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The Effects of Locally Administered Morphine Over the Dura on Postoperative Morphine Consumption and Pain After Lumbar Disc Surgery: A Prospective, Randomised, Double-Blind and Placebo-Controlled Study

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Abstract

Objective: Effective pain management by avoiding side effects in the perioperative period is essential for patient outcome. Lumbar disc surgery is associated with moderate to severe postoperative pain, and opioids are widely used. The primary aim of the present study was to compare the effects of 1 mg and 2 mg morphine-impregnated absorbable cellulose haemostat material placed over the dura on morphine consumption, and the secondary aims were to compare pain scores and opioid-related side effects during postoperative 24 h.

Methods: The study included 44 patients (American Society of Anesthesiologists I and II). After the discectomy procedure and before the closure, in Group A (n=15), 1 mg morphine-impregnated absorbable cellulose haemostat material placed over the dura was used. In Group B (n=14), 2 mg morphine was used for the same technique, and in Group C (n=15) (control), normal saline was used. All patients used intravenous morphine patient-controlled analgesia pumps for 24 h following lumbar disc surgery. Morphine consumption, pain scores and opioid-related side effects were recorded at 10 min, 1, 2, 6, 12 and 24 h postoperatively.

Results: Morphine consumption, pain scores and opioid-related side effects were similar among the groups.

Conclusion: Morphine-impregnated absorbable cellulose haemostat material placement over the dura after single level lumbar discectomy did not reduce postoperative morphine consumption, pain scores and incidence of opioid-related side effects.

Keywords: Lumbar disc surgery, morphine, pain

Introduction

The surgical stress response due to local inflammation and systemic neuroendocrine process may affect postoperative mortality and morbidity. One of the contributing factors of surgical stress response is pain, thus pain management becomes essential in the perioperative period (1, 2).

There are many drugs and administration routes for perioperative pain management. Although systemic opioids were widely used for this purpose, their use is now limited with enhanced recovery after surgery protocols to reduce opioid-related side effects, such as sedation, respiratory depression, nausea, vomiting and ileus, in the postoperative period (3-5). Regional and local administration routes are proposed rather than systemic administration for this purpose (4, 6).

Lumbar disc surgery is associated with moderate to severe postoperative pain (7, 8). Ineffective pain management after lumbar disc surgery may cause immobilisation, thromboembolic events, pneumonia and increased sympathetic

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activity leading to increased myocardial oxygen consumption (9, 10).

Thus, the primary aim of this prospective, randomised and placebo-controlled study was to compare the effects of 1 mg and 2 mg morphine-impregnated absorbable cellulose haemostat material (Surgicel®; Ethicon, NJ, USA) placed over the dura on morphine consumption during postoperative 24 h. The secondary aims were to compare pain scores and opioid-related side effects during postoperative 24 h.

Methods

This prospective, randomised, double-blind and placebo-controlled study was performed between February 2017 and April 2018. The ethics committee of Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine (ethical committee no. 83045809-604.01.02; 5 January 2017) approved the study. Written informed consent was obtained from every patient. Patients with an American Society of Anesthesiologists (ASA) physical status class I–II, aged between 18 and 70 years and scheduled for microscopic single level lumbar discectomy were included in the study. Patients presenting with neurological disorders hindering communication, drug or alcohol addiction, chronic pain, allergies to any of the drugs used in the present study, hepatic or renal dysfunction and perioperative dural injury were excluded from the study.

Patients were randomised to one of three groups using a computer-generated list (in opaque sealed envelopes). All patients were previously instructed on patient-controlled analgesia (PCA) pumps (Abbott Provider®; Abbott Laboratories, Chicago, IL, USA) and visual analogue scale (VAS) from 0 to 10, with 0 being no pain and 10 being the worst pain imaginable.

