Treatment of Pain after Spinal Surgery in the Recovery Room by Single Dose Lornoxicam: A Randomized, Double Blind, Placebo-Controlled Trial

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Background : *Lornoxicam has been used in microsurgical lumbar discectomy. However, there is no data about controlling pain after open discectomy or laminectomy.*
Objective : *To compare the efficacy of a single dose of 16 mg of lornoxicam for the treatment of pain after disectomy or laminectomy with placebo in the PACU.*
Study design : *Randomized, double blind, placebo-controlled trial.*
Material and Method : *Fifty-six patients who underwent disectomy or laminectomy were randomly allocated to receive 16 mg lornoxicam (Group L), or placebo (Group P) at the beginning of wound closure. Pain scores at rest (using a verbal numeric rating scale: VNRS 0-10), time to first analgesia requirement, morphine consumption during the first 2 hr after surgery and adverse effects were all recorded. The outcomes were assessed on admission to the PACU (T0), then at 1 (T1) and 2 (T2) hr after surgery.*
Results : *Baseline data were comparable between the two groups. The proportion of patients with VNRS > 5 at T0 in both groups were not significantly different (44.4% in group P vs 50.0% in group L, CI of difference: - 32.4%, 21.3%, p = 0.68). The mean VNRS scores, at T0 and T1 were > 5 and at T2 was < 5 in both groups. There was no difference between the two groups.*

The morphine consumption in both groups was not different (9.0 mg vs 9.3 mg) as well as the time to first analgesia requirement (35 min vs 40 min).

Patients in the two groups had no significant difference in the symptoms or degree of nausea/ vomiting. The number of patients with excessive sedation and the proportion of patients needing oxygen during transportation to the ward were not different.
Conclusion : *Lornoxicam 16 mg given intravenously before wound closure provides inadequate pain relief immediately after disectomy or laminectomy in the PACU. However, adequate pain relief was demonstrated at 2 hr after surgery, which was similar to the placebo.*

Keywords : *Lornoxicam, Postoperative pain, Spinal surgery, PACU*

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Many patients with lumbar spine surgery experience moderate to severe pain in the recovery room or post-anesthesia care unit (PACU). Although opioids are the traditional first-line treatment in this setting[1], this potential adverse effects often make physicians reluctant to increase the dosage to achieve adequate analgesia[2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) provide effective analgesia for acute pain after minor and major surgery as a substitute for or as an adjunct to opioid analgesia[3-12]. Lornoxicam, an NSAID belongs to the enolic acid chemical class shared by piroxicam and tenoxicam, has short plasma elimination half-life of 3-5 hr, which is suitable for

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acute use in the postoperative period. It has been used successfully for postoperative pain control in microsurgical lumbar discectomy[13]. However, there is no data about controlling pain after open discectomy or laminectomy in the PACU.

Since lornoxicam was the only intravenous NSAID the authors had at the time of this study, a randomized, double-blind, placebo controlled study was designed to assess the efficacy of a single intra-operative dose of 16 mg lornoxicam for postoperative pain relief after discectomy or decompressive laminectomy of the lumbar spine in the PACU. A fixed dose of 16-mg lornoxicam was chosen according to the result of a previous study that most patients had sufficient pain relief at this dosage[13]. The authors' hypothesis was that immediate postoperative pain would be less in the lornoxicam group.

Material and Method

Patients

The Ethics Committee of the Faculty of Medicine, Khon Kaen University, approved the protocol. The authors obtained written informed consent and enrolled 56 patients scheduled for discectomy or decompressive laminectomy (1 or 2 levels) of the lumbar spine: ASA physical status I-II, between 15 and 70 years of age. The authors excluded patients who had contraindications for, or were allergic to NSAIDs, known or suspected to be drug abusers and patients with a history of peptic ulcer. During the preoperative interview, patients were instructed how to assess postoperative pain by using the verbal numeric rating scale (VNRS) 0-10, 0 = no pain, 10 = the worst imaginable pain.

