Periarticular Infiltration of 0.25% Bupivacaine on Top of Femoral Nerve Block and Intrathecal Morphine Improves Quality of Pain Control after Total Knee Arthroplasty: A Randomized Double-Blind Placebo Controlled Clinical Trial

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Objective: *Find out if the addition of periarticular local anesthetic infiltration enhances the quality of postoperative pain control in patients with knee arthroplasty (TKA) in spinal anesthesia and intrathecal morphine plus single shot femoral nerve block (FNB).*

Material and Method: Ninety-nine patients scheduled for TKA under spinal anesthesia were enrolled after written informed consent, and randomized into two groups with either periarticular injection of 20 ml 0.25% bupivacaine (B-gr, n = 50) or isotonic saline solution (S-gr, n = 49). All patients had intrathecal morphine 0.2 mg and single shot FNB with 20 ml bupivacaine 0.25% and were adjusted postoperative analgesic requirement via patient controlled analgesia with morphine. Effect of postoperative pain control and requirement of additional analgesics were recorded.

Results: Randomization created comparable groups. Periarticular infiltration of bupivacaine in addition to femoral nerve block and intrathecal morphine was efficient and superior to saline regarding pain control, morphine consumption, and patient's satisfaction. More patients in B-gr did not require any supplement morphine in the first 24 hours (26% compared to 12.2%, $p \leq 0.01$). In patients who required morphine, B-gr had longer pain free period (25 hours compared to 14.8 hours, $p < 0.001$) and needed lower dose of morphine (5.16 mg compared to 8.67mg, $p = 0.005$). No significant side effects were recorded.

Conclusion: *Adding periarticular infiltration to femoral block and intrathecal morphine significantly enhances the quality of postoperative pain therapy in TKA patients. However, combining three methods for analgesic therapy may be too much effort. Modifying infiltration techniques including continuous application needs further research.*

Keywords: *Periarticular infiltration, Pain control, Knee arthroplasty*

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Pain after total knee arthroplasty (TKA) is a major concern as it is known to impair early rehabilitation[1]. An increasing number of reports have demonstrated significant improvement of postoperative pain control in arthroplasty of the knee thus leading to early rehabilitation and ambulation[2-4]. In Siriraj Hospital, more than 500 cases of TKA are performed each year. Intrathecal morphine for postoperative pain relief is routinely used since 1998. Single shot femoral nerve block was added to this method in 2002. Unfortunately, this combination leads to a pain free postoperative interval shorter than 24 hours. Approximately 60% of TKA patients need at least one dose of strong opioid during the first 12 to 24 postoperative hours, even when paracetamol, Dynastat™ or Arcoxia™ have been additionally administered immediately after operation. The routine use of IV PCA is desirable but limited due to costs and availability.

There is an increasing interest in periarticular local anesthetics infiltration for pain control after TKA; the method has been proven to be efficient and safe[5-7]. However, most of the studies were done in patients with general anesthesia. Furthermore, there are no conclusive suggestions yet which combination

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of analgesic methods may be most efficient and safe. Therefore, the authors conducted the present study adding periarticular bupivacaine infiltration to routinely applied intrathecal morphine and single shot femoral nerve block.

Material and Method

Study population and randomization

This is a randomized, placebo-controlled, double-blind trial conducted between December 2009 and May 2010, enrolling patients undergoing TKA at Siriraj Hospital. After approval by the Institutional Review Board, Siriraj Medical Center, one hundred consecutive patients scheduled for elective TKA were recruited.

Inclusion criteria were age 40 to 80 year, American Society of Anesthesiologists (ASA) physical status I-III, body mass index 20 to 35 kg/m^2, acceptance of spinal anesthesia, intrathecal morphine, femoral nerve block, and periarticular infiltration. Additionally, there had to be no history of drug allergy to local anesthetics, analgesic drugs, and adjuvant drugs. All participants could read, understand and communicated well with evaluation techniques. Patients were excluded if they were not suitable for spinal block for anatomical or functional (neurologic) reasons, and if they were already suffering from severe knee pain (pain score > 5 at rest) prior to surgery.

