An investigation of the effects of dexmedetomidine and fentanyl as an adjuvant to ropivacaine on pain scores and hemodynamic changes following laparoscopic cholecystectomy

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Abstract

Postoperative pain control is recognized as a challenging surgical issue receiving high priority in the healthcare system, and opioids are routinely prescribed for anesthesia and pain relief. This study aimed to investigate the effects of ropivacaine administered intraperitoneally alone or combined with dexmedetomidine or fentanyl on postoperative pain control following laparoscopic cholecystectomy. This randomized double-blind clinical trial recruited three equal-size block-randomized groups of patients ($n = 138$) scheduled for elective laparoscopic cholecystectomy at Valiasr Hospital, Arak, Iran, in 2019–2020 who received ropivacaine (40 mL/0.5%), ropivacaine (40 mL/0.5%) + dexmedetomidine (1 µg/kg), and ropivacaine (40 mL/0.5%) + fentanyl (1 µg/kg). No significant differences were observed among the three groups according to the vital signs (mean arterial pressure/heart-rate/oxygen saturation) in the study period and during surgery ($P > 0.05$). Lower pain was revealed in the ropivacaine + dexmedetomidine group ($P = 0.001$), with the lowest opioid dose in postoperative 24 hours ($P = 0.001$). Moreover, no clinically significant differences were observed in complications among the three groups ($P = 0.483$), and no patient developed ileus. Intraperitoneal ropivacaine administered with dexmedetomidine could relieve pain and reduce opioid use in postoperative 24 hours, without any complication and ileus. Therefore, intraperitoneal ropivacaine administered with dexmedetomidine is recommended for postoperative pain control in patients undergoing laparoscopic cholecystectomy. This study was approved by the Ethical Committee of Arak University of Medical Sciences (approval No. IR.ARAKMU.REC.1397.267) on December 30, 2018 and was registered in the Iranian Registry of Clinical Trials (No. IRCT 20141209020258N117) on July 13, 2019.

Key words: adjuvant; dexmedetomidine; fentanyl; hemodynamic changes; intraperitoneal; laparoscopic cholecystectomy; pain score; ropivacaine

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Introduction

Postoperative pain control (PPC) is recognized as a challenging surgical issue receiving high priority in the healthcare system.[1] Pain feeling is the cause of patients' delayed return to normal activities, prolonged hospital stay, increased atelectasis, venous thrombosis, and ultimately lower patient satisfaction level.[2] When opioids are employed as a potent postoperative analgesic, they can contribute to a host of complications including dizziness, decreased respiratory function, ileus, nausea and vomiting, itching, and urinary retention. Postoperatively administrated analgesics help improve such complications and accordingly enhance pulmonary function. Furthermore, venous thromboembolic complications and constipation are lessened owing to the earlier resumption of regular activity, and the convalescence is thus shortened.[2,3]

Analgesia is usually not sufficient in most cases in which PPC is achieved using opioids without reference to the patient's needs within the specified time frames. Thus, pain-relieving medicines that do not have the above side effects and can provide a better and more continuous analgesic effect after the operation are more desirable.[4,5] Unlike opioids, local anesthetics have been increasingly recognized for treating surgical pain on account of analgesic properties and unharmful effects.[6] If acute pain is not well-controlled, severe detrimental outcomes can be achieved on various body systems: inability to clear respiratory secretions, gastrointestinal ileus, elevated blood pressure and heart rate (HR), sweating, paleness, prolonged bed rest, and consequently increased risk of deep vein thrombosis.[7] Therefore, systemic analgesia techniques, including opioids and non-opioids, along with regional analgesia are among the therapies currently available for PPC.[8]

A highly significant issue following laparoscopic surgery is thus to find a drug that produces the fewest complications, the longest duration of postoperative analgesia, and patient comfort.[9] Among various drugs relieving pain are opioids and other non-opioids. The latter drugs have the following advantages over the former: no respiratory depression, no potential for drug abuse, less nausea, early return of bowel function, and faster recovery.[5,10] The increasing use of laparoscopic abdominal surgery results in less trauma and postoperative pain in which patients also experience postoperative pain, occasionally severe, leading to delayed

discharge. No effective pain therapy has been reported, despite various pain control studies including those in which bupivacaine was injected or sprayed at the site of surgery intraoperatively, making the technique easy and cost-effective while some studies have suggested that it is not effective in PPC.[11]

Dexmedetomidine is an α2-adrenergic agonist and can relieve postoperative pain.[12-14] Much of the scientific literature has documented the efficacy of dexmedetomidine added to ropivacaine.[6,15,16] For instance, Sharma et al.'s[17] study on ropivacaine 2.0% for femoral nerve block indicated that dexmedetomidine could prolong the duration of postoperative analgesia. Numerous studies have explored the intravenous or intrathecal dexmedetomidine separately.[18-20] Kucuk et al.'s[21] study reported the better ecacy of peritoneal ropivacaine compared to peritoneal bupivacaine on PPC. In another study, Shukla et al.[22] reported that combined bupivacaine with dexmedetomidine or tramadol would relieve pain and prolong the duration of analgesia.

