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Original Research Article

Comparison of postoperative analgesia and sedation responses of intravenous dexmedetomidine and esmolol during laparoscopic cholecystectomy

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ABSTRACT

Background: Although, the concept of laparoscopic surgeries has revolutionised the surgical practice and has markedly reduced the incidence of complications especially postoperative pain. However, the menace of postoperative pain still remains challenge, especially in first 24 hours. The present study was conducted to comparatively analyse the postoperative pain and sedation using intravenous dexmedetomidine and intravenous esmolol during laparoscopic cholecystectomy.
Methods: Study was conducted on 90 adult patients aged 18-60 years of ASA grade I or II of both genders, scheduled for laparoscopic cholecystectomy under general anaesthesia. Patients were randomized into three groups of 30 patients each. Patients of group A received esmolol infusion (loading: 1 mg/kg and maintenance: 5-15 µg/kg/min), patients of group B received dexmedetomidine infusion (loading: 0.7 µg/kg and maintenance: 0.4 µg/kg/hour) and group C (control group) received normal saline infusion. During the post-operative period of 24 hours, patient were monitored for sedation using Ramsay sedation score like pain, using visual analogue score (VAS), incidence of post-operative nausea and vomiting and use of any drug for pain, vomiting and any other side effect.
Results: Frequency of pain was highest in group C at all post periods, followed by group A and was least in group B. The mean sedation score of group B was comparatively higher as compared to both group C and group A.
Conclusions: The inference authors drew was that dexmedetomidine is better analgesic with aurousable sedation.

Keywords: Dexmedetomidine, Esmolol, Laparoscopic cholecystectomy, Postoperative pain, Sedation

INTRODUCTION

Laparoscopic surgery, also known as minimally invasive surgery (MIS), band aid or keyhole surgery is a modern surgical technique in which operations in the abdomen are performed through small incisions.

There are a number of advantages to the patient with laparoscopic surgery versus an open procedure. These include:

- Reduced blood loss.

- Smaller incision, which reduces pain and shortens recovery time,
- Less pain, leading to less pain medication needed,
- Short duration of hospital stays and often patients are often discharged on same day which leads to a faster return to everyday living,
- Reduced exposure of internal organs to possible external contaminants thereby reduced risk of acquiring infections.[1]

Although the concept of laparoscopic surgeries has revolutionized the surgical practice and has markedly reduced the incidence of complications especially postoperative pain. However, the menace of postoperative pain still remains challenge, especially in first 24 hours.[2]

For a long period, opioids have remained as gold standard drugs for analgesia during and after laparoscopic cholecystectomy. However, their use is also associated with undesirable side effects such as respiratory depression, nausea and vomiting, urinary retention and pruritus. To minimize these side effects of opioids author added two drugs which were dexmeditomidine and esmolol.

Dexmedetomidine is a new generation highly selective α2 adrenoreceptor agonist, that dose-dependently reduces blood pressure (BP) and heart rate (HR) and has a sedative and analgesic effect without activation of α1 receptors. It also induces a centrally mediated reduction of sympathetic nervous system activity thereby decreasing the hemodynamic and plasma catecholamine response to stressful events of surgery.[3] Effective attenuation of the sympathoadrenal stress responses is an important goal in anaesthesiology. These properties make it a suitable agent for use as an adjuvant in anaesthetic regimen.

Esmolol is the first intravenous titratable β-blocker available for use in critical care and surgical settings. It is a cardio-selective β1 receptor blocker with rapid onset, and a short duration of action. However, its role in contemporary intraoperative anesthesia practice has not yet been established and there have been few studies on the cardiovascular parameters in humans during continuous infusion of the drug in the perioperative period in laparoscopic surgeries.

Esmolol has significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. In addition to its effect on the sympathetic nervous system, esmolol influences core components of an anaesthetic regimen, such as analgesia, hypnosis, and memory function.[4,5] It is a class II antiarrhythmic.

The present prospective randomized study was designed to compare the effects of intravenous dexmedetomidine and esmolol on postoperative pain and sedation after laparoscopic cholecystectomy.

METHODS

After getting approval from ethical committee, the study was conducted on ASA physical status I and II patients aged 18-60 years of either sex, being admitted for laparoscopic cholecystectomy to be done under general anesthesia. An informed consent was taken from all patients.