Anesthesia management

All patients received oral diazepam (5 mg) 2 hr before surgery. Morphine 0.15 $mgkg^{-1}$ and diazepam 0.1 $mgkg^{-1}$ were slowly given intravenously before induction of general anesthesia with thiopentone 4-5 $mgkg^{-1}$. After intubation with vecuronium 0.1 $mgkg^{-1}$, anesthesia was maintained with 70% nitrous oxide in oxygen, isoflurane 0.2-1.5% and vecuronium. During surgery, 2-mg morphine was given every 2.5 hr. The patients were extubated after reversal of muscle relaxant and then admitted to the PACU for 2 hr.

Study design and randomization

The study was a randomized, double blind, placebo controlled trial. By permutated block randomization using a computer generated random number, the patients were allocated to receive either 16 mg lornoxicam (Group L) or placebo (normal saline: Group P), respectively. The study drug was given intravenously at the beginning of surgical wound closure. In the PACU, supplemental analgesia was provided by 2 mg morphine IV for VNRS $\geq$ 5 every 5 minutes until VNRS score < 5 or patients required no more analgesia. Nausea and vomiting if occurred were treated with 10 mg intravenous metoclopramide.

Outcome measurements

Outcome measurements including pain scores (VNRS) at rest, time to first analgesia requirement, morphine consumption during 2 hr of the study and adverse effects such as sedation (4-point rating scale), nausea/vomiting (4-point rating scale) and oxygen supplement during transportation to the ward were all recorded. Excessive sedation was defined as sedation score $\geq$ 3. Outcomes were assessed on admission to the PACU as soon as patients regained consciousness (T0), then at 1 (T1) and 2 (T2) hr after surgery.

Statistics

The authors estimated the sample size required for testing the hypothesis that postoperative pain would be less in Group L than Group P. A 40% difference in the proportion of patients with VNRS > 5 at admission to the PACU was considered as clinically relevant. Based on the pilot study, the proportion of patients with VNRS > 5 was 80%. Therefore, a sample size of 27 patients per group was required to give 80% power, with a type I error of 0.05.

Descriptive statistics were used for demographic and clinical variables such as age, body weight and duration of anesthesia. The *Z* test with a 95% confidence interval was used to compare the proportion of VNRS > 5. To test the difference of VNRS and morphine consumption between the two groups, repeated measure ANOVA and student-t test were used, respectively. Time to first analgesia requirement was tested using survival analysis. The proportion of adverse effects was tested using the ^{2} test for trend. A $p < 0.05$ was considered statistically significant.

Results

Demographics

Between August 2001 and March 2003, 56 patients, 28 per group, fulfilling the inclusion criteria were recruited into the study. No patients dropped out before the end of the study. However, 2 patients

in Group L were deviated from the protocol by receiving additional fentanyl for postoperative analgesia. The authors were unable to obtain VNRS from 2 patients in Group L, one at T0, the other at T0 and T2 because of drowsiness. And one patient in Group P was unable to report VNRS at T0 and T1 for the same reason. Therefore, data for VNRS scores at T0, T1, T2 and morphine consumption were analyzed from the remaining 54, 53, 55 and 55 patients respectively.

The baseline characteristics of the patients in both groups regarding age, ASA status and duration of anesthesia were comparable, except for body weight and types of operation (laminectomy) which were slightly greater in Group L than Group P. Corresponding with the body weight, patients in Group L received a total dose of morphine intraoperatively more than Group P. The ratio of male to female was slightly greater in Group P than Group L (Table 1).

Pain relief

The proportion of patients with VNRS > 5 in both groups evaluated at T0, T1 and T2 was not significantly different, especially the main outcome which was VNRS > 5 at T0 (44.4% in Group P vs 50.0% in Group L, CI of difference:- 32.4%, 21.3%, p = 0.68) (Table 2).

The mean VNRS scores (Table 3), at T0 and T1 were > 5 and at T2 was < 5 in both groups. There was no significant difference between the two groups.

