

Clinical Trial

Continuous “three-in-one” Femoral Block for Analgesia after Unilateral Total Knee Replacement; the Value of Adding Verapamil

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Abstract

This study was designed to investigate the possible analgesic role of verapamil in the continuous 3-in-1 femoral block after total knee replacement (TKR). Forty two patients scheduled for TKR were randomly assigned to one of two groups. Group “R” received 15 ml Ropivacaine 0.75 % and a bolus of 5 ml normal saline. Group “R-V” received 15 ml Ropivacaine 0.75 % and verapamil 2.5 mg diluted in 5 ml normal saline. General anesthesia was standardized for all study groups. After recovery: In group “R”, Ropivacaine 0.2 % was given in a rate of 5 ml / hr., whereas in group “R-V”, Ropivacaine 0.2 % mixed with verapamil was given at the same rate. Hemodynamic changes, intensity of resting and moving pain by VAS, consumption of systemic analgesia, amplitude of knee flexion, hospital stay and general or local adverse effects were assessed. Two cases were excluded due to complete failure. Both groups were comparable regarding the progress of sensory and motor block. The mean VAS scores were significantly lower ($P < 0.05$) in group R-V than group R during rest and during physical therapy sessions. We concluded that the addition of verapamil potentiates the analgesic effect of Ropivacaine in 3-in-1 block without side effects. More studies are required to clarify dose-responses of verapamil.

Keywords: Knee Replacement; Analgesia; Femoral; Verapamil

Introduction

Postoperative pain is a major concern after TKR. When inadequately treated, it intensifies reflex stress responses [1] and hinders early intensive physical therapy, the most influential factor for good postoperative knee rehabilitation [1,2]. Postoperative pain relief after TKR was achieved by a variety of techniques such as IV patient-controlled analgesia [3], epidural analgesia with narcotics and/or local anesthetics [4,5] and lumbar plexus blockade (3-in-1-block) [6,7]. It has been shown that continuous femoral nerve block is a more effective pain reliever after TKA compared to IV patient controlled analgesia [8], epidural analgesia [6] or single injection block [9]. In an attempt to improve duration and potency of analgesia for continuous femoral nerve block, Ropivacaine in a concentration of 0.2% - 0.75% showed better analgesic quality than other anesthetic agents [10-12]. The mechanism of action of local anesthetics is primarily through sodium channel and axonal conduction block, but it also has extensive effects on presynaptic calcium channels that must function to stimulate the release of neurotransmitters. Thus, calcium channel blockers may potentiate the analgesic properties of both local anesthetics and opioids [13]. This fact was confirmed by demonstrating the potentiating anesthetic and analgesic effect of verapamil in epidural analgesia [14], spinal anesthesia [15], subcutaneous injection [16] and brachial plexus block [17]. According to that fact, we hypothesize that addition of verapamil to the local anesthetics for “3-in-1” continuous femoral nerve block may improve the analgesic quality after TKR. This study was designed to demonstrate if addition of verapamil to Ropivacaine

for 3-in-1 femoral block would potentiate its analgesic effect or not.

Patients and Methods

This prospective randomized double-blind controlled study was carried out on 42 patients subjected to primary unilateral TKR at Mansoura University Hospital. After approval of the protocol by our institute, patients of ASA I or II, of either sex, aged 50 -70 years were included in the study. Patients were excluded if they have any contraindications to regional anesthesia, allergy to amide local anesthetics, pre-existing neurological diseases of lower extremities, preoperative use of opioids, have psychic diseases or failure of the technique. After routine preoperative assessment, the details of the technique and postoperative VAS pain scale assessment were discussed with the patient and a written consent was obtained. In the operating suit, patients were connected to non-invasive standard monitoring, basal hemodynamic parameters were recorded, I.V. line was secured and 500 ml normal saline was given.

Femoral nerve block

Midazolam (0.02 mg /kg I.V.) was given before insertion of the femoral catheter. Continuous “three-in-one-block” was performed before induction of general anesthesia following Winnie et al landmarks [18]. An 18 G Tuohy needle (Perifix; Braun, Melsungen, Germany) attached to the nerve stimulator (Neurosign 100, MAGSTIM,UK) was inserted just lateral to the femoral artery. With a starting output of 1.5 mA, the needle was advanced in a cephalad plane at an angle of 30° to the skin until contraction of the quadriceps femoris muscle (patella ascension) was elicited. Its position was then

optimized and judged adequately when an output lower than 1 mA (usually 0.2-0.5 mA) still elicited contractions of the quadriceps. A 20-G multiperforated catheter was then threaded upwards 10-15 cm within the femoral nerve sheath.