Exclusion criteria included patients having allergy, hypersensitivity or contraindication to anesthetic or analgesic medication, patients with clinically significant medical conditions, endocrine or liver diseases, peptic ulcer disease or bleeding disorders, pregnant or lactating women, subjects with history of alcohol or drug abuse within three months. Patients were randomized into three groups of 30 each using computer generated random tables.

- Group A (esmolol group) patients received esmolol infusion (loading: 1 mg/kg and maintenance: 5-15 µg/kg/min),
- Group B (dexmedetomidine group) patients received dexmedetomidine infusion (loading: 0.7 µg/kg and maintenance: 0.4 µg/kg/hr),
- Group C (control group) patients received normal saline infusion.

According to respective groups, on arrival of patients in OR, all standard monitors were attached, and baseline heart rate (HR), mean arterial pressure (MAP), ECG and SPO2 were recorded.

According to respective groups, infusions were initiated and 10 minutes after the infusion was started, anaesthesia was induced with Inj. propofol (2 mg/kg) and Inj. fentanyl (1 µg/kg) I.V. After induction, vecuronium was given at a dose of 0.08 mg/kg body intravenously to facilitate intubation. Intraoperative relaxation was also achieved by vecuronium 0.05 mg/kg. Patient were on controlled mechanical ventilation to maintain EtCO2 at 30 to 40 mmHg.

Patients were monitored at 5 mins, 10 mins, induction, intubation, skin incision, CO_2 insufflation, 5 mins after insufflation, 10 mins after insufflation and thereafter at every 15 mins till the end of surgery.

At the start of surgical wound closure, the study drug infusion was stopped, and the neuromuscular block was be antagonized with neostigmine (0.04 mg/kg) and glycopyrrolate (5 microgram/Kg). Timing of extubation was recorded.

During the post-operative period of 24 hours, patient was monitored for sedation using Ramsay sedation score, pain using visual analogue score (VAS), incidence of post-operative nausea and vomiting and use of any drug for pain, vomiting and any other side effect. Rescue medication in post-operative room for pain was

paracetamol 100 ml infusion while for nausea or vomiting, Inj. ondansetron I.V. was given.

Ramsay sedation score

- Score 1, response- anxious or restless or both,
- Score 2, response- cooperative oriented and tranquil,
- Score 3, response- responding to commands,
- Score 4, response- brisk response to stimulus,
- Score 5, response- sluggish response to stimulus,
- Score 6, response- no response to stimulus.

Visual Analogue Scale (VAS)

It is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. Operationally a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimetres from the left-hand end of the line to the point that the patient marks.

Data were tabulated as mean±SD. One-way analysis of variance (ANOVA) and the significance of mean difference between the groups was done by Tukey's post hoc test. Groups were also compared by two factor repeated measures ANOVA using general linear models (GLM) and the significance of mean difference within and between the groups was done by Tukey's post hoc test. Discrete (categorical) groups were compared by chi-square (χ^2) test. A two-sided (α=2) p value less than 0.05 ($p < 0.05$) was considered statistically significant. All analyses were performed on SPSS software (windows version 17.0).

RESULTS

The present study was conducted on 90 patients of either sex between 18-60 years of age ASA Grade I and II undergoing laparoscopic cholecystectomy for cholelithiasis.

Table 1: Basic characteristics of three groups.

Characteristics	Group C (n=28) (%)	Group A (n=30) (%)	Group B (n=29) (%)	χ^2/F value	P value
Age (yrs) Mean±SD	39.43±6.87	39.57±9.42	39.83±9.26	0.02	0.984
Sex					
Females	22 (78.6)	20 (66.7)	19 (65.5)	1.42	0.492
Males	6 (21.4)	10 (33.3)	10 (34.5)		
Weight (kg) Mean±SD	57.86±9.25	62.53±9.87	57.66±6.88	2.92	0.059
ASA grade					
I	17 (60.7)	20 (66.7)	16 (55.2)	0.82	0.664
II	11 (39.3)	10 (33.3)	13 (44.8)		

Out of the 90 patients three patients were excluded from the study (2 from control group and one from dexmedetomidine group) as their laparoscopic cholecystectomy was changed to open cholecystectomy due to some complication. So, authors had 30 patients in group A, 29 in group B and 28 in group C. Otherwise the three groups were similar to each other on the basis of demographic characteristics. The higher number of female patients in all the three group indicates normal demographic distribution of the disease and its increased prevalence in the female sex.