Table 1. Patients demographics

Characteristics	Group P (N = 28)	Group L (N = 28)
Age (yr)	49.7 ± 11.1	49.4 ± 11.1
Weight (kg)	59.4 ± 8.2	65.8 ± 10.4
Gender : Female	11 (39.4)	15 (53.6)
: Male	17 (60.7)	13 (46.4)
ASA status : I	15 (53.5)	15 (53.5)
: II	13 (46.4)	13 (46.4)
Type of operation		
Discectomy	16	11
Laminectomy	12	17
Duration of anesthesia (min)	122.3 ± 34.6	119.6 ± 42.0
Total dose of morphine during anesthesia (mg)	8.9 ± 1.2	9.6 ± 1.4
VNRS scores during venous cannulation	3.3 ± 1.8	3.5 ± 1.8

Data are presented as the mean ± SD and number (%) for gender and ASA status

Table 2. Proportion of patients with VNRS > 5

Measurement Time	Group P	Group L	Diff (CI)	P-value
T0	12/27 (44.4%)	13/26 (50.0%)	-5.5% (-32.4%,21.3%)	0.68
T1	13/27 (48.1%)	11/27 (40.7%)	-7.4% (-19.0%,33.8%)	0.58
T2	3/28 (10.7%)	3/27 (11.1%)	-0.4% (-16.8%,16.8%)	0.96

Data are presented as ratio (percent)

Table 3. Mean VNRS

Measurement Time	Group P	Group L	P-value*
T0	5.2 ± 3.9	5.0 ± 4.0	
T1	5.4 ± 2.9	5.9 ± 1.8	0.76
T2	3.9 ± 2.0	3.9 ± 1.5	

* Repeated ANOVA, Data are presented as the mean ± SD

Rescue medication

The morphine consumption evaluated at T1, and total morphine consumption evaluated at T2 were not significantly different between the two groups (Table 4).

The time to first analgesia requirement in the two groups was not significantly different. Five patients (2 in Group P, 3 in Group L) did not require morphine for analgesia during the first 2 hr after surgery. The survival curves of the time to first analgesia requirement of the two groups are shown in Fig. 1.

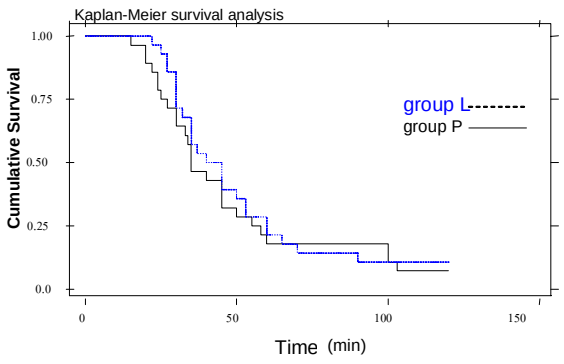

Fig. 1 The survival curve of the time to first analgesia of the two groups

Side effects

There was no significant difference in the symptoms or degree of nausea/vomiting (Table 5). Two patients in Group P and one in Group L had severe nausea/vomiting, which was successfully treated.

The number of patients with excessive sedation (sedation score $\geq$ 3) either at admission to or at discharge from the PACU in both groups was not different, but one patient in Group P developed upper airway obstruction which was successfully treated by insertion of an oral airway. According to the sedation score, the proportion of patients needing oxygen supplement during transportation to the ward in the two groups was not significantly different. Four patients (3 in Group P, 1 in Group L) had dizziness which improved without any medical treatment.

Table 4. Morphine consumption and time to first analgesia requirement

	Group P	Group L	P-value*
Morphine consumption at 1 hr	7.1 $\pm$ 4.9	6.7 $\pm$ 4.9	0.77
Total morphine consumption	9.0 $\pm$ 5.0	9.3 $\pm$ 6.0	0.86
Time to first analgesia Requirement (min)	35(32-53)	40(32-53)	0.52

* T- test, Data are presented as the mean $\pm$ SD and median (range) for time to first analgesia requirement

Table 5. Comparing the adverse events between the two groups

Adverse events	Group P (N=28)	Group L (N=28)	P value
Severity of Nausea/Vomiting			
Grade 1	1	3	
Grade 2	0	1	0.89*
Grade 3	2	1	
Excessive sedation at admission			
Score 3	8	11	0.40*
Score 4	3	3	
Excessive sedation at discharge			
Score 3	0	1	0.49*
Score 4	0	0	
Need oxygen supplement at ward	11(39.3%)	9(32.1%)	0.57**
Dizziness	3	1	

*Mann-Whitney *U*, ** Z –test for proportion, Data are presented as number, and proportion for oxygen supplement

Discussion

Non-steroidal anti-inflammatory drugs have been found to enhance analgesia by reducing pain scores and reducing the amount of morphine used for analgesia[14].

