The Effect of Epidural Low-Dose Morphine-Soaked Microfibrillar Collagen Sponge in Postoperative Pain Control after Laminectomy and Instrumented Fusion: A Randomized Double-Blind Placebo-Controlled Study

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Objective: *To evaluate the postoperative analgesic effect and postoperative nausea and vomiting (PONV) after using epidural low-dose morphine-soaked microfibrillar collagen sponge (MMCS), as compared with placebo.*
Material and Method: *A prospective randomized double-blind placebo-controlled study was performed on patients undergoing single-level posterior lumbar spinal decompression and instrumented fusion at the Department of Orthopedic Surgery, Siriraj Hospital, between August 2012 and December 2013. Patients were randomly allocated into two groups to receive either an epidural MMCS or an epidural normal saline-soaked microfibrillar collagen sponge (placebo). Intensity of pain, PONV, and total amount of morphine were recorded at 4, 24, 48, and 72 hours, postoperatively.*
Results: *The analgesic effect was enhanced significantly in the epidural MMCS group, as the amount of morphine used was statistically less than in the placebo group at 4 and 24 hours ($p<0.05$).*
Conclusion: *A single low-dose epidural MMCS is effective for pain control after posterior lumbar spinal surgery with a low incidence of PONV.*

Keywords: *Epidural morphine, Randomized controlled trial, Pain after spinal surgery, Microfibrillar collagen sponge*

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Posterior lumbar spinal surgery is a major operative procedure that causes intense postoperative pain. Multimodal analgesia is mandatory for patients undergoing this type of procedure[1-3]. The use of an opioid is common but carries many side effects, such as nausea, vomiting, and respiratory depression[1,2,4]. Patients who receive different opioid administrations may need varying opioid dosages and each route of opioid usage may have different rates of side effects[4]. It is a common practice to administer intravenous (IV) morphine as patient-controlled analgesia (PCA) and oral analgesics to patients undergoing posterior lumbar spinal surgical procedures[1,4,5].

Epidural opioid usage is a common practice for postoperative pain control[4,6,7]. Epidural infusion, using local anesthetics with or without opioid, is effective for pain control, although it may impede mobilization in some patients. Fisher et al reported the effectiveness of IV-PCA fentanyl and patient-controlled epidural analgesia (PCEA) with fentanyl and bupivacaine in patients undergoing lumbar spinal surgeries[4]. Joshi et al found that continuous epidural fentanyl infusion is superior to IV-PCA morphine, in terms of pain control[7]. In 2011, Wu et al demonstrated that epidural low dose MMCS placed over the dural sac is effective for postoperative pain control in posterior lumbar spinal surgery, while carrying a low rate of side effects[8]. However, the retrospective nature of their study and the variety of surgical procedure may contain bias and other uncontrolled factors.

The purpose of the present study is to evaluate the postoperative analgesic effect of epidural MMCS and the side effects, including nausea and vomiting, pruritus, and respiratory depression.

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Material and Method

The present study was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital (COA: Si387/2012). Study populations included degenerative spondylolisthesis patients undergoing single level laminectomy and instrumented fusion in Siriraj Hospital from August 2012 to December 2013. Exclusion criteria were opioid or sulfonamide allergy, American Society of Anesthesiologists (ASA) physical status classification ≥3, body mass index (BMI) ≥35, pre-operative opioid use within 6 weeks, and intra-operative blood loss >1,000 ml.

Nineteen patients were enrolled in the present study and randomly allocated into two groups. In the study group, 1 ml of 1 mg morphine was applied to the microfibrillar collagen sponge and placed over the intact dural sac. The control group was treated in the same manner but 1 ml of normal saline was applied instead. All patients were counseled by the orthopedists one day before surgery. Patient understanding and apprehension regarding IV-PCA were evaluated and a computerized randomization was performed. All patients and surgeons were blind to the treatment.

All operative procedures were performed using a standard posterior midline approach. All patients underwent single-level laminectomy and instrumented fusion using local bone graft and pedicle screw and rod system. The wound was irrigated and meticulous hemostasis was achieved. At that time, the scrub nurse checked and prepared the soaked microfibrillar collagen sponge (2.5 x 2.5 cm^2) according to the computerized randomization. The surgeon placed it over the surface of the dural sac and Gelfoam (Johnson & Johnson Medical Ltd., Livingston, United Kingdom) was placed over the sponge. A vacuum drain was placed and the wound was closed within 30 minutes.