Pain score at the end of the surgery

The 24 hours post-operative pain scores of three groups are summarized in Table 2 and also shown graphically in Figure 1. The pain scores differed significantly among the groups at all post periods and the frequency (%) of higher level of pain was significantly higher in group C at all post periods as compared to both group A and especially group B.

Sedation

The sedation score at the end of the surgery of three groups are summarized in Table 3 and also depicted graphically in Figure 2. Especially, from 0 hr to 12 hrs, the mean sedation score of group B was comparatively higher as compared to both group C and group A. Comparing the mean sedation scores of three groups and periods together, ANOVA revealed significant effect of both groups ($F=27.88$, $p < 0.001$) and periods ($F=30.33$, $p < 0.001$) on sedation score. Further, the interaction (groups X periods) effect of both on sedation score was found also found significant ($F=22.14$, $p < 0.001$). Further, Tukey's test also revealed significantly ($p > 0.05$)

different and lower mean sedation score of group B from 1 to 24 hours as compared to respective baseline (0 min) (Table 4).

However, it remains insignificant (p >0.05) in both group C and group A when compared to their respective baselines.

Table 2: Pain score of three groups at the end of the surgery.

Periods (hrs)	Pain score (cm)	Group C (n=28) (%)	Group A (n=30) (%)	Group B (n=29) (%)	χ^2 value	p value
0 hrs	0	0 (0.0)	10 (33.3)	29 (100.0)	74.20	<0.001
	1	1 (3.6)	5 (16.7)	0 (0.0)		
	2	17 (60.7)	14 (46.7)	0 (0.0)		
	3	2 (7.1)	0 (0.0)	0 (0.0)		
	4	4 (14.3)	1 (3.3)	0 (0.0)		
	6	4 (14.3)	0 (0.0)	0 (0.0)		
1 hr	0	0 (0.0)	0 (0.0)	7 (24.1)	55.82	<0.001
	1	0 (0.0)	4 (13.3)	9 (31.0)		
	2	7 (25.0)	15 (50.0)	13 (44.8)		
	3	4 (14.3)	6 (20.0)	0 (0.0)		
	4	11 (39.3)	5 (16.7)	0 (0.0)		
	5	2 (7.1)	0 (0.0)	0 (0.0)		
	6	4 (14.3)	0 (0.0)	0 (0.0)		
2 hrs	0	0 (0.0)	0 (0.0)	2 (6.9)	75.40	<0.001
	1	0 (0.0)	2 (6.7)	14 (48.3)		
	2	2 (7.1)	8 (26.7)	8 (27.6)		
	3	2 (7.1)	6 (20.0)	5 (17.2)		
	4	1 (3.6)	8 (26.7)	0 (0.0)		
	5	4 (14.3)	1 (3.3)	0 (0.0)		
	6	7 (25.0)	3 (10.0)	0 (0.0)		
	7	9 (32.1)	1 (3.3)	0 (0.0)		
	8	3 (10.7)	1 (3.3)	0 (0.0)		
6 hrs	0	0 (0.0)	2 (6.7)	12 (41.4)	45.25	<0.001
	1	0 (0.0)	2 (6.7)	4 (13.8)		
	2	10 (35.7)	6 (20.0)	4 (13.8)		
	3	8 (28.6)	2 (6.7)	4 (13.8)		
	4	1 (3.6)	4 (13.3)	3 (10.3)		
	5	2 (7.1)	1 (3.3)	0 (0.0)		
	6	4 (14.3)	12 (40.0)	2 (6.9)		
	7	3 (10.7)	1 (3.3)	0 (0.0)		
12 hrs	0	2 (7.1)	5 (16.7)	19 (65.5)	47.80	<0.001
	1	1 (3.6)	2 (6.7)	0 (0.0)		
	2	4 (14.3)	9 (30.0)	1 (3.4)		
	3	1 (3.6)	6 (20.0)	0 (0.0)		
	4	2 (7.1)	3 (10.0)	0 (0.0)		
	6	12 (42.9)	3 (10.0)	6 (20.7)		
	7	6 (21.4)	2 (6.7)	3 (10.3)		
18 hrs	0	5 (17.9)	12 (40.0)	24 (82.8)	42.02	<0.001
	1	0 (0.0)	4 (13.3)	0 (0.0)		
	2	7 (25.0)	6 (20.0)	4 (13.8)		
	3	4 (14.3)	1 (3.3)	0 (0.0)		
	6	9 (32.1)	2 (6.7)	1 (3.4)		
	7	3 (10.7)	5 (16.7)	0 (0.0)		
24 hrs	0	18 (64.3)	22 (73.3)	29 (100.0)	13.34	0.038
	1	1 (3.6)	1 (3.3)	0 (0.0)		
	2	8 (28.6)	7 (23.3)	0 (0.0)		
	3	1 (3.6)	0 (0.0)	0 (0.0)		

