Postoperative Analgesia with Intravenous Paracetamol and Dexmedetomidine in Laparoscopic Cholecystectomy Surgeries: A Prospective Randomized Comparative Study

Abstract

**Background and Aim:** Therapeutic use of nonopioid analgesic such as paracetamol (PCM) is an alternative to opioids, so to avoid the established side effects associated with opioids, PCM is commonly used due to its analgesic and antipyretic effects. Recently, dexmedetomidine has also emerged on the anesthesia front with a potential role of providing postoperative analgesia. The present study was conducted to compare and assess the quality and duration of analgesia with PCM and dexmedetomidine using visual analog scale (VAS). **Methods:** One hundred patients between the age of 18 and 60 years of the American Society of Anesthesiologists grade I and II undergoing laparoscopic cholecystectomy surgery were randomly allocated into two groups (n = 50). Each patient received either 1 g intravenous PCM, in 100 ml solution before incision (Group I), or i.v. dexmedetomidine 1 µg/kg as bolus over 10 min followed by infusion of 0.5 µg/kg/h (Group II). Postoperatively, the following parameters were observed: quality and duration of analgesia, hemodynamic parameters, time to the first dose of rescue analgesia, sedation, and any postoperative complication or side effects. Statistical analysis was carried out using an unpaired t-test for quantitative parameters and nonparametric data using Wilcoxon signed-rank test and Mann–Whitney U-test. Qualitative data were analyzed using Chi-square or Fishers’ exact test. **Results:** Postoperative analgesic requirement significantly decreased (P = 0.001), with a lower score on VAS, better patient satisfaction scores, and Ramsay Sedation Score ranges from 3 to 5 (62%) in Group I. The incidence of nausea and vomiting, hypotension, and bradycardia was comparable in both the groups except shivering, which was found significantly less in Group II. **Conclusion:** Incorporation of dexmedetomidine as a part of multimodal analgesia provides better hemodynamic profile, analgesic, sedative, and amnesic properties along with negligible serious adverse effects.

**Keywords:** Dexmedetomidine, laparoscopic cholecystectomy, paracetamol, postoperative analgesia

Introduction

Best practices in anesthesia come from detailed knowledge of physics, physiology, and pharmacology which are then applied scientifically to individual patient’s requirement, 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 a major challenging issue for the attending anesthesiologist, especially during the first 24 h. The emerging role of the anesthesiologist as a perioperative physician further heightens the expectation for him/her to manage postoperative pain so as to enhance patient satisfaction and comfort during a hospital stay. 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, but established, side effects such as respiratory depression, nausea and vomiting, urinary retention, and pruritus. To minimize these side effects associated with the use of opioids, various methods have been adopted such as administration of nonopioid analgesics such as PCM.[1] Recently, newer studies have been published which have highlighted the possible role of intravenous (i.v.) dexmedetomidine in providing postoperative analgesia through the reduction of opioid consumption.[2] Although i.v. paracetamol (PCM) and i.v. dexmedetomidine have individually been studied to see their efficacy in reducing

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postoperative narcotic requirement and other side effects after laparoscopic cholecystectomy, only few studies have compared them with each other for the same purpose. In this backdrop, this study was aimed to evaluate this lacuna by comparing i.v. PCM with i.v. dexmedetomidine administered preoperatively in laparoscopic cholecystectomy to evaluate postoperative narcotic requirement, assessing quality of analgesia using visual analog scale (VAS) and Patient Satisfaction Scale (PSS) along with the assessment of any undesirable side effects.