Randomization

According to addition of verapamil or not to the injected solution, eligible patients were randomly allocated into 2 equal groups by using a computer-generated list of random permutations. Group “R” received 15 ml Ropivacaine 0.75 % (Narophin® Astra, Dietikon, Switzerland) and a bolus of 5 ml normal saline in separate syringes. Group “R-V” received 15 ml Ropivacaine 0.75 % and verapamil 2.5 mg (Isopten®; Knoll AG, Ludwigshafen, Germany) diluted in 5 ml normal saline in separate syringes. The study solutions were prepared and injected by an attending anesthetist who was not involved in the patient care or data collection while the managing anesthetist was masked about the used solution. The sensory block of the 3 nerves was assessed every 10 minutes during the first 30 minutes post injection using a 25-G needle. Testing was performed on the anterior aspect of the knee (femoral nerve), medial aspect of the knee (Obturator nerve) and lateral aspect of the thigh (lateral femoral cutaneous nerve). The block was considered complete when no sensation was observed to pinprick test, partial when sensation to pinprick test was decreased and absent when normal sensation to pinprick test was observed. Motor block was assessed during the same period by testing knee extension (complete, partial or failure). A block failure was defined as a complete absence of both sensory and motor block in each nerve territory after 30 minutes. In case of failure, the patient was excluded from the study and systemic analgesia was given according to our institutional policy.

General anesthesia

After ensuring the success of the femoral block, general anesthesia was standardized for all study groups. Induction was done by Fentanyl (1 µg/kg), thiopentone (3-5 mg/kg) and maintenance by N₂O-O₂, atracurium, Isoflurane and incremental doses of Fentanyl (0.25 µg /kg). One of 3 surgeons belonging to the same team (using the same technique) performed all the operations.

Recovery and analgesic protocol

After full recovery, patients were transferred to the post anesthesia care unit (PACU) and stayed there for 6 hours under full monitoring. The postoperative analgesic protocol was initiated in PACU and continued in the surgical ward for 48 hours. Infusion pumps containing the randomized analgesic solution were activated immediately after recovery. In group “R”, Ropivacaine (0.2 %) in 50 ml was given in a rate of 5 ml / hr., whereas in group “R-V”, Ropivacaine (0.2 %) mixed with verapamil (2.5 mg) in 50 ml was given at the same rate. The intensity of resting pain was determined by VAS and recorded 1, 2, 4, 6, 12, 24, and 48 hours after recovery. Early rehabilitation was initiated on the 1st day after surgery by asking patients to put patella up (contraction of quadriceps muscles) and by using continuous passive movement splint. In accordance with the surgical team, knee flexion of 40° was progressively attempted for 30 minutes on 1st postoperative day and of 50° on the 2nd postoperative day. Pain during mobilization was evaluated during target flexion at the 1st and 2nd postoperative days. Excessive pain (VAS > 5) was avoided by decreasing the amplitude of flexion.

Acquisition of the clinical variables

The primary outcome was the quality of postoperative analgesia as assessed by VAS. If VAS was > 5, non steroidal anti-inflammatory drugs e.g. Diclofenac 75 mg I .M. were given. Other secondary outcomes included: Time and dose of systemic analgesia, amplitude of knee flexion, hospital stay and general or local adverse effects. Hemodynamic changes (Heart rate and Mean arterial blood pressure) were recorded in the following times: basal, 30 minutes after FNB, during GA (30 min, 1 h, 2 h), in PACU (1 h, 2 h and 6 h). On the morning of the 3rd postoperative day, the pump was deactivated and the catheter was removed.

Statistical analysis

The power of this clinical trial was retrospectively calculated using the GPower analysis program. Using post-hoc power analysis with accuracy mode calculations and assuming type-I error protection of

Table1: Demographic and clinical characteristics of Ropivacaine (R) group and Ropivacaine- Verapamil (R-V) group. Values are mean ± SD (range) or number (%).