This study examined the effects of a single dose of lornoxicam given at the time of surgical wound closure for treatment of immediate postoperative pain after discectomy or decompressive laminectomy of the lumbar spine in the PACU. A dose of 16 mg was used according to the studies by Rosenow et al[13] and Staunstrup et al[12], which reported that this dosage was sufficient for the treatment of moderate to severe postoperative pain. Time to peak pain relief, also reported by Staunstrup et al, was about 30 min, which corresponded to the time the patients received the study drug until the patients gained good consciousness and reported reliable pain intensity measurements.

The proportion of patients with VNRS > 5 at T0 was 50% and the mean VNRS score was 5.2 in the lornoxicam group. It seemed that 16-mg lornoxicam given before closing the surgical wound was insufficient for the treatment of immediate postoperative pain in this setting. Some factors might have confounded the present results such as four patients in the lornoxicam group who were excluded from the analysis. Two of these patients received 25 g and 50 g of fentanyl (equivalent to 2.5 mg and 5 mg of morphine), the other two fell asleep, which meant that these four patients had low pain intensity. Patients with excessive sedation in the first hour of the study also had some effects on the results by reporting less reliable pain intensity than fully consciousness patients. However, this was an unavoidable factor because the more rescue morphine for analgesia needed, the more the result of excessive sedation. The different types of operation might have contributed some effects to the result as well, since the lornoxicam group had a higher number of laminectomy operation (more invasive than discectomy) than the placebo group.

There were a few limitations in this study. First, for the additive analgesic effect or multimodal analgesia, it has been suggested that a triad of opioids, NSAIDs and local anesthetic agents should be used[15]. The authors considered local infiltration but did not use this technique in this study because it was different from our routine practice. Although patients in the present study received morphine at a dose of 0.15 mg/kg before surgery and IV lornoxicam

at surgical wound closure, these pharmacologic interventions might not play enough action to prevent such painful stimuli. A combination of NSAIDs such as ketoprofen with propacetamol also produced additive analgesic effect shown by reduced pain scores after disc surgery as reported by Fletch et al[16]. Second, pain during movement was not assessed, because most of the patients in this setting were not ready to ambulate while they stayed in the PACU. Third, the power calculation in this study was based on a pilot study, in which 80 percent of the patients had VNRS > 5. However, only 44 percent of the patients in the placebo group actually had VNRS > 5, reflected that the sample size was smaller than expectation. The cause of the different results might be the additional dose of 2-mg morphine 2.5 hr after surgery in the study protocol.

The undesirable side effects of lornoxicam in this study could not be concluded. Although nausea/vomiting, excessive sedation and dizziness were frequently found, causes were hardly differentiated, because these symptoms were induced by rescue morphine as well as by lornoxicam. Therefore, the use of lornoxicam for a short duration, if indicated, was thought to be safe[17].

Conclusion

Lornoxicam 16 mg given intravenously before wound closure provides inadequate pain relief immediately after discectomy or laminectomy. However, adequate pain relief appeared 2 hr after surgery, similarly to the placebo group. To increase the efficacy of lornoxicam, a combination with other analgesic drugs such as local anesthetic agents and opioids, or given before the incision as preemptive analgesia should be considered.

