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Analgesic efficacy of intraperitoneal vs intravenous dexmedetomidine as adjuvant to levobupivacaine 0.25% in laparoscopic cholecystectomy under general Anaesthesia

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Abstract
Background and Aims: Recently, low□dose intravenous (IV) dexmedetomidine has been evaluated for its analgesic efficacy in laparoscopic cholecystectomy. Methods: Hundred□five patients, 18–60 years, ASA I & II scheduled for laparoscopic cholecystectomy under general anaesthesia were included. Patients in group B received intravenous 10 mL normal saline (NS) over 10 minutes before extubation along with intraperitoneal [IP] instillation of 28 mL levobupivacaine 0.25% + 2mL of NS. Patients in group BD received intravenous 10 mL NS over 10 minutes before extubation and intraperitoneal 28 mL levobupivacaine 0.25% + 0.5 µg/kg dexmedetomidine (2 mL). Patients in group D received dexmedetomidine 0.5 µg/kg IV in 10 mL NS over 10 minutes before extubation and intraperitoneal instillation of levobupivacaine 0.25% (28mL) to total volume of 30 mL. The primary outcome was visual analogue pain score and secondary outcomes were sedation scores, rescue analgesic requirement.
Results: VAS score was significantly lower in dexmedetomidine group D, BD from 1hr to 8hr. From 8 hr to 24 hr, VAS score in group IV dexmedetomidine was significantly less than the other groups (*P*=0.01). In the postoperative period, sedation scores were more in IV dexmedetomidine group as compared to other groups till 4 hrs. The requirement of rescue analgesia in IV dexmedetomidine + IP levobupivacaine was significantly less from zero hrs to 8 hrs.
Conclusion: Low bolus dose of IV dexmedetomidine is more efficacious as compared to IP dexmedetomidine (0.5 µg/kg) along with IP bupivacaine in laparoscopic cholecystectomy.

Keywords: Laparoscopic cholecystectomy, intraperitoneal, dexmedetomidine, analgesia

Introduction
Postoperative pain after laparoscopic surgery is the most important limiting factor in early discharge of the patients [1]. As laparoscopic procedures are done on outpatient basis, there is great emphasis on rapid recovery and freedom from postoperative pain and nausea. Therefore, there is more emphasis on multimodal methods of pain relief including local anaesthetic administration via intraperitoneal route, to shorten the hospital stay. adjuvants have been tried for intraperitoneal instillation along with local anaesthetic to reduce the dose of local anesthetics and thereby decreasing probable adverse effects [2]. Dexmedetomidine 1 µg/kg as adjuvant to 0.25% bupivacaine in elective laparoscopic cholecystectomy shows encouraging results by reduces the post-operative pain and analgesic requirement in post-operative period.
This study aimed to compare the antinociceptive efficacy of intraperitoneal vs intravenous dexmedetomidine as adjuvant to levobupivacaine in laparoscopic cholecystectomy patients.

Material and Methods
After obtaining Institutional Ethics approval and written informed consent from the patients, study enrolled 105 patients (n=35 in three group each) aged 20 to 45 years and American Society of Anaesthesiologists (ASA) physical status I and 2, scheduled under general anaesthesia requiring endotracheal intubation for elective laparoscopic cholecystectomy procedures.

Patients with significant cardiovascular and respiratory comorbid diseases including hypertension, obesity (BMI> 30kg /m2), diabetes, difficult anticipated airway, history of sleep apnoea were excluded from the study. Patients with requirement of intra-abdominal drains in the postoperative period were also excluded. During the preoperative interview detailed information regarding the visual analogue scale and communication regarding need for rescue analgesics in the postoperative period, was explained to the patients.

Patients were kept nil orally for solid food for eight hours and clear fluid was allowed till 2 hours prior to surgery. On the day of surgery tablet metoclopramide 10 mg and tablet ranitidine 150 mg was given to the patients at 6 am. In the operating theatre, intravenous (IV) line was secured and drip was started with normal saline (NS). After instituting routine monitoring ie three lead electrocardiogram (ECG), non-invasive blood pressure (NIBP) and saturation of oxygen (SpO_2), the baseline parameters were recorded.