Postoperative pain control for all patients included IV morphine PCA, acetaminophen 500 mg per oral (PO) every 6 hours, celecoxib 400 mg PO once on the day after the operation, and 200 mg PO per day for the next 2 days. IV morphine PCA was set up (PCA bolus dose of 1 mg, 5-minute lockout, no basal rate) and connected to the patient immediately in the Post Anesthesia Care Unit (PACU). No prophylaxis was administered for pruritus or nausea and vomiting. All ward nurses were familiar with surgical nursing care for spinal surgery patients and the assessment of postoperative pain and side effects of opioids.

Data were collected, including gender, age, BMI, underlying diseases, ASA classification, operative time, and perioperative blood loss. All patients were evaluated for pain intensity, nausea and vomiting, pruritus, respiratory depression, and hypotension by orthopedists, Acute Pain Service (APS) nurses, and ward nurses. All evaluators were blind to the treatment given to the patients. Timely assessment was performed at 4, 24, 48 and 72 hours after operation. Time to first needed IV morphine PCA and accumulated amount of morphine were recorded. Patients rated their pain intensity using verbal rating scale (VRS) score from 0 to 10, with 0 = no pain and 10 = worst pain imaginable. The evaluators rated pruritus and nausea and vomiting scores from 0 to 3, with 0 = none; 1 = mild, no medication required; 2 = medication required; 3 = not relieved with regular medication.

Statistical analysis

A sample size calculation was performed using 24-hour pain scores of an epidural MMCS and IV-PCA group, as described in a study by Wu et al. As determined by the calculation, eight patients per group were required for this study. Data were analyzed using SPSS version 16.0. Continuous variables were analyzed using the Student's t-test. Categorical variables were analyzed using the Chi-squared test. A *p*-value of less than 0.05 was considered statistically significant.

Results

Demographic data are presented in Table 1 and overall results are presented in Table 2. There were no significant differences between the groups in terms of gender, age, underlying diseases, ASA classification,

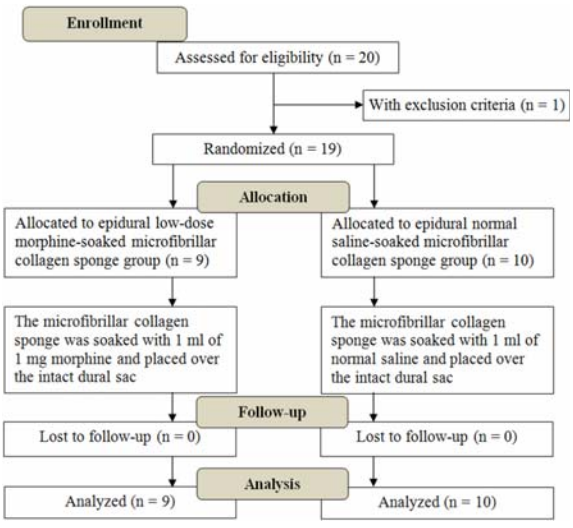

Fig. 1 CONSORT flow diagram.

Table 1. Demographic and perioperative data

	MMCS (n = 9)	Placebo (n = 10)	*p*-value
Gender: female	9 (100)	6 (60)	0.054
Age (years)	57.3±10.9	57.3±7.6	0.994
ASA classification			0.484
1	3 (33.3)	5 (50)	
2	6 (66.6)	5 (50)	
Underlying diseases			
Hypertension	5 (62.5)	1 (16.7)	0.050
Diabetes mellitus	1 (12.5)	2 (33.3)	0.542
Dyslipidemia	2 (25)	3 (50)	0.556
Operative time (min)	176.1±37.3 (110-210)	184.5±44.4 (120-250)	0.663
Postoperative bleeding (ml)			
4 hr	65.6±39.4	87.1±45.9	0.290
24 hr	158.9±103.3	167.0±107.8	0.869
48 hr	62.2±57.2	70.0±76.9	0.807
72 hr	6.7±10.0	15.0±21.7	0.295

Values are number (percentage) and mean ± SD (min-max)

Table 2. Pain scores, numbers of patients who had no nausea and vomiting and no pruritus, time to first morphine injection, and accumulated amount of morphine use