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References

1. Schug SA, Merry AF, Acland RH. Treatment principles for the use of opioids in pain of nonmalignant origin. Drugs 1991; 42: 228-39.
2. Nuutinen LS, Laitinen JO, Salomaki TE. A risk-benefit appraisal of injectable NSAIDs in the management of postoperative pain. Drug Saf 1993; 9: 380-93.
3. Cashman J, McAnulty G. Nonsteroidal anti-inflammatory drugs in perisurgical pain management. Mechanisms of action and rationale for optimum use. Drugs 1995; 49: 51-70.
4. Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. Br J Anaesth 1991; 66: 703-12.
5. Perttunen K, Nilsson E, Kalso E. I.v. diclofenac and ketorolac for pain after thoracoscopic surgery. Br J Anaesth 1999; 82: 221-7.
6. Elhakim M, Amine H, Kamel S, Saad F. Effects of intraperitoneal lidocaine combined with intravenous or intraperitoneal tenoxicam on pain relief and bowel recovery after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2000; 44: 929-33.
7. Aubrun F, Langeron O, Heitz D, Coriat P, Riou B. Randomised placebo-controlled study of the post-operative analgesic effects of ketoprofen after spinal fusion surgery. Acta Anaesthesiol Scand 2000; 44: 934-9.
8. Gupta A, Axelsson K, Allvin R, Liszka-Hackzell J, Rawal N, Althoff B, Augustini BG. Postoperative pain following knee arthroscopy: the effects of intra-articular ketorolac and/or morphine. Reg Anesth Pain Med 1999; 24: 225-30.
9. Kostamovaara PA, Laitinen JO, Nuutinen LS, Koivuranta MK. Intravenous ketoprofen for pain relief after total hip or knee replacement. Acta Anaesthesiol Scand 1996; 40: 697-703.
10. Collins SL, Moore RA, McQuay HJ, Wiffen PJ, Edwards JE. Single dose oral ibuprofen and diclofenac for postoperative pain. The Cochrane Library, Oxford, Issue 2, 2003.
11. Smith LA, Carroll D, Edwards JE, Moore RA, McQuay HJ. Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis. Br J Anaesth 2000; 84: 48-58.
12. Staunstrup H, Ovesen J, Larsen UT, Elbaek K, Larsen U, Kroner K. Efficacy and tolerability of lornoxicam versus tramadol in postoperative pain. J Clin Pharmacol 1999; 39:834-41.
13. Rosenow DE, Albrechtsen M, Stolke D. A comparison of patient-controlled analgesia with lornoxicam versus morphine in patients undergoing lumbar disk surgery. Anesth Analg 1998; 86: 1045-50.
14. Reuben SS, Connelly NR, Steinberg R. Ketorolac as an adjunct to patient-controlled morphine in post-operative spine surgery patients. Reg Anesth 1997; 22: 343-6.
15. Jin F, Chung F. Multimodal analgesia for postoperative pain control. J Clin Anesth 2001; 13: 524-39.

16. Fletcher D, Negre I, Barbin C, Francois A, Carreres C, Falgueirettes C, Barboteu A, Samii K. Postoperative analgesia with i.v. propacetamol and ketoprofen combination after disc surgery. Can J Anaesth 1997; 44(5 Pt 1): 479-85.

17. Warrington SJ, Lewis Y, Dawnay A, Johnston A, Kovacs IB, Lamb E, Ravic M. Renal and gastrointestinal tolerability of lornoxicam, and effects on haemostasis and hepatic microsomal oxidation. Postgrad Med J 1990; 66 (Suppl 4): S35-40.

การรักษาอาการปวดภายหลังการผ่าตัดกระดูกสันหลังเปรียบเทียบระหว่างลอร์นอซิเคมกับยาหลอกโดยให้ก่อนเสร็จการผ่าตัด: การศึกษาแบบสุ่มปกปิดสองฝ่าย

สมบูรณ์ เทียนทอง, กิตติ จิระรัตนโพธิ์ชัย, วิมลรัตน์ กฤษณะประกรกิจ, สุธันนี สิมะจารึก, วัฒนา ตันทนะเทวินทร์, อักษร สาธิตการมณี

บทนำ *: Lornoxicam เป็น NSAIDs ชนิดฉีดทางหลอดเลือดดำชนิดเดียวที่มีในประเทศไทยในขณะทำการศึกษานี้ มีรายงานการใช้ lornoxicam ระงับปวดหลังผ่าตัดกระดูกสันหลังแบบ microsurgery ได้ผลดี แต่ยังไม่มีการศึกษาเกี่ยวกับการระงับปวดหลังผ่าตัดกระดูกสันหลังแบบเปิดซึ่งมีระดับความปวดปานกลางถึงรุนแรง จึงเป็นที่มาของการศึกษาในครั้งนี้ โดยมีสมมติฐานว่ายา lornoxicam สามารถระงับปวดหลังผ่าตัดได้ดีกว่ายาหลอก*

