Post-Op Pain and Blood Loss in Total Knee Arthroplasty: An RCT Using Periarticular Injection with Diclofenac-Based Multimodal Drugs

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Objective: *To study post-operative pain and blood loss after intraoperative periarticular injection with the multimodal drugs diclofenac, adrenaline, marcaine (bupivacaine) and morphine in total knee arthroplasty.*
Material and Method: *A prospective randomized controlled trial of knee osteoarthritis patients age more than 55 years undergoing total knee arthroplasty at Maharat Nakhon Ratchasima hospital from January 2011 through June 2012 was performed. A group receiving intra-operative periarticular injections was compared to a control group receiving no injections. Half of a group of forty-two patients, 2 males and 40 females, average age 67.9 years (range 57-84 years), were randomly assigned to receive the periarticular injection (the injection group), the others to the control group. Pain was measured by two methods: visual analog score at 6, 12, 24 and 48 hours post-operation and by patient controlled analgesia (PCA) measuring the daily amount of intravenous morphine used. The amount of blood loss post operation (in the redivac drain), degree of knee flexion, time to onset of assisted ambulation, length of hospital stay and any complications were also analyzed.*
Results: *The mean VAS at 6 and 12 hours post operation of the injection group were 2.67 and 2.48, whereas the values for the control group were 6.10 and 4.95, respectively ($p<0.05$). Mean quantities of morphine used by PCA by the injection group during the first day was 9.43 mg, significantly lower than the 18.81 mg used by the control group. Average blood loss of the injection group at 263.8 ml was also significantly below the 362.1 ml of the control group ($p<0.05$). The degree of knee flexion, time to onset of assist ambulation, length of hospital stay and complications, however, were not significantly different between the groups.*
Conclusion: *Multimodal drugs, periarticular injections consisting of diclofenac, adrenaline, Marcaine plus a patient controled anesthetic machine (PCA) with morphine can significantly reduce post-operative pain and blood loss in total knee arthroplasty without significant adverse effects.*

Keywords: *Periarticular injection, Multimodal drugs, Diclofenac, Total knee arthroplasty, Blood loss*

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Total knee arthroplasty is a major procedure that results in significant post-operative pain. Intraoperative periarticular multimodal drug injection during total knee arthroplasty has been reported to provide many advantages such as reduced analgesia requirements, improved patient satisfaction, safe provision of excellent pain control and functional recovery. Multimodal drug injection has even been used to replace conventional pain control modalities[1,2].

There are four main actions of most multimodal drugs used: bupivacaine for anesthetic effect, morphine as an opioid receptor agonist, adrenaline or epinephrine to induce vasoconstriction which prolongs the effect of local anesthetics and reduces blood loss, and ketorolac as an anti-inflammatory. In the present study, diclofenac replaced ketorolac. Diclofenac, like ketorolac, is an active form of aceclofenac but no study of diclofenac as part of a multimodal drugs therapy for periarticular injection in total knee arthroplasty has been accomplished.

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Material and Method

A prospective randomized controlled trial of patients diagnosed with osteoarthritis of the knee and undergoing unilateral total knee arthroplasty at Maharat Nakhon Ratchasima Hospital from January 2011 through June 2012 was performed. Inclusion criteria consisted of primary osteoarthritis, age over 55 years, and weight of 50 to 120 kg. Patients who had a history of major psychological problems, previous drug dependency, allergic reaction to any of the

ingredients in the injection, renal insufficiency, abnormal liver enzymes, a history of stroke or major neurological deficit, uncontrolled angina and bifascicular blocks with prolonged QT intervals or revision total knee arthroplasty were excluded. Sample size was calculated using the PS program which indicated that twenty one subjects for each group was sufficient. Using block randomization, 21 patients were assigned to the periarticular multimodal drug injection group and the other 21 patients were assigned to the control group.

Total knee arthroplasty was performed by an expert arthroplasty orthopedic surgeon using the midvastus approach and with the patient under spinal anesthesia. The anesthetic regimen was standardized for all patients. No long-acting analgesics were used, and spinal anesthesia was achieved using 10 to 15 mg of bupivacaine.

The multimodal drug injection contained diclofenac (75 mg) 3 ml, levobupivacaine (5 mg/ml) 20 ml, 5 mg of morphine, and 1 ml of adrenalin (1:1,000). In the operating room those were mixed with sterile normal saline solution to make up a combined volume of 100 ml. The first 50 ml of the mixture was injected just prior to implantation of the prosthesis into the posterior aspect of the capsule and the medial gutter, and the other 50 ml was injected at the lateral gutter, patella fat pad and tissues around quadriceps area. Care was taken to avoid excessive infiltration in the area of the common peroneal nerve.

