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Özgün Araştırma / *Original Article*

Effect of Dexmedetomidine as an Adjuvant to 0.25% Bupivacaine for Local Infiltration of Port Site in Laparoscopic Cholecystectomy in Terms of Quality and Duration of Post-op Analgesia

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Laparoskopik Kolesistektomide Port Sahasına %0.25 Bupivakain İnfiltrasyonuna Adjuvan Olarak Eklenen Deksmedetomidinin Postoperatif Analjezi Kalitesi ve Süresine Etkisi

ABSTRACT

Objective: *Laparoscopic cholecystectomy (LC) technically has evolved as a day case procedure even to a extent that ASA III patients are also not a exclusion. Pain is one of the cause for unexpected overnight hospital stay. The recent PROSPECT (PROcedure SPECific Postoperative Pain Management) working Group has recommended port site infiltration along with NSAIDS and paracetamol as the preferred mode of analgesia for laparoscopic cholecystectomy. Hence, we studied about efficacy of dexmedetomidine as an adjuvant for local anesthetic portsite wound infiltration with bupivacaine in patients undergoing laparoscopic cholecystectomy.*
Methods: *120 patients of ASA I-II scheduled for LC were randomly allotted to two groups. Group A received port site wound infiltration with 24 mL of 0.25% bupivacaine and dexmedetomidine 2 µg kg^{-1} while Group B received wound infiltration with 24 mL of 0.25% bupivacaine divided equally for all the four laparoscopic port sites. A standard general anesthesia technique was used in all the patients. Pre-emptive analgesia with paracetamol 1 g IV given 30 minutes before skin incision. Tramadol 1 mg kg^{-1} and ketorolac 0.5 mg kg^{-1} IV infusion was administered as rescue analgesic. Postoperative pain score, duration of effective analgesia, need for rescue analgesic, time of ambulation and hospital discharge was recorded.*
Results: *Dexmedetomidine group has better pain score, longer duration of effective analgesia, lower percentage of patients requiring rescue analgesic, and earlier ambulation and hospital discharge.*
Conclusion: *We conclude that dexmedetomidine 2 µg kg^{-1} is an effective adjuvant to bupivacaine for port site wound infiltration in terms of quality and duration of postoperative analgesia following laparoscopic cholecystectomy.*

Keywords: *Laparoscopic cholecystectomy, dexmedetomidine, general anesthesia, tramadol, bupivacaine*

ÖZ

Amaç: *Laparoskopik kolesistektomi (LK), teknik açıdan, ASA III hastaların bile dışlanmadığı günübirlik bir işlem haline gelmiştir. Ağrı, beklenmedik gece hastanede yatış nedenlerinden biridir. PROSPECT (PROcedure SPECific Postoperative Pain Management) çalışma grubu, NSAİİ'lar ve parasetamol ile port sahası infiltrasyonunu laparoskopik kolesistektomi için tercih edilen analjezi şekli olarak önermektedir. Buradan yola çıkarak, laparoskopik kolesistektomi yapılan hastalarda, port sahasına yara yeri infiltrasyonunda bupivakaine adjuvan olarak eklenen deksmedetomidinin etkinliğini çalıştık.*
Yöntem: *LK planlanan 120 ASA I-II hasta rastgele iki gruba ayrıldı. Grup A'ya 24 mL %0.25 bupivakain ve 2 mcg kg^{-1} deksmedetomidin ile, Grup B'ye 24 mL % 0.25 bupivakain ile yara infiltrasyonu dört laparoskopik port bölgesi için eşit olarak bölünmüş dozda uygulandı. Tüm hastalarda standart bir genel anestezi tekniği kullanıldı. Cilt insizyonundan 30 dk önce parasetamol 1 g iv ile pre-emptif analjezi uygulandı. Tramadol 1 mg kg^{-1} ve ketorolak 0.5 mg kg^{-1} iv ile kurtarıcı analjezi sağlandı. Postoperatif ağrı skoru, etkili analjezi süresi, kurtarıcı analjezik ihtiyacı, ile mobilizasyon ve taburculuk zamanları kaydedildi.*
Bulgular: *Deksmedetomidin grubunda, ağrı skoru daha iyi, etkili analjezi süresi daha uzun, kurtarıcı analjezik gerektiren hasta oranı daha düşük ve mobilizasyon ve taburculuk daha erkendi.*
Sonuç: *2 µg kg^{-1} deksmedetomidinin, laparoskopik kolesistektomiyi takiben postoperatif analjezi kalitesi ve süresi açısından port sahası yara infiltrasyonu için etkili bir bupivakain adjuvanı olduğu sonucuna vardık.*