	MMCS (n = 9)	Placebo (n = 10)	*p*-value
Pain scores			
4 hr	2 (1.5, 4.3)	3 (1.4, 6.0)	0.199
24 hr	2 (1.8, 3.7)	3.5 (1.7, 4.7)	0.299
48 hr	0 (0.7, 1.8)	2 (0.7, 2.3)	0.357
72 hr	0 (0.4, 1.7)	2 (0.6, 2.4)	0.106
Nausea and vomiting score = 0			
4 hr	8 (88.9)	8 (80)	0.622
24 hr	5 (55.6)	9 (90)	0.212
48 hr	7 (77.8)	10 (100)	0.211
72 hr	7 (77.8)	8 (80)	0.667
Pruritus score = 0			
4 hr	9 (100)	9 (90)	0.526
24 hr	9 (100)	9 (90)	0.526
48 hr	8 (88.9)	10 (100)	0.474
72 hr	9 (100)	10 (100)	-
Time to first morphine injection (min)	57.9±34.3 (25-137)	47.6±29.1 (19-110)	0.489
Accumulated amount of morphine use (mg)			
4 hr	5.3±2.1 (3-9)	16.5±5.4 (11-27)	<0.001
24 hr	18.8±6.8 (10-29)	38.7±21.0 (13-69)	0.016
48 hr	28.1±14.9 (10-52)	49.5±30.6 (16-99)	0.070
72 hr	31.2±31.5 (10-51)	56.2±38.3 (19-124)	0.079

Values are median (95% CI), number (percentage) and mean ± SD [min-max]

operative time and postoperative bleeding. Pain scores revealed no significant differences between the two groups. The number of patients who had no vomiting or pruritus showed some difference, but the difference was not statistically significant. The accumulated amount of morphine used at 4 and 24 hours was significantly less in the MMCS group than in the placebo group. There were no patients with respiratory

depression or hypotension in either group.

Discussion

Multimodal postoperative pain control is effective for spinal surgery. However, dose-dependent opioid side effects have been the concern of postoperative opioid usage[1]. There have been many techniques for multimodal pain management in spinal surgery and the use of an epidural opioid was an alternative option[4,5,7-13]. Epidural morphine is a good alternative option for pain control after spinal surgery and many researchers reported its safety and efficacy[3,7,9,14]. Epidural catheter insertions for pain medication were useful for postoperative pain control although this technique might cause serious complications, such as respiratory depression[14], epidural hematoma, or infection. Epidural MMCS was performed to eliminate such complications. In the present study, there was no infection in either of the groups of interest. The authors administered oral analgesics to both groups in the same manner. IV-PCA morphine without basal rate was used as a pain rescuer to reflect the efficacy of epidural low-dose MMCS. The authors found that morphine consumption for one-level laminectomy and instrumented fusion was reduced at 4 and 24 hours. There was also a trend towards lower morphine use at 72 hours, postoperatively. The authors reported the accumulated amount of morphine together with the side effects and pain scores at 4, 24, 48 and 72 hours postoperatively, because it was practical for clinical application. A low dose of epidural MMCS appeared safe as no patients in the MMCS group had respiratory depression or deep sedation. Wu et al reported lower PONV rates from epidural MMCS when compared to IV-PCA. The present study revealed low rates of PONV in both groups. Reduced morphine use may reduce its dose-dependent side effects, but the present study could not show the difference between the groups because the number of patients was too small. Our sample size was calculated from the pain score difference, so our study could not prove any differences in the incidence of side effects between the groups. The extended effect of epidural morphine may be due to the hydrophilic property of morphine and the stabilized clotting effect of the microfibrillar collagen sponge.

Conclusion

This randomized double-blind placebo-controlled study revealed that epidural low-dose morphine-soaked microfibrillar collagen sponge was effective as part of multimodal pain control for single-level posterior lumbar laminectomy and instrumented fusion.

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Potential conflicts of interest

None.

References

1. Garcia RM, Cassinelli EH, Messerschmitt PJ, Furey CG, Bohlman HH. A multimodal approach for postoperative pain management after lumbar decompression surgery: a prospective, randomized study. J Spinal Disord Tech 2013; 26: 291-7.
2. Mathiesen O, Dahl B, Thomsen BA, Kitter B, Sonne N, Dahl JB, et al. A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. Eur Spine J 2013; 22: 2089-96.
3. Sekar C, Rajasekaran S, Kannan R, Reddy S, Shetty TA, Pithwa YK. Preemptive analgesia for postoperative pain relief in lumbosacral spine surgeries: a randomized controlled trial. Spine J 2004; 4: 261-4.
4. Fisher CG, Belanger L, Gofton EG, Umedaly HS, Noonan VK, Abramson C, et al. Prospective randomized clinical trial comparing patient-controlled intravenous analgesia with patient-controlled epidural analgesia after lumbar spinal fusion. Spine (Phila Pa 1976) 2003; 28: 739-43.
5. Yu L, Ran B, Li M, Shi Z. Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. Spine (Phila Pa 1976) 2013; 38: 1947-52.
6. Cata JP, Noguera EM, Parke E, Ebrahim Z, Kurz A, Kalfas I, et al. Patient-controlled epidural analgesia (PCEA) for postoperative pain control after lumbar spine surgery. J Neurosurg Anesthesiol 2008; 20: 256-60.
7. Joshi GP, McCarroll SM, O'Rourke K. Postoperative analgesia after lumbar laminectomy:

