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Effect of Addition of Magnesium Sulphate and Fentanyl to Ropivacaine Continuous Femoral Nerve Block in Patients Undergoing Elective Total Knee Replacement

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This prospective double blinded study was designed to compare the effect of magnesium or fentanyl addition to ropivacaine in continuous femoral nerve block in patients undergoing elective total knee replacement under general anesthesia. Sixty patients undergoing elective TKR under general anesthesia, were randomly allocated into three equal groups, Group (R): given 30 mL Ropivacaine 0.2%. Group (R+F): given 30 mL Ropivacaine 0.2% and 4 $\mu\text{g mL}^{-1}$ fentanyl. Group (R+M): given 30 mL Ropivacaine 0.2% and 50 mg mL^{-1} of magnesium sulphate, through femoral catheter. The following parameters were evaluated: (1) demographic data of the patients and duration of the surgery, (2) intraoperative and postoperative hemodynamics, (3) intraoperative fentanyl requirements, (4) the severity of postoperative pain for 24 h, (5) time to first request of analgesia and (6) amount of postoperative morphine consumed in 0-6, 6-12, 12-18, 18-24 and 0-24 h, postoperatively. There were no difference among the three groups as regards the demographic data, the duration of the surgery, the pre and postoperative hemodynamics, the total intraoperative fentanyl consumption and the VAS during the 1st postoperative hour. The postoperative pain showed significant lower values in groups (R+F) and (R+M) compared to group (R) when measured at 6, 12, 18 and 24 postoperative hours. The time for the first postoperative request for analgesia was statistically longer in the (R+M) group and (R+F) group compared with group (R). The postoperative morphine consumption was statistically lower in groups (R+F) and (R+M) compared to group (R) but insignificant between groups (R+F) and (R+M). The admixture of magnesium sulphate or fentanyl to ropivacaine for continuous femoral nerve block provided a significant prolongation of postoperative analgesia than ropivacaine alone.

Key words: Total knee replacement, ropivacaine, continuous femoral nerve block, magnesium sulphate and fentanyl

INTRODUCTION

The use of peripheral regional analgesic techniques as a single or continuous infusion can provide superior analgesia compared with systemic opioid (Nguyen *et al.*, 2001) and has several advantages over systemic opioid and decrease opioid related side effects (Liu and Salinas, 2003) with greater patient satisfaction (Wu *et al.*, 2001). More effective pain relief in the early postoperative period, as a result of the sensory block produced by local anesthetics, facilitates recovery by enabling earlier ambulation and discharge home (i.e., fast-track recovery) (Song *et al.*, 2000; Li *et al.*, 2000).

Pain after Total Knee Arthroplasty (TKA) is often severe and may hinder participation in early intensive physical therapy, considered one of the most important factors for optimal postoperative knee rehabilitation (Wang *et al.*, 2002).

Multiple techniques of postoperative pain control have been used after TKA, including oral or IM opioids, patient-controlled IV opioids, Patient-Controlled Epidural Analgesia (PCEA) and single-dose or Continuous Femoral Nerve Block (CFNB) (Williams *et al.*, 1996; Capdevila *et al.*, 1999).

The addition of Single-injection of Femoral Nerve Block (SFNB) to postoperative IV analgesia after TKA resulted in significantly better pain control, less frequent morphine-related side effects, more rapid achievement of physical therapy milestones and shorter hospital stay (Wang *et al.*, 2002; Ng *et al.*, 2001).

Placement of a femoral nerve catheter allows prolonged site-specific regional analgesia. This may be beneficial, because previous studies have shown that duration of analgesic effect from a SFNB is typically 12 to 24 h (Allen *et al.*, 1998), but may be as long as 48 h, whereas severe pain after TKA, especially during physical therapy, may persist through the second day after surgery (Ng *et al.*, 2001).

Magnesium has antinociceptive effects in animal and human models of pain. These effects are primarily based on the regulation of calcium influx into the cell (Kara *et al.*, 2002). Co-administration of magnesium for postoperative epidural (Bilir *et al.*, 2007) and intraarticular (Bondok and Abd El-Hady, 2006) analgesia results in a reduction in fentanyl consumption without any side-effects (Bilir *et al.*, 2007). Magnesium infusion, including the pre-, intra- and postoperative periods reduces analgesic requirements. These results demonstrate that magnesium can be an adjuvant for perioperative analgesic management (Kara *et al.*, 2002).

The aim of this study was to compare the effect of addition of magnesium or fentanyl to ropivacaine for

Continuous Femoral Nerve Block (CFNB) in patients undergoing elective unilateral [Total Knee Replacement] under general anesthesia, as a double blinded randomized prospective clinical trial.

