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Comparative Study between Intrathecal (Dexmedetomidine versus Fentanyl) in Laparoscopic Cholecystectomies under Spinal Anesthesia

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ABSTRACT

Background: General anesthesia was once believed to be the exclusive option for laparoscopy. However, regional anesthesia, including combination spinal epidural, spinal anesthesia, and epidural anesthesia, has advantages over general anesthetic these days.

Objective: An analysis of the clinical intraoperative results of intrathecal fentanyl and intrathecal dexmedetomidine in treating shoulder tip pain (STP) in patients undergoing laparoscopic cholecystectomy.

Patients and Methods: Patients undergoing cholecystectomy were randomly assigned into two equal groups based on a predefined randomization protocol. Group (D) was administered spinal anesthesia (SA) consisting of 3.0 ml levobupivacaine combined with 5 µg dexmedetomidine, making a total volume of 3.5 ml. Meanwhile, Group (F) received an intrathecal injection of 10 µg fentanyl (0.5 ml) along with 3.0 ml of 0.5% hyperbaric levobupivacaine.

Results: Spinal anesthetic combined with either fentanyl or dexmedetomidine was a viable option for treating shoulder tip discomfort in individuals undergoing laparoscopic cholecystectomy; the dexmedetomidine group experienced more improvement. Regarding hemodynamics, shoulder discomfort, and time to rescue analgesia, there were notable variations between the two groups.

Conclusion: The two groups' rates of pneumoperitoneum, postoperative complications, muscle relaxation quality, and operational space adequacy were comparable.

Keywords: Laparoscopic cholecystectomy, Spinal anesthesia, Intrathecal fentanyl, Dexmedetomidine.

INTRODUCTION

General anesthesia was once believed to be the exclusive option for laparoscopy. However, regional anesthesia, including combination spinal epidural, spinal anesthesia, and epidural anesthesia, has advantages over general anesthetic these days [1-3]. The main reason spinal anesthesia is not used during laparoscopy is because of the patient's discomfort associated with pneumoperitoneum and the resultant STP [4-6].

Although numerous studies have explored the practicality and safety of performing laparoscopic cholecystectomy under regional anesthesia [7,8], only a limited number have offered in-depth anesthetic protocols. Specifically, detailed information on intrathecal anesthetic dosages, the necessity for supplemental intravenous pain relief, the optimal sensory block level, and strategies for managing intraoperative discomfort is often lacking. To enhance the quality of analgesia without extending the duration of motor block, intrathecal opioids are frequently administered alongside local anesthetics in spinal anesthesia [9].

Spinal anesthesia remains the preferred approach for surgeries involving the lower abdomen due to its cost-effectiveness and ease of administration. Over time, various agents have been incorporated as adjuvants to intrathecal local anesthetics. Among these, α2 adrenergic agonists have gained attention for their ability to enhance anesthetic effects while allowing the use of lower local anesthetic doses. Clonidine, a partial α2 agonist administered intrathecally, has demonstrated both safety and efficacy. When combined with local anesthetics, it significantly prolongs both sensory and motor block durations [10-13].

Strategies to reduce STP during laparoscopic surgeries under spinal anesthesia have been the subject of several investigations [4,5]. Although intrathecal opioids and local anesthetics have both been studied for this purpose, their application has frequently been restricted because of adverse effects such itching, nausea, and vomiting following surgery. Numerous investigations have employed intrathecal clonidine at dosages as high as 1 µg/kg [10,11]. However, because of its analgesic and sympathetic nervous system-suppressing properties, such concentrations are known to result in adverse effects such as bradycardia, or a slowed heartbeat, and hypotension, or a drop in blood pressure. There has been concentrated investigation on the effectiveness of a 1 µg dosage of intrathecal clonidine in managing STP during laparoscopy [14].

Dexmedetomidine is a selective α2 adrenergic agonist that has received FDA approval for use in intravenous sedation and analgesia, has about eightfold greater α2 versus α1 receptor selectivity compared to clonidine [6]. Several studies have examined intrathecal dexmedetomidine combined with levobupivacaine for spinal anesthesia, yet its specific role in reducing STP during laparoscopic cholecystectomy remains underexplored[15–17].