Patients were recruited with written informal consent the day before surgery and written informal consent were obtained. Blocked of four randomization were generated by a computer program. Scaled envelopes of sequential numbers were used and opened only by the investigational drugs service who prepared sterilized 20 ml syringes with either 0.9% isotonic saline solution (Group S) or 0.25% bupivacaine (Group B). The syringes were handed to the intra-operative nurse for periarticular injection. After prosthesis implantation, before joint capsule closure, 20 ml of 0.25% bupivacaine or 0.9% saline solution were injected along the borders of and into anterior joint capsule, infrapatellar ligament, the cruciate ligaments, and soft tissue surrounding the joint.

Femoral block and spinal anesthesia

Every patient received balanced crystalloid solution 80 to 100 ml/hour started in the morning of the operation day. On patient's arrival to the operating room baseline vital signs monitoring, such as automatic non-invasive blood pressure measurement, pulse oximetry and EKG was applied. Femoral nerve block (FNB) was performed with 50 mm, 22 gauge insulated needle (Stimuplex™ A; B Braun) by one of the authors experienced in the technique using nerve stimulator (Stimuplex® HNS II; B Braun, Melsungen, Germany). Successful location was indicated by quadriceps motor response and ascension of patella with cessation of contraction at ≤ 0.5 mA. 20 ml of 0.25% bupivacaine were injected. In all patients, sensory block was verified by loss of cold sensation, reduced sensibility of the skin at anterior part of knee and thigh, and inability to flex knee.

Spinal anesthesia was performed in lateral decubitus position at L2-L3 or L3-L4. Hyperbaric bupivacaine (0.5% in 8.75% dextrose) and 0.2 mg morphine, totally 2.5 to 3 ml were administered intrathecally via 26-gauge pencil-point spinal needle. Intraoperative sedation was limited to 2.5 mg midazolam IV.

Pain therapy and data collection

After operation patients, were placed on intravenous patient controlled analgesia (PCA) for 48 hours with no basal rate, morphine one milligram available every five minutes and a maximal dose of four milligram in four hours. In addition, all patients received oral paracetamol 1,000 mg every six hours for five days. Finally, intravenous Dynastat™ 40 mg was given 12 and 24 hours after operation plus Arcoxia™ 120 mg daily for three days. Ondansetron 8 mg intravenously was started intraoperatively and continued postoperatively every eight hours for two days. For treatment of pruritus and nausea/vomiting Chlorpheniramine 10 mg and metoclopramide 10 mg respectively were ordered.

Postoperatively patients were evaluated by a research assistant at 2, 6, 12, 24, and 48 hours to evaluated numeric rating scale of pain, sensory and motor recovery from spinal anesthesia and femoral nerve block, occurrence and severity of side effects. Morphine consumption and time of demand were recorded. In addition overall pain scores after 24 and 48 hours was evaluated, judging the effectiveness of pain control by "Patient Global Assessment, PGA" in four levels, 'excellence, good, acceptable and bad' together with "Patient satisfactory visual analogue scoring".

Earlier observations within our department showed that 60% of patients with TKA under spinal anesthesia with intrathecal morphine 0.2 mg and femoral nerve block, evaluated pain control 'excellent' or 'good'. Our primary objective of this study was if

the addition of periarticular infiltration with 0.25% bupivacaine 20 ml could increase this ratio from 60 to 75%.

Statistics

Using analysis of variances for comparison of continuous variables, with a two-sided α of 0.05 and equivalence margin of β at 0.10 (power 90), minimal sample size amounted to 44 patients each group. For drop out risk from the failure of FNB or spinal block, 50 patients on each group were designed. Data were recorded and analyzed by SPSS version 11.5. Descriptive statistics were used to analyze demographic variables. Chi-square was used for categorical variable and for continuous variable the used of student-t-test or Mann Whitney U-test was use according to the data distribution. The survival curve analysis was used to analyze the consumption of morphine and its first postoperative requirement. P-value of less than 0.05 was considered statistically significant.

Results

One hundred patients joined the present study after informed consent, being randomly allocated to two groups with 50 each. One patient (S-gr) changed her mind before operation and was excluded, thus reducing the group to 49. All patients were operated by one of three experienced surgeons (Table 1).

There were no significant differences between the two groups regarding sex, age, body mass index, ASA Classification, and operative time (Table 1). Laboratory data did not show any abnormalities.

