Original Article

Preemptive morphine suppository for postoperative pain relief after laparoscopic cholecystectomy

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Abstract

Background: Postoperative pain is a major problem following laparoscopic cholecystectomy, and there is no general agreement on the effective method of pain relief. Rectal morphine suppositories are one of the newly released morphine forms. The aim of this study is to compare the impact of suppository morphine with placebo on pain relief after laparoscopic cholecystectomy.

Materials and Methods: Seventy patients scheduled for elective laparoscopic cholecystectomy under general anesthesia, were randomly allocated to two groups according to the drug used for postoperative analgesia: Group morphine suppository (MS - 10 mg) just before induction of anesthesia And Group placebo suppository (PS) (the pills were made from cocoa butter, physically similar to the real drug). Pain intensity based on visual analog scale (VAS) and opioid consumption were assessed 30 and 60 min, and 2, 4, 8, 16, and 24 h after arrival of the patient to the recovery room.

Results: VAS scores were significantly lower in MS group (from 3.8 ± 1 to 5.3 ± 1.6) compared with PS group (from 4.9 ± 0.9 to 6.7 ± 1) from 30 min after arrival to the recovery room until 16 h postoperatively ($P < 0.05$). There were no additional analgesic requirements in the first 2 h after the entrance of the patient to the recovery room in MS group. The number of patients requiring pethidine was significantly different between two groups ($P < 0.05$) in all periods except for 24 h postoperatively.

Conclusion: Suppository morphine administration is more effective than placebo to reduce pain and analgesic requirements after laparoscopic cholecystectomy.

Key Words: Cholecystectomy, laparoscopic, morphine, pain, postoperative, preemptive

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INTRODUCTION

Acute postoperative pain causes serious complications such as chronic pain, impairment of rehabilitation, increased length of stay and/or hospital readmission, and adverse events related to excessive analgesic use, like over sedation.[1]

Lack of pain relief increases the risk of adverse effects and of developing chronic postoperative pain.[2] A revolution in the management of acute postoperative pain has occurred during the past four decades.[3] Widespread recognition of the under treatment of acute pain by clinicians, economists, and

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health policy experts has led to the development of a national clinical practice guidelines for management of acute pain by the Agency for Healthcare Quality and Research.[3] Many patients experience considerable pain after cholecystectomy, so there is no general agreement on effective pain control.[4]

The various methods used with variable success include intraperitoneal local anesthetics and interpleural block,[4] no steroidal anti-inflammatory drugs,[5] infiltration of wounds with local anesthetics,[6] intermittent intramuscular narcotics,[5,7] etc., By preventing central sensitization, preventive analgesia may reduce acute and chronic pains.[8] Although studies overwhelmingly support the concept of preemptive analgesia, the evidence from clinical trials is equivocal because of methodologic issues.[8] The systemic administration of high doses of opiates has been associated with a side effects ranging from pruritus, nausea and vomiting to sedation, and respiratory depression.[9] Morphine is an opioid analgesic, which have a direct effect on the central nervous system and is one of the most powerful analgesic drugs in controlling and treatment of acute and severe chronic pains. Rectal morphine suppositories are one of the newly released morphine forms. Each rectal suppository can contain 5, 10, 20, and 30 mg of morphine, approximately two-thirds of which is absorbed through the gastrointestinal tract and maximum effect is after 20–60 min and its metabolism occurs in the liver.[10]

To the best of our knowledge, there was no previous study to evaluate the analgesic effect of suppository morphine for pain prevention after laparoscopic cholecystectomy and as this method of preemptive analgesia by morphine is not routinely used in our university hospitals especially in ophthalmologic operating rooms, and some studies have showed beneficial effect of this method in other surgeries so we designed the present study to assess the effect of suppository morphine on postoperative pain relief in patient's candidate for laparoscopic cholecystectomy and we hope that this method of analgesia become routine in our operating rooms as a new routine route.

MATERIALS AND METHODS

After institutional approval and obtaining an informed patient consent, 70 American Society of Anesthesiologists (ASA) physical status I–II patients, scheduled for elective laparoscopic cholecystectomy, under general anesthesia, were included in this double-blind prospective randomized study (power analysis with $\alpha = 0.01$ and $\beta = 0.05$ suggested that a sample size of 35 patients per group was needed to detect a 20% reduction in postoperative pain score and also postoperative analgesic requirements). Other inclusion criteria of patients into the study was as follows: Age span from 18 to 65 years, body mass index (BMI) <30, lack of sensitivity to morphine and or similar compounds, lack of addiction to opioids and no renal, and liver failure.