epidural fentanyl infusion versus patient-controlled intravenous morphine. Anesth Analg 1995; 80: 511-4.
8. Wu MH, Wong CH, Niu CC, Tsai TT, Chen LH, Chen WJ. A comparison of three types of post-operative pain control after posterior lumbar spinal surgery. Spine (Phila Pa 1976) 2011; 36: 2224-31.
9. Guilfoyle MR, Mannion RJ, Mitchell P, Thomson S. Epidural fentanyl for postoperative analgesia after lumbar canal decompression: a randomized controlled trial. Spine J 2012; 12: 646-51.
10. Gurbet A, Bekar A, Bilgin H, Korfali G, Yilmazlar S, Tercan M. Pre-emptive infiltration of levobupivacaine is superior to at-closure administration in lumbar laminectomy patients. Eur Spine J 2008; 17: 1237-41.
11. Hee HI, Tan YS, Hee HT. Commentary: Post-operative analgesia after lumbar laminectomy: is there a role for single-shot epidural fentanyl? Spine J 2012; 12: 652-5.
12. Klatt JW, Mickelson J, Hung M, Durcan S, Miller C, Smith JT. A randomized prospective evaluation of 3 techniques of postoperative pain management after posterior spinal instrumentation and fusion. Spine (Phila Pa 1976) 2013; 38: 1626-31.
13. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Fluoroscopic caudal epidural injections in managing post lumbar surgery syndrome: two-year results of a randomized, double-blind, active-control trial. Int J Med Sci 2012; 9: 582-91.
14. Kumar RJ, Menon KV, Ranjith TC. Use of epidural analgesia for pain management after major spinal surgery. J Orthop Surg (Hong Kong) 2003; 11: 67-72.

ผลของการใช้แผ่นใยคอลลาเจนชุบด้วยยามอร์ฟีนขนาดต่ำวางบน dural sac เพื่อระงับปวดหลังการผ่าตัด laminectomy และ instrumented fusion: การวิจัยเชิงทดลองแบบสุ่มและมีกลุ่มควบคุม

ศิริชัย วิลาศรัศมี, วิมลลักษณ์ สนั่นศิลป์, ธเนศ อริยะวัตรกุล, จตุพร โชติกวณิชย์, วิทเชษฐ พิชัยศักดิ์, อารีศักดิ์ โชติวิจิตร, ปัญญา ลักษณะพฤกษา

วัตถุประสงค์: เพื่อศึกษาผลการระงับปวดและอาการคลื่นไส้อาเจียนจากการวางแผ่นใยคอลลาเจน (microfibrillar collagen sponge) ชุบด้วยยามอร์ฟีนขนาดต่ำบน dural sac บริเวณที่ได้รับการผ่าตัด laminectomy และ instrumented fusion เปรียบเทียบกับยาหลอก

วัสดุและวิธีการ: ศึกษาเปรียบเทียบในผู้ป่วยที่เข้ารับการผ่าตัด laminectomy และ instrumented fusion ที่กระดูกสันหลังส่วนเอว 1 ระดับ ในโรงพยาบาลศิริราชช่วงเดือนสิงหาคม พ.ศ. 2555 ถึง เดือนธันวาคม พ.ศ. 2556 โดยแบ่งเป็นสองกลุ่ม กลุ่มศึกษาใช้แผ่นใยคอลลาเจน ชุบยามอร์ฟีน 1 มิลลิกรัมใน 1 มิลลิลิตรวางบน dural sac ส่วนกลุ่มควบคุมใช้น้ำเกลือแทนยามอร์ฟีนเก็บข้อมูลผลการระงับปวด อาการคลื่นไส้อาเจียน อาการคัน และปริมาณการใช้ยามอร์ฟีนทางหลอดเลือดดำ ที่ 4, 24, 48 และ 72 ชั่วโมงหลังการผ่าตัด

ผลการศึกษา: กลุ่มที่ใช้แผ่นใยคอลลาเจนชุบยามอร์ฟีนในขนาดต่ำวางบริเวณที่ได้รับการผ่าตัดใช้ยามอร์ฟีนทางหลอดเลือดดำปริมาณน้อยกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญทางสถิติที่ 4 และ 24 ชั่วโมงหลังการผ่าตัด

สรุป: การใช้แผ่นใยคอลลาเจนชุบยามอร์ฟีนในขนาดต่ำวางบริเวณที่ได้รับการผ่าตัด laminectomy และ instrumented fusion 1 ระดับมีประโยชน์ในการลดอาการปวดโดยมีอุบัติการณ์ของอาการคลื่นไส้อาเจียนต่ำ