All subjects received patient controlled analgesia (a morphine bolus of 1 mg with a lock-out of six minutes, and a maximum of 15 mg/hr) for forty-eight hours after the surgery. The consumption of patient-controlled analgesia was measured at different times during the forty-eight hour post-operative period, and the patient's overall analgesic consumption was measured and converted to morphine equivalents to allow for comparison between the two groups. The visual analog scale was also used to assess pain, both at rest and during activity, on the day of the surgery, in the post-anesthetic care unit and during the in-hospital period. The VAS scale for pain ranges from 0 (indicating no pain or completely satisfied) to 10 (indicating extreme pain or completely dissatisfied) in 1 unit increments. VAS scores at 6, 12, 24 and 48 hours post operation were analyzed.

Blood loss (measured from the redivac drain), the degree of knee flexion, time to onset of assisted ambulation and length of hospital stay were also analyzed. Any signs of cardiac or central nervous system toxicity or wound complications were specifically noted. Mann-Whitney U test by SPSS 13.0 was used to statistically to compare the continuous ordinal data between groups.

Results

Patients' mean age, body weight, pre-operative range of motion, pre-operative knee society score and pre-operative visual analog score are shown in Table 1. There were no statistically significant differences in these characteristics between the two groups.

Comparison of VAS, quantity of PCA morphine used, total blood loss and degree of knee flexion between the injection group and control group are shown in Table 2. Patients who received the diclofenac-based multimodal drug periarticular injection had significantly better post-operative pain relief, especially at 6 and 12 hours post-operation. Mean VAS scores (Fig. 1) were significantly lower in the injection group than in the control group at 6 and 12 hours post-operation (2.67 versus 6.10 and 2.48 versus 4.95, respectively). At 24 hours, the mean VAS of the injection group was still lower, but the difference was not statistically significant.

The mean of PCA morphine consumption by the two groups is shown in Fig. 2. The amount of morphine used within the first day by the injection group was 9.43 mg, significantly less than the 18.81 mg

Table 1. Characteristics of the injection group and the control group

Demographic variables	Injection group, mean (SD)	Control group, mean (SD)	*p*-value
Age (years)	68.9 (6.82)	66.8 (6.06)	0.441
Body weight (kg)	65.3 (14.13)	64.1 (12.80)	0.880
Pre op ROM (degree)	107.9 (31.17)	98.1 (29.30)	0.168
Knee society score	46.1 (12.89)	40.8 (16.19)	0.232
Pre op VAS	5.43 (1.502)	5.05 (1.465)	0.319

ROM = range of motion; VAS = visual analog scale

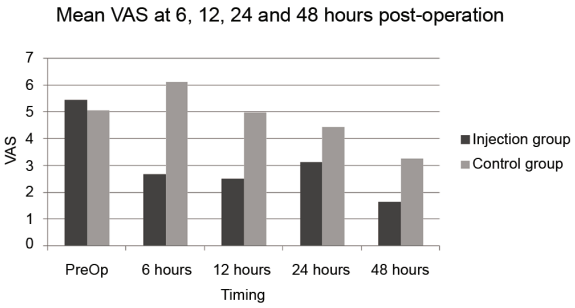

Fig. 1 Mean VAS pre op and at 6, 12, 24 and 48 hours post-operation.

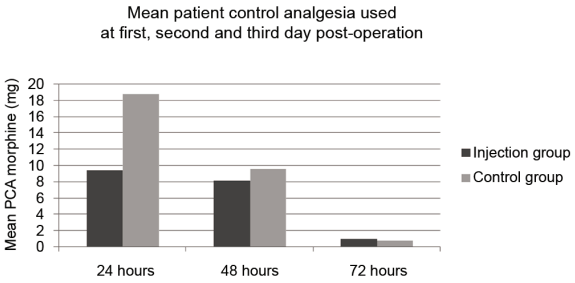

Fig. 2 Consumption of patient controlled analgesia at 24, 48 and 72 hours post-operation measured in milligrams of morphine used.

of the control group. However, there was no statistically significant difference in usage for the second or the third day post-operation.

There was a significant difference in average blood loss in the redivac drain between the injection group and control group: 263.8 ml vs. 362.1 ml, respectively. In addition, the mean degrees of knee flexion of the injection group was significantly better than the control group in the first, second and third day post-operation as shown in Table 2. However, there was no statistically significant difference between groups for time to onset of assisted ambulation or length of hospital stay. The time to onset of assisted ambulation of the injection group was 51.43 hours, while for the control group it was 60.57 hours; the average length of hospital stay of the injection group was 4.14 days whereas the control group average was 5.16 days. Two cases in each group had a serum oozing wound, one in each group had redness of the wound edge and one in the control group had a subcutaneous hematoma collection. None of the cases had adverse effects in their cardiac or central nervous system.