วัตถุประสงค์ *: เพื่อเปรียบเทียบผลการรักษาความปวดที่ห้องพักฟื้นและผลข้างเคียงของ lornoxicam 16 มก.กับยาหลอก เมื่อฉีดให้ทางหลอดเลือดดำครั้งเดียวก่อนสิ้นสุดการผ่าตัดกระดูกสันหลัง*

วิธีการศึกษา *: ศึกษาแบบ randomized-controlled trial ในผู้ป่วย 56 ราย โดยกลุ่มทดลอง (กลุ่ม L) จะได้รับยา lornoxicam 16 มก. ส่วนกลุ่มควบคุม (กลุ่ม P) จะได้ยาหลอกโดยฉีดทางหลอดเลือดดำเมื่อเริ่มเย็บปิดแผลผ่าตัด ประเมินอาการปวดขณะผู้ป่วยนอนพักโดยใช้ verbal numeric rating scale: VNRS 0-10 ที่เวลาแรกรับในห้องพักฟื้น (T0) และที่ 1 (T1) และ 2 (T2) ชั่วโมงหลังผ่าตัด บันทึกระยะเวลาที่ผู้ป่วยเริ่มขอยาระงับปวดครั้งแรก ปริมาณ morphine ที่ใช้ระงับปวด และอาการแทรกซ้อนที่เกิดขึ้น*

ผลการศึกษา *: สัดส่วนของผู้ป่วยที่มีระดับความปวด VNRS > 5 ที่เวลา T0 ระหว่างกลุ่ม P และกลุ่ม L ไม่แตกต่างกันทางสถิติ (44.4% vs 50.0%, CI of difference: -32.4%, 21.3%, P = 0.68) ระดับความปวดเฉลี่ย (Mean) ในผู้ป่วยทั้งสองกลุ่มพบว่าไม่แตกต่างกัน โดยที่เวลา T0 และ T1 พบมี VNRS > 5 ส่วนที่ T2 มี VNRS <5 ในผู้ป่วยทั้งสองกลุ่ม*

ระยะเวลาที่เริ่มขอยาระงับปวดครั้งแรกของทั้งสองกลุ่มพบว่าไม่แตกต่างกัน (35 นาทีในกลุ่ม P vs 45 นาทีในกลุ่ม L) เช่นเดียวกับปริมาณ morphine เฉลี่ยที่ใช้ในการระงับปวดใน 2 ชั่วโมงแรกหลังผ่าตัดของกลุ่ม P และกลุ่ม L พบว่าไม่แตกต่างกัน (9 มก. vs 9.3 มก.)

อาการคลื่นไส้อาเจียน ของทั้งสองกลุ่มพบว่าไม่แตกต่างกัน แต่จำนวนผู้ป่วยในกลุ่ม L มีอาการง่วงนอนที่เวลา T0 สูงกว่ากลุ่ม P เล็กน้อย (11 ราย vs 14 ราย) อย่างไรก็จำนวนผู้ป่วยที่ต้องการใช้ออกซิเจนในระหว่างการนำส่งผู้ป่วยกลับหอผู้ป่วยของทั้งสองกลุ่มไม่แตกต่างกัน

สรุป *: การให้ยา lornoxicam 16 มก. ฉีดก่อนเสร็จการผ่าตัดกระดูกสันหลังไม่สามารถลดสัดส่วนของผู้ป่วยที่มีความปวดในระดับ VNRS > 5 ในระยะเริ่มฟื้นจากยาสลบลงได้ อย่างไรก็ตามที่เวลา 2 ชั่วโมงหลังการผ่าตัดผู้ป่วยก็ได้รับการระงับปวดที่เพียงพอเช่นเดียวกับกลุ่มที่ได้รับยาหลอก*