Resting NRS pain scores in the bupivacaine group (B-gr) were significantly lower than those of the saline group (S-gr) at 6 and 12 hours postoperatively, but did not differ at 24 and 48 hours (Table 2). Thirteen B-group patients (26%) did not require supplement morphine within the first 24 hours, which was significantly higher compared to S-group (6 cases; 12.24%, $p \leq 0.01$). Mean pain free period was significantly ($p < 0.001$) longer in B-group (25 ± 2 hours, 95% CI = 21.1, 28.9) compared to S-group (14.8 ± 1.9 hours, 95% CI = 11.1, 18.5). This finding is confirmed by survival analysis (Fig. 1). Thirty-seven patients in group B needed 'rescue' morphine compared to 43 S-group patients, with no differences in the single dosages used. The average morphine consumption in group B was significantly lower (Table 2) within the first 24 postoperative hours ($p = 0.005$).

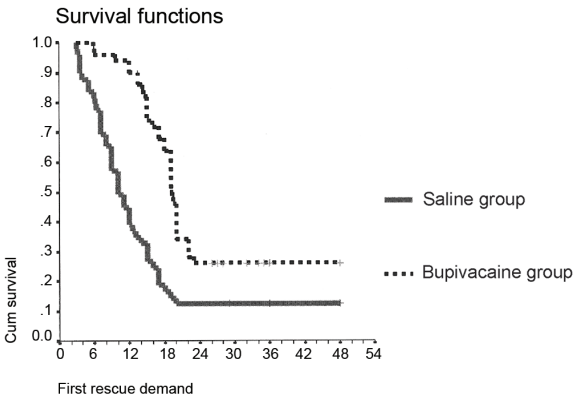

Fig. 1 Survival curve of first rescue demand between infiltration with 20 ml of 0.25% bupivacaine and 0.9% saline

Satisfactory score for post-operative pain control in patients with bupivacaine (B) was

Table 1. Demographic data

	Group B (n = 50)	Group S (n = 49)	p-value
Age (yr)	70.54 ± 6.71	68.16 ± 7.81	0.11
Sex (female:male)	47:3	44:5	0.45
Body weight (kg)	64.77 ± 10.65	63.36 ± 10.65	0.52
Height (cm)	155.11 ± 6.55	152.46 ± 7.29	0.06
Body mass index	26.82 ± 3.33	27.13 ± 3.47	0.65
ASA (1:2)	3:47	7:42	0.36
Operative time (min)	111.90 ± 29.31	115.00 ± 32.77	0.62
Site of operation (right:left)	22:28	23:26	0.77
Surgeon			
Dr K	28	27	0.69
Dr P	11	10	
Dr W	11	12	

Table 2. VAS and morphine consumption

	Group B (n = 50)	Group S (n = 49)	p-value
Postoperative VAS at			
6 hours	0.38 ± 0.80	1.04 ± 1.64	0.01*
12 hours	0.90 ± 1.36	1.71 ± 1.80	0.01*
24 hours	2.06 ± 1.72	2.69 ± 1.96	0.09
48 hours	2.24 ± 1.71	2.51 ± 1.83	0.45
Morphine consumption (mg), mean ± SD (range)			
First 24 hours	5.16 ± 4.65 (0-18)	8.67 ± 7.26 (0-40)	0.005*
24-48 hours	11.10 ± 8.88 (0-40)	11.76 ± 11.25 (0-67)	0.72
Number of patients			
No morphine in 24 hr	13 (26%)	6 (12.24%)	<0.001*
Survival time (hr)			
Mean	25.0 ± 2.0	14.8 ± 1.9	<0.001*
Range	21.1-28.9	11.1-18.5	
Median	19.0 ± 0.5	10.0 ± 1.2	
Percentile			
25	0	16	<0.001*
50	19	10	
75	15	7	

* Statistically significant

Table 3. Satisfactory score

	Group B (n = 50)	Group S (n = 49)	p-value
Satisfactory score			
24 hours	8.68 ± 1.56	7.63 ± 1.86	0.003*
48 hours	8.76 ± 1.45	8.27 ± 1.64	0.16
Satisfactory scale			
Day 1			
Excellent	34 (68%)	20 (40%)	0.035*
Good	14 (28%)	23 (46%)	
Enough	2	5	
Bad	0	1	
Day 2			
Excellent	30	24	0.5
Good	19	23	
Enough	1	2	
Bad	0	0	