Discussion

According to studies of the pathophysiology of pain caused by surgical trauma, TKA was found to be a major procedure that is associated with considerable post-operative pain. Periarticular injection plays a role in the blockage of peripheral sensitization. Good pain relief is important for encouraging post-operative knee rehabilitation and may influence overall outcomes.

In 2006, Busch et al[1] reported on a randomized trial of the efficacy of periarticular multimodal drug injection in total knee arthroplasty. The multimodal drug given contained ropivacaine, ketorolac, morphine and epinephrine. Patients who received the injection used significantly less patient-controlled analgesia

Table 2. Comparison of VAS, PCA morphine, total blood loss and degree of knee flexion in the injection group and the control group

Variables	Injection group, mean (SD)	Control group, mean (SD)	*p*-value
VAS			
6 hours	2.67 (2.76)	6.10 (2.12)	0.000
12 hours	2.48 (3.03)	4.95 (2.73)	0.197
24 hours	3.10 (2.98)	4.43 (3.20)	0.055
48 hours	1.62 (2.09)	3.24 (2.84)	0.004
PCA morphine (mg)			
24 hours	9.43 (6.19)	18.81 (8.35)	0.000
48 hours	8.14 (7.94)	9.62 (7.72)	0.447
72 hours	0.95 (2.87)	0.76 (1.64)	0.742
Total blood loss (ml)	263.81 (139.91)	362.14 (166.71)	0.047
Degree of knee flexion			
1st day	43.6 (24.40)	24.3 (17.34)	0.005
2nd day	67.9 (26.39)	47.4 (18.07)	0.010
3rd day	88.1 (17.14)	70.0 (17.46)	0.000

VAS = visual analog scale; PCA = patient controlled analgesia

at six, twelve and twenty-four hours after surgery. In addition, their VAS for pain was lower during activity in the post-anesthetic-care unit and at four hours after the operation. No cardiac or central nervous system toxicity was observed.

In contrast, in 2011, Joo[4] reported a randomized double blind prospective study that found periarticular multimodal drug injection during total knee arthroplasty had no post-operative pain relief benefit.

The diclofenac-based periarticular injection in this study provided pain relief benefits, especially at six hours, twelve hours, and during the first day after total knee arthroplasty, the same outcome as reported by Busch. The pain relief may be a result of the half-life of the periarticular injection ingredients, the action of which could be prolonged for up to twenty-four hours.

It has been reported that the efficacy of ketolorac-based periarticular injection in pain relief is equivalent to spinal morphine but with fewer complications[5]. The present study, however, did not compare diclofenac-based periarticular injection to spinal morphine or to ketolorac-based periarticular injection. More studies of those options are needed.

Concerning post-operative blood loss, there has been disagreement about the effect of periarticular multimodal drugs in the reduction of bleeding. Bersanek et al[6] found no significant difference in post-operative blood loss with or without periarticular injection. Lombardi et al[7], however, reported that periarticular injection could decrease post-operative blood loss significantly. The reduction in blood loss in the present study might be due to the effect of epinephrine. As epinephrine was used as part of the ingredients in both control and study groups, there may be the other factors influencing bleeding after TKA. In any event, the relatively lower blood loss in the injection group in the present study was similar to the findings of Lombardi.

In terms of improvement of early post-operative knee ROM, Parvataneni et al[2] reported no significant differences with or without periarticular injection. That observation is contrary to the present study which found a significantly improved degree of knee flexion in the injection group during the early post-operative period. One reason for the better flexion in the injection group in the present study could be that the significantly improved pain relief in that group encouraged early rehabilitation. However, there was no significant difference in the time to onset of assist ambulation or length of hospital stay between the injection group and the control group.

Because of the low number of wound complications in both the injection group and the control group, it was not possible to determine if multimodal drug injection results in adverse effects on the wound. Further study with a larger number of patients is suggested.

Some doubts may remain regarding the safety of diclofenac-based periarticular injection. For example, Elron-Gross et al[8] reported on the beneficial local anti-inflammatory effect after periarticular injection of diclofenac of animal joints. Shakeel et al[9] compared local steroid injections to diclofenac injections in humans for treatment of trigger finger and found that diclofenac was effective and had no apparent adverse effects. In the present study, none of cases had immediate cardiac or central nervous system adverse effects. However, the patients in this study should be followed-up for longer term adverse effects and complications.