Patients were sedated with intravenous (IV) midazolam (0.05 mg kg^{-1}) before surgery. In the operating room, after routine monitoring, anaesthesia was induced with propofol (2 mg kg^{-1}), rocuronium (0.5 mg kg^{-1}), remifentanil (0.1 µg kg^{-1}) and 0.7 FiO_2 oxygen/air and maintained with sevoflurane 1 MAC in oxygen/air (FiO_2=0.40) and remifentanil (0.05–0.1 µg kg^{-1} h^{-1}) infusion. After orotracheal intubation, patients were then turned into the prone position supported by three surgical bolsters, one on the chest and two on the pelvis. Intraoperative analgesia was maintained with remifentanil and tenoxicam 20 mg IV. Additional remifentanil 25 µg IV was administered if the mean arterial pressure (MAP) and heart rate (HR) increased >20% of the baseline in all groups.

After the discectomy procedure and before the closure, in Group A (n=15), 1 mg morphine-impregnated absorbable cellulose haemostat material (Surgicel®) placed over the dura was used. In Group B (n=14), 2 mg morphine was used for the same technique, and in Group C (n=15) (control), normal saline was used.

Sugammadex (2 mg kg^{-1}) was used to reverse residual muscle relaxation at the end of surgery. Ondansetron (8 mg IV) was administered as an antiemetic prophylaxis. All patients were extubated at the end of surgery, admitted to the post-anaesthesia care unit and then transferred to the ward when their Aldrete score reached >9 (11). All patients received IV morphine using a PCA pump for postoperative 24 h. The PCA solutions contained 100 mg morphine in 100 mL normal saline. The PCA was set to administer a bolus dose of 1 mg morphine on demand with a lockout period of 10 min and maximum 20 mg for 4 h. Two mg IV morphine was administered every 20 min in addition to PCA delivery until the pain score decreased <4.

Age, gender, ASA physical status, body mass index (BMI), duration of surgery and size of the surgical incision were recorded.

Postoperative cumulative morphine consumption and pain scores were recorded at postoperative 10 min, 1 h, 2 h, 6 h, 12 h and 24 h. Moreover, morphine-related side effects, such as nausea, vomiting, pruritus and rash, were recorded at the same time intervals and defined by a scale with 0=absent and 1=present. HR, MAPs and Ramsey sedation scores were also recorded at the same time intervals (12).

The patient and the anaesthesiologists who recorded postoperative data were blinded to the study groups.

The primary aim of the present study was to compare the effects of 1 mg and 2 mg morphine-impregnated absorbable cellulose haemostat material placed over the dura on morphine consumption during postoperative 24 h. The secondary aims were to compare pain scores and opioid-related side effects during postoperative 24 h.

Statistical analysis

A power analysis was performed prior to the study. According to the power analysis, a total of 14 patients per group should be enrolled in the study to detect at least a 10% difference in morphine consumption among the groups, with an alpha error of 0.05 and a beta error of 0.2.

Statistical analysis was performed using NCSS 10 (2015; NCSS, LLC, Kaysville, UT, USA). The Pearson chi-square test with Yates correction was used for comparison of qualitative variables between the groups, such as gender, ASA physical status and opioid-related side effects, which showed binary change. The Shapiro–Wilk normality test was used to evaluate the distribution of data. The one-way ANOVA

was used to compare normally distributed variables among the groups. The Kruskal–Wallis test was used to compare the non-normally distributed variables. The analysis of repeated measures was performed by repeated measures of ANOVA in normally distributed variables, and the Friedman test and post-hoc Wilcoxon test with Bonferroni correction were performed in non-normally distributed variables. The normally distributed values were expressed as mean (standard deviation), and the non-normally distributed values were expressed as median and interquartile range. A p value of <0.05 was considered to be statistically significant.

Results

A total of 44 patients were enrolled in the study. There was no patient excluded before and after randomisation (Figure 1).