Before the study began, a random number table was used to generate a randomized schedule specifying the group to which each patient would be assigned upon entry into the trial. In case of exclusion, the next patient was randomized per schedule.

The included patients were divided into two groups each with 35 members. The patients in the first group (morphine suppository [MS] group) were randomly assigned to their treatment (10 mg morphine rectal suppository) and placebo suppository (PS) group (control group) received rectal placebo just before induction of anesthesia.

General anesthesia was used in patients by injecting of sodium thiopental (5 mg/kg), Atracurium (0.6 mg/kg), and fentanyl (2 μgr/kg); followed by 1.2% isoflurane and 50% oxygen with 50% N_2O as maintenance of anesthesia. At the end of surgery, muscle relaxation was completely reversed by injecting of 0.04 mg/kg of neostigmine and 0.02 mg/kg of atropine, after getting back to normal respiration at full consciousness the patient was extubated.

All patients underwent pain assessment with visual analog scale (VAS, ranges 0–10 cm) from 30 min after recovery to 24 h after surgery. In the recovery room controlling of pain, consciousness, systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and respiratory rate (RR) was done at the time of admission to the recovery room 30 and 60 min and 2, 4, 8, 16, and 24 h after surgery by someone who was not aware of the group type of the patients.

Moreover, the first request for additional analgesic and the related dosage along with implications were recorded in both groups. In the case VAS > 3, intravenous pethidine with a dose of 0.5 mg/kg was injected intravenously. When vomiting or marked nausea (VAS > 3) was observed, intravenous ondansetron with a dose of 0.1 mg/kg was injected. BMI (BMI - the ratio of body weight in kg to body surface area in m^2), age, sex, and duration of anesthesia (the time from induction of anesthesia to extubation of the patient), duration of surgery (the time from skin incision to skin closure), recovery time (the time from entrance of the patient to recovery room to discharging

from recovery) were also recorded. Also, questions about drug complications were asked from the patients and any complication recorded. At the end of 24 h, questions about patients' satisfaction were asked using the following: Excellent, very good, good, and poor.

The analysis of obtained data was by the statistical software SPSS (version-20) and statistical tests, including Student's *t*-test and Chi-square test as well as analysis of variance with repeated observation. These results were considered significant if the *P* value was <0.05.

RESULTS

We performed a double-blind, prospective, randomized clinical trial to assess the effect of morphine suppositories on postoperative pain relief, pethidine requirement, patient satisfaction, and side effects after elective laparoscopic cholecystectomy. Seventy patients were studied in two groups [Figure 1].

The two study groups comparable with respect to age, sex, duration of anesthesia, duration of surgery, recovery time, and BMI [Table 1].

Pain intensity and additional postoperative opioid consumption in patients are separately shown in Table 2 from 30 min after recovery to 24 h after surgery.

Performing *t*-test on mentioned data revealed that mean pain intensity was significantly different between two groups from 30 min to 16 h after surgery; however, this was not meaningful after 24 h. In addition, according to an analysis of variance with repeated observations, changes in pain intensity were significant between two groups from 30 min to 24 h after surgery ($P < 0.001$).

According to the Chi-square test there was a significant difference between two groups in terms of mean total added opioid dose ($P < 0.001$) so that 2 h after surgery no additional drugs were used for subjects in the MS group, whereas in the PS group, a total of 26 additional pain relief were requested in the case of postoperative complications.