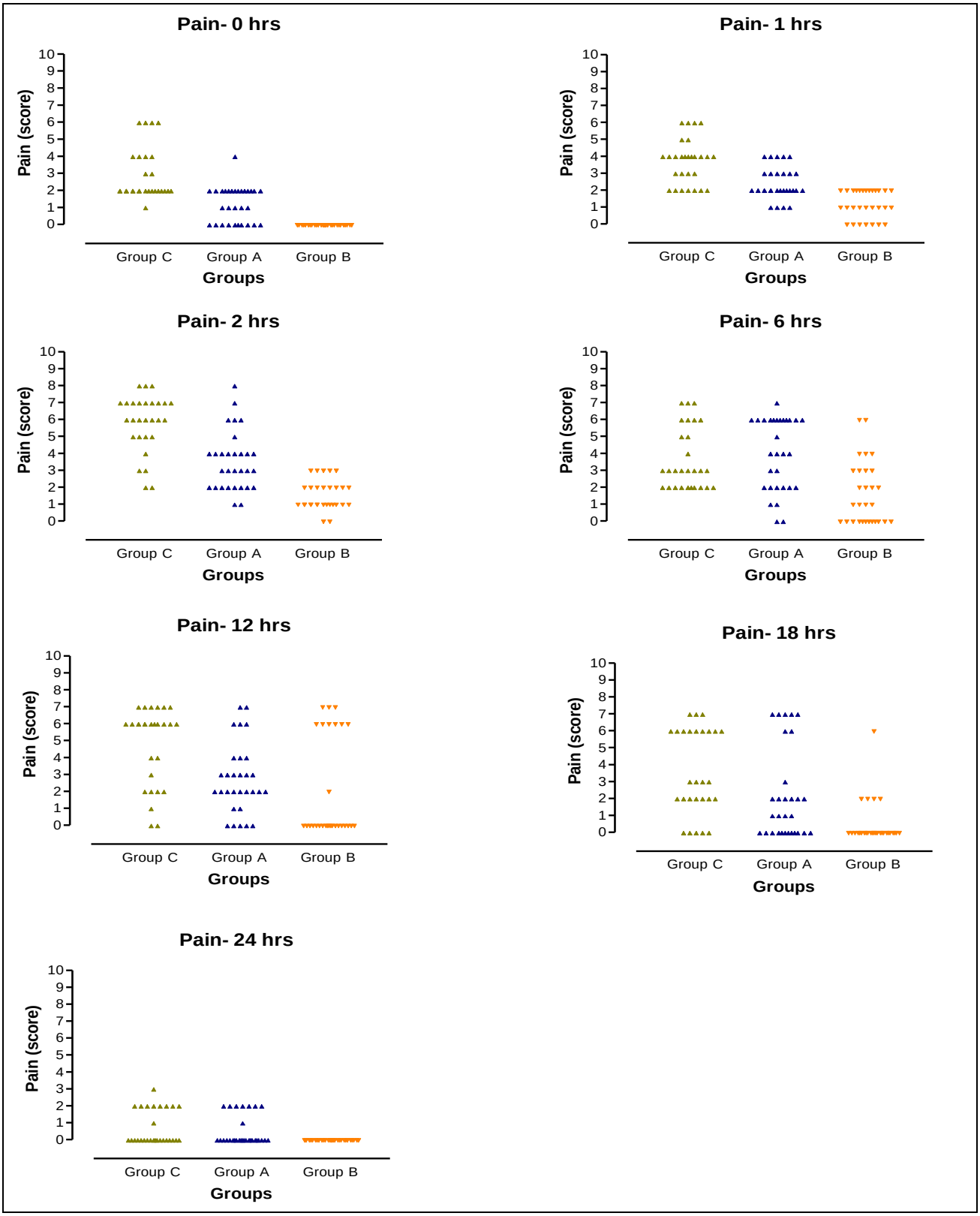

Figure 1: Pain score at different time intervals. A) Pain score at 0 hr in three grups B) Pain score at 1 hr in three groups C) Pain score at 2 hrs in three groups D) Pain score at 6 hrs in three group E) Pain score at 12 hrs F) Pain score at 18 hrs G) Pain score at 24 hrs.