**Methods**

The present prospective randomized double-blinded study was conducted after obtaining approval from hospital’s ethical and research committees. A total of 100 American Society of Anesthesiologists physical status I and II patients aged between 18 and 60 years undergoing laparoscopic surgery were enrolled in the study. Patients with known hypersensitivity to PCM or dexmedetomidine or with any hyperactive airway disorder, psychiatric, opioid or alcohol addiction, patients taking nonsteroidal anti-inflammatory drugs or any other analgesic, reluctance to participate, operation of <1 h or >3 h, intraoperative bleeding of more than 6 cc/kg body weight, chronic pain syndrome, and prior treatment with steroids were excluded from the study. Preoperatively, the patients were instructed about their role in the study and the use of 10 cm VAS with end point to be labeled as 0 = no pain and 10 = excruciating worst possible pain. Computer randomization with allocation concealment was carried out, and all patients were evenly assigned into two groups of equal number. On arrival of the patient in the operating room, all standard monitors were attached, and baseline heart rate (HR), mean arterial pressure, and oxygen saturation (SpO₂) were recorded. All the patients were premedicated with i.v. glycopyrrolate (0.005) and midazolam (0.02 mg/kg). The standard anesthetic technique was used in all the patients of both the groups, and muscle relaxation was achieved by vecuronium bromide (0.1 mg/g). Patients in Group I received i.v. PCM bolus (1 g PCM in 100 ml of 0.9% NaCl) immediately after induction of anesthesia over 15 min, while during the same period, Group II patients received i.v. dexmedetomidine (1 µg/kg as an infusion) over 10 min and then (0.5 µg/kg/h) continuously until the removal of gall bladder. Maintenance of anesthesia was achieved with 66% N₂O in O₂ and 0.6%–1.2% isoflurane. Muscle relaxation was maintained with injection vecuronium (0.01 mg/kg i.v.) as and when required. Tidal volume of 6–10 ml/kg body weight and end-tidal carbon dioxide were maintained between 35 and 45 mmHg. During surgery, intra-abdominal pressure was maintained at 12–15 mmHg. All patients were administered injection ondansetron (0.1 mg/kg i.v.) 20 min before the end of surgery for postoperative nausea and vomiting (PONV) prophylaxis. At the end of the surgery, neuromuscular blockade was reversed by administration of injection neostigmine (0.05 mg/kg i.v.) and injection glycopyrrolate (0.01 mg/kg i.v.), and patients were extubated when adequate spontaneous breathing returned. The total duration of surgery and anesthesia was observed and recorded. All patients were kept in the postanesthesia care unit for 2 h. HR, blood pressure, SpO₂, and VAS were explained to the patients preoperatively were observed and recorded at 1 and 2 h postoperatively. Ramsay Sedation Score (RSS) was observed at 1 h postoperatively after which the patients were shifted to the ward. HR, blood pressure, SpO₂, and VAS were again observed and recorded at 4, 12, and 24 h postoperatively. In case of inadequate analgesia (VAS score >4), patients of both groups received 100 mg tramadol i.v. in 100 ml normal saline as the starting dose and the same dose was repeated to a maximum of 400 mg daily. Timing of the first dose of rescue analgesia was observed and recorded. Side effects such as hypotension and bradycardia were also looked for and recorded both intra- and post-operatively. Ephedrine 6 mg bolus was administered i.v. if intra- or post-operative hypotension occurred with systolic blood pressure <90 mmHg. Any intra- or post-operative bradycardia with HR <50 beats/min was treated with injection atropine 0.6 mg i.v. bolus. Other side effects such as nausea and vomiting and shivering were also observed and recorded postoperatively till the first 24 h. Patient satisfaction was assessed at the end of 24 h on a scale of 0–4 with 0 = poor, 1 = moderate, 2 = good, 3 = very good, and 4 = excellent. At the end of the study, all data were compiled and tabulated and were analyzed using SPSS software version 17 (SPSS Inc., Chicago) for Windows. The results of the quantitative variable were presented as mean and standard deviation while categorical variables were analyzed as an absolute number and percentage. Sample size calculations were based on a previous study. Assuming an α value of 0.05 and power value of 80%, 47 patients were required, for better results, and in view of dropouts from the study, we took 100 patients (50 in each group). The data were checked for normality before statistical analysis using Shapiro–Wilks test. Quantitatively, parameter data were analyzed using t-test while nonparametric data were analyzed using Wilcoxon signed-rank test and Mann–Whitney U-test. Qualitative data were analyzed using Chi-square or Fisher’s exact test. The difference was considered statistically significant if \( P < 0.05 \) was obtained.