Although mean heart rate was higher in MS group compared with PS group, other hemodynamic variables such as mean blood pressure and oxygen

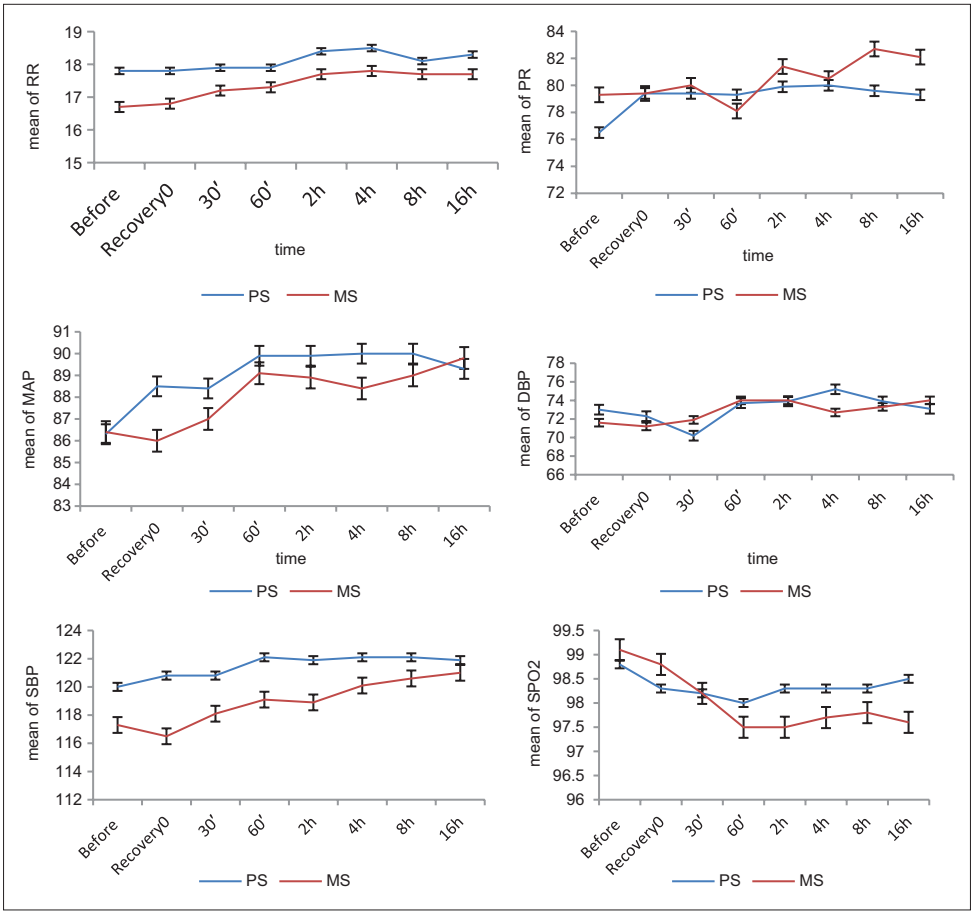


Figure 1: Mean and standard deviation of hemodynamic variables in two groups

saturation (SPO_2) as well as mean RR were lower in MS group. There was no reporting of $SPO_2 < 92\%$ in any of groups. However, analysis of variance with repeated observations showed that there were no significant differences in the mean changes in each hemodynamic parameters and respiratory status between two groups since before anesthesia until 24 h after surgery [Table 3].

Table 1: Demographic data of patients and recovery, operation and anesthesia time in the two groups

Group variable	MS group	PS group	*P*
Age (year)	44.2±10.8	47.4±11.7	0.24
Sex ratio (male/female) (*n*)	17.18	13.22	0.4
Duration of anesthesia (h)	1.69±0.47	1.67±0.36	0.8
Duration of operation (h)	1.2±0.44	1.3±0.29	0.32
Recovery time (h)	1.43±0.76	1.58±0.46	0.33
BMI	24.7±1.8	24.4±1.4	0.63

All data mentioned as mean±SD unless otherwise indicated. MS group: Morphine suppository group, PS group: Placebo suppository group, BMI: Body mass index, SD: Standard deviation

Table 2: VAS and frequency of pethidine consumption in two groups

Group time	VAS			Pethidine consumption *n* (%)		
	PS group	MS group	*P*	PS group	MS group	*P*
30’	6.1±0.9	5±1	<0.001	2 (5.7)	0 (0)	0.49
60’	6.7±1	4.7±0.6	<0.001	12 (34.3)	0 (0)	<0.001
2 h	6.6±1.1	4.7±0.8	<0.001	12 (34.3)	0 (0)	<0.001
4 h	6.4±1.1	5.3±1.6	0.002	12 (34.3)	15 (42.9)	0.46
8 h	6±1.2	4.5±1.3	<0.001	11 (31.4)	21 (60)	0.016
16 h	4.9±0.9	3.8±1	<0.001	0 (0)	0 (0)	1
24 h	3±0.7	2.7±1.1	0.19	0 (0)	0 (0)	1
P	<0.001	<0.001	<0.001			