Furthermore, the mean sedation score of group B was also found significantly ($p < 0.01$ or $p < 0.001$) different and higher as compared to both group C from 0 to 6 hours while group A from 0 to 1 hour (Table 3). However, it remains similar between group A and group C at all periods (Table 3).

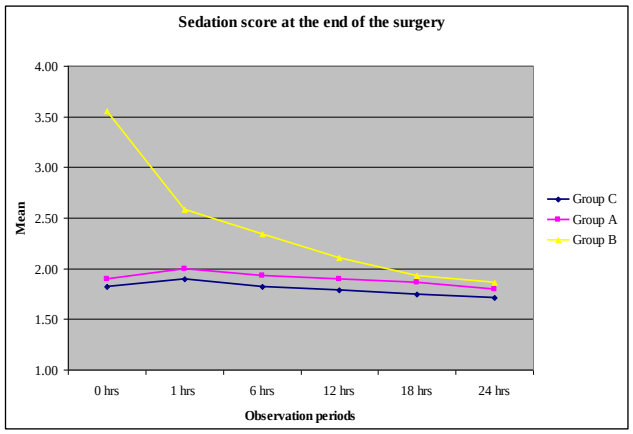

Figure 2: Mean sedation scores of three groups at the end of the surgery to post 24 hrs.

Rescue analgesic used

The number of rescue analgesic (paracetamol 100 ml infusion) used (3 doses) by the subjects of three groups are summarized in Table 5. The frequency (%) of use of all three-rescue analgesic of group C was significantly different and higher as compared to both group A and especially group B (χ^2=15.71, p=0.003).

Table 3: Sedation score (Mean±SD) of three groups at the end of the surgery.

Time (hrs)	Group C (n=28)		Group A (n=30)		Group B (n=29)	
	Mean	SD	Mean	SD	Mean	SD
0	1.82	0.39	1.90	0.31	3.55	0.78
1	1.89	0.31	2.00	0.00	2.59	0.68
6	1.82	0.48	1.93	0.25	2.34	0.55
12	1.79	0.57	1.90	0.31	2.10	0.31
18	1.75	0.65	1.87	0.43	1.93	0.26
24	1.71	0.71	1.80	0.61	1.86	0.44

Complications

The post-operative complications of three groups are summarized in Table 6. The post-operative complications frequency (%) of nausea and nausea/vomiting were significantly different and higher in group C as compared to both group A and group B (χ^2=19.87, p=0.011).

Table 4: For each period, significance (p value) of mean difference of sedation scores at the end of the surgery between the group's ANOVA followed by Tukey's test.

Comparisons	0 hr	1 hr	6 hrs	12 hrs	18 hrs	24 hrs
Group C vs Group A	1.000	1.000	1.000	1.000	1.000	1.000
Group C vs Group B	<0.001	<0.001	0.006	0.554	0.996	1.000
Group A vs Group B	<0.001	0.001	0.102	0.981	1.000	1.000

Table 5: No of rescue analgesic used by the subjects of three groups.

Rescue analgesic	Group C (n=28) (%)	Group A (n=30) (%)	Group B (n=29) (%)	χ^2 value	P value
1st dose	28 (100.0)	22 (73.3)	10 (34.5)	15.71	0.003
2nd dose	21 (75.0)	8 (26.7)	2 (6.9)		
3rd dose	15 (53.6)	0 (0.0)	0 (0.0)		

Table 6: Post-operative complications of three groups.

