0.007) in the dexmedetomidine group(Table-4) and the number of rescue analgesia doses were also significantly less (P=0.007). Only one patient complained of headache in the post-operative period suggestive of post-dural puncture headache and responded very well to treatment. One patient in group 2 had PONV requiring treatment with 4mg IV ondansetron.

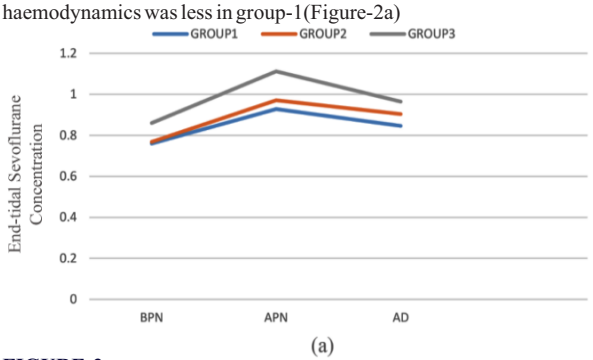
DISCUSSION:

Our study results showed stable and comparable haemodynamics (Table-3) during stressful periods of pneumoperitoneum in all the groups. The entropy level was comparable and was within a safe range of 40-60 in all the three groups during post-pneumo creation stage of surgery(Figure-2b),



(b)

but the end-tidal concentration of sevoflurane to maintain stable haemodynamics was less in group-1(Figure-2a)



(a)

FIGURE-2:

a) End-tidal sevoflurane concentration at different stages of pneumoperitoneum
b) Entropy at different stages of pneumoperitoneum

as compared to group-3 (P=0.036), which indirectly denotes exaggerated haemodynamic response in group-3. The sevoflurane sparing effect was less as compared to intravenous route in other studies,[17] which can be attributed to less dosage of dexmedetomidine in our study and probably intrathecal route does not produce much sedation. Intrathecal fentanyl did not offer any significant advantage over the control group with respect to consumption of inhalation anesthetics during the creation of pneumoperitoneum phase was concerned (P=0.142). Although it was not our objective in the present study we found that the intubation response was stabilized early in group 1, as denoted by significant initial fall in heart rate despite comparable end-tidal inhalation agent (P= 0.158) and entropy value (P =0.088) and significantly higher (P=0.033) systolic blood pressure (SBP) in group-3 patients as compared to group-1 in pre-pneumo phase(Table-2).

Intrathecal dexmedetomidine and fentanyl are frequently used drugs which prolong the duration of anaesthesia and analgesia when used as an adjuvant to local anesthetic drugs [11,12].In a study conducted by Abdalla et al.,[9] where a combination of intrathecal fentanyl and dexmedetomidine significantly reduced the intraoperative opioid requirement as compared to the intravenous group. We chose the drug dosage based on the literature.[12,13,14,15] The end-tidal sevoflurane concentration of 1.2% with opioids achieved the optimal balance between the quality, and recovery from anaesthesia [16] and intravenous dexmedetomidine has sevoflurane sparing effect up to 41% per hour.[17] Intravenous requirement of dexmedetomidine ranges from 20-30 µg/hour for a 50kg adult [3,4]in contrast 10µg of intrathecal dexmedetomidine in our study, made a significant difference as compared to control group which proves that, not only the intrathecal dose requirement was less but also an effective drug to reduce consumption of inhalation agent.

The recovery profile of dexmedetomidine group was better (P=0.007) without any increase in extubation time. The quality of post-operative analgesia was superior in the dexmedetomidine group(Table-4) in terms of lesser requirement of rescue analgesia and duration of analgesia was superior(P=0.009). The results were consistent with the finding in the studies where dexmedetomidine was used as an adjuvant.[18]

Another interesting finding in our study was that though there was a rise in blood sugar levels intraoperatively in all the three groups which was comparable, but in group-2 the curve was less steep with significant low blood sugar levels compared to control group(P=0.02) suggesting a more gradual rise in the value, however, the explanation for this could not be provided.

The results of this study consistent with the finding that the use of intrathecal dexmedetomidine is an effective way to control haemodynamic response to pneumo-peritoneum and reduces the requirement of inhalation anesthetics. To add, it provides good patient comfort during extubation and provides excellent post-operative analgesia without any adverse effects.

The limitation of our study was the amount of inhalation agents utilized was not taken in to account, which could have given an added assessment of anesthetic agent used. Probably future studies in this regard with larger sample size may add to the literature.

CONCLUSION:

Intrathecal dexmedetomidine is a safe and effective adjunctive to general anaesthesia to attenuate the intra-operative haemodynamic stress response to pneumo-peritoneum with superior post-operative analgesia and recovery profile in laparoscopic cholecystectomy. It can be used in the armamentarium of the multimodal analgesia.

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