All data mentioned as mean±SD unless otherwise indicated. MS group: Morphine suppository group, PS group: Placebo suppository group, VAS: Visual analog scale, SD: Standard deviation

Although none of the patients had a high level of consciousness on arrival to the recovery room, the use of morphine suppositories did not cause coma and hypoxia in any of the patients. As shown in Table 4, the incidence of nausea and vomiting, and ondansetron consumption had no significant difference between two groups.

During hospitalization, 5 patients had pruritus. All of them were in the intervention group and self-limited. And no special treatment used. However, according to Fisher’s exact test, there was no significant difference was observed in the incidence of pruritus between the two groups ($P = 0.5$). Patient’s satisfaction was significantly higher in the intervention group when compared with the control group [Table 5, Figure 1 and Flow Diagram 1].

DISCUSSION

Our data showed that VAS scores were significantly lower in MS group when compared with PS group

Table 3: Mean and SD of hemodynamic variables in two groups

Variable	RR		PR		MAP		DAP		SAP		SPO2	
Time	PS group	MS group	PS group	MS group	PS group	MS group	PS group	MS group	PS group	MS group	PS group	MS group
Before anesthesia	18.2±1	17.9±1.1	79.7±6.4	82.6±3.6	90.6±8.3	89.8±7.7	74.5±8.1	73.1±8	112.8±11.4	121.6±11	98.3±1	96.9±1
Recovery 0	17.8±1	16.7±0.9	76.5±15.5	79.3±4.4	86.3±17.2	86.4±7.1	73±8.4	71.6±8	120±13.2	117.3±8.2	98.8±1.1	99.1±0.56
30’	17.8±1	16.8±0.8	79.4±7.9	79.4±4.3	88.5±7.8	86±6.4	72.3±7	71.2±7.1	120.8±11.3	116.5±7.9	98.3±1.3	98.8±0.7
60’	17.9±0.9	17.2±0.7	79.4±7.1	80±3.9	88.4±8.1	87±6.2	70.2±13.6	71.9±6.1	120.8±11.3	118.1±8.7	98.2±1.2	98.2±0.7
2 h	17.9±0.8	17.3±0.9	79.3±6.2	78.1±14	89.9±7.1	89.1±6.3	73.7±6.3	74±6.6	122.1±10.9	119.1±8.1	98±1.1	97.5±0.93
4 h	18.4±1	17.7±1.1	79.9±5.7	81.4±2.7	89.9±6.2	88.9±5	73.9±5.8	74±5.1	121.9±9.4	118.9±7.5	98.3±1.1	97.5±0.93
8 h	18.5±1.2	17.8±0.8	80±5.3	80.5±13.4	90±5.7	88.4±5.2	75.2±5.9	72.7±5.6	122.1±8.9	120.1±7.2	98.3±1.1	97.7±0.9
16 h	18.1±1	17.7±1	79.6±5.8	82.7±2.7	90±5.7	89±5.7	73.9±5.4	73.3±5.8	122.1±9.6	120.6±7.6	98.3±0.71	97.8±15.4
24 h	18.3±1	17.7±0.9	79.3±6.2	82.1±2.8	89.3±5.5	89.8±5.3	73.1±5	74±5.9	121.9±8.1	121±6.7	98.5±0.78	97.6±0.74
P	0.07		0.26		0.45		0.71		0.21		0.053	

All data mentioned as mean±SD unless otherwise indicated. MS group: Morphine suppository group, PS group: Placebo suppository group, SD: Standard deviation, RR: Respiratory rate, PR: Pulse rate, SBP: Systolic blood pressure, DAP: Diastolic blood pressure, MAP: Mean arterial pressure, SPO2: Oxygen saturation, SAP: Systolic arterial pressure

Table 4: Frequency of nausea, vomiting, and ondansetron consumption in the two groups