We hypothesized that intrathecal dexmedetomidine at five µg and clonidine at one µg would exhibit equipotency and comparable effects on the properties of bupivacaine in spinal anesthesia, as

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supported by previous studies [14,16-18]. Dexmedetomidine provides analgesia, sedation, and anxiety relief in a dose-dependent manner, all without causing respiratory depression. When used postoperatively, it offers pain control without inducing deep sedation [9].

Opioids are useful for treating pain, but their use is frequently restricted by adverse effects e.g., respiratory depression, nausea, vomiting, itching, and urine retention, which can result in extended hospital stays [19].

Fentanyl is simple to administer and reliably effective. When combined with bupivacaine, it enhances the quality of both intraoperative anesthetic and early postoperative nerve block [20].

In this study, patients having laparoscopic cholecystectomy had shoulder tip discomfort assessed in relation to the clinical intraoperative effects of intrathecal fentanyl versus dexmedetomidine

The study evaluated a variety of outcome measures. Hemodynamic measures, the surgeon's evaluation of the operating settings, and the intraoperative clinical effect of pneumoperitoneum on shoulder discomfort and the corresponding need for analgesics were the main results. However, the quality of muscular relaxation, the duration of the first rescue analgesia, the Bromage score's advancement and regression, and the frequency of postoperative sequelae were all included in the secondary outcomes.

PATIENTS AND METHODS

60 patients of either sex, aged 30 to 60, undergoing elective laparoscopic cholecystectomies with American Society of Anesthesiologists (ASA) grades I and II, were prospectively randomized into two equal groups for our study. Angiotensin converting enzyme inhibitors, calcium channel blockers, α2-adrenergic receptor antagonists, patients experiencing ASA grade >II, patient rejection, dysrhythmia, vertebral deformity, history of study medication allergies, pregnancy, coagulopathy, neurological disorders, and known contraindications to spinal anesthesia were all excluded from our study.

Every patient had to undergo an examination and fast overnight the day before surgery. They received intravenous injections of ondansetron (8 mg) and atropine (0.2 mg) as premedication. The following measures were tracked in the operating room while the patient was preloaded with 15 ml/kg of ringer lactate: baseline pulse, blood pressure (BP), saturation, electrocardiography (ECG), respiratory rate (RR), and ETCO2. These patients were divided into two groups. 3.0 ml of levobupivacaine and 5 µg of dexmedetomidine were given to group (D) (no = 30) to make 3.50 ml, and 3.0 ml of levobupivacaine and 10 µg of fentanyl (0.5 ml) were given to group (F) (n = 30).

Spinal anesthetic was administered in the L3-L4 interspace using a 26-gauge Quincke needle. Two-segment regression, pinprick-based sensory block onset, Bromage-scale-based motor block onset, and time to rescue analgesia request were among the important characteristics that were assessed when the patient was in a supine position. A T4 sensory level was attained by adjusting the operation table. At induction, post-induction, during the formation of the pneumoperitoneum, and every 15 minutes throughout and 30 minutes after surgery, vital signs such as pulse, systolic blood pressure (SBP), respiratory rate (RR), oxygen saturation (SpO_2), and electrocardiogram (ECG) were recorded. The CO_2 pressure in the pneumoperitoneum was maintained below 15 mmHg. Atropine was used to treat bradycardia (HR <60/min), whereas IV fluids and ephedrine were used to treat hypotension (SBP decrease >20%). Demographic information, sensory block onset (pinprick test), motor block onset (Bromage scale), and evaluation of shoulder tip discomfort during pneumoperitoneum were among the observations. A 10-point visual analogue scale (VAS), with 0 denoting no pain and 10 the greatest pain, was used to assess shoulder discomfort, a common complaint, and it was scored on a 0–3 scale according to severity and analgesic response.

The administration of ephedrine or rescue analgesia in the form of a 75 mg intravenous infusion of diclofenac sodium, the use of ketamine and fentanyl to alleviate shoulder pain, and clinical side effects like hypotension were among the other intraoperative observations. Apart from evaluating the suitability of the operating room, the level of muscle relaxation was evaluated and classified as mild, moderate, or severe. Lastly, the following postoperative adverse effects were recorded: headache, nausea, vomiting, lightheadedness, and hallucinations.

Ethical approval:

Sohag Faculty of Medicine Ethical Committee approved this research IRB number (Soh-med-24-12_2PD), (Clinical Trial No : NCT06970574). Informed written consent was gained from the cases or their legal representatives based on the case's condition prior to enrollment. The Helsinki Declaration was followed throughout the course of the study.