Fentanyl produces a potent analgesic effect with rapid onset and short duration of action; hence, it is used to relieve pain in repairing skin tears in emergency centers and has been reported to be a potent mu-opioid receptor agonist. A strong opioid with analgesic properties is 80 times more potent than morphine; opioid was first introduced into medicine in the 1960s as an intravenous anesthetic while being widely used as a premedication and analgesic in the operating room.[23]

Nowadays, opioids are routinely prescribed for anesthesia and pain relief.[2,24] The present trial was designed due to the mixed findings of previous studies and a lack of a three-group comparative study to administer fentanyl and dexmedetomidine in combination with ropivacaine, as well as intraperitoneal ropivacaine alone for providing postoperative analgesia after laparoscopic cholecystectomy.

Subjects and Methods

Study design

This double-blind randomized clinical trial study included 138 patients (aged 18–65 years old) undergoing elective laparoscopic abdominal surgery for cholecystectomy at Valiasr Hospital, Arak, Iran, in 1 year (January 2019 to January 2020). This study was registered in the Iranian Registry of Clinical Trials (No. IRCT20141209020258N117) on July 13, 2019.

The written informed consent obtained indicated patients' full knowledge of the aims and methods of operation, and possible risks and benefits associated with laparoscopic surgery from all eligible patients. This study was approved by the Ethical Committee of Arak University of Medical Sciences on December 30, 2018 (approval No. IR.ARAKMU.REC.1397.267) (**Additional file 1**).

Subjects

Inclusion criteria included the following: patients' age (18 to 65 years old), American Society of Anesthesiologists class I and II,[25] undergoing laparoscopic abdominal surgery, no history of allergy to medications used, no underlying cardiac, renal or endocrine disease, no smoking and drug use, no chronic pulmonary disease (asthma and chronic obstructive pulmonary disease), no pregnancy, consent to participate in the study, body mass index < 35 kg/m^2, no history of laparoscopy or no history of laparotomy. In addition, patients who were reluctant to continue the study, refused to receive intraperitoneal injections and required no intra-abdominal drainage for any reason were excluded from the study. The eligible patients were hospitalized at least 1 day before the surgery and kept nothing by mouth for 8 hours.

Surgical preparation and interventions

Intravenous lines were placed on arrival in the operating room through which all patients received 10 mL/kg of crystalloid (Ringer's solution). Baseline HR, mean arterial pressure (MAP) (by non-invasive blood pressure), oxygen saturation (SaO_2), and electrocardiogram were measured and recorded. Each patient was endotracheally intubated with an appropriately sized cuffed endotracheal tube and mechanically ventilated by a ventilator. Anesthesia was maintained with oxygen and N_2O (50:50) and isoflurane 1%; afterward, ventilation was controlled to maintain normocapnia (end-tidal carbon dioxide 35–40 mmHg). All patients were limited to 10–12 mmHg intra-abdominal pressure. After ensuring complete homeostasis at the end of the surgery, each patient received 50 mL of the prepared solution instilled intraperitoneally with a sterile syringe and was placed in the Trendelenburg position for 5 minutes and then returned to the initial position. The reverse Trendelenburg position was applied to the patient over a period of 5 minutes. Prepared solution in each group was different. In ropivacaine group 2 mg/kg ropivacaine 0.5% was calculated and up to total volume of 50 mL normal saline was added. In ropivacaine + dexmedetomidine group also 2 mg/kg ropivacaine 0.5% was calculated and 1 μg/kg dexmedetomidine added to ropivacaine and then up to total volume of 50 mL normal saline was added. In ropivacaine + fentanyl group 2 mg/kg ropivacaine 0.5% was calculated and 1 μg/kg fentanyl added to ropivacaine and then up to total volume of 50 mL normal saline was added.