Anahtar kelimeler: *Laparoskopik kolesistektomi, deksmedetomidin, genel anestezi, tramadol, bupivakain*

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INTRODUCTION

Laparoscopic cholecystectomy is the mainstay treatment of benign biliary disease. Pain continues to be an important issue after laparoscopic cholecystectomy resulting in prolonged admissions or readmissions [(1)]. Inadequately controlled pain has undesirable physiologic and psychologic consequences such as increased postoperative morbidity, delayed recovery, a delayed return to normal daily living, and reduced patient satisfaction [(2)]. Postoperative pain management not only minimizes patient suffering but also can reduce cardio-respiratory morbidity and facilitate rapid recovery. Although regional anesthetic techniques, such as epidural analgesia or perineural catheters, have proven to provide excellent analgesia, many of these analgesic modalities are time-consuming, expensive, and not without side-effects. As a significant proportion of surgical pain originates from the surgical wound, it would seem logical to use local anesthetics at the site of surgery to manage perioperative pain. The recent PROSPECT (PROcedure SPECific Postoperative Pain Management) Working Group has recommended port site infiltration along with NSAIDS and paracetamol as the preferred mode of analgesia for laparoscopic cholecystectomy [(1)]. Recent reviews has shown that dexmedetomidine usage intraoperatively has better postoperative outcomes in terms of improved morbidity and mortality [(3)]. Moreover, dexmedetomidine was proved to be an effective adjuvant to local anesthetic in nerve blocks [(4)]. Hence, we evaluated dexmedetomidine as an adjuvant to the commonly used local anesthetic bupivacaine for portsite infiltration in patients scheduled for laparoscopic cholecystectomy under general anesthesia. Hence, this study hypothesised that addition of dexmedetomidine as an adjuvant to bupivacaine will improve the quality of analgesia in the postoperative period following laparoscopic cholecystectomy. We also attempted to study the effect on postoperative ambulation and discharge following laparoscopic cholecystectomy.

MATERIAL and METHODS

After ethics committee approval and informed consent, this prospective randomized double blinded study enrolled 120 patients of ASA physical status I and II scheduled for laparoscopic cholecystectomy. Sample size for the study was determined by power analysis based on the results of pilot study conducted. The patients were randomly allocated into two groups A and B, consisting of 60 each. Randomisation was done by random computer generated numbers and concealed by sealed envelope technique. The following conditions were excluded: Imaging evidence or surgical diagnosis of empyema gall bladder or expected surgical difficulty by the surgeon, emergency laparoscopic cholecystectomy, if the BMI >30 kg m^{-2} patients with previous clinical history of chronic pain with or without medications and allergic to study drugs. The expected drop outs were prolonged duration of surgery >120 minutes, technical difficulty needing more than 4 ports, need for a surgical site drainage tube and conversion to open cholecystectomy. Group A - (Dexmedetomidine group) patients received port site wound infiltration with 24 mL of 0.25% bupivacaine and dexmedetomidine 2 mg kg^{-1} divided equally for all the four laparoscopic port sites.