Statistical analysis: The statistical analysis was conducted using SPSS version 22.0. To ensure 90% power, a sample size of 30 per group was selected at a significance level of 0.05. To ascertain if continuous data were normal, the Kolmogorov–Smirnov test was employed. Depending on the data distribution, continuous variables (represented as mean ± SD) were assessed using either the Student's t-test or the Mann-Whitney U-test. Categorical variables were compared using either the X^2-test or Fisher's exact test, as appropriate. A X^2-test for trends was used to assess the degree of STP. Statistical significance was defined as P-values below 0.05.

RESULTS

Group F received 3.0 ml of 0.5% hyperbaric bupivacaine and 10 µg of fentanyl, while group D received 3.0 ml of 0.5% hyperbaric bupivacaine and 5 µg of injection dexmedetomidine. We recruited 60 patients undergoing elective laparoscopic procedures under SA and divided them into two groups.

There was no statistically significant difference between the two groups as regard to demographic data (Table 1).

Table (1): Demographic data of the two groups

	Group D (n=30)	**Group F (n=30)**	**P value**
	Mean ± SD	Mean ± SD	
Age in years	35.5±5.22	35.6±6.23	0.98
Weight in kg	60.4±7.45	58.6±6.7	0.76

There was no statistically significant difference between the two groups at the start of the Bromage score, however there was significant difference at the regression to 0 score and in terms of the time to rescue analgesia (Table 2).

Spinal anesthetics were adequate for procedures, and none of the patients had any issues during the process. Dexmedetomidine has no influence on the onset of SA, as demonstrated by Figure 1, which compares the quality of SA. The sensory and motor level onsets were similar in both groups. The two-segment regression occurred earlier in group (F) than group (D) and was statistically significant. Additionally, dexmedetomidine was found to significantly extend the duration of SA and motor block (Table 2), which prolongs analgesia as seen by the postoperative period's delayed need for rescue analgesia (Figure 1).

Table (2): Onset and regression of Bromage expressed as mean and standard deviation.

	Group D (n=30)	**Group F (n=30)**	**P value**
	Mean ± SD	Mean ± SD	
Onset to Bromage 3 in min	11.6±7.5	11.5±7.2	0.76
Regression to Bromage 0 in min	417.3±6.4	146.7±4.3	0.001
Time of rescue analgesia in min	511.±3.5	188.4±8.3	0.0007

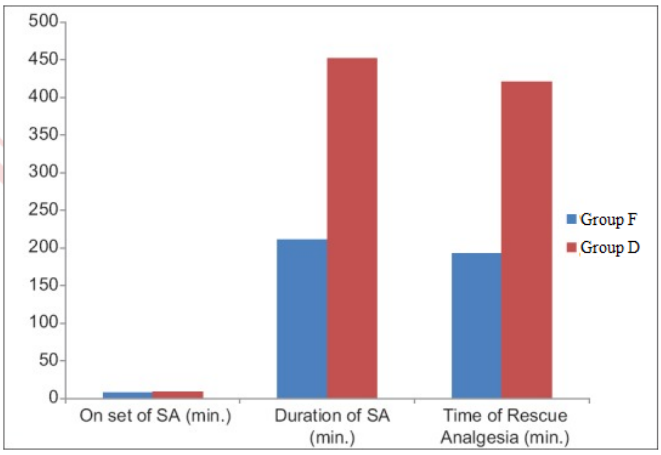

Figure (1): Comparison of the 2 groups regarding onset, duration and time to rescue analgesia.

The surgeon's evaluation revealed no discernible difference between the two groups in terms of the frequency of pneumoperitoneum brought on by peritoneal rupture, the suitability of the operating area, or the degree of muscle relaxation (Table 3).

Table (3): Comparison of frequency of pneumoperitoneum, the suitability of the operating area and the degree of muscle relaxation in the 2 groups

	Group D (n=30)	**Group F (n=30)**	**P value**
Quality of muscle relaxation Good Moderate Poor	 25 5 0	 22 8 0	**Not significant**
Operative space Adequate Inadequate	 24 6	 25 5	**Not significant**
Pneumoperitoneum	15	10	**Not significant**

Figure 2 Displays a comparison of the two groups' SBP. Following induction, the SBP dropped in both groups, but it dropped more in group (F) than in group (D). Following pneumoperitoneum, both groups experienced a small rise in SBP, with group F experiencing a greater increase than group D. After that, group D's SBP was constant, while group F's showed a minor rise. The two groups' postinduction SBP differences were statistically significant.