* Statistically significant

Table 4. Side effects

	Group B (n = 50)	Group S (n = 49)	p-value
Nausea			
No	39	38	0.04*
Mild	4	0	
Moderate	7	11	
Severe	0	0	
Vomiting			
No	43	43	0.33
Mild	2	0	
Moderate	4	6	
Severe	1	0	
Itching			
No	23	19	0.91
Mild	12	15	
Moderate	11	12	
Severe	4	3	

* Statistically significant

significantly higher ('better') than in patients with saline (S), which was true for visual satisfactory score as well as global assessment satisfactory scale (p-value = 0.003 and 0.035 respectively; Table 3). This difference disappeared in 24 to 48 hours after operation. Incidence and severity of side effects such as nausea, vomiting and pruritus was similar for both groups (Table 4), except severity of nausea, which was higher in S-group patients (p = 0.04). No further relevant side effects regarding anesthetic technique or drugs administered became obvious.

Discussion

Our double-blind, randomized, placebo-controlled trial demonstrates periarticular injection of 0.25% bupivacaine 20 ml significantly increased efficiency of first 24 hours pain control after TKA under several evaluation aspects, including pain free period, morphine consumption, VAS and patient satisfactory score. The effect of single shot FNB and intrathecal morphine, applied to all patients, was significantly enhanced by additional periarticular bupivacaine, but not by saline.

Periarticular infiltration as well as intraarticular injection of local anesthetics and its effect on pain control, additional opiate consumption and patients satisfaction but also functional recovery has been investigated frequently, but not in combination with FNB plus intrathecal morphine. Joo et al[8] investigated the effect of intraarticular multimodal drug injection included local anesthetics on postoperative pain relief, patient's satisfaction and range of motion in bilateral TKA, the patients serving as their own control. They did not find any effect compared to placebo. In their randomized trial comparing FNB and peri-/intraarticular infiltration of ropivacaine, ketorolac, and epinephrine in TKA patients, Affas et al[9] found both methods to be sufficient, without one being significantly superior. They suggested though infiltration might be the better choice as it is cheaper and easy to perform. Sean et al[10] performed single-dose periarticular infiltration in TKA patients comparing bupivacaine alone and mixed with steroid (triamcinolone), the latter patients having significantly better pain control. The study of Mullaji et al demonstrated the beneficial effect of periarticular bupivacaine, fentanyl, and prednisolone in patients with bilateral TKA not only on postoperative pain control but also on functional recovery two and four weeks after surgery[11]. All these studies used a mixture of local anesthetics and different agents with analgesic potency for periarticular infiltration. One of these studies was conducted by Carli et al[12]. As the authors did, they performed a randomized double-blind study. Patients with TKA had continuous femoral block (catheter) with ropivacaine being compared to patients with infiltration of posterior capsule using ropivacaine plus ketorolac and epinephrine. It is remarkable in the present study that the injection in the posterior capsule was performed after all the bony cuts but before cementing the implants, thus trying to treat the well known popliteal pain after TKA, which is not sufficiently controlled by femoral block. However, the efficiency of the femoral block was superior to infiltration including functional recovery after six weeks.

Periarticular local anesthetic infiltration could reduce pain from the posterior and medial sides of the knee. They are supplied by sciatic and obturator nerves, which cause severe pain in the patients who receive only femoral nerve block for postoperative analgesia. Some studies chose higher dose of ropivacaine or levobupivacaine (200-400 mg) due to their lower toxicity or using articular catheter to give another dose on the day after surgery or continuous infusion, which undoubtedly produce longer analgesic effect[13-15]. The authors limited dose of bupivacaine for periarticular in filtration to 100 mg because we did femoral nerve block with 0.25% bupivacaine 20 ml. Therefore, the total bupivacaine was 150 mg.

The present study may have limitations. The investigated patients had three therapeutic measures for postoperative pain control, femoral block, intrathecal morphine, and periarticular infiltration with bupivacaine. This combination of highly effective methods may raise concern about interactions, making it difficult to distinguish between the effects of particular techniques. Consequently, one may ask if the effect of pain therapy methods additional to intrathecal morphine can be clearly estimated. However, the authors believe periarticular infiltration in our patients can be well evaluated, as femoral block and intrathecal morphine has been applied to ALL patients. In addition the design of the present study was double-blind including randomizing patients to either periarticular bupivacaine or saline. In conclusion, the efficiency of the periarticular infiltration on pain control and patients satisfaction could be demonstrated.