While all groups received 2 mg/kg of 0.5% ropivacaine (L. Molteni & C. dei F.Iii Alitti Societa di Esercizio S.p.A., Scandicci, Italy), once the target dose of adjuvant (dexmedetomidine and fentanyl) was diluted to 50 mL with normal saline, 1 μg/kg dexmedetomidine (Eksir Co., Lorestan, Iran) and 1 μg/kg fentanyl (Caspian Tamin Co., Rasht, Iran) were added for the patients in the ropivacaine + dexmedetomidine and ropivacaine + fentanyl groups, respectively. Subsequently, the administration of inhaled anesthetics was stopped and the patient was ventilated with 100% oxygen. The skin incision was then repaired and dressed and the patient was reversed with neostigmine (0.05 mg/kg; Caspian Tamin Co., Rasht, Iran) and atropine (0.02 mg/kg; Caspian Tamin Co.).

Measurements

We recorded MAP/HR/SaO_2 after endotracheal intubation throughout and up to the postoperative two hours every 30 minutes and the Visual Analog Scale (VAS) pain scores at recovery time and certain postoperative time points (2, 4, 6, 12, and 24 hours) in all groups whereas hypotension was defined as a decrease of pressure by 20% from the baseline and

bradycardia as HR < 45 beat/min and SaO_2 < 92%. As with a VAS scale, zero represents the lowest and 10 the highest. If VAS > 4, 1 µg/kg fentanyl was intraperitoneally administered postoperatively, we recorded the overall dose and the time of opioid administration. Moreover, any complication, including cardiovascular issues, drug allergy, nausea, and vomiting, occurring within postoperative 24 hours was recorded for patients in the three groups, and necessary monitoring and treatment were performed.[17] The incidence of postoperative ileus was assessed up to 72 hours postoperatively.

Randomization

The patients were assigned to three groups ($n = 46$) using the balanced-block randomization method. A random allocation plan was generated by an epidemiologist and remained with him, and the sequence in which individuals were placed in groups was determined individually in the study period. The block size was six, and the three groups received ropivacaine alone, ropivacaine with dexmedetomidine, and ropivacaine with fentanyl, respectively. After random allocation, all patients were pre-oxygenated with oxygen 100% and then received fentanyl (2 µg/kg), midazolam (0.02 mg/kg), propofol (2 mg/kg), and atracurium (0.05 mg/kg) for the induction of general anesthesia intravenously.

Blinding

All the data were measured or recorded by a medical student who was unaware of the patients' grouping to ensure a double-blind study. The drugs were prepared by an anesthetist in each group and instilled by the surgeon who was also unaware of the drugs in each syringe. Furthermore, all surgeries were performed by only one surgeon.

Sample size

Using Stata 13 software (Stata Corp, College Station, TX, USA), taking into account alpha 5% and power 80% and according to previous study,[26] the mean VAS pain scores 24 hours after the intervention in the levobupivacaine group and the group of levobupivacaine plus dexmedetomidine were estimated to be 23 ± 8.4 and 17.1 ± 11.3, respectively. The sample size required in this study was estimated to be 46 individuals in each group with a total of 138 patients.

Statistical analysis

The data were described by the mean, standard deviation (SD), tables, and charts. Likelihood ratio Chi-square test, one-way analysis of variance with Scheffe *post hoc* test, and repeated measure analysis of variance were used to compare the variables of the study among the three groups. Stata 13 was used to analyze the data at a significant level of less than 0.05.

Results

The patient's enrollment procedure is shown in **Figure 1**. A total of 151 patients who were planned for elective laparoscopic abdominal surgery for cholecystectomy referred to Valiasr Hospital in Arak, Iran, were assessed for eligibility, out of which 13 patients did not meet the inclusion criteria. Finally, 138 patients were allocated to three groups (n = 46 per group) and were included in the final analysis.

Table 1 presents the baseline comparison of demographic and clinical characteristics among the three groups. In total, the mean age of participants was 40.26 ± 5.2 years old and