	R (n=20)	R-V (n=20)
Age (Y)	62.9 ±5	62.7 ±4
Sex (M/F)	6/14	1/19
BMI (kg/m ²)	29.2 ±2 (25-33)	30.4±2 (27-33)
Duration of surgery (min)	179.8±19 (150-210)	178.8±13 (150-200)
Preoperative medical diseases:		
- Hypertension.	12 (60)	10 (50)
- Diabetes mellitus.	7 (35)	8 (40)
- Ischemic heart diseases.	4 (20)	3 (15)
- Hepatic diseases.	2 (10)	2 (10)

Table2: Hemodynamic variables of Ropivacaine group (R) and Ropivacaine Verapamil group (R-V). Values are mean ± SD.

	Heart rate (bpm)		Mean Arterial Pressure (mmHg)	
	R	R-V	R	R-V
Basal	84 ± 8	85 ± 5	84 ± 8	79 ± 7
30 min after block	82 ± 8	87 ± 7	84 ± 5	77 ± 6
After GA:				
30 min	83 ± 8	80 ± 9	85 ± 6	78 ± 6
1 h	80 ± 8	79 ± 6	82 ± 5	77 ± 6
2 h	83 ± 3	79 ± 6	84 ± 6	77 ± 7
At recovery	86 ± 7	81 ± 7	83 ± 6	76 ± 6
Postoperative:				
1 h	81 ± 6	76 ± 5	83 ± 5	84 ± 5
2 h	80 ± 6	74 ± 6	85 ± 5	82 ± 5
6 h	79 ± 5	75 ± 5	84 ± 6	81 ± 6

Note : Basal readings were recorded in 21 patients in each group; all other readings were recorded in 20 patients only.

Table 3: Pattern of motor and sensory blocks in Ropivacaine (R) and Ropivacaine-Verapamil (R-V) groups. Values are number (%).

	Motor block		P-value	Sensory block		P-value
	R (n=21)	R-V (n=21)		R (n=21)	R-V (n=21)	
10 min after block:						
Complete	0	0	0.16	0	0	0.1
Partial	7 (33.3)	9 (42.9)		9 (42.9)	11 (52.4)	
No block	14 (66.7)	12 (57.1)		12 (57.1)	10 (47.6)	
20 min after block:						
Complete	7 (33.3)	9 (42.9)	0.22	9 (42.9)	11 (52.4)	0.3
Partial	13 (62.0)	11 (52.4)		11 (52.4)	9 (42.9)	
No block	1 (4.7)	1 (4.7)		1 (4.7)	1 (4.7)	
30 min after block:						
Complete	20 (95.3)	20 (95.3)	0.05	20 (95.3)	20 (95.3)	0.05
Partial	0	0		0	0	
No block	1 (4.7)	1 (4.7)		1 (4.7)	1 (4.7)	

- Complete motor block: No extension of the knee was observed.
- Complete sensory block: No sensation was detected to pinprick.
- Partial motor block: quadriceps motor force was decreased
- Partial sensory block: sensation to pinprick was decreased
- No motor block: Normal quadriceps function was observed.
- No sensory block: normal sensation to pinprick test was observed.

Table 4: Visual analogue score (VAS) of Ropivacaine (R) and Ropivacaine – Verapamil (R-V) groups during rest and during physical therapy sessions. Values are mean ± SD (range).

After recovery	During rest		During physical therapy sessions	
	R (n=20)	R-V(n=20)	R (n=20)	R-V(n=20)
1 h	0.8 ± 0.6 (0-2)	0.1 ± 0.3* (0-2)	-	-
2 h	1.4 ± 0.7 (0-2)	0.8 ± 0.5* (0-2)	-	-
4 h	1.7 ± 1.0 (0-3)	1.1 ± 0.5* (0-3)	-	-
6 h	2.9 ± 0.9 (0-4)	1.8 ± 0.8* (0-4)	-	-
12 h	1.6 ± 0.9 (0-3)	0.9 ± 0.3* (0-2)	-	-
POD 1	0.7 ± 0.4 (0-3)	0.2 ± 0.5* (0-2)	3.3 ± 1.8 (1-4)	1.3 ± 1.4* (1-2)
POD 2	0.3 ± 0.4 (0-1)	0 ± 0*	3.2 ± 1.4 (1-4)	0.9 ± 1.3* (0-2)

POD=Postoperative day
*Significant (P<0.05)

Table 5: Amplitude of knee flexion, hospital stay, analgesia consumption and complications in Ropivacaine (R) and Ropivacaine – Verapamil (R –V) groups. Values are mean ± SD (range) or numbers (%).