The premedication was given with midazolam 0.03mg/kg and fentanyl 2µg/kg intravenously followed by induction with propofol 2mg/kg and injection cisatracurium 1.5mg/kg for tracheal intubation. After intubating the trachea with proper sized cuffed oral endotracheal tube, nitrous oxide and oxygen (70:30) with isoflurane (0.5-1vol%) were used to maintain anaesthesia. End tidal carbon-dioxide [$EtCO_2$] was kept in the range of 35- and 40-mm Hg intra operatively by adjusting minute ventilation. After the creation of pneumoperitoneum, the patients were put in 15-20^0 reverse trendelenberg position. Intraabdominal pressure was restrained between 8-12 mm of Hg in the intraoperative period. Before the completion of surgery, injection paracetamol 10mg/kg was given as per the institutional protocol and after ensuring complete haemostasis by the surgeon, the allocated drug preparations was given according to computer generated randomized table to three groups.

Surgeon and the anaesthetist in the postanesthesia care unit were unaware of the treatment to which each patient is randomized. In group B patients bolus of intravenous 10 mL normal saline (NS) was given slowly over 10 minutes before extubation along with intraperitoneal instillation of 28 mL levobupivacaine 0.25% (70 mg) with 2mL of NS. The patients in group BD received bolus of 10 mL NS over 10 minutes before extubation along with intraperitoneal 25 mL levobupivacaine 0.25% (70 mg) + 2 mL dexmedetomidine (0.5µg/kg). Whereas, dexmedetomidine 0.5 µg/kg intravenous (IV) in 10 mL NS bolus was given over 10 minutes before extubation along with levobupivacaine intraperitoneally in group D patients.

At the end of surgery, under the direct guidance of the camera, the study drug was administered under the diaphragm and gall bladder fossa and in trendelenberg position to facilitate dispersion of drug solution in sub hepatic region. At the same time the intravenous drug solution was given over a period of 5 minutes.

Injection neostigmine 0.05 mg/kg and 0.01mg/kg glycopyrrolate were administered for reversal of neuromuscular blockade. The parameters recorded were heart rate, systolic, diastolic and mean blood pressure at the time of extubation and thereafter at 1, 3 and 5 minutes following extubation for 30 minutes. We observed for any adverse events like laryngospasm, bronchospasm, vomiting, hypotension or bradycardia and undue sedation in the postoperative period.

Postoperative sedation was evaluated on a 6 point scale (Ramsay Scale): [3] 1 = Anxious or agitated and restless or both, 2 = Cooperative, oriented and tranquil, 3 = Drowsy but responds to commands, 4 = Asleep, brisk response to light glabellar tap or loud auditory stimulus, 5 = Asleep, sluggish response to light glabellar tap or loud auditory stimulus, 6 = Asleep and unarousable. The intensity of the pain was assessed using visual analogue scale (VAS) at 0.5 h, 1 h, 4 h, 8 h, 12 h, 18 h, and 24 h. Where zero score corresponds to 'no pain' and 10 corresponds to the 'maximum' or 'worst pain'. For the first 24 h, for post□operative pain relief injection diclofenac 75 mg was administered intramuscularly, if VAS score was equal or more than 4. For breakthrough pain, IV tramadol 2 mg/kg was administered as and when required.

Statistical Analysis

The MS Excel 2010 was used for data collection and statistical analysis was performed using SPSS software 15. The One-Sample Kolmogorov-Smirnov Test was used for assessing the data distribution. Mann–Whitney U-test was used for non-uniform distributed data and ANOVA was employed for assessing normally distributed data. The Chi-square test was applied for analysing categorical data and the unpaired t test was applied in normally distributed data for comparison between two groups

Results

One hundred and ten patients were recruited, scheduled for laparoscopic cholecystectomy requiring endotracheal intubation under general anaesthesia. However, due to surgical indications in the intraoperative period, open cholecystectomy was done in three and two patients in group BD and B respectively, therefore one hundred and five patients were recruited in the study [Fig 1]. The demographic profile age, gender, basal metabolic index and duration of surgery were statistically insignificant in all the groups [Table 1].

In the present study, VAS score of the patients were recorded till 24 hours in the postoperative period. We observed that VAS score was comparable in all the groups till third hours (P≥.05). After 4 hours VAS score was significantly decreased in group D and BD (mean±SD: 2.28±0.72,2.48±1.78) than group B (mean±SD:: 2.63±1.70::P=.002 in gp B vs D). We observed that beyond 8 hours to 24 hours, VAS score was significantly less in group D as compared to other two groups (P=0.00) [Figure-2].