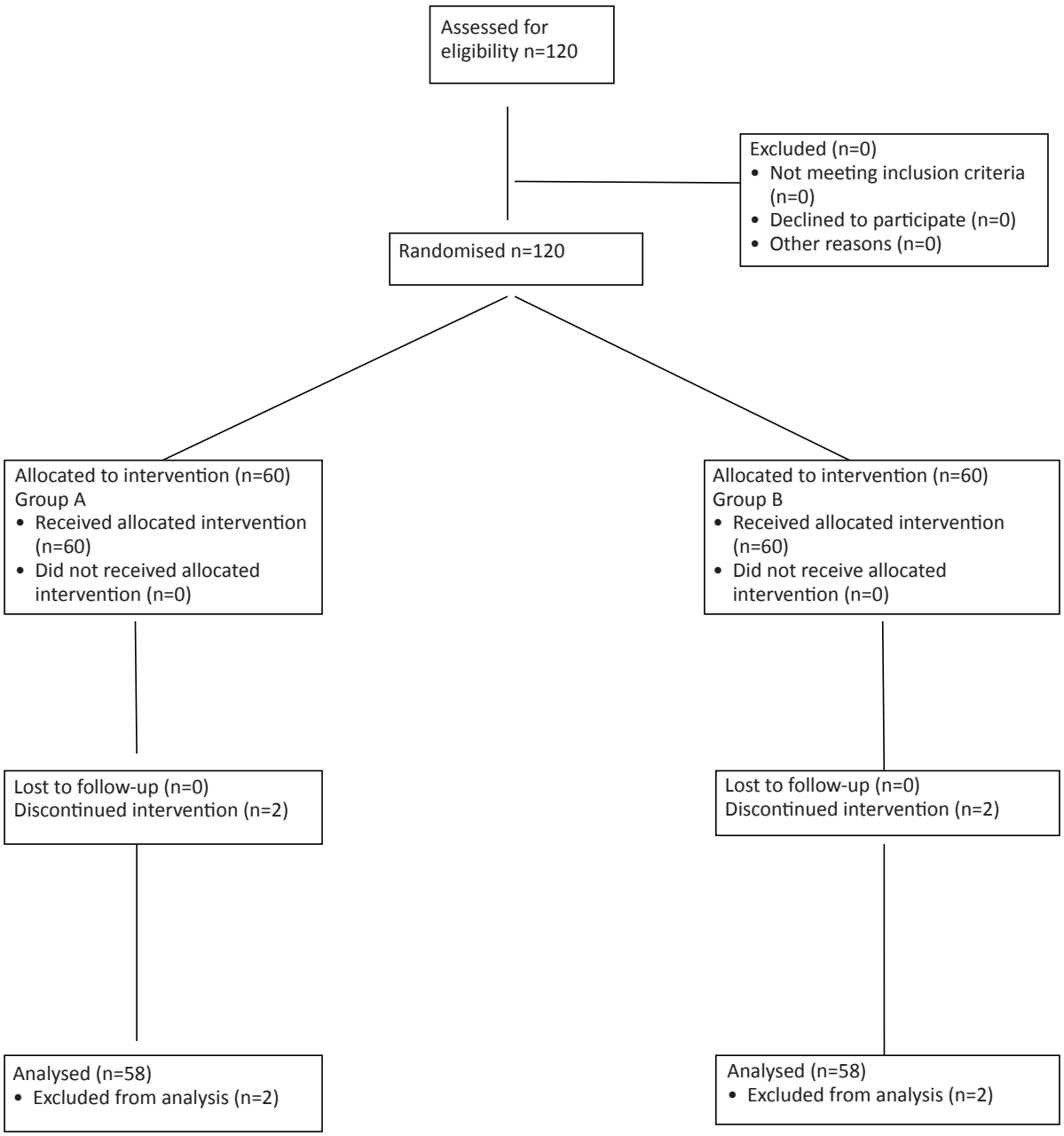
Group B - (control group) all the patients received wound infiltration with 24 mL of 0.25% bupivacaine divided equally for all the four laparoscopic port sites.