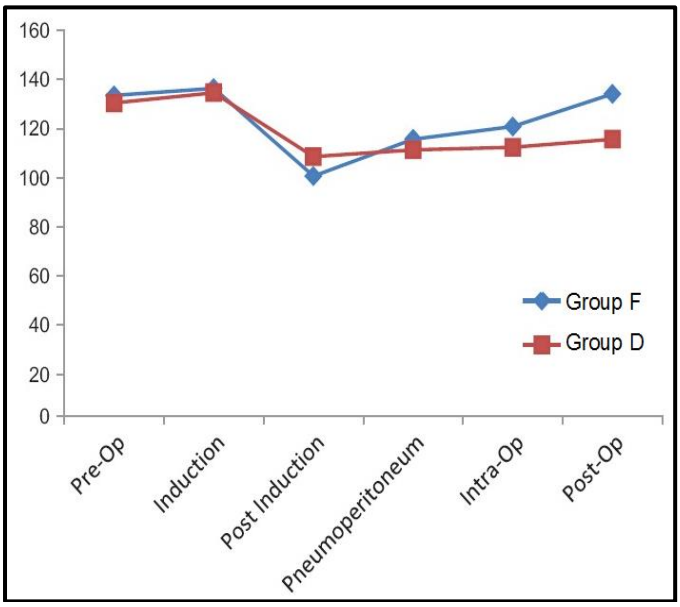

Figure (2): Comparison between two groups as regard to SBP.

With 22 versus 14 patients, respectively, group F had a significantly higher frequency of hypotension than group D. Compared to group (F), group (D) received a significantly lower dosage of ephedrine. The shoulder tip discomfort was worse in group (F) than in group (D). The number of patients in group (F) who required ketamine and the amount of ketamine required were significantly higher than those in group (D) (Table 4).

Table (4): Intraoperative characteristics assessment in the two groups.

	Group D anesthesia	**Group F anesthesia**	**P value**
	Mean ± SD	Mean ± SD	
Hypotension Patients number	14	22	0.035
Vasopressor Ephedrine (in mg) Atropine (in mg)	 2.4±5.4 0.1±0.2	 3.2±3.4 0.2±0.3	 0.02 0.64
STP Patients number 0 1 2 3	 22 6 2 0	 10 12 8 0	0.024
Ketamine Patients number Total dose (in mg)	 8 11.4±5.6	 17 20.7±5.8	 0.018 0.024
Fentanyl Patients number Total dose (in ug)	 1 0.1±0.0	 6 5.3±4.7	 0.044 0.026

Postoperative side effects showed no statistically significant difference between the two groups.

Table (5): Postoperative side effects in the 2 groups

	Group D (n=30)	**Group F (n=30)**	**P value**
Postoperative nausea and vomiting	5	6	Not significant
Urinary retention	3	3	Not significant
Headache	4	5	Not significant
Dizziness	1	0	Not significant
Hallucination	4	2	Not significant

DISCUSSION

One of the primary challenges anesthesiologists encounter during laparoscopic surgeries performed under SA is the occurrence of STP [4-6]. While the exact origin of this discomfort remains unclear, it is most commonly attributed to irritation of the diaphragm. This type of pain is referred in nature, making it difficult to manage effectively. In this study, we evaluated and compared the ability of intrathecal dexmedetomidine and fentanyl to alleviate STP. This type of discomfort is a leading reason why patients undergoing laparoscopic cholecystectomy with SA often require conversion to general anesthesia (GA). Notably, this pain is seldom directly caused by pneumoperitoneum itself. Rather, it results from irritation of the diaphragm and peritoneum by carbon dioxide, with the pain signals transmitted through the phrenic and cervical spinal nerves[21].