MATERIALS AND METHODS

After approval of Local Ethical and Research Committee in Dar Alshifa hospital (in The State of Kuwait) during the period from February 2007 to January 2008. The informed written consents were obtained from 60 patients (45-65 year), ASA physical status 1 and 2, scheduled for unilateral primary TKR under general anesthesia whom were included in this prospective, randomized study.

Exclusion criteria included: ASA physical status more than III, age below 45 years or above 65 years; inability to give informed consent for language or cognitive reasons, body mass index more than 35, allergy to local anesthetics or other medications used in this study, chronic opioid use, difficulties in understanding Visual Analog Scale (VAS) pain scores or use of an PCA device and any contraindications to CFNB (e.g., patient refusal, infection overlying the injection site or previous femoro-popliteal bypass surgery, pre-existing lower extremity neurological abnormality, platelet count below $100 \times 10^9 \text{ L}^{-1}$ or coagulopathy).

The study protocol, the procedure, the Visual Analogue Scale (VAS) for pain and the use of PCA device were explained to each patient during the preoperative visit.

All patients were premedicated with oral midazolam 5 mg, approximately 60-90 min prior to surgery. Upon arrival to the operating room, a wide bore intravenous cannula was inserted and 8 mL kg^{-1} normal saline was infused intravenously. Electrocardiogram (lead 2 and 5 with ST segment analysis), pulse oximetry and non-invasive arterial blood pressure at 5 min intervals, were monitored.

With the patient is in the supine position with both legs extended a thorough cleaning with an antiseptic solution, skin infiltration with local anesthetic at the injection site using a 1½" 25 G needle. The palpating hand is used to keep the middle finger on the pulse of the femoral artery, just below the inguinal crease the entire hand is slightly pulling the skin caudally to keep it from wrinkling on needle insertion. A 90 mm, 17-gauge insulated stimulating Tuohy needle (Arrow International, Reading, PA) connected to the nerve stimulator (B-Braun, Bethlehem, PA) (1.0 mA, 2 Hz, 100 μsec) is inserted and advanced at a 45-60° cephalad.

After the quadriceps muscle twitch is obtained (patella twitch) at 0.5 mA, a 19-gauge stimulating catheter (connected to the nerve stimulator) was advanced 4-5 cm past the needle tip via the catheter while quadriceps contractions were still being elicited. The final position of the femoral catheter was acceptable only when quadriceps contractions were still elicited at ≤ 0.5 mA via the catheter. The catheter is then secured to the skin using a clear dressing applied over the catheter.

Patients were randomly allocated (Using Table of Randomization) into three equal sized groups (n = 20, each):

- Group (R): Given 30 mL Ropivacaine 0.2% (Naropin, Astra Zeneca) through femoral catheter
- Group (R+F): Given 30 mL Ropivacaine 0.2% (Naropin, Astra Zeneca) with fentanyl 4 $\mu\text{g mL}^{-1}$, through femoral catheter
- Group (R+M): Given 30 mL Ropivacaine 0.2% (Naropin, Astra Zeneca) with magnesium sulphate 50 mg mL^{-1} through femoral catheter

The drugs were prepared and given to the investigator who was blinded to the identity of drugs.

Initial femoral block in all groups was confirmed by loss of pinprick sensation over both the mid-anterior thigh (anterior division of femoral nerve) and the medial aspect of the calf above the medial malleolus.

Continuous infusion of the same concentration in each group was then continued for the next 24 h at a rate of 6 mL h^{-1} .

Then general anesthesia was induced in all patients with propofol 2-3 mg kg^{-1} IV, fentanyl 2 $\mu\text{g kg}^{-1}$ IV, cisatracurium 0.15 mg kg^{-1} IV. The trachea was intubated with oral cuffed tube lubricated with lidocaine jell 2% 3 min after cisatracurium administration guided by peripheral nerve stimulation, lidocaine 1.5 mg kg^{-1} IV was given 1.5 min before intubation.

Anesthesia was maintained using isoflurane 0.6-0.8%, 100% O_2 , additional doses of cisatracurium was given guided by peripheral nerve stimulation and additional doses of fentanyl was given guided by hemodynamics.

At the end of surgery neuromuscular blockade was reversed with neostigmin 2.5 mg and atropine 1.2 mg IV and the trachea was extubated when the patient responded to commands. All patients were transferred to PACU (for the next hour) where the hemodynamics were monitored (each 5 min).

The postoperative pain was assessed using Visual Analogue Scale (VAS), where zero score corresponds to no pain and 10 to the maximum or worst pain.