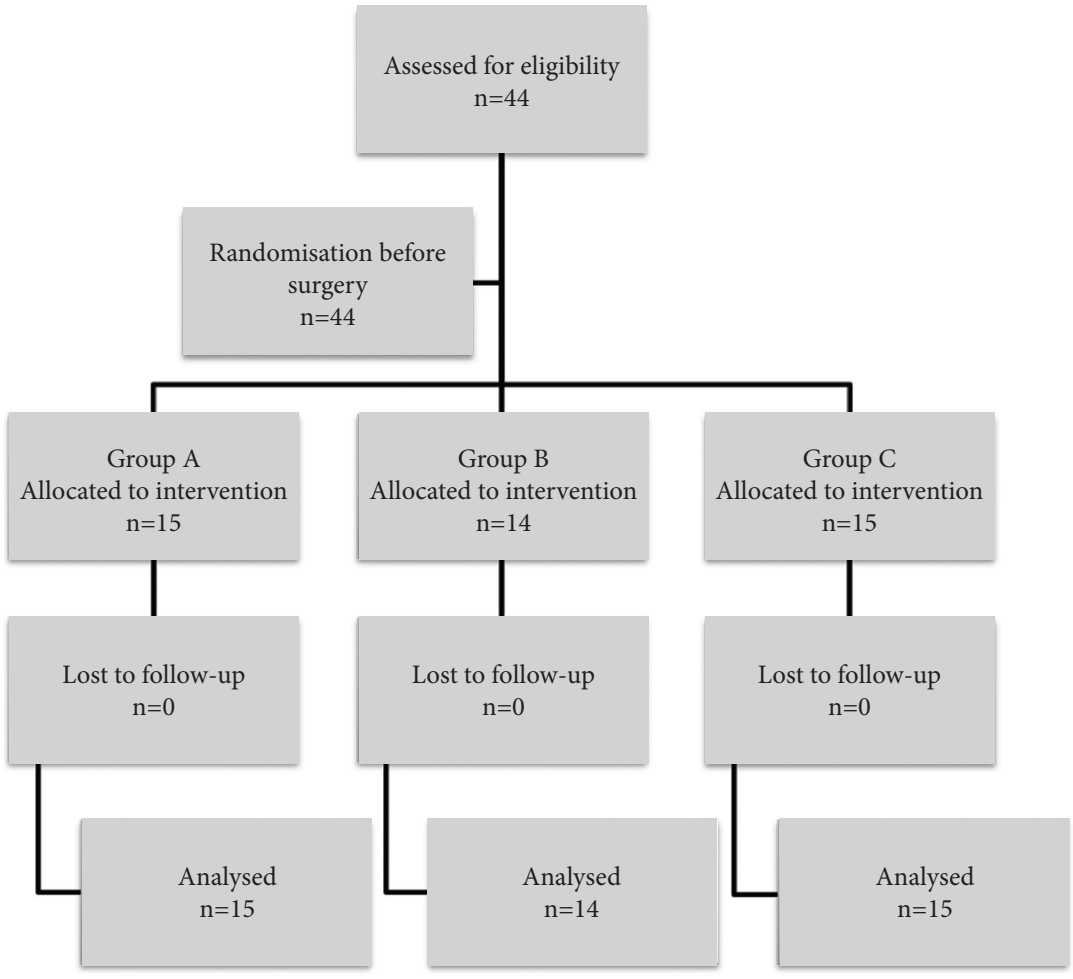

Figure 1. Consort flow diagram

Table 1. Patient characteristics, duration of surgery and size of incision

	Group A 1 mg morphine (n=15)	Group B 2 mg morphine (n=14)	Group C Control (n=15)	p
Age (year), mean (SD)	43.3 (11.0)	48.1 (13.0)	48.4 (14.7)	0.47
Gender (female/male) (n)	8/7	7/7	11/4	0.38
ASA (I/II) (n)	9/6	9/5	5/10	0.19
BMI, mean (SD)	27.0 (5.5)	28.3 (4.7)	28.5 (6.3)	0.73
Duration of surgery (min), mean (SD)	118.6 (47.1)	130 (59.9)	138.2 (51.6)	0.60
Size of incision (cm), median (IQR)	5 (5–6)	8 (5–10)	6 (5–10)	0.05*

*The size of the surgical incision was statistically longer in Group B than in Group A (p=0.05). n: number

The study groups were similar with respect to age, gender, ASA physical status scores, BMI and duration of surgery. The size of the surgical incision was statistically longer in Group B than in Group A (p=0.05) (Table 1).