Group time	Nausea *n* (%)			Vomiting *n* (%)			Ondansetron consumption *n* (%)		
	PS group	MS group	*P*	PS group	MS group	*P*	PS group	MS group	*P*
30’	2 (5.7)	1 (2.9)	0.99	2 (5.7)	1 (2.9)	0.99	2 (5.7)	1 (2.9)	0.99
60’	2 (5.7)	4 (11.4)	0.67	0 (0)	0 (0)	1	2 (5.7)	2 (5.7)	1
2 h	4 (11.4)	3 (8.6)	0.99	0 (0)	0 (0)	1	0 (0)	0 (0)	1
4 h	8 (22.9)	8 (22.9)	1	4 (11.4)	6 (17.1)	0.5	4 (11.4)	6 (17.1)	0.73
8 h	6 (17.1)	10 (28.6)	0.26	4 (11.4)	10 (28.6)	0.07	4 (11.4)	10 (28.6)	0.22
16 h	1 (2.9)	3 (8.6)	0.3	1 (2.9)	3 (8.6)	0.61	2 (5.7)	3 (8.6)	0.48

MS group: Morphine suppository group, PS group: Placebo suppository group

from 30 min after the entrance of the patients to a recovery room until 16 h after surgery. Previous works demonstrated that preemptive morphine can be superior to morphine given postoperatively for pain relief after surgery.[11] Also, it was shown in another study that nonparenteral morphine provides better analgesia than parenteral route but with an effect limited to the first postoperative day.[12] In the present study the need for additional analgesics was lower in the MS group; again the finding of the other studies in this regard is in accordance with the results of our study.[13]

Also pain process after the surgery was shorter for the intervention group compared to the control group. These results are similar to finding of the study of Cole *et al*. and Beaver and Feise. Cole *et al*. and Beaver and Feise demonstrated that morphine hydrogen suppository can be effective in controlling postoperative pains.[13,14]

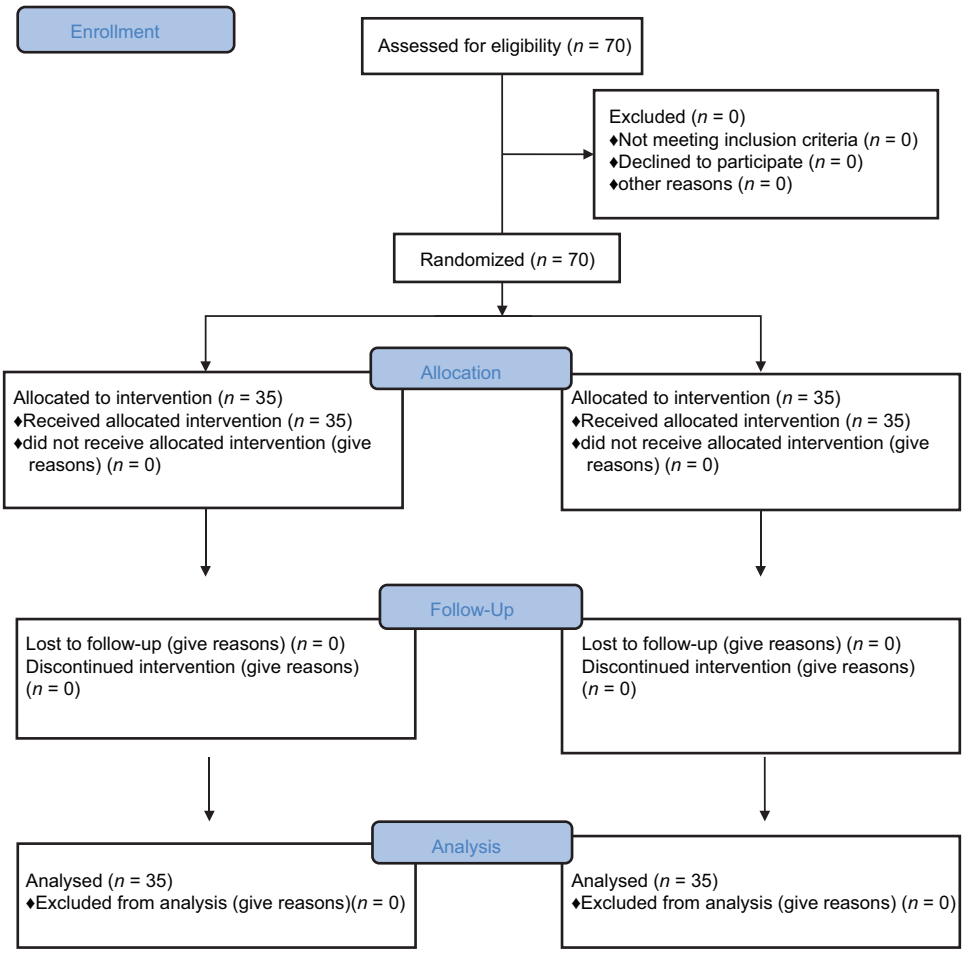
Table 5: Satisfaction scores in the two groups