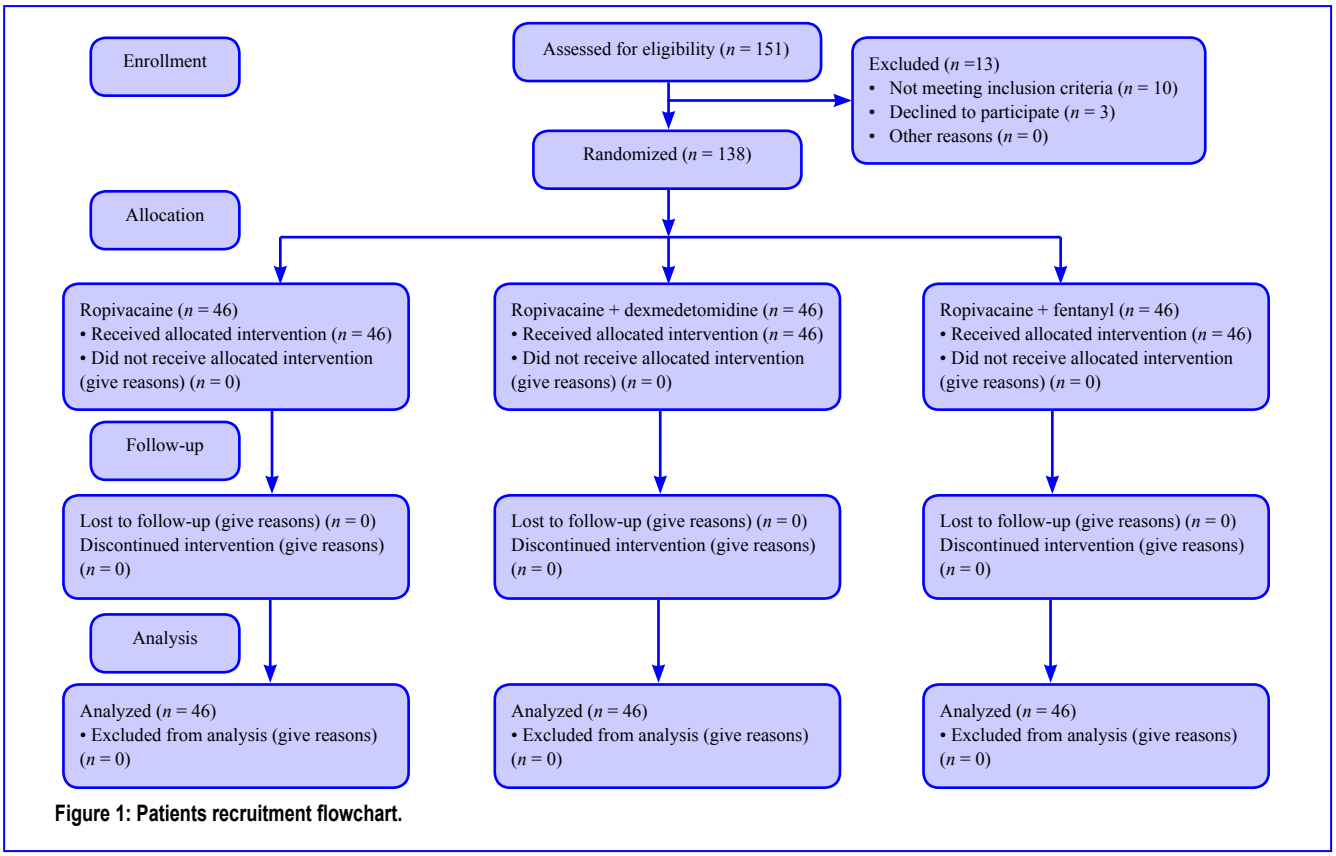

Figure 1: Patients recruitment flowchart.

Table 1: Baseline demographic and clinical characteristics of laparoscopic cholecystectomy patients

	Ropivacaine (n = 46)	Ropivacaine + dexmedetomidine (n = 46)	Ropivacaine + fentanyl (n = 46)	Total (n = 138)
Age (yr)	40.28±5.45	40.28±5.11	40.23±5.09	40.26±5.18
Body mass index (kg/m^2)	31.41±1.96	31.41±2.02	31.43±2.34	31.42±2.10
Sex	24(52.17)	24(52.17)	24(52.17)	72(52.17)
Mean arterial pressure (mmHg)	99.02±7.33	99.02±6.58	99.02±6.06	99.02±6.63
Heart rate (beats/min)	93.84±6.16	93.91±5.87	93.95±6.51	93.90±6.14
Oxygen saturation (mmHg)	97.97±0.57	97.97±0.68	97.93±0.71	97.96±0.65

Note: The data are presented as the mean ± SD, except for sex, expressed as number (percentage).

52.2% (72/138) of them were female. The mean of body mass index was 31.42 ± 2.1 kg/m^2 and also the means of MAP, HR, and SaO_2 at the baseline were 99.02 ± 6.6 mmHg, 93.90 ± 6.1 beats/min and 97.96 ± 0.65 mmHg, respectively.

