The effect of addition of pregabalin and s-ketamine to local infiltration analgesia on the knee function outcome after total knee arthroplasty

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Abstract: Pain reduction is important for early mobilization after total knee arthroplasty. Recent studies show that local infiltration analgesia and addition of anti-hyperalgesic drugs (pregabalin and s-ketamine) may improve postoperative analgesia and mobilization. This pilot study was meant to evaluate if this new method of analgesia might improve patients’ ability to exercise in the first postoperative days. The secondary goal was to determine what side effects could be expected by using this drug combination. A pilot study showed that patients achieved knee flexion of 88.5 °(SD 9.6) already on the second postoperative day. The side effects were mild and mostly self-limiting.

Key words: corticosteroids, local infiltration analgesia, pregabalin, s-ketamin, total knee arthroplasty

Reduction of pain is an important factor in the early rehabilitation after total knee arthroplasty (TKA). It is difficult to achieve adequate analgesia after TKA using opioids alone, even in combination with non-steroidal anti-inflammatory drugs (1). The reduction in postoperative pain and morbidity with peripheral nerve blocks is well recognized. Previous studies emphasize analgesic benefits of a (continuous) femoral nerve block (CFNB) (2), although popliteal fossa, innervated by the sciatic nerve, remains painful in 15-20% of patients (3). More importantly, CFNB induces quadriiceps paresis delaying the ability to walk.

There is, however, some evidence that the addition of anti-hyperalgesic drugs, such as pregabalin and s-ketamine, may reduce postoperative pain and even the incidence of chronic pain after surgery (4, 5). Studies also show that intra-articular injection of corticosteroids may be beneficial and shorten hospital stay (6).

Recent studies show that local infiltration analgesia (LIA) after TKA, as simple technique with low complication risk and lack of motor block, might be a good alternative to peripheral nerve blocks (7). However, none of these techniques is sufficient as a single method of postoperative pain treatment and must be used as a part of multimodal analgesic approach (8).

The aim of this study was to evaluate a new multimodal analgesic approach, which would allow the use of fast physiotherapy protocol, with early mobilization and quicker discharge from the hospital.

Methods

After approval of Local Ethics Committee, patients scheduled for primary TKA, at the Radboud University Nijmegen Medical Centre, The Netherlands, were informed about the new analgesia method and were asked to participate in this pilot study. Adult patients ASA class I-III were included.

Exclusion criteria were: patient’s refusal, pre-existing neurological or psychiatric illnesses, chronic pain syndromes, alcohol or drug abuse, suspected possibility of delirium, rheumatoid arthritis, revision knee surgery.

Patients were preoperatively informed about local knee infiltration and additional medication (pregabalin and s-ketamin), (LIA-PREGABA-KET).
The orthopedic surgeon informed patients about the new institutional physiotherapy protocol. The anesthesiologist explained that also a patient-controlled-analgesia (PCA) would be available during 48 hours.

Paracetamol (1000 mg) and pregabalin (150 mg) were given per os, as premedication. Pregabalin was further continued for four days, 150 mg twice a day. Dose reduction to 75 mg twice a day, was applied for ASA-class III patients and > 65 years.

TKA was performed under spinal or general anesthesia. For spinal anesthesia 12.5-15 mg of 0.5% bupivacaine – plain was used. General anesthesia patients did not receive long-acting opioids during surgery.

After induction of anesthesia, patients received an intravenous bolus 10 mg s-ketamine, followed by 24 hours infusion (10 mg/hour). Bolus dose was reduced to 5 mg and the continuous infusion to 5 mg/hour in ASA-class III patients and the patients > 65 years.

After cementing the components, 100 ml of ropivacaine 0.2% with epinephrine (1 mcg/ml) and 40 mg of triamcinolone acetonide (kenacort®) was used by the surgeon for infiltration of the posterior and the anterior knee capsule. Another 50 ml of ropivacaine 0.2% without additives was injected in the subcutaneous tissue.

After surgery, patients were admitted to the recovery room. Piritramide-PCA device was explained. Paracetamol (1000 mg) and diclofenac (50 mg) were prescribed four and three times daily, respectively.

S-ketamine infusion was stopped next morning at 8:00 am; pregabalin was continued three more days.

Side effects of combined medication (drowsiness, dizziness, PONV, anxiety, hypertension etc), were observed. Beside the vital signs, AVPU (A for ‘alert’, V for ‘reacting to vocal stimuli’, P for ‘reacting to pain’, U for ‘unconscious’) was used. NRS-pain scores and patient’s satisfaction were noted.

A fast track physiotherapy protocol was implemented. On the day of surgery patients stayed in bed, but were allowed to flex and extend the knee. On the first and second postoperative day patients exercised twice a day, and were encouraged to make transfers from bed to chair and to start walking. By day 3, patients should be able to walk with elbow crutches, without assistance, and were expected to start climbing stairs.

The primary goal of this study was to determine if addition of pregabalin and s-ketamine to LIA could improve mobilization in the first postoperative days after a TKA. Knee flexion angle was measured from day one until the day of discharge.

The secondary goal was to determine if this medication could reduce the acute pain without causing side effects interfering with patients’ safety and comfort. Numeric Rating Scale (NRS) 0-10 was used to measure pain. A nurse in the ward recorded NRS four times a day, at rest. Physical therapist noted dynamic pain scores, twice a day.

Patients could use PCA-piritramide on demand and the consumption was noted. The state of sedation was assessed as AVPU-scores. Side effects were registered: PONV (mild, moderate, severe), diplopia, dizziness, drowsiness and anxiety.