Characteristics	Group C (n=28) (%)	Group A (n=30) (%)	Group B (n=29) (%)	χ^2 value	P value
Bradycardia	0 (0.0)	1 (3.3)	0 (0.0)	19.87	0.011
Hypotension	0 (0.0)	1 (3.3)	0 (0.0)		
Nausea	10 (35.7)	4 (13.3)	1 (3.4)		
Nausea/vomiting	2 (7.1)	0 (0.0)	0 (0.0)		
None	16 (57.1)	24 (80.0)	28 (96.6)		

DISCUSSION

In present study, pain scores differed significantly among groups and frequency (%) of higher level of pain was significantly more in group C as compared to both group A and especially group B. Observation of this study was that dexmedetomidine is far better analgesia as compared to esmolol. Mean sedation score was highest in group B as compared to group A and C which were almost similar.

Coinciding results were seen with the use of dexmedetomidine in various studies done by Málek J et al, Tufanogullari et al, Dholakia et al, and Bakhmees et al, and with use of esmolol in studies done by Alavarez S. et al, Lee and Lee.[6-11]

Málek J et al, did a randomized control trial to see the effect of a combination of dexmedetomidine with ketamine and opioids on hemodynamics and postoperative pain in patients of lap cholecystectomy.[6] They found decreased need for analgesia during GA and prolonged postoperative analgesia in dexmedetomidine group. However, they also used ketamine in their study which also possesses analgesic property which was not used in this study.

Tufanogullari et al, conducted a study to evaluate the effect of dexmedetomidine on both early and late recovery after laparoscopic bariatric surgery.[7] The amount of rescue fentanyl administered in the PACU was significantly less in the dexmedetomidine groups versus control group (113+/- 85, 108+/- 67, and 120+/- 78 vs 187+/- 99 microg, respectively, P <0.05).

Dholakia et al, conducted a study to see the effect of dexmedetomidine infusion in laparoscopic bariatric surgeries and concluded that dexmedetomidine infusion perioperatively is safe and may help to minimize narcotic requirements and decrease duration of stay after laparoscopic bariatric procedures.[8] Gastric bypass patients who received a dexmedetomidine infusion required fewer narcotics (66 vs 130 mg of morphine equivalents) than control patients. In present study, postoperative rescue analgesia was given by paracetamol 100 ml infusion (not by narcotic analgesics) and similar results were seen as dexmedetomidine group required post-operative analgesia only 12 times as compared to 64 times in control group.

Bakhmees et al, evaluated the effect of dexmedetomidine on anesthetic requirements during surgery, hemodynamic, recovery profile and morphine use in the postoperative period.[9] The intraoperative infusion of dexmedetomidine decreased the total amount of propofol and fentanyl required to maintain anesthesia, offered better control of intraoperative and postoperative hemodynamics, decreased postoperative pain level, decreased the total amount of morphine used and showed better recovery profile compared with placebo which was again in concordance with the present study.

Alavarez S et al, conducted a randomized control trial using esmolol vs ketamine-remifentanil combination for early postoperative analgesia after laparoscopic cholecystectomy.[10] They used verbal numerical rating scale (VNRS) for pain intensity and observed higher pain scores in ketamine-remifentanyl group as compared to esmolol group. It was also seen that intraoperative esmolol infusion reduces morphine requirements and provides more effective analgesia as compared with a combination of remifentanil-ketamine given by infusion in patients undergoing LC. In present study also, authors observed less pain scores (VAS score) in patients of esmolol group as compared to control and postoperative analgesia was given to 30 times in esmolol group as compared to 64 in control group during the 24 hours postoperative period.

Lee SJ et al, studied 60 patients who underwent a laparoscopic appendectomy under total intravenous anesthesia using propofol and remifentanil and compared a control group with another group that received continuously injected esmolol during anesthesia.[11] Postoperative 30 minute visual analog scale (VAS) scores and analgesic use for postoperative pain control during the first 24 hours decreased significantly in the esmolol group. Similar results were concluded in present study when author compared esmolol group with the control group.

Also, Hall JE et al, implicated that dexmedetomidine has sedation and analgesic properties.[12] Their study quantified these effects as well as cardiorespiratory, memory and psychomotor effects in healthy volunteers. Dexmedetomidine infusion resulted in reversible sedation, mild analgesia and memory impairment without cardiorespiratory compromise.

CONCLUSION

Thus, authors concluded that dexmedetomidine is better analgesic as compared to esmolol regarding analgesia though analgesic properties were also shown by esmolol. Sedation was maximum in dexmedetomidine group, control group and esmolol group were less sedated. The inference author drew was that dexmedetomidine is better analgesic with aurousable sedation.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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