With regards to rescue analgesics, our study observed that patients in group D demand less rescue analgesics as compared to group B and BD at 8-hour, 18 hour, and 24 hours. Total boluses of injection diclofenac 75 mg used in each patient group in postoperative period were calculated. Total number of boluses used in group B was maximum followed by BD and D group. The group B required doses from first hr upto 24 hr with maximum boluses usage at 4th hour and 18th and 24 hr, indicating shorter pain free period and more requirement of analgesia postoperatively. The maximum bolus usage was at 8, th 12 th and 24 hr in group BD with requirement started at 4 hrs. The group D patients, required rescue analgesic at around 8 hrs with maximum demand at 12, 18 and 24 hrs [Fig 3]. In the postoperative period over 24 hrs, the mean dose of rescue analgesic required was 1.2 in group D in comparison to group BD and

B (1.5 and 2.2: P=0.00 [gp D, BD: gp B]) respectively.

The sedation score in group D was significantly higher in the first 4 hours (3.26±0.78, 3.21±0.89, 3.16±0.87 and 3.10±1.17) at 0 min, 0.5 hr, one hr and at 4 hr respectively, as in comparison to group BD (3.01±0.87, 2.91±0.49, 2.96±0.72 and 2.90±1.56 (P=0.00 b/w gp D and BD). Whereas in group B the sedation score was statistically less (2.10±0.83, 2.08±0.57, 2.01±0.81 and 2.00±1.78) in comparison to group B and BD at 0 min 0.5 hr, 1 and 4 hr. Beyond fourth hour the patients in three groups had comparable scoring. [Fig 4]

HR at extubation was significantly increased in group B in comparison to group BD and D (80.86±11.62 vs. 76.20±10.87; P=0.088 and 67.00±10.29;P=0.007) with significantly less rise in group D. HR at 1min was comparable in group B and group BD (82.23±11.08 &77.91±10.81; P=0.104). Significantly higher HR was observed in group B as compared to patients in group D (82.23±11.08 and 77.29±9.69; P=0.049). However, the HR up to 30 minutes in the postoperative period was statistically insignificant. The rest of hemodynamic variables were comparable at all study time intervals, except single episode of increases in systolic blood pressure at extubation in group B. We didn't encounter any adverse effect in any group.