Drugs were prepared in 10 mL syringes by an anesthesiologist who is not involved in the data collection and administered by the surgeon at the proposed port site prior to inserting the port. Both the anesthesiologist involved in the data collection and the infiltrating surgeon were blinded for the drug contained in the syringe. The standard four port surgical laparoscopic method was followed by the operating surgeons. The pneumoperitoneum was established with a 5-mm umbilical trocar.

During the preoperative visit, the patients were introduced to the concept of the visual analog scale (VAS), with a 10-cm vertical score ranged from 0=no pain to 10=worst pain imaginable. Standard fasting guideline was followed in all patients. All patients received no premedication, and when they arrived at the operating room, venous access was established for lactated Ringer's solution infusion. Baseline vital parameters (heart rate, oxygen saturation, non-invasive blood pressure) was documented. Intravenous access was secured. 30 minutes prior to

start of surgery paracetamol 1 g IV is given in all patients. Vitals monitoring includes (Phillips IntelliVue MP50, Philips Healthcare, Netherlands) - electrocardiogram, pulse oximetry (SpO_2), non invasive blood pressure. Preoxygenated with 6 litres of oxygen for 3 minutes and induced with fentanyl 2 mg kg^{-1} IV; propofol 2 mg kg^{-1} IV; vecuronium 0.1 mg kg^{-1} IV.

Intubated with 7.5 cuffed endotracheal tube in female patients and 8.5 cuffed endotracheal tube in male patients; nasogastric tube was inserted and stomach deflated. Anesthesia maintained with sevoflurane of 2% in air/O_2 with inspired oxygen concentration of 40% throughout the procedure. Minute ventilation was adjusted to keep end-tidal CO_2 pressures at 35 to 45 mmHg. During laparoscopy, intra-abdominal pressure was maintained at 12 mmHg by using CO_2.



Consort Diagram:

Technique of injection:

After sterile drapping of the surgical area, the surgeon infiltrates the proposed four standard port sites in layers through a spinal needle 20 G including skin, subcutaneous, fascial layer, muscle plain, preperitoneal space, and parietal peritoneum. The infiltrating surgeon was blinded to the drug in the syringe. Same amount of drug was used in both the groups at the corresponding port sites for infiltration.

Any intra-operative signs of inadequate analgesia was managed by increasing the inhaled concentration of sevoflurane accordingly at the dispense of the anesthesiologist. At the end of the procedure, complete evacuation of CO_2 was done by manual compression of the abdomen with open trocars. Ondansetron (4 mg) was given IV 15 minutes prior to the end of surgery for postoperative nausea and vomiting (PONV) prophylaxis. At the end of the procedure, after recovering from the neuromuscular blockade reversed with neostigmine and glycopyrrolate the patients were extubated and observed in the postoperative care unit during the study period.

Postoperative pain management includes if pain scale is >3 treated with injection tramadol 1 mg kg^{-1} IV, pain reassessed after 15 minutes if still pain score is >3 further analgesia given with ketorolac 0.5 mg kg^{-1} given as slow iv infusion over 10 minutes.

The parameters measured were: duration of effective analgesia - from time of extubation to pain score ≥3 in the PACU, pain assessed by visual analogue scale at the following duration 0,1/2,1,2,4,6 and 8 hrs, need for rescue analgesia, sedation score *Richmond Agitation-Sedation Scale* (RASS), day of ambulation (on which day ambulated) and delayed discharge (defined as discharge after first postoperative day).

As a standard institutional protocol, all patients undergoing uncomplicated laparoscopic cholecystectomy of ASA physical status I-II were discharged on the evening of first postoperative day provided if the postoperative period is uneventful. Hence in this study, delayed discharge was defined as discharge after the evening of first postoperative day. Also all the patients are ambulated in the evening on the day of surgery after 6 hours of the procedure.