	R (n=20)	R-V (n=20)
Amplitude of knee flexion (degree)	25.8 ± 4.7 (15-30)	24.3 ± 4.1 (15-30)
Hospital stay (days)	21.3 ± 3.5	19.5 ± 3.9
Patients required systemic analgesics.	2 (10)	0
Complications:		
- Systemic:		
- Vomiting	1 (5)	0
- Hypotension (MBP < 60 mmHg)	0	1 (5)
- Local:		
- Difficulty of the catheter insertion	2 (10)	1 (5)
- Kink	0	0
- Hematoma	2 (10)	0

MBP= Mean Blood Pressure

0.05 and medium effect size convention of 0.3, a total sample size of 42 patients produced a power of 0.98.

Data were collected and analyzed by SPSS program Version 14. Normal distribution of the collected data was first verified with the Kolmogrov-Smirnov test. Normally distributed data was compared with Student t-test. Paired sample t-test was used for intragroup comparison. Chi-square test was used for comparison of proportions. P value < 0.05 was considered as a level of significance.

Results

Two patients (one from each group) were excluded from the study due to complete sensory and motor block failure. The patients' characteristics showed no significant differences between the 2 studied groups. Hypertension and Diabetes were the most common preoperative co-morbid diseases (table 1).

Hemodynamic variables did not display significant differences between both groups or inside each group as compared with basal values. In addition, all readings of heart rate and mean arterial blood pressure remained within the accepted normal ranges throughout the study period (table 2).

No cases showed complete motor block 10 min after the procedure but gradual partial motor block was achieved in 35 % and 45 % in R and R-V groups respectively. After 20 minutes, 20/21 patients had either complete block (33.3 %, 42.9 %) or partial block (62 %, 52.4 %) in R and R-V groups respectively. By the end of 30 minutes, 20/21 in each group showed complete motor block. Although sensory block was achieved earlier than motor block, it showed the same pattern as motor block in both groups. No significant differences were detected between the 2 groups regarding either motor or sensory block through the three timings. Only one patient in each group showed complete failure (table 3).

The resting VAS scores and peak scores during physical therapy sessions are presented in table 4. In the first 12 hours after recovery, all readings of resting VAS were significantly lower in Ropivacaine-Verapamil group compared with Ropivacaine group. On the first and second postoperative days, significant differences were detected between VAS of the studied groups during rest and during physical therapy sessions. However, all values of VAS were accepted in both groups either during rest or physical activities (table 4).

There were no significant differences regarding amplitude of knee flexion and hospital stay (table 5). Two patients in Ropivacaine group (at 5h and 7h postoperatively) needed additional analgesia (Diclofenac Sod. 75 mg I.M.) as VAS exceeded 5. One patient in Ropivacaine group had vomiting 6 hours postoperatively which needed rescue treatment. One patient in Ropivacaine –Verapamil group had mild hypotension 12 hours postoperatively due to blood loss which needed blood transfusion. Technical difficulties were recorded during insertion of the femoral catheter in 3 patients; two of them due to development of hematoma which necessitated a firm compression for about 10 minutes, and the third one due to obesity (table 5).

Discussion

In the present study, we demonstrated that Ropivacaine alone

in the used regimen for “3-in-1” femoral block showed satisfactory postoperative analgesic results after TKR. Moreover, our results showed significant differences in resting and moving VAS between the two groups indicating that addition of verapamil improved the analgesic quality after TKR. We used Ropivacaine and not bupivacaine as it is a long acting local anesthetic and has less cardiovascular and central nervous toxicity compared to equivalent doses of bupivacaine. Thus, it is suitable for our patients undergoing TKR as most of them are commonly old and have limited cardiac and pulmonary reserves. There is a conflict about the proper dose of Ropivacaine for femoral nerve block [10-12]. Previous studies used Ropivacaine 0.5 % as a bolus dose of 30 ml and infusion rate 10-15 ml/hr of 0.2- 0.3 % [10] or 20 ml of Ropivacaine 0.5 % combined with sciatic block followed by infusion rate of 2-3 ml/hr of 0.2% [11] or Ropivacaine 15 ml of 0.75 % in combination with sciatic block without general anesthesia [12]. On the other hand, another report showed analgesia up to 9 hours with a single injection femoral nerve block using 30 ml of bupivacaine 0.25 % concomitant with epidural analgesia [19]. We used Ropivacaine for “3-in-1” femoral block in a bolus dose of 15 ml Ropivacaine 0.75 % in combination with general anesthesia. This dose achieved a successful complete sensory and motor block in 95% of patients within 30 minutes. That result is in agreement with the previous reports which concluded that complete sensory femoral and obturator block was achieved in 95 % of patients with 20 ml Ropivacaine 0.5 % [11] or 10 ml Ropivacaine 0.75 % [12]. The last research confirmed also that the given dose achieved analgesia up to 10 hours and motor block up to 6 hours. In our study, we started infusion immediately after recovery from general anesthesia as our aim was to test the value of adding verapamil to Ropivacaine. However, in group “R” the infusion of Ropivacaine 0.2 % in an infusion rate of 5 ml/h led to a satisfactory postoperative analgesia as manifested by a low VAS either during rest or physiotherapy and minimal requirement of systemic analgesia.