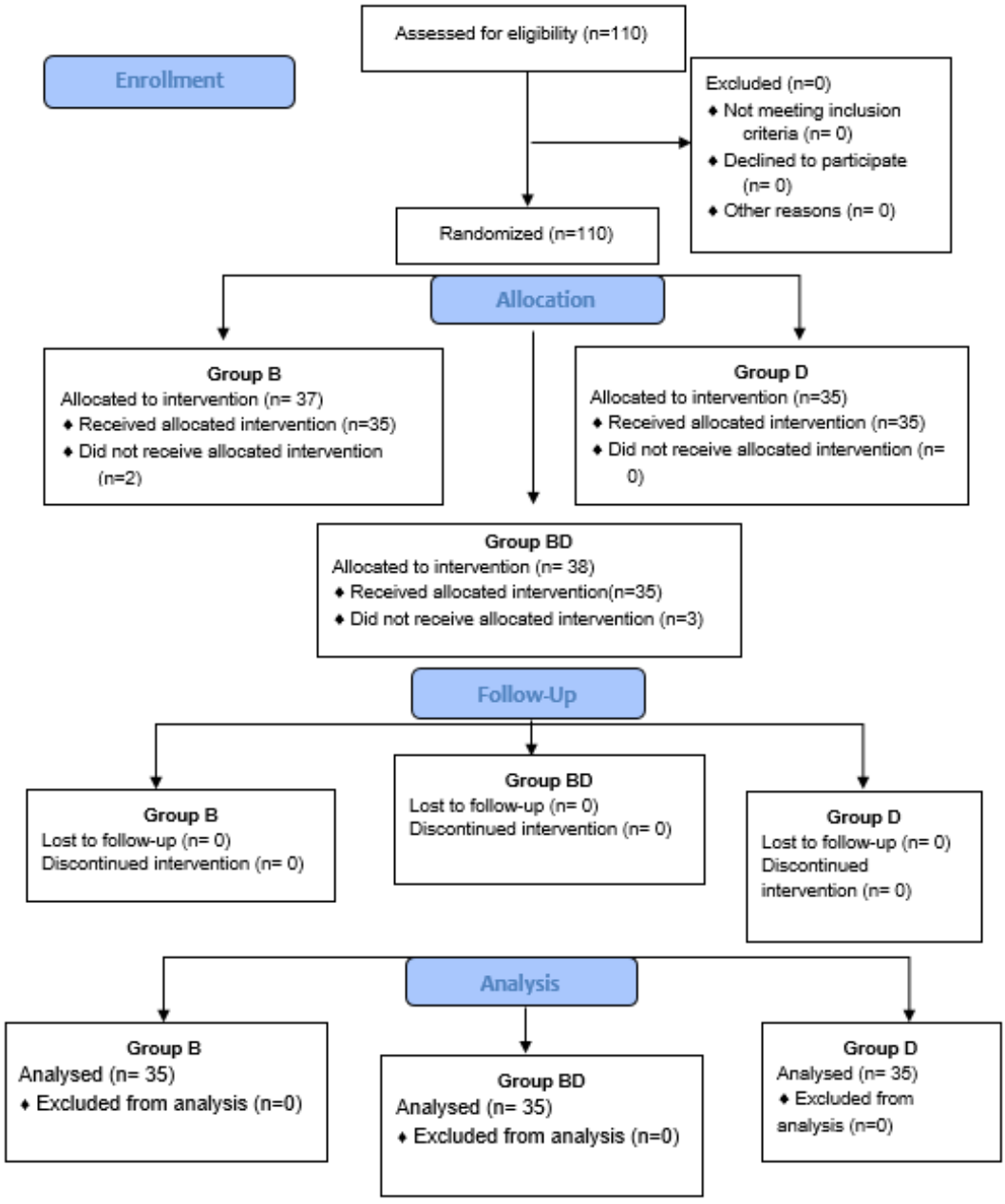

Fig 1: Flow chart of patients recruited and analyzed in three groups: consort 2010 flow diagram

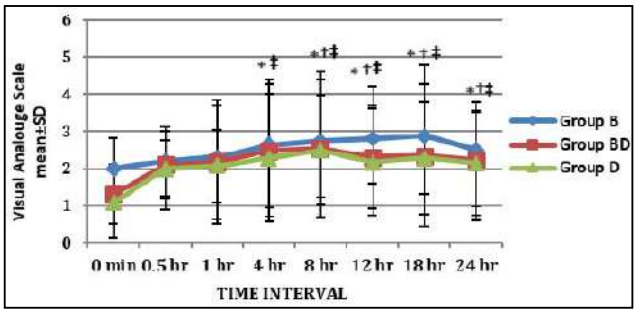

Fig 2: Graphical presentation of Visual Analogue Scale in three groups. Data expressed as mean±SD. *P*<0.05: * =gp D vs gp B:, †= gp BD vs gp D, ‡= gp B vs BD.

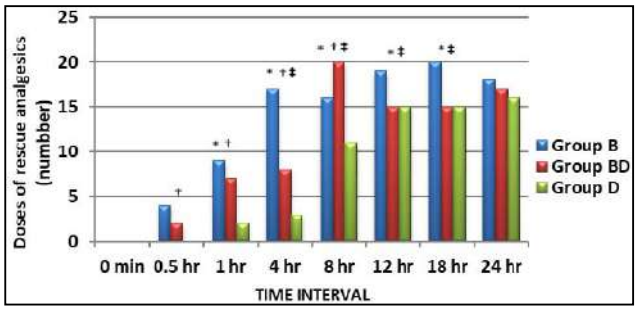

Fig 3: Total dose of rescue analgesics required in three groups over a period of 24 hrs, expressed as number. *P*<0.05: * =gp D vs gp B:, †= gp BD vs gp D, ‡= gp B vs BD.

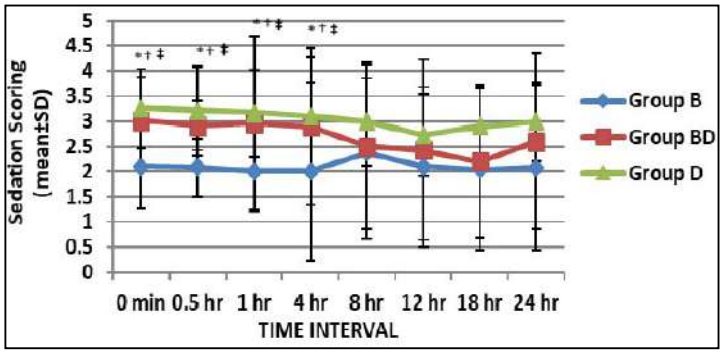

Fig 4: Comparative evaluation of sedation score in three groups up to 24 hrs in the postoperative period. *P*<0.05: * =gp D vs gp B:, †= gp BD vs gp D, ‡= gp B vs BD.