The collected data were analyzed with SPSS Inc., for windows, version 16.0, Chicago, IL, USA. To describe the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables, and the mean and SD were used for continuous variables. To find the significant difference between the bivariate samples in independent groups, the Mann-Whitney U-test was used. To find the significance in categorical data, Chi-square test was used. In all the above statistical tools, the p=0.05 is considered as significant level. Sample size calculation was calculated from a pilot study done with 10 patients in each. A total of 92 cases was required for an effect size of 45 minutes difference in the duration of effective analgesia at a power of 80% and an alpha error of 0.05. Total sample size of 120 patients with 60 patients in each group at an expected drop rate of 25% was arrived. The parameters are collected by an anesthesiologist who is blinded for the drug given for infiltration in all the patients.

RESULTS

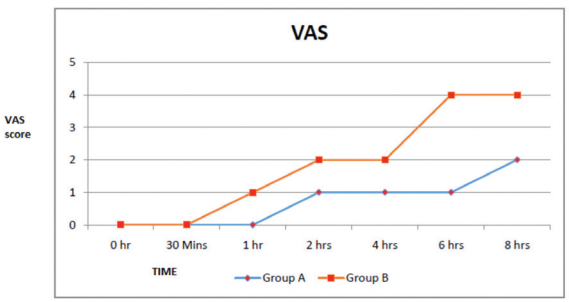
Both groups are comparable with respect to distribution of age, height, sex and weight as shown in Table I, there was no statistically significant difference between the two groups. The difference in duration of

Table I. Comparison of demographic and study parameters among the two groups

	Mean ± SD		
Parameters	**Group A**	**Group B**	**p value**
Age in years	43.27±12.390	44.20±12.047	0.794 (p>0.05)
Weight in kg	65.60±9.1	64.63±9.733	0.724 (p>0.05)
Height in cm	165.10±6.54	162.11±7.12	0.842 (p>0.05)
Gender	Male=11 (36.7%) Female=19 (63.3%)	Male=9 (30%) Female=11 (70%)	0.792 (p>0.05)
Duration of Surgery (minutes)	50.90±19.96	58.83±27.32	0.157 (p>0.05)
Duration of Analgesia (minutes)	444.00±88.57	337±136.38	0.006

SD-standard deviation, Kg-kilograms, cm-centimeters
Group A: dexmedetomidine group, Group B: control group

surgery across two groups was not significant (p>0.05). The difference in duration of effective analgesia between group A and B has been found to be statistically significant (p<0.05). Group A has a prolonged duration of effective analgesia compared to group B which was statistically significant (p<0.05) as shown in Table I. Mann-Whitney U test was used to detect the statistical significance between the two groups in terms of duration of effective analgesia (P=0.006).



Group A: Dexmedetomidine group, Group B: Control group, VAS-Visual analogue scale.

Figure 1. Distribution of pain scores among the two groups

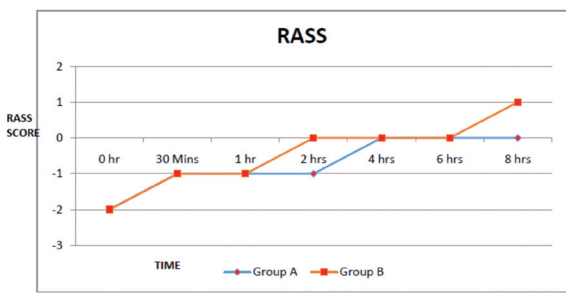
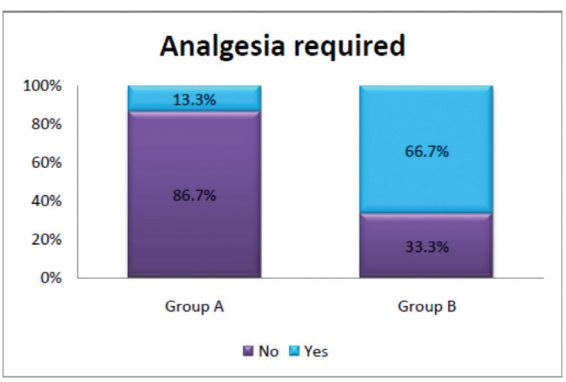