The cumulative morphine consumption was not statistically different among the groups (Figure 2).

The groups were statistically similar with respect to VAS scores (Figure 3).

There was no statistically significant difference with respect to opioid-related side effects (p=0.71 for nausea and vomiting and p=0.37 for pruritus and rash among the groups) (Table 2).

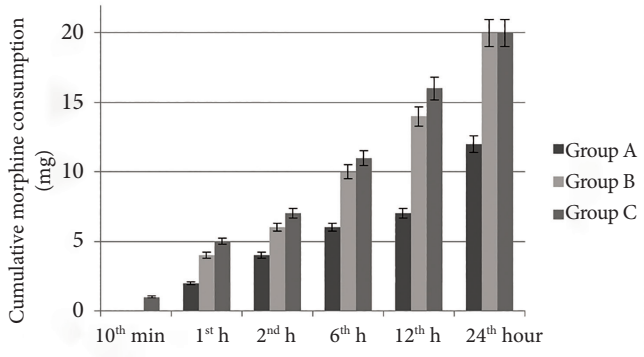

Figure 2. Cumulative morphine consumption. The cumulative morphine consumption was not statistically different among the groups (p>0.05)

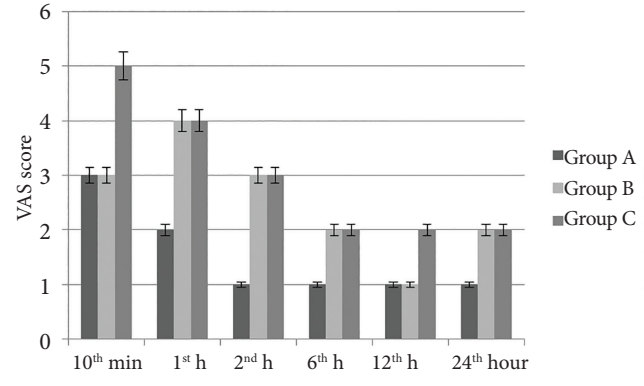

Figure 3. VAS scores. The groups were statistically similar with respect to VAS scores (p>0.05)
VAS: visual analogue scale

The groups were similar with respect to HR, MAP and Ramsey sedation scores.

Discussion

The present study showed that locally administered morphine over the dura did not decrease postoperative morphine consumption after lumbar disc surgery. Although a statistically significant difference was not observed among the groups, the lowest morphine consumption was observed in Group A (1 mg morphine); moreover, morphine consumption was almost the same in Group B (2 mg morphine) and Group C (control). This result may be due to the longer surgical incision size in Group B (2 mg morphine). Pain scores were also lower in Group A (1 mg morphine) than in Group B (2 mg morphine) and Group C (control), but the differences were not statistically significant.

Perioperative multimodal pain management aims to provide analgesia by different neurophysiological pathways and to reduce opioid consumption, side effects and abuse. Many different modalities, such as regional and local techniques, are described for this purpose (13-16). Mastronardi et al. (17) placed 1 mg morphine-impregnated anti-adhesion gel (Adcon-L®; Gliatech Inc., Cleveland, OH, USA) over the dura after lumbar discectomy and found that analgesic requirements are lower than the control group. Wilartratsami et al. (18) placed 1 mg morphine-impregnated microfibrillar collagen sponge over the intact dural sac during single level posterior lumbar laminectomy and instrumented fusion operation and found that postoperative morphine consumption is lower than the control group during 24 h. The common feature of all of these materials is that they are composed of absorbable materials when placed in the tissue. These materials are preferred to achieve prolonged analgesic activity by the slow release of morphine. Although it is thought that the analgesia is provided by the effects of morphine on the dorsal root ganglia, a more probable mechanism of action is the opioid receptors that increase with inflammation due to surgical incision (17). The difference with these studies and our results may be due to our material properties and the ability of morphine absorbance. The material that we use in our institution may not be appropriate for this purpose. We recommend the use of gel or sponge materials for future studies.