Postoperative pain (VAS > 3) was initially managed with a bolus of 1 mg i.v. morphine. Patients were then instructed to start using intravenous Patient-Controlled Analgesia (PCA) morphine pump (IVAC 5000). The PCA pump was adjusted to deliver morphine boluses in 1 mg increments with a lockout interval of 10 min and a maximum hourly dose of 5 mg. The PCA regimen was reviewed if analgesia proved to be inadequate.

Following parameters were evaluated in all of the studied groups:

- Demographic data of the patients and duration of the surgery
- Intraoperative and postoperative heart rate, systolic, diastolic and mean arterial blood pressure
- Intraoperative fentanyl requirements (in micrograms).
- The severity of postoperative pain for 24 h (the severity of postoperative pain measured at 1, 6, 12, 18 and 24 h postoperatively using (VAS).
- Time to first request of analgesia.
- Amount of postoperative morphine consumed in 0-6, 6-12, 12-18, 18-24 and 0-24 h, from the end of surgery

Statistical analysis: All data were presented as mean \pm SD or as median and range, comparison among groups was done using Analysis of Variance test (ANOVA) and post hoc test was performed in case of significant difference. Significance was considered where p was > 0.05. Statistical analysis was performed using the statistical computer program SPSS version II.

RESULTS AND DISCUSSION

There were no statistically significant differences among the three groups as regards the demographic data and the duration of the surgery (Table 1).

There were statistically insignificant differences among the three groups or within each group as regards the intraoperative and postoperative hemodynamics [SPB, DBP, MBP and HR] (Table 2).

Similarly, the difference among the three groups, as regards the intraoperative fentanyl consumption, was statistically insignificant (Table 3).

Table 1: Demographic data and duration of the surgery

Parameters	Group (R) (n = 20)	Group (R+F) (n = 20)	Group (R+M) (n = 20)
Age (year)	55 \pm 7	54 \pm 6	55 \pm 5
Gender (male/female)	12/8	11/9	7/13
Body weight (kg)	75 \pm 5	74 \pm 6	76 \pm 4
Height (m)	1.77 \pm 0.3	1.75 \pm 0.7	1.76 \pm 0.6
Duration of surgery (min)	121 \pm 7	120 \pm 8	122 \pm 6

Values presented as (mean \pm SD or number), R: Ropivacaine group, R+F: Ropivacaine+Fentanyl group, R+M: Ropivacaine+Magnesium group, No statistically significant difference among the three groups

Table 2: Mean intraoperative and postoperative hemodynamics

Hemodynamic Parameters	Group (R) (n = 20)	Group (R+F) (n = 20)	Group (R+M) (n = 20)
Intraoperative SBP (mmHg)	123±8	122±7	119±8
Intraoperative DBP (mmHg)	75±4	74±5	73±7
Intraoperative MBP (mmHg)	66±5	67±4	66±6
Intraoperative HR (bpm)	74±3	72±6	71±5
Postoperative SBP (mmHg)	126±8	126±6	122±8
Postoperative DBP (mmHg)	77±3	76±4	121±6
Postoperative MBP (mmHg)	68±5	69±3	68±7
Postoperative HR (bpm)	79±4	76±5	75±4

Values presented as (mean±SD or number), R: Ropivacaine group, R+F: Ropivacaine+Fentanyl group, R+M: Ropivacaine+Magnesium group, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MBP: Mean Blood Pressure, HR: Heart Rate, No statistically significant difference among the three groups or within the same group

Table 3: Intraoperative fentanyl requirement (µg)

Intraoperative fentanyl requirement	Group (R) (n = 20)	Group (R+F) (n = 20)	Group (R+M) (n = 20)
Total dose (µg)	180±3	176±4	178±2

Values presented as (mean±SD or number), R: Ropivacaine group, R+F: ropivacaine+Fentanyl group, R+M: Ropivacaine+Magnesium group, No statistically significant difference among the three groups or within the same group

The severity of postoperative pain measured by VAS showed statistically insignificant differences among the three groups during the 1st postoperative hour, but showed statistically significant lower values in groups (R+F) and (R+M) compared to group (R) when measured at 6, 12, 18 and 24 postoperative hours (p<0.05) but the VAS values were insignificant between groups (R+F) and (R+M) when measured all over the postoperative 24 h (Table 4).

The time for the first postoperative request for analgesia was statistically significant longer in the (R+M) group and (R+F) group compared with the ropivacaine group (R), being [320 (6), 315 (7) and 113 (9) min] respectively, but insignificant between groups (R+F) and (R+M) (Table 4).