As presented in **Table 2**, the means of HR, MAP, and SaO_2 were compared and the repeated measure analysis of variance revealed that there were no significant differences among three groups ($P > 0.05$).

Statistically significant differences were found in VAS scores among the three groups ($P = 0.001$); a significant time trend was also observed ($P = 0.001$). As shown in **Table 2**, the results showed that the mean of VAS scores was significantly lower in the ropivacaine + dexmedetomidine group and higher in the ropivacaine group ($P < 0.001$). In addition, the need for opioid use was significantly lower in ropivacaine + dexmedetomidine and ropivacaine + fentanyl groups than the ropivacaine group.

The results revealed that 76.1% and 52.2% of cases in ropivacaine + dexmedetomidine and ropivacaine + fentanyl groups did not use opioid and just 23.9% and 47.8% needed to use opioid one time, respectively; besides, no patient received more than one dose of opioid use whereas all cases in ropivacaine group received at least one dose of opioid, and about 89% of patients in ropivacaine group needed to use opioid at least 2 times during surgery. As observed in **Table 3**, the one-way analysis of variance suggested that the means of opioid use were significantly different among the three groups ($P = 0.001$). The Scheffe *post hoc* test also showed that the mean of opioid use was significantly lower in the ropivacaine + dexmedetomidine and ropivacaine + fentanyl than the ropivacaine group ($P = 0.001$). Moreover, the mean of opioid use was lower in the ropivacaine + dexmedetomidine group than the ropivacaine + fentanyl group but not significantly different ($P = 0.117$).

Moreover, ileus was not observed in any of the patients, and the results showed that there were no significant differences between the three groups in terms of side effects ($P = 0.483$).

Discussion

This double-blind trial recruited three groups of patients scheduled for elective laparoscopic abdominal surgery. The results showed that HR, MAP, and SaO_2 were the same with no significant differences in the study period and during the surgery. Moreover, there was not a significant difference regarding side effects among the three groups, and no patient had ileus. Nevertheless, the mean pain scores across the three groups were significantly different, and the lowest pain score was observed in the ropivacaine + dexmedetomidine group with the highest pain scores observed in the ropivacaine group. Overall, ropivacaine with dexmedetomidine was adopted to relieve pain and reduce opioid use without any complication within postoperative 24 hours without any hemodynamic changes in patients during and after surgery.

Various studies have demonstrated that dexmedetomidine results in longer postoperative analgesia and duration of sensory and motor block[6,15-17] while many have focused on the IV and IT dexmedetomidine separately.[18-20,27] However, the present study explored the intraperitoneal effect of dexmedetomidine, based on which dexmedetomidine combined with intraperitoneal ropivacaine was found to relieve pain significantly. A study by Mena et al.[28] compared intraperitoneal ropivacaine and bupivacaine in LC, suggesting that ropivacaine provides a highly statistically significant beneficial effect on PPC as also confirmed in our study. In agreement with our findings, Shukla et al.[22] conducted a study comparing bupivacaine administered intraperitoneally alone or with dexmedetomidine or tramadol in LC and reported that combined bupivacaine could relieve pain and prolong the duration of analgesia. However, it should be noted that whereas we administered ropivacaine, they used bupivacaine in their study.

Given the higher pain scores in the ropivacaine group, the higher rate of opioid use was observed in this group, but the lower opioid use was in the ropivacaine + dexmedetomidine group for 24 hours. The reason is that dexmedetomidine is an α2-adrenergic agonist that can relieve postoperative pain.[14,29,30] It can provide more effective analgesia during the postoperative period and a prolonged duration of sensory-motor block with the least complications, as reported by Anderson et al.[15] In line with our results, one study on 50 abdominal hysterectomy patients by Ülgey et al.[31] in Turkey revealed that pain intensity was reduced in the levobupivacaine + dexmedetomidine group while opioid use decreased. Another study assessed analgesia with ropivacaine administered intraperitoneally with or without fentanyl after cholecystectomy and reported that combined ropivacaine reduces the severity of pain and opioid administration.[32] Additionally, our study found reduced pain and opioid use in patients receiving ropivacaine and fentanyl, but greater efficiency in those using dexmedetomidine-ropivacaine.