Figure 2. Distribution of sedation score among the two groups

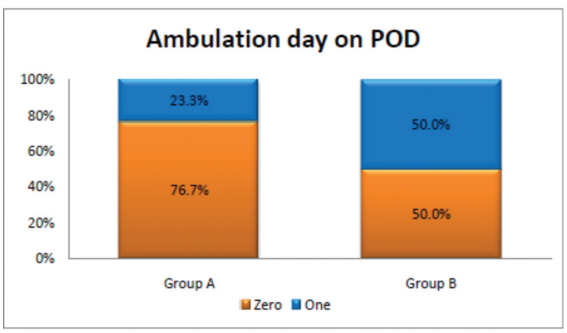


Group A: Dexmedetomidine group, Group B: Control group

Figure 3. Distribution of need for rescue analgesic in both groups

The distribution of VAS score among the two groups was found to be statistically significant at the following intervals of 1/2hr, 1hr, 2hrs, 4hrs, 6hrs and 8hrs. Mann-Whitney U test was used to compare the pain score between the two groups. VAS score distribution shows that Group A has better analgesia at the above mentioned intervals than group B as shown in figure 1. The distribution of RASS score among the two groups was found to be statistically significant at the following intervals of 6hrs and 8hrs (p<0.001) as shown in figure 2. Mann-Whitney U test was used to compare the pain score between the groups. Mean RASS score was significantly lower in Group A compared to Group B at all time intervals of the study up to 8 hours into the postoperative period (p<0.05).

In Group A, the need for rescue analgesic is less compared to group B as shown in the figure 3, the difference in the distribution of need for rescue analgesic was found to statistically significant (p<0.0005). Chi-square test was used to compare the significance of



Group A: Dexmedetomidine group, Group B: Control group

Figure 4. Comparison of day of ambulation between the two groups

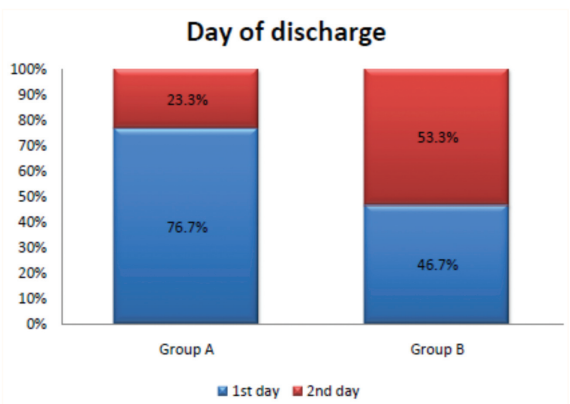


Figure 5. Day of discharge

need for rescue analgesic between the two groups. In group A, more percentage of patients were ambulated earlier compared to patients in group B, but the difference was found to be statistically insignificant (p=0.06) as shown in figure 4. Higher percentage of patients in group A were found to be discharged earlier compared to the patients in group B as shown in figure 5. The difference in the percentage distribution of earlier discharge among the two groups was found to be statistically significant (p<0.03). Chi-square test was used to compare the significance of day of discharge and ambulation between the two groups.

Thus, dexmedetomidine when added as an adjuvant to bupivacaine for local port site infiltration, prolonged the duration of analgesia and hence delayed the need for rescue analgesia and furthermore, it has improved the mean pain scores in the postoperative period. The addition of dexmedetomidine also was associated with earlier discharge from the hospital with better pain scores and decreased need for rescue analgesics in the first 8h of the postoperative period.