The postoperative morphine consumption was statistically significant lower in groups (R+F) and (R+M) compared to group (R) when measured every 6 h during the postoperative 24 h (p<0.05) but insignificant between groups (R+F) and (R+M) (Table 5).

Effective pain control is a major concern in the postoperative management of TKR and one that has a significant impact on our health care system. The FNB has become the technique of choice after TKR, it is as efficient as epidural analgesia, has fewer side effect and is easier to manage in the surgical ward (Vloka *et al.*, 1997).

Intraoperative fentanyl requirement was comparable in the three studied groups. This may be attributed to the fact that, FNB does not consistently produce anesthesia of the obturator nerve. Consequently, the intact sensation in the back of the knee after a FNB alone could be attributable to either the obturator or the sciatic nerve, which also supplies the knee joint (Macalou *et al.*, 2004).

Table 4: The severity of postoperative pain for 24 h (VAS)

Time	Group (R) (n = 20)	Group (R+F) (n = 20)	Group (R+M) (n = 20)
1st h postoperative	1 (0-2)	1 (0-2)	1 (0-2)
6 h postoperative	3 (2-3)	2 (0-2)*	2 (0-2)*
12 h postoperative	3 (2-3)	2 (1-2)*	1 (0-2)*
18 h postoperative	4 (3-5)	2 (2-3)*	2 (1-3)*
24 h postoperative	5 (3-6)	3 (2-3)*	2 (1-3)*
Time for the first request for analgesia (min)	113±9	315±7*	320±6*

Values presented as [median (range)] and Time for the first request for analgesia. Values presented as (mean±SD), R: Ropivacaine group, R+F: Ropivacaine+Fentanyl group, R+M: Ropivacaine+Magnesium group, *Statistically significant compared to group (R), (p<0.05)

Table 5: Amount of postoperative morphine consumed

Time	Morphine consumption (mg)		
	Group (R) (n = 20)	Group (R+F) (n = 20)	Group (R+M) (n = 20)
0-6 h	5.7±0.8	2.4±0.9*	2.1±1.1*
6-12 h	7.4±1.2	3.4±0.6*	3.2±1.0*
12-18 h	9.8±1.5	4.6±0.5*	4.5±0.9*
18-24 h	10.3±1.4	5.8±0.7*	5.5±0.7*
0-24 h	33.3±2.9	17.3±1.3*	16.5±1.4*

Values presented as (mean±SD), R: Ropivacaine group, R+F: Ropivacaine +Fentanyl group, R+M: Ropivacaine+Magnesium group, *Statistically significant compared to group (R), (p<0.05)

The present study demonstrated that CFNB with ropivacaine 0.2% with MgSO₄ or fentanyl was associated with better postoperative analgesia after TKR compared with ropivacaine 0.2% alone and prolonged duration of analgesia than ropivacaine 0.2% alone, this can be explained by potentiation of the action and prolongation of the duration of local anesthetics by either MgSO₄ or fentanyl. And the results of MgSO₄ or fentanyl combination with ropivacaine were comparable.

In agreement with present results, the study done by De Ruyter *et al.* (2006) showed that femoral nerve catheters with continuous infusion of ropivacaine provide satisfactory analgesia, improve rehabilitation and shorten hospital stay than iv opioid pc after TKR

Also the study done by Gunduz *et al.* (2006) showed that the admixture of magnesium 150 mg to prilocaine for axillary brachial plexus block provided a pronounced prolongation of sensory and motor block without side effects in patients scheduled for forearm and hand surgery under axillary brachial plexus block and Bilir *et al.* (2007) showed that co-administration of 50 mg magnesium sulphate epidural as an initial bolus dose followed by a continuous infusion of 100 mg day⁻¹ for postoperative epidural analgesia resulted in a reduction in fentanyl PCEA consumption without any side effects than patients received fentanyl PCEA only in patients undergoing hip surgery.

On the other hand, there is one study against our results done by Yu-Chun Hung *et al.* (2007) where MgSO₄ co-administered with amide-type LAs shortened the

duration of sciatic-nerve block in rats, therefore they suggested it does not seem to be useful as an adjuvant for peripheral-nerve block. The mechanism of this observed antagonism is unclear but appears to be independent of the action of LAs and MgSO₄ at the LA receptor within the Na⁺ channel.

We conclude that the admixture of magnesium sulphate 1.5 g as initial bolus followed by 300 mg h⁻¹ to ropivacaine 0.2% for continuous femoral nerve block provided a significant prolongation of postoperative analgesia in patients scheduled for unilateral TKR under general anesthesia than patients received ropivacaine 0.2% alone and was comparable to combination of fentanyl and ropivacaine.

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