Length of hospital stay was noted as number of days between surgery and discharge. The patient’s satisfaction was rated on a 4 point scale; 1 = poor, 2 = fair, 3 = good, or 4 = very good.

STATISTICAL ANALYSIS

Descriptive demographic characteristics of the patients, clinical variables of surgery and postoperative physiotherapy results are reported as mean ± standard deviation for continuous variables, and count or percentages for dichotomous variables.

RESULTS

Twenty patients (12 females/8 males), scheduled for a primary TKA, were included in this LIA-PREGABA-KET pilot study. The mean age (SD) was 64 (12) years, ASA-class II (I-III), and BMI of 27 (5). Eight patients received spinal, twelve, general anaesthesia. The average length of surgery was 137 (24.8) minutes, blood loss 248 (106.2) ml.

There were no adverse events after local anesthetic infiltration.

The following functional physiotherapy results were achieved (Table 1), together with the following NRS scores (Table 2):

D-1 : Knee flexion angle of 82.3°, walking distance of 28.6 m, mean NRS at rest 2.0 and 3.9 during exercise.

D-2 : Knee flexion angle of 88.5°, walking distance of 60.8 m, NRS : 1.2 at rest and NRS : 2.6 during exercise.

D-3 : Knee flexion angle reaches 89.8°; walking distance of 82.5 m. NRS further decreases to 0.7 at rest and 2.4 during exercises.
PCA-piritramide was only needed during the first 24 hours. An average use of 5.8 mg was registered in 13 patients.

Adverse events, possibly related to pregabalin and S-ketamine were noted. One patient experienced temporary diplopia in the recovery room. Four patients complained of dizziness in the first 24 hours. Notably, one of these patients was also anemic and required blood transfusion. Two patients experienced mild anxiety and s-ketamine was stopped after twelve, instead of 24 hours. Although some patients experienced possible side effects of study medication, pregabalin did not have to be stopped. All patients were scored “alert” on the sedation scale. PONV was scored “mild” in two cases and “severe” in one case.

There were no complications leading to significant morbidity. On the second postoperative day, one patient developed swelling of the foot on the operated limb. Deep venous thrombosis was suspected (not confirmed), but the hospitalization had to be prolonged. Satisfaction was rated “very good” by 18 patients (90%) and “good” by two patients.

**DISCUSSION**

The present study on patients undergoing primary TKA showed that the multimodal analgesic approach, where LIA was combined with low dose of s-ketamine and pregabalin, offered good analgesia, excellent mobilization results and shortened the hospital stay.

From 1994 to 2004, the TKA patients in our institution followed a conservative physiotherapy protocol. Keeping in mind primarily wound healing, patients were prescribed “5-days bed rest” and received oxygen 48 hours. Our archive results in 455 TKA patients since 1994, showed that the hospital stay used to be 7 to 15 days. The protocol changed with the use of loco-regional techniques. “Bed rest” was reduced to two days. This was appropriate with the use of CNFB during 48 hours, which produced good analgesia, but also a quadriceps paresis and inability to walk safely. Introduction of CFNB reduced hospital stay to five days. With the introduction of LIA-PREGABALIN-S-KET technique, average hospital admission is further reduced to three days (Fig. 1), with excellent mobilization results and low pain scores. Due to good analgesia, patients exercised efficiently, achieving an average knee flexion of 88 degrees and walking distance of 60 m on the second postoperative day. On the third day, knee flexion angle and walking distance further increased, the pain scores decreased and patients were ready for discharge.

However, the adjunct anti-hyperalgesic drugs caused known transitory side effects in several patients: dizziness, PONV, diplopia and anxiety. On suspicion of anxiety, s-ketamine infusion was stopped and the recovery was quick. Also the other side effects were mild and selflimiting. Despite these side effects, 90% of the patients rated their satisfaction as “very good” and 10% as “good”.

<table>
<thead>
<tr>
<th>Day</th>
<th>Knee flexion degrees</th>
<th>Walk (m)</th>
</tr>
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<tbody>
<tr>
<td>DAY-1</td>
<td>82.3 (10.7)</td>
<td>28.7 (19.7)</td>
</tr>
<tr>
<td>DAY-2</td>
<td>88.5 (9.6)</td>
<td>60.8 (28.4)</td>
</tr>
<tr>
<td>DAY-3</td>
<td>89.8 (8.2)</td>
<td>82.5 (17.0)</td>
</tr>
</tbody>
</table>

**Table 1**

The mean (SD) mobilization results during the first three postoperative days

<table>
<thead>
<tr>
<th>NRS</th>
<th>at rest and during exercises</th>
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<tbody>
<tr>
<td>NRS-D1</td>
<td>2.0 (1.4)</td>
</tr>
<tr>
<td>NRS-D2</td>
<td>1.2 (1.1)</td>
</tr>
<tr>
<td>NRS-D3</td>
<td>0.7 (1.0)</td>
</tr>
</tbody>
</table>

**Table 2**

The mean (SD) NRS pain scores at rest and during exercises on the first three postoperative days after a TKA

![Fig. 1. — The average duration of hospitalization after a TKA from 1994-2011 (July) at the Orthopaedic Department of UMC Nijmegen, The Netherlands.](image)
In conclusion, preliminary findings from this observational study where LIA-PREGABA-KET technique was applied after TKA, showed good analgesic and excellent mobilization results, with shorter hospital stay. There were no toxic reactions to dose of LIA-cocktail used and only mild side effects of pregabalin and s-ketamine were noted. However, randomized controlled trials are needed, before definitive conclusions can be made.

References