Conclusion

Intra-operative periarticular injection with diclofenac-based multimodal drugs can significantly reduce the requirement for patient-controlled analgesia and improve pain VAS in the first day post total knee arthroplasty. It can also decrease blood loss and promote early knee flexion with no apparent risk.

What is already known on this topic?

The periarticular injection techniques were used for post-operative pain in total knee arthoplasty but in difference medicine. Dicolfenac was not used for periarticular injection before. The efficacy of periarticular injection is better than control group.

What this study adds?

Diclofenac in periarticular injection give a good results in both pain control and bleeding control and without complication. The cost effective in diclofenac periarticular injection is better than other NSAIDs.

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Potential conflicts of interest

None.

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การศึกษาผลของการลดความปวดการเสียเลือดในการผ่าตัดเปลี่ยนข้อเข่าเทียมโดยใช้ยาผสมกับยา diclofenac ฉีดรอบ ๆ ข้อเข่า

มนูญ เลียวนรเศรษฐ, นฤพล เรืองศิลปานันต์

วัตถุประสงค์: เพื่อศึกษาผลการฉีดยาผสมรอบข้อ ประกอบด้วยยา diclofenac, adrenaline, marcaine และ morphine ในการลดความเจ็บปวด และการเสียเลือดหลังผ่าตัดเปลี่ยนข้อเข่าเทียม

วัสดุและวิธีการ: ทำการศึกษาแบบ prospective randomized controlled trial ในผู้ป่วยข้อเข่าเสื่อม อายุมากกว่า 55 ปี ได้รับการผ่าตัดเปลี่ยนข้อเข่าเทียมตั้งแต่ เดือนมกราคม พ.ศ. 2554 ถึง เดือนมิถุนายน พ.ศ. 2555 ที่โรงพยาบาลมหาราชนครราชสีมา เปรียบเทียบกลุ่มที่ได้รับการฉีดยาผสมรอบข้อระหว่างผ่าตัดกับกลุ่มควบคุมที่ไม่ได้ฉีด ประเมินความเจ็บปวดด้วย visual analog score ที่ 6, 12, 24 และ 48 ชั่วโมง และปริมาณ morphine ที่ผู้ป่วยใช้แบบ patient control analgesia วิเคราะห์ปริมาณเลือดที่สูญเสียทาง redivac drain พิสัยการงอเข่า ระยะเวลาก่อนเริ่มเดินด้วยเครื่องช่วยพยุงเดิน จำนวนวันนอนในโรงพยาบาล และภาวะแทรกซ้อน

ผลการศึกษา: ผู้ป่วย 42 ราย ชาย 2 ราย หญิง 40 ราย อายุตั้งแต่ 57-84 ปี เฉลี่ย 67.9 ปี กลุ่มฉีดยามีค่าเฉลี่ย VAS ที่ 6 และ 12 ชั่วโมง เท่ากับ 2.67 และ 2.48 ตามลำดับ ในขณะที่กลุ่มควบคุมมีค่าเฉลี่ย 6.10 และ 4.95 ($p<0.05$) กลุ่มฉีดยาผสมรอบข้อมีค่าเฉลี่ยของปริมาณ morphine ที่ใช้ในวันแรกหลังผ่าตัดเท่ากับ 9.43 มิลลิกรัม แตกต่างอย่างมีนัยสำคัญจากกลุ่มควบคุมซึ่งมีค่าเฉลี่ยเท่ากับ 18.81 มิลลิกรัม ค่าเฉลี่ยของปริมาณเลือดที่สูญเสียของกลุ่มฉีดยาผสมมีค่าเท่ากับ 263.8 มิลลิลิตร น้อยกว่ากลุ่มควบคุมซึ่งมีค่าเท่ากับ 362.1 มิลลิลิตร พิสัยการงอเข่าของกลุ่มฉีดยามากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ ไม่พบความแตกต่างของระยะเวลาก่อนเริ่มเดิน จำนวนวันนอนโรงพยาบาล และภาวะแทรกซ้อน

สรุป: การฉีดยาผสมรอบข้อซึ่งประกอบด้วยยา diclofenac, adrenaline, marcaine และ morphine ขณะผ่าตัดเปลี่ยนข้อเข่าเทียมสามารถลด ความเจ็บปวดและจำนวนเลือดที่สูญเสียหลังผ่าตัดได้อย่างมีนัยสำคัญโดยปราศจากผลไม่พึงประสงค์