Group satisfaction	PS group *n* (%)	MS group *n* (%)
Excellent	5 (14.3)	9 (25.7)
Very good	8 (22.9)	15 (42.9)
Good	5 (14.3)	5 (14.3)
Poor	17 (48.5)	6 (17.1)
Total	35 (100)	35 (100)

P=0.048. MS group: Morphine suppository group, PS group: Placebo suppository group

In another study, Beaver and Feise demonstrated that single rectal oxymorphone has lower and more delayed peak analgesia and a longer duration of action than intramuscular oxymorphone administration on postoperative pain. He concluded that because intramuscular oxymorphone is 9–10 times as potent as intramuscular morphine, 5–10 mg suppository oxymorphone provides better analgesic effects than routinely used parenteral narcotics, and suggested that the rectal route is an acceptable and practical way of administering potent analgesics and is probably being underutilized by physicians in the control of moderate to severe pain.[14]

In another study, Bourke *et al*. concluded that oral sustained release morphine sulfate tablet is a suitable alternative to the intramuscular route for relieving postoperative pain.[15] So it seems that



Flow Diagram 1: Consort 2010 flow diagram

low-dose mucosal opioid administration like a rectal prescription to be safe compared with other systemic routes.[14]

Some other researchers show an anomalous response to morphine in patients with unexplained pain in the upper abdomen which persists or recurs after cholecystectomy.[16] Some authors have reported side effects of rectal morphine administration due to inattention to the narrow therapeutic ratio for opioid drugs and staff education and clinical protocols.[17] In our study, the total amount of used analgesic in the postoperative period was significantly less in MS group compared with PS group. Furthermore, basic science investigations suggest that opioids decrease central and peripheral sensitization via direct central nervous system effect.[18]

Hemodynamic parameters such as blood pressure, heart rate, RR and blood SPO_2 were not significantly different between two groups just before anesthesia and during the first 24 h after surgery. In addition, no case of hemodynamic instability and respiratory difficulty were seen in both groups. So we concluded that suppository morphine prescription before surgery may induce hemodynamic stability during anesthesia. This is in accordance with basic science investigations that postoperative pain relief stabilizes patient hemodynamics.[19]

Again there was no significant difference between two groups in mean arterial blood pressure, and RR; this finding is comparable to other studies.[20] Ventilator rate is considered a more reliable and adequate index of hypoventilation in most studies.[20]

Although nausea and vomiting were higher implications in the MS group than in the PS group, however, no significant difference were observed between two groups; other studies have shown a similar result. Nausea and vomiting have been major side effects of opioid used for postoperative analgesia.[21-23]

In our study, patient's satisfaction was significantly higher in PS group compared with PS group.

However, it should be remembered that the analgesic efficacy is likely dependent upon multiple variables. First, it is possible that by altering the volume and concentration of the drug administered, an improved analgesia may be achieved. Second, the relative efficacy of the analgesic regimens investigated is study design – dependent. Therefore, we suggest that by altering the delivery set-up, different results may be achieved. However, this hypothesis requires further investigations.

Our study demonstrates that the use of preoperative morphine suppositories may considerably be more effective in reducing postoperative pain in patients and since the morphine suppositories have no adverse impact on the hemodynamic status of patients and also have no other severe complication we recommend to use it as an analgesic medication in laparoscopic cholecystectomy surgical procedures in the absence of contraindication and under control of anesthesiologist. The limitation of this study was the small sample size and the fact that we followed patients with age span from 18 to 65 years, BMI < 30, and ASA physical status I–II only for 24 h postoperatively; however, the findings seem particularly robust in spite of this. Also, we suggest altering the study design and further investigation.

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Conflicts of interest

There are no conflicts of interest.

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