A highly selective and specific α2-adrenergic agonist, dexmedetomidine has analgesic, sedative, and anxiolytic properties. It functions as a selective α2 agonist by preventing presynaptic terminals from releasing norepinephrine. For α2 receptors, it is sixteen times more selective than clonidine. It stabilizes hemodynamics while maintaining ventilator drive and has sedative, analgesic, and anxiolytic effects. Additionally, it has calming effects and prolongs the sensory and motor blockage of regional anesthesia. The sympatholytic effect that dexmedetomidine produces is caused by this action [17].

Sedation and anxiolysis are caused by the central nervous system stimulating parasympathetic outflow and inhibiting sympathetic outflow from the brainstem's locus ceruleus. Inhibiting substance P release and activating α2-adrenergic receptors in the spinal cord's dorsal horn produce primary analgesic effects and intensify opioid-induced analgesia. Adult cases of bradycardia and hypotension have been documented, particularly when concomitant heart disease is present, when the medication is taken with other drugs that have adverse chronotropic effects, during vagotonic

procedures (laryngoscopy), or after high or quick bolus doses. It activates the α2-adrenergic receptor in the locus ceruleus, which results in drowsiness and anxiolysis. It significantly reduces the need for opioids by 30 to 50% and has a strong analgesic effect. In addition to peripheral sympatholysis, dexmedetomidine also reduces catecholamine release in the brain, which results in analgesia. Patients undergoing laparoscopy under SA with intrathecal dexmedetomidine may experience less STP as a result of all these effects. It has been demonstrated that intrathecal dexmedetomidine prolongs the effects of local anesthetics. Additionally, it has been observed to improve postoperative analgesia following intrathecal administration [14,17].

The justification for when fentanyl is combined with levobupivacaine, STP is reduced as through a neurally mediated mechanism, fentanyl administered intrathecally would have analgesic effects in areas distinct from the site of administration [22]. Within 30 minutes of lumbar intrathecal administration, opioids were found in the cisterna magna and were re-distributed within the cerebrospinal fluid (CSF). The clinically severe side effects that follow lumbar spinal injection, like respiratory depression, may be explained by the dispersion of opioids in the CSF [22,23].

When a pneumoperitoneal tear occurs, the effective execution of laparoscopic cholecystectomy under regional anesthesia is significantly influenced by the management of intraoperative STP [24]. In the current trial, intravenous ketamine and fentanyl were effective in treating STP, even when the pneumoperitoneum was not present. Ketamine provides potent analgesic and sedative effects while maintaining protective airway reflexes and minimal respiratory depression, although it also typically elevates BP and HR [25].

A somewhat high degree of anesthetic block is necessary for a laparoscopic cholecystectomy performed under SA, which is linked to respiratory depression, bradycardia, and hypotension. As a result, ketamine was the primary choice for an analgesic. A modest starting dose of 0.5 mg/kg and subsequent incremental use of up to 1 mg/kg effectively controlled STP without causing cardiovascular problems. For laparoscopic surgeries, spinal anesthetic offers good muscle relaxation, ideal surgical circumstances, and exceptional postoperative pain management. By lowering opioid need, reducing pain, and providing stable hemodynamics and efficient sedation, intrathecal dexmedetomidine amplifies these advantages. Obese individuals who are prone to reflux and respiratory problems may benefit from dexmedetomidine, but they were not included in the trial because of the danger of aspiration. The use of dexmedetomidine increased comfort and cost-effectiveness, and no patient needed to be switched to GA [24,25].

At the beginning of the Bromage score (p value 0.76), there was no statistically significant difference between the two groups in our study; nevertheless, at the regression to 0 score (p value 0.001), there was. For surgeries, spinal anesthetic was sufficient, and none of the patients experienced any problems throughout the procedure. When the two groups' levels of SA are compared, it is clear that the fentanyl and dexmedetomidine groups have no bearing on when SA starts. In both groups, the onsets at the sensory and motor levels were comparable. Compared to group D, group F had two-segment regression earlier, and the difference was statistically significant (P = 0.0001). Dexmedetomidine considerably lengthens the duration of spinal anesthetic and motor block, delaying the need for rescue analgesia after surgery. For laparoscopic cholecystectomy under SA, the ideal intrathecal anesthetic dosage and necessary block level are still unknown. For TEP hernia repair, **Luck *et al.*** [26] found that 3–3.5 ml of 0.5% hyperbaric bupivacaine produces a T10 sensory block with sufficient analgesia. **Ismail and Garg** [7] did not specify the ideal anesthetic dosage, however they did utilize 4 milliliters of 0.5% hyperbaric bupivacaine for TEP. **Lal *et al.*** [27] **and Azurin *et al.*** [28] suggested reaching sensory levels above T6 and T4, respectively, for successful TEP under epidural anesthesia. A T6 block level was the focus of our investigation in light of these findings [7,21,28]. In both groups, 3 ml of levobupivacaine was given due to the smaller and older patient population [7,29].