**Results**

All the patients after screening were enrolled in the study [Flow Chart 1]. Patients from both the groups had a comparable demographic profile with no significance statistically. All the patients who were enrolled completed the study without any dropout. Hemodynamic parameters remained stable in both the groups and did not show any comparative difference when analyzed statistically. However, there was a significant difference between the...
groups in the VAS score measured at intervals of 1, 2, 3, 4, 12, and 23 h postoperatively [Figure 1]. In Group I (PCM) patients, mean value of VAS was more (4.86) as compared to dexmedetomidine group at 1 h interval postoperatively. In Group I, 44% of the patients had a RSS of 2 while 4% had RSS of 4, whereas in Group II, the RSS was observed to be 4 and 5 in 26% and 18% of patients, respectively [Figure 2]. The difference was significant as a higher number of patients in Group II were in the phase of conscious sedation as compared to the PCM group, who were anxious, agitated, and tranquilized at 1 h interval postoperatively, that is, RSS of 1–2. Time to administration of the first dose of rescue analgesia for the PCM group was 79.25 ± 50.85 min while it was 143.63 ± 137.17 min for dexmedetomidine group [Table 1]. Three patients in Group I did not require rescue analgesia dose throughout the period of 24 h, whereas in Group II, only (dexmedetomidine) 17 patients required. Total dose of rescue analgesia administered was much higher significantly in Group I (236 ± 106.44 mg) as compared to Group II (80 ± 69.98) (P < 0.001). Observation of PSS revealed good-to-excellent scoring in the dexmedetomidine group (42%) as compared to (96%) PCM group [Figure 3]. The comparative incidence of nausea and vomiting and other side effects such as hypotension and bradycardia was not significant statistically except for the incidence of shivering in dexmedetomidine group (2%) as compared to PCM group (16%).

**Discussion**

In our study, mean value of VAS was more in PCM group compared to dexmedetomidine group at all time intervals, 4.86 in Group I (PCM) compared to 3.62 in Group II (dexmedetomidine) at 1 h postoperatively. Several studies suggested that VAS score was less in PCM group at 8, 16, and 24 h postoperatively as compared
to dexmedetomidine group\textsuperscript{[3]} in contrast to our finding, which observed a lesser VAS score in dexmedetomidine group. The present study is in line with an earlier study of Jung-kyu park\textsuperscript{[3]} who highlighted lower VAS score in patients receiving dexmedetomidine at 1 h postoperatively. Salihoglu \textit{et al} \textsuperscript{[6]} studied the effect of i.v. PCM administration on postoperative pain and recovery in patients undergoing laparoscopic cholecystectomy and concluded that a VAS score of dexmedetomidine group was lower at 1 h postoperatively and concluded that VAS score of PCM was significantly lower than that of control (saline) group.

Lack of a control group with i.v. dexmedetomidine did not allow researchers of previous studies to comment on the potential effect of dexmedetomidine in having lower VAS score as compared to PCM.

In one of the previous studies\textsuperscript{[7]} it was demonstrated that mean sedation scores were higher in dexmedetomidine groups as compared to normal saline. The authors compared three groups and concluded that Group I patients (dexmedetomidine [dexmed group]) had better sedation score (0.4) than Group II (dexmedetomidine) (0.2), whereas in normal saline group (control), sedation score was less. None of the patients in dexmedetomidine groups developed significant sedation level, and all the patients were cooperative, oriented, and tranquil all the time, which was in line with our study that also showed patients in i.v. dexmedetomidine group were more in the phase of conscious sedation.