It has been shown that verapamil significantly prolongs the anesthetic duration of lidocaine when used for brachial plexus block [17] or for epidural analgesia with bupivacaine after lower abdominal surgery [14], and potentiates antinociceptive effects of morphine at the spinal cord level in an animal model [15]. Different doses of verapamil were used in different techniques. Epidural verapamil 5 mg was given with 10 ml bupivacaine 0.5 % and achieved good postoperative analgesia [14]. Verapamil 2.5 mg was chosen as a bolus dose for our study because this dose has previously shown to potentiate the antinociceptive properties of morphine in humans [20] and prolongs the duration of sensory anesthesia when used for brachial plexus block [17]. In the used bolus dose of verapamil we did not detect any significant change in the pattern of motor and sensory blocks between Ropivacaine and Ropivacaine- Verapamil groups. However, there was a trend – although non significant – towards faster onset of both motor and sensory block for R-V group. That is also consistent with study’s overall observation that verapamil is an effective adjunct. It seems that verapamil may enhance the start of the block if the dose is increased.

Verapamil in our study- potentiates the postoperative analgesic property of Ropivacaine as shown by the significant reduction of VAS in patients that received verapamil throughout the studied period after recovery. We could not confirm from that study if

verapamil prolongs the analgesic action or not as we started infusion of verapamil immediately after recovery from general anesthesia, so we are not sure if this effect is due to the bolus dose or infusion. What is confirmed in our study is that VAS of verapamil group displayed significant decrease compared with the other group. This effect continued during rest in the first 12 hours after surgery and during physiotherapy in the second and third postoperative days. This result confirms the previous reports [14-17]. However, although both resting and active VAS scores were statistically different, resting VAS was already so low by the effect of Ropivacaine that additional reduction was not clinically meaningful but a VAS reduction of > 2 is probably clinically significant for VAS with activity.

It was shown that the combined administration of local anesthetics and verapamil results in a significant drug interaction increasing the toxicity of local anesthetics when administered to mice [21]. They recommended that caution should be exercised in giving verapamil to patients during regional anesthesia. Our study showed that administration of verapamil with Ropivacaine in “3-in-1” FNB is safe and did not result in local toxic effect or systemic hemodynamic changes. While there appears to be a trend towards lower HR/BP in the R-V group, it is both statistically and clinically non significant and may be due to slightly less sympathetic discharge due to less pain or direct systemic calcium channel blocker effects. Hypotension that happened in one patient of the R-V group after 12 hours was due to blood loss and not due to verapamil. However, further studies should be performed using different doses of verapamil with Ropivacaine for “3-in-1” FNB after TKR to determine the optimal dose that definitely potentiates the analgesic effect without possible side effects. In our study, we couldn’t clarify the role of verapamil in affecting the duration of hospital stay. We performed a complete physical rehabilitation in our hospital so; the total duration of hospital stay included the postoperative period and rehabilitation phase of recovery. Our result is comparable with other studies that showed hospital stay of 17 ± 3 days [22]. The second limitation of our study is that we did not assess the difference of density of motor block between the 2 groups in the days 1&2 after surgery. However-from our observation-the used small dose of Ropivacaine caused just light numbness in the operated side without great affection of motor power. This is together with the free non-operated limb enabled the patient to walk with the aid of a walker.

From this study, we can conclude that addition of verapamil potentiates the analgesic effect of Ropivacaine in “3-in-1” continuous femoral nerve block.

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