Table 1: Demographic Profile of patients in three groups. Values mentioned as mean ±SD* and number† as appropriate. BMI – Basal metabolic Index; ASA – American Society of Anesthesiologists ; SD – Standard deviation.

S No.	Characteristic	Group B (n=35)	Group BD (n=35)	Group D (n=35)	Statistical Significance
1.	Age (Yrs) mean±SD	42.86±11.28	39.74±12.62	42.46±10.02	*P*=0.072
2.	**Gender (n)**				
	Male (n=30)	9	9	12	*P*=0.67
	Female (n=75)	26	26	23	
3.	BMI (Kg/m^2) mean ±SD	21.63±1.80	21.63±1.78	20.74±1.61	*P*=0.352
3.	**ASA Grade (n)**				
	I	30	32	31	χ^2=0.609
	II	5	3	4	*P*=0.738
4.	Mean Duration of surgery (min) mean±SD	40.00±11.43	40.65.±10.70	41.70±12.44	*P*=0.630

Discussion

In laparoscopic surgeries the raised intraperitoneal pressure as consequence of gas insufflation leads to peritoneal inflammation and neuronal rupture and are strong predictors of severity of the postoperative pain.

Therefore, we opted for intraperitoneal route for local anaesthetic, as these agents has inhibitory effect on visceral afferent signals therefore the perception of pain is suppressed. The local anaesthetic provide analgesia by virtue of its effect on nerve membrane and secondly decreased release of prostaglandins, which is primarily responsible for inflammation [4]. The analgesic efficacy of dexmedetomidine is due to its action at the level of dorsal root neuron, leading to decreased release of substance P. Dexmedetomidine also have effect on inhibitory G protein, resulting in increased conductance through the potassium channels [5].

Levobupivacaine, safer isomer of bupivacaine is advantageous for intraperitoneal use by virtue of its beneficial profile in providing cardio stability. The levobupivacaine (0.25%) and ropivacaine (0.25%) through intraperitoneal route are effective for providing analgesia following laparoscopic cholecystectomy, though levobupivacaine relieved pain for a longer duration, without noticeable adverse effects [6]. The results of the study favoured 0.25% levobupivacaine in preventing pain and reducing the need for postoperative analgesic through intraperitoneal instillation per se or along with pre incisional local infiltration. Therefore, we used 0.25% levobupivacaine in our study, by virtue of its safety and better therapeutic response.

In another study, [7] the authors observed that intravenous dexmedetomidine resulted in decreased requirement of opioid analgesics and anesthetics in the intraoperative period. The incidence of severe hemodynamic fluctuations during traumatic phases of surgeries were also prevented by premedication with dexmedetomidine 0.5 µg/kg. Dexmedetomidine has been shown to reduce the

intraoperative propofol requirement in addition to have beneficial effect on postoperative analgesia. The authors observed increased postoperative satisfaction and sedation level in patients undergoing laryngoscopic biopsy under total intravenous anesthesia [8].

In the study by Ranjita *et al*. [9] intraperitoneal dexmedetomidine 0.5µg/kg as adjuvant to ropivacaine was found to be beneficial in reducing the VAS scores, decreasing the total rescue analgesic requirement in the postoperative period. The time for demand of rescue analgesia was also prolonged in laparoscopic hysterectomy procedures.

Therefore, we hypothesized that the intravenous bolus of dexmedetomidine 0.5µg/kg bolus injected over ten minutes prior to extubation will enhance the efficacy of intraperitoneal levobupivacaine. We evaluated and compared the analgesic efficacy of intraperitoneal dexmedetomidine versus intravenous dexmedetomidine as an adjuvant to levobupivacaine in patients scheduled for laparoscopic cholecystectomy.

In the present study, the VAS score was comparable in all the three groups in initial three hrs. Beyond 4 hours VAS score was significantly less in group D and BD than group B, whereas from 8 hr till 24 hr, VAS score in group D was significantly less than the other two groups(P=0.00).