The incidence of postoperative nausea and vomiting in group B was statistically significant difference than the group A. There was 12 (20%) cases of PONV in group B while there was only 5 (12%) cases in group A. We had 2 cases as drop outs in each group, two because of conversion to open cholecystectomy and another two because of duration greater than 2 hours according to the study design.

DISCUSSION

We found that addition of dexmedetomidine as an adjuvant to bupivacaine 0.25% for local port site infiltration has more prolonged duration of effective analgesia, improved VAS scores and reduced rescue analgesia requirement in the postoperative period. Early rate of hospital discharge and early ambulation are the other benefits observed in the dexmedetomidine group.

Pain accounts to 4.7% as the reason for unexpected overnight stay in a planned daycase laparoscopic cholecystectomy [5]. At the same time, the recent PROSPECT (PROcedure SPECific Postoperative Pain Management) Working Group 2018 has recommended port site infiltration along with NSAIDS and paracetamol as the preferred mode of analgesia for laparoscopic cholecystectomy [1].

The uniqueness about our study was that there was no similar comparison with bupivacaine and dexmedetomidine done in laparoscopic cholecystectomy before in the literature, also the effect of early ambulation and hospital discharge has not been studied following laparoscopic cholecystectomy with postoperative wound infiltrative analgesia.

Wound infiltrative analgesia is a standard method of providing analgesia in surgical patients especially following laparoscopic cholecystectomy [6]. Previous studies have shown that dexmedetomidine is an effective adjuvant to bupivacaine in wound infiltrative analgesia following open surgeries [7,8]. Recent study has shown that dexmedetomidine is an effective adjuvant to ropivacaine following laparoscopic cholecystectomy [8]. This study also showed that dexmedetomidine when used as an adjuvant improves quality of analgesia as well as increases early ambulation with effective pain management. So we found that dexmedetomidine improves the quality of postoperative wound infiltrative analgesia with bupivacaine but also adds to early ambulation as well as hospital discharge.

It was suggested that infiltration with local anesthetics might increase the risk of postoperative wound infection and also may local tissue toxicity [2]. This concern has not been substantiated by clinical studies and it appears that local anaesthetics, particularly bupivacaine, may have both bacteriostatic and bactericidal actions [2].

The limitations with our study are; first, we have studied only the first 8 hours of the postoperative period. The characteristic of pain [10] in the postoperative period after laparoscopic cholecystectomy has been studied earlier which shows significant pain only till the first eight hours in the postoperative period. Hence, we studied the first eight hours of postoperative period. We did not compare varied doses of dexmedetomidine as adjuvant to bupivacaine.

Also the technique of wound infiltration with local anesthetic differs with each surgeon. Ideally, the local anesthetic should be infiltrated to all the layers namely the skin, subcutaneous tissue, muscle tissue in line with adequate quantity of local anesthetic. We made measures such that we included patients of a particular unit of surgeons with a common protocol in their surgical technique as well as the analgesic and other postoperative care measures. The other limitation was, earlier studies have shown that intraperitoneal infiltration of local anesthetic solution improves the postoperative analgesia following laparoscopic cholecystectomy. Our study didn't include the intraperitoneal instillation of local anesthetic and dexmedetomidine which would have benefitted the patients in terms of postoperative analgesia. Recent literature evidence has recommended port site infiltration along with NSAIDS and paracetamol as the preferred mode of analgesia for laparoscopic cholecystectomy [(1)].

To conclude, dexmedetomidine is found to be an effective adjuvant to bupivacaine for local wound infiltration analgesia in terms of effective analgesic duration, need for rescue analgesic and better pain scores in the immediate postoperative period.

Ethics Committee Approval: Ramachandra University Instutitional Ethics Committee approval was obtained (CSP-MED/15OCT/25/82).
Conflict of Interest: None
Funding: None
Informed Consent: The patients' consent were obtained.

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