In a research study\textsuperscript{[8]} comparing dexmedetomidine and dexamethasone, one of the groups received single dose of 1 µg/kg of dexmedetomidine (dexmed group) while the second group received 8 mg dexamethasone (dxea group) before skin incision and it was found that, after 6 h of arrival in postanesthesia care unit, the mean RSS was significantly higher in the dexmed group (4.2 ± 0.8). The present study also showed that the time to first dose of rescue analgesia was more in dexmedetomidine group, in line to other studies\textsuperscript{[2,4]}

Another study concluded that the amount of rescue analgesia required during 24 h postoperatively was 43.5 ± 18 mg in dexmed group compared to 66 ± 39.6 in normal saline group\textsuperscript{[3]}

Our study showed that degree of patients’ satisfaction was good to excellent in dexmed group. Few researchers have also compared the efficacy of preemptive i.v. PCM (Group 1) with normal saline (Group 2) and placebo (Group 3) and concluded that patient satisfaction was 78%, 56%, and 11%, respectively, in the three groups.

There was significant reduction in systolic and diastolic blood pressure and HR at 1, 2, 3, 4, 12, and 24 h postoperatively in dexmedetomidine group as compared to PCM group. These observations were supported by Swaika \textit{et al}\textsuperscript{[5]} who concluded that mean HR was less in dexmedetomidine group (0.005) at 4 and 24 h postoperatively.

The adverse effects including nausea and vomiting along with other complications such as hypotension and bradycardia were comparable in both groups in our study in contrast to a study by Arslan \textit{et al}\textsuperscript{[4]} who showed that the incidence of nausea and vomiting was higher in saline group compared to PCM group (\textit{P} < 0.05).

One meta-analysis on PONV showed that the efficacy of dexmedetomidine in reducing postoperative nausea when compared with placebo. with an effective dose of 0.5g/kg\textsuperscript{[9]}

In one study, author\textsuperscript{[10]} suggested less shivering in dexmedetomidine group compared to saline group, undergoing elective abdominal hysterectomy and concluded

\begin{table}[h!]
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\begin{tabular}{|l|l|l|}
\hline
Parameter & Paracetamol & Dexmedetomidine & \textit{P} \\
\hline
Time to first dose of rescue analgesia (min) & 79.25±50.85 & 143.63±137.17 & 0.004 \\
Total analgesic requirement (mg) & 236±106.44 & 80±69.98 & <0.001 \\
SD: Standard deviation & & & \\
\hline
\end{tabular}
\caption{Comparison of rescue analgesia and total analgesic requirement}
\end{table}

\begin{figure}[h!]
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\includegraphics[width=\textwidth]{image1}
\caption{Comparison of Ramsay Sedation Scale scores}
\end{figure}

\begin{figure}[h!]
\centering
\includegraphics[width=\textwidth]{image2}
\caption{Patient Satisfaction Scale score}
\end{figure}
that postanesthetic shivering was observed in 21 patients in the saline group and in 7 patients in the dexmedetomidine group \((P = 0.001)\) similar to our findings. Furthermore, opioid-sparing effect of dexmedetomidine in early postoperative period concluded the decreased risk of PONV.

The main limitation of our study was that it required more systemic reviews of high-quality randomized control trials (RCTs) to be conducted regarding the use of i.v. dexmedetomidine as opioid-sparing agent in case of laparoscopic cholecystectomy to provide us with level I evidence for evidence-based study.

Several studies tried to investigate the postoperative analgesic effect of PCM compared with normal saline, in contrast to our study that compared dexmedetomidine. More studies are needed to establish the safe dose and timing of dexmedetomidine administration, especially in patients having hepatic and renal failure as well as in pediatric age group.

Taken together all the data according to our study, we recommended the use of i.v. dexmedetomidine to be given preoperatively in case of laparoscopic cholecystectomy to decrease the requirement of postoperative narcotics.

Conclusion

We conclude that addition of dexmedetomidine as an i.v. adjuvant significantly reduced the intensity of postoperative pain and prolonged the duration of analgesia with significant advantage of good-to-excellent patient satisfaction. In addition to this, the incidence of postoperative shivering also decreased significantly.

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Conflicts of interest

There are no conflicts of interest.

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