Our results were consistent with those of **Park *et al.*** [30], who reported that intravenous dexmedetomidine administration (1 μg/kg 10 min before induction and then 0.5 μg/kg/h by intravenous infusion until the gall bladder removal) in laparoscopic cholecystectomy caused postoperative pain score reduction only during the first hour postoperatively, with significant analgesia reduction in the first postoperative 24 hours. The two groups' time to rescue analgesia was statistically significantly different, as indicated by a p value of 0.0007. Furthermore, also **Bhatia *et al.*** [31] observed that intrathecal dexmedetomidine (5 μg) caused significant prolongation of SA, thereby extending analgesia, as indicated by delayed analgesic-requirement-postoperatively. SBP dropped following induction in both groups, although it fell more in group F than in group D, according to our study's assessment of the two groups' SBP. In our investigation, we discovered that 5 μg of intrathecal dexmedetomidine does not cause concerning hypotension. This is because the formation of pneumoperitoneum causes an increase in peripheral vascular resistance, which offsets the drop in BP. Bradycardia does happen at this dosage, however it rarely needs to be treated [31].

Table (4) showed a significant difference in the ephedrine therapy, with a p-value of 0.02. Following pneumoperitoneum, both groups experienced a small increase in SBP, with group F experiencing a greater increase than group D. After that, the SBP in group (D) was constant, but it slightly increased in group (F). With a P value of 0.0001, the two groups' differences in post-induction SBP were statistically significant. Though **Sharma and Shankaranarayana** [32] noted that

intrathecal fentanyl (25 µg) significantly reduced heart rate and mean arterial pressure at pneumoperitoneum until extubation compared to intravenous fentanyl (2 µg/kg) during laparoscopic hysterectomies under GA. There was regrettably no comparative study between the hemodynamic effects of intrathecal and intravenous dexmedetomidine during laparoscopic cholecystectomy under GA.

In contrast to our study **Niu *et al.* [24]** examined the effect of intravenous and intrathecal dexmedetomidine in SA and noticed that dexmedetomidine did not increase the incidence of hypotension.

With P-values of 0.024 and 0.005, respectively, shoulder tip discomfort was considerably more common and severe in the fentanyl group (F) than in the dexmedetomidine group (D). Furthermore, group F had more patients in need of ketamine and needed more of it overall (P = 0.03 and P = 0.024). These results are consistent with those of **Bhatia *et al.* [31],** who found that adding intrathecal dexmedetomidine to bupivacaine significantly decreased shoulder tip discomfort during laparoscopic procedures (3 out of 30 patients impacted) as opposed to using bupivacaine alone (27 out of 30 patients).

There are no episodes of apnea, pruritus, or postoperative nausea and vomiting when opioids were given as intrathecal adjuvants along with a local anesthetic, as is occasionally the case. Together, the hypnotic and analgesic effects of dexmedetomidine keep patients relaxed and pain-free. While there were no appreciable differences in the postoperative side effects between the two groups in our study, a study by **Magdy *et al.* [33]** comparing the effects of intrathecal (5 µg) versus intravenous (0.5 µg/kg/h) dexmedetomidine as an adjuvant to spinal bupivacaine anesthesia for cesarean sections, found that the incidence of nausea and vomiting was lower in the intravenous group than in the intrathecal group. Different kinds of procedures, anesthesia, or the use of intravenous dexmedetomidine infusion could be the cause of this.

CONCLUSION

For patients undergoing laparoscopic cholecystectomy, spinal anesthetic combined with either fentanyl or dexmedetomidine was a viable and effective way to control shoulder tip discomfort, with the dexmedetomidine group experiencing more improvement. The two groups differed significantly in terms of hemodynamics, shoulder discomfort, and time to rescue analgesia. The two groups' rates of pneumoperitoneum, postoperative complications, muscle relaxation quality, and operational space adequacy were comparable.

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