The pain was relieved in the patients who were treated with ropivacaine administered intraperitoneally alone or combined with dexmedetomidine, and hence there was a reduction in the amount of opioid use throughout postoperative 24 hours. Given that no complication and ileus were developed in the patients and intraperitoneally administered ropivacaine could

Table 2: The comparison of HR, MAP, and SaO_2 among laparoscopic cholecystectomy patients

	Ropivacaine (n = 46)	Ropivacaine + Dexmedetomidine (n = 46)	Ropivacaine + fentanyl (n = 46)	P-value
Mean arterial pressure (mmHg)				P_{Groups}=0.521 P_{Time}=0.001 $P_{Interaction}$=0.023
Recovery	98.95±5.79	98.50±4.02	98.60±3.86	
30 min post-operation	98.76±5.71	97.82±3.70	98.13±3.47	
60 min post-operation	98.43±5.57	97.06±3.19	97.54±2.93	
90 min post-operation	98.28±5.42	96.60±2.78	97.23±2.49	
120 min post-operation	98.28±5.32	96.52±2.73	97.08±2.22	
Heart rate (beats/min)				P_{Groups}=0.818 P_{Time}=0.001 $P_{Interaction}$=0.040
Recovery	94.39±5.48	93.93±5.07	94.04±5.29	
30 min post-operation	94.00±5.29	93.06±4.90	93.43±5.21	
60 min post-operation	93.86±5.26	92.93±4.87	93.23±5.28	
90 min post-operation	93.84±5.27	92.93±4.89	93.23±5.22	
120 min post-operation	93.86±5.26	92.93±4.87	93.23±5.28	
SaO_2 (mmHg)				P_{Groups}=0.688 P_{Time}=0.932 $P_{Interaction}$=0.999
Recovery	97.89±0.73	97.97±0.77	97.86±0.71	
30 min post-operation	97.89±0.73	97.97±0.71	97.86±0.68	
60 min post-operation	97.89±0.67	97.97±0.74	97.86±0.65	
90 min post-operation	97.89±0.70	97.97±0.71	97.86±0.77	
120 min post-operation	97.89±0.73	97.97±0.71	97.86±0.68	
Visual Analog Scale				P_{Groups}=0.001 P_{Time}=0.001 $P_{Interaction}$=0.001
In recovery	0.34±0.49	0.0±0.0	0.0±0.0	
2 h post-operation	0.61±0.49	0.0±0.0	0.0±0.0	
4 h post-operation	2.10±0.64	0.0±0.0	0.0±0.0	
6 h post-operation	4.02±0.74	1.17±0.38	1.45±0.54	
12 h post-operation	4.93±0.39	2.30±0.66	3.02±0.49	
24 h post-operation	5.30±0.51	4.23±0.52	4.54±0.62	

Note: The data are presented as the mean ± SD, and were analyzed by one-way analysis of variance and Scheffe *post hoc* test. HR: Heart rate; MAP: mean arterial pressure; SaO_2: oxygen saturation.

Table 3: The received opioid dose (mg) among laparoscopic cholecystectomy patients

Group	Opioid dose	P value
Ropivacaine (n = 46)	154.89±50.99	
Ropivacaine + dexmedetomidine (n = 46)	17.93±32.34	
Ropivacaine + fentanyl (n = 46)	35.86±37.87	
Total	69.56±73.41	0.001

Note: The data are presented as the mean ± SD, and were analyzed by one-way analysis of variance and the Scheffe *post hoc* test.

significantly relieve pain, it is recommended that ropivacaine be used in patients with laparoscopic surgery for PPC.

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Author contributions
Study conception, design, and manuscript drafting: MP, BY, AAH, HM; data collection: MP, HM; data analysis and interpretation: AAH, HM. All authors revised the manuscript and approved the final version.

Conflicts of interest
All the authors declare no conflict of interest.

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Institutional review board statement
This study was approved by the Ethical Committee of Arak University of Medical Sciences (approval No. IR.ARAKMU.REC.1397.267) on December 30, 2018 and was registered in the Iranian Registry of Clinical Trials (No. IRCT 20141209020258N117) on July 13, 2019.

Declaration of patient consent
The authors certify that they have obtained patients consent forms. In the form, patients gave their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published.

Reporting statement
The writing and editing of the article were done in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) Statement.

Biostatistics statement
The statistical methods of this study were reviewed by an epidemiologist at Arak University of Medical Sciences, Iran.

Data sharing statement
The data could be shared if requested but the patients completed the informed consent.
Plagiarism check
Checked twice by iThenticate.
Peer review
Externally peer reviewed.

Additional file
Additional file 1: Hospital Ethics Approval.

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