In another study by Bez *et al*. [10] 105 patients for laparoscopic cholecystectomy were enrolled and divided into three study groups. Intraperitoneal instillation of normal saline 40 mL was done in control group (C). In group L, 40 mL 0.25% levobupivacaine was given and in group LD patients received intraperitoneal infiltration of levobupivacaine 0.25% (40 mL) and dexmedetomidine 1 µg/kg. Postoperative VAS scores were statistically significantly less in group LD than group L and C at different time intervals up to 12 hrs postoperatively. We observed reduced pain scores in group BD till 8 hrs in comparison to group B. The difference may be due to the fact that lesser volume of the local anaesthetic (40mL vs 30 mL) and the low doses of dexmedetomidine (0.5µg/kg vs 1µg/kg) were used in the present study.

The dose of rescue analgesic injection diclofenac was less in group LD in comparison to group C and L (203.5±42.9 vs 117.8±63.7 and 46.3±41.3; *P*< 0.001).

There is single study [11] till date to compare the IV vs IP dexmedetomidine (0.5µg/kg) as adjuvant to 0.5% bupivacaine. Seventy□five patients, ASA physical status I and II, aged 18 to 60 yrs were recruited for laparoscopic cholecystectomy. Patients in control group (C) received bupivacaine 0.5% (40 mL). In group IV dexmedetomidine 0.5µg/kg IV bolus was given after removal of gall bladder +IP bupivacaine. Whereas dexmedetomidine 0.5µg/kg in 40 mL of bupivacaine IP was given in group IP. The authors observed that the mean VAS pain score were significantly less in groups IV and IP as compared to control group from 0.5 to 12 h, with the exception at the sixth hour in the postoperative period. Whereas in our study, the pain scores were comparable in all groups till 4 hr and beyond that scores were comparable in group BD and D till 8 hrs. Afterwards the VAS was significantly less in group D. Again, the discrepancies in the results could be attributed to larger volume of bupivacaine (40 mL) in the study by Chilkoti *et al*.

Our study observed that requirement of rescue analgesia in IV dexmedetomidine + IP levobupivacaine was significantly lower from 8 hours to 24 hours than IP dexmedetomidine + IP levobupivacaine and IP levobupivacaine only. Oza *et al*. [12] compared the antinociceptive efficacy of IP instillation of dexmedetomidine and bupivacaine to that of plain bupivacaine in patients posted for laparoscopic surgeries. The authors concluded that the demand for the rescue analgesic was less in group D (1.76) as compared to group B (2.56) postoperatively (*P*<0.05).

In the present study, the demand for rescue analgesic was observed beyond first hr in group B, whereas in group BD, requirement started at 4 hrs as compared to 8 hrs in IV group. Whereas, in the study, [11] the mean time to demand for the first rescue analgesic was statistically more in the IV dexmedetomidine group (210.52 ± 161.17 min) as compared to IP group. So the results of both study correlates well.

Our study observed that IV dexmedetomidine + IP levobupivacaine provided better sedation than IP dexmedetomidine + IP levobupivacaine and IP levobupivacaine only. The patients were arousable on verbal command in group D vs BD up to four hour and beyond that time interval the sedation scores were comparable in all three groups. The duration of approximately 4 hrs could be the result of elimination half-life of dexmedetomidine of upto 2 to 3 hrs. However in the study, [11] the patients were observed to have higher sedation scores in dexmedetomidine groups as compared to control group till 2 h. Dexmedetomidine induces a peculiar state called "cooperative sedation, " and is thought to be associated with attention [13].

Regarding haemodynamic there was less rise in heart rate during and upto one-minute postextubation in group BD and D in comparison to B. The stable haemodynamic in the present study are because of dexmedetomidine in low dose of 0.5µg/kg through either route as adjuvant to levobupivacaine in laparoscopic cholecystectomy procedures. Whereas the studies utilizing higher doses or infusion of dexmedetomidine are associated with significant haemodynamic fluctuations presenting as hypotension or bradycardia.

We have few limitations of the study like we have assessed the pain scores at rest only and dynamic pain scores were not included. Secondly the individual variation in the pain scores could not be verified using objective assessment.

Therefore, present study concluded that intravenous dexmedetomidine along with intraperitoneal instillation of levobupivacaine comparatively provides better prevention of postoperative pain, better sedation, and decreased demand for rescue analgesics without any adverse effects. The patients were haemodynamically stable during extubation with intravenous dexmedetomidine especially with regard to heart rate changes.

So it is recommended that intravenous dexmedetomidine 0.5µg/kg can be used as an adjuvant to intraperitoneal levobupivacaine 0.25% in patients for laparoscopic cholecystectomy, for better postoperative pain scores and increased duration of analgesia. Thereby, reducing the rescue analgesic requirement with arousable sedation without any adverse effect.

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