Even these three methods used for pain control may be too much effort. However, infiltration techniques are simple and modifiable, whereas other methods such as intrathecal morphine should be replaceable, the more as they have the potential to create unpleasant side effects. Further investigations about infiltration techniques should focus on combination of agents, site of application and continuous administration of local anesthetic via catheters.

Potential conflicts of interest

None.

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การฉีดบิวพิวาเคน 0.25% ในบริเวณ periarticular สามารถเพิ่มประสิทธิภาพของการระงับปวดภายหลังการผ่าตัดเปลี่ยนข้อเข่าในผู้ป่วยที่ได้รับการฉีดยาขัดขวางการทำงานของเส้นประสาทฟีเมอรัลและการฉีดมอร์ฟีนเข้าในช่องไขสันหลัง

ฐิติมา ชินะโชติ, อังคณา เหลืองนทีเทพ, มานี รักษาเกียรติศักดิ์

วัตถุประสงค์: *การศึกษาครั้งนี้เพื่อแสดงว่าผู้ป่วยที่ได้รับการระงับความรู้สึกโดยวิธีฉีดยาชาเฉพาะที่เข้าช่องไขสันหลังพร้อมกับมอร์ฟีนร่วมกับการฉีดยาขัดขวางการทำงานของเส้นประสาทฟีเมอรัลสำหรับการผ่าตัดเปลี่ยนข้อเข่า การฉีดยาชาเฉพาะที่บริเวณ periartcular ก่อนเย็บปิดแผลจะสามารถเพิ่มประสิทธิภาพของการระงับปวดภายหลังการผ่าตัดได้มากหรือน้อยเพียงใด*

วัสดุและวิธีการ: *ดำเนินการศึกษาในผู้ป่วย 99 ราย ที่ได้รับการผ่าตัดเปลี่ยนข้อเข่าภายใต้การระงับความรู้สึกโดยวิธีดังกล่าวภายใต้กระบวนการศึกษาแบบ randomized double-blind placebo controlled clinical trial โดยผู้ป่วย 50 ราย จะได้รับการฉีดบิวพิวาเคน 0.25% 20 มล. และผู้ป่วย 49 ราย ได้รับการฉีดน้ำเกลือ 0.9% ปริมาณ 20 มล. บริเวณ periarticular หลังการผ่าตัดผู้ป่วยได้รับการระงับปวดโดย intravenous patient controlled analgesia ด้วยมอร์ฟีน ทำการตรวจประเมินระดับความปวดหลังการผ่าตัด ความต้องการมอร์ฟีน ความพึงพอใจของผู้ป่วยที่เวลา 24 และ 48 ชั่วโมงหลังผ่าตัด*

ผลการศึกษา: *พบว่าวิธีการสุ่มสามารถเลือกผู้ป่วยที่มีคุณสมบัติใกล้เคียงกัน และการฉีดยาชาบริเวณperiarticular เพิ่มประสิทธิภาพของการระงับปวดชัดเจนในระยะหลังการผ่าตัด ประกอบด้วยจำนวนผู้ป่วยที่ต้องการมอร์ฟีนเพิ่มน้อยกว่า (26% เปรียบเทียบกับ 12.2%, $p \leq 0.01$) ระยะเวลาที่ไม่ปวดหลังการผ่าตัดนานกว่า (25 ชั่วโมง เปรียบเทียบกับ 14.8 ชั่วโมง, $p < 0.001$) จำนวนมอร์ฟีนที่ต้องการน้อยกว่า (5.16 มก. เปรียบเทียบกับ 8.67 มก., $p = 0.005$) และผู้ป่วยมีความพึงพอใจมากกว่า โดยไม่พบผลข้างเคียงใด ๆ ในผู้ป่วยทั้งสองกลุ่ม*

สรุป: *การฉีดยาชาบริเวณ periarticular ช่วยเพิ่มประสิทธิภาพของการระงับปวดภายหลังการผ่าตัดเปลี่ยนข้อเข่า โดยต้องใช้วิธีการระงับปวดร่วม 3 วิธี พร้อม ๆ กัน อาจเป็นการกระทำที่มากเกิน ควรต้องมีการศึกษาเพิ่มเติมว่าสมควรดัดแปลงวิธีการฉีด periarticular อย่างไรให้ได้ประสิทธิภาพดีขึ้น เช่นการฉีดยาชาอย่างต่อเนื่องบริเวณรอบ ๆ ข้อเข่า*