Table 2. Opioid-related side effects

	Group A 1 mg morphine (n=15)	Group B 2 mg morphine (n=14)	Group C Control (n=15)	p
Nausea–vomiting (n)	6	6	4	0.71
Pruritus–rash (n)	3	0	0	0.37

The groups were statistically similar with respect to opioid-related side effects (p>0.05). n: number

Wu et al. (4) placed 1 mg morphine-impregnated microfibrillar haemostasis sponge (Avitene®; Davol Inc., Cranston, RI, USA) on the dura at the end of the posterior lumbar spinal decompression and fusion operations and reported that pain scores are similar with IV morphine PCA and are statistically lower than intramuscular meperidine. Chen et al. (19) found that 3 mg morphine and 80 mg methylprednisolone-impregnated microfibrillar collagen placed over the dural sac improve pain scores after lumbar multilevel laminectomy. Mastronardi et al. (17) found that pain scores are statistically lower in the 1 mg morphine-impregnated anti-adhesion gel (Adcon-L®) group than in the control group in lumbar discectomy. Wilartratsami et al. (18) also found that pain scores are lower in the 1 mg morphine-impregnated microfibrillar collagen sponge group than in the control group. We did not observe a statistically significant difference with respect to pain scores among the groups. Pain scores were <5 in all groups. Spinal fusion surgery is one of the most painful surgeries (20). Different results in pain scores may be due to the difference in the types of surgery. Our study was single level lumbar discectomy, whereas other previous studies were spinal decompression with instrumented fusion operations where pain intensity could be more severe.

The systemic administration of opioids even with PCA is associated with dose-dependent side effects, such as sedation, respiratory depression, nausea, vomiting and ileus (21). It is demonstrated that a low dose of epidural morphine administration (10–20 μg kg^{-1}) provided adequate analgesia, but vomiting was not reduced even with low dose (22). We evaluated two doses of morphine in our study and did not find any difference with respect to side effects. Wu et al. (4) found postoperative nausea and vomiting to be lower in the morphine-impregnated microfibrillar haemostasis sponge (Avitene®) group than in the IV morphine PCA group. We administered prophylactic antiemetic ondansetron intraoperatively, and they used IV morphine PCA continuously; therefore, postoperative nausea and vomiting were lower in our study than in Wu et al.'s study (4).

Our study groups were similar with regard to age, gender, ASA physical status scores, duration of surgery that may have influence on postoperative pain scores and development of opioid-related side effects (23-28).

The present study has some limitations. First, it is powered to determine a 10% difference in morphine consumption; perhaps a bigger sample size was needed to analyse the difference in pain scores. Second, remifentanil as analgesic was used intraoperatively. Remifentanil is supposed to have an opioid-induced hyperalgesia (OIH) effect and may cause acute opioid tolerance that may confound our results (29). The activation of spinal N-methyl-D-aspartate receptors by pure μ receptor agonists, such as remifentanil, is proposed as the main mechanism of OIH (30). Intraoperative remifentanil infusion was found to be associated with increased early (within postoperative 4 h) postoperative pain and morphine requirements (31). The higher pain scores in the early postoperative period in our study might be due to this effect.

Conclusion

Morphine-impregnated absorbable cellulose haemostat material (Surgicel®) placement over the dura did not reduce postoperative morphine consumption, pain scores and incidence of opioid-related side effects; more larger sample-sized studies are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine (83045809-604.01.02; 5 January 2017).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – O.K., Y.T. Design – O.K., Y.T.; Supervision – Ö.K.D., Y.T. ; Resources – Ö.K.D., Y.T. Materials – O.K.; Data Collection and/or Processing – O.K. ; Analysis and/or Interpretation – O.K., E.F.A., Ö.K.D., Y.T.; Literature Search – O.K.; Writing Manuscript – O.K., Ö.K.D., Y.T., E.F.A.; Critical Review – O.K.D., Y.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

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