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Abstract

Pain management is a main determinant of functional recovery after total knee arthroplasty (TKA). We performed a randomized, controlled, double blind study to evaluate additive efficacy of periarticular anesthesia in patients undergoing TKA in reducing post-operative pain, operated limb edema and improving post-operative mobility. Patients were randomly assigned to study or control group; all subjects received the same analgesic protocol; before wound closure, the study group received also a periarticular anesthesia (ropivacaine 1% 20 mL). The results show no statistical differences in any of the variable evaluated. Our data suggest that additive periarticular anesthetic protocol with ropivacaine 1% 20 mL is not superior to oral and intravenous analgesia alone in patients undergoing TKA, regarding post-operative pain control, operated limb edema reduction and post-operative mobility improvement.

Keywords: analgesia; arthroplasty; knee replacement; outcome; periarticular injection; range of motion.

Introduction

Pain is a major concern in patients undergoing total knee arthroplasty (TKA) and it is an acknowledged limitation to functional recovery. Pain perception is a complex process mediated by multiple pathways and mechanisms in both central and peripheral nervous systems. Each class of analgesic agents acts on different pain pathways based on their target receptor and combining different classes of drugs and techniques, to target more than one pathway at the same time (multimodal analgesia), is gaining increasing attention for clinical management of pain syndromes of different etiology [1]. Multimodal analgesia aims to maximize control of pain while limiting side effects of analgesic therapies and it has been shown to be superior compared to a single therapeutic choice in the reduction of post-operative pain and local response to surgical stress [2]. In practice a multimodal analgesia protocol consists in the administration of an opioid plus a second or more class of analgesic drugs like nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (CCS) and anesthetics. In recent years there has been a growing interest in periarticular multidrug infiltration (PMDI) [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16] consisting in associations of anesthetic, opioid, epinephrine, NSAID and CCS, in patients undergoing TKA. These PMDI protocols showed encouraging results regarding pain relief, post-operative analgesic consumption reduction and functional outcome improvement. The combinations of analgesic drugs used in PMDI act on peripheral opioid receptors, nociceptors and local mediators of inflammation, inhibiting the central transmission of the painful experience and stimulating the production of prostaglandins with analgesic, anti-inflammatory and antipyretic effect. Three meta-analyses have evaluated the efficacy and safety of PMDI in patients undergoing hip and knee joint arthroplasties [17], [18], [19]: the results showed that PMDI could be recommended for post-operative pain management; however, little is known about the role of each single drug in determining such benefits. Thus, the real effectiveness in post-operative pain reduction, range of motion (ROM) improvement and outcome of local anesthetic infiltration alone after total joint arthroplasty remains still unclear [20], [21]. In light of these considerations, the aim of this study was to evaluate the efficacy of adding periarticular anesthesia in patients undergoing TKA in reducing post-operative pain and improving post-operative mobility, through ROM evaluation. Secondarily, we evaluated the impact of additive periarticular anesthesia on edema of the operated limb and functional outcome in these patients.

Materials and methods

Study Population

The study was designed as a prospective, randomized, double-blind, controlled trial. Eligible subjects were recruited among patients admitted for primary, unilateral, TKA between January and December 2013. The inclusion criteria were the following: primary knee osteoarthritis, age > 60 years; the exclusion criteria were: cognitive impairment, sensory or motor disorders in the operated limb, known allergy to the study medications or history of drug abuse. No other inclusion/exclusion criteria were considered in order to obtain a population more similar to everyday clinical practice. After enrollment patients were randomly divided in two groups; the first group (A) received multimodal analgesia protocol with additive periarticular anesthesia while the second group (B) received multimodal analgesia protocol only. Randomization was done by the anesthetist, prior to procedure, using a computer-generated randomization block. Patients, physiotherapists, nursing staff, the surgeon and the physician who performed all the evaluations, were blind regarding whether the subject received periarticular analgesia or placebo. All patients signed a written informed consent. The procedures in this study were in accordance with the Declaration of Helsinki.

Procedures

As previously described, patients included in the study were randomly allocated to group A or group B. All subjects underwent single shot spinal anesthesia, induced at L4-L5 or L3-L4 using 25G Pencan spinal needle with bupivacaine 0.5% 12 mg. All patients received the same oral and intravenous (i.v.) multimodal analgesic protocol described as follows: oxycodone/naloxone 10/5 mg every 12 hours the day before surgery; 20/10 mg every twelve hours the surgery day, 10/5 mg or 20/10 mg twice a day until day 2 after the operation and 5/10 mg or 10/5 mg day 3, in relation to patients weight; a single dose of methylprednisolone 250 mg (2 mL) i.v. just before performing anesthesia; etoricoxib 90 mg daily for 15 days after surgery. The two protocols are resumed in Fig. 1. An intramuscular injection of ketorolac 10 mg (1 mL) repeatable every six hours, was used on the day of surgery as rescue dose when patients reported pain greater than 4 on Numeric Rating Scale (NRS) [22]. Prior to wound closure, subjects assigned to group A received periarticular injections with ropivacaine 1% (20 mL). The total dose of ropivacaine administered was 200 mg. The solution was injected into posteromedial and posterolateral

corners, posterior capsule, quadriceps and wound margins. The same surgeon performed all the injections. Subjects of group B received a placebo injection with 20 mL of normal saline. Patients did not have any nerve blocks. All implants were posterior-stabilized and did not include patellar resurfacing. Both groups participated in the same rehabilitation program of three hours daily for three weeks starting the day after surgery. After discharge, all the patients enrolled in the study followed a standardized home rehabilitative program.

Outcome Measures

The severity of pain was assessed at rest, during active motion and during the night, using NRS; all evaluations were performed the day before surgery, the surgery day (2-4-6-12 hours after surgery) and at days 1–4, 5, 10, 15, and 21 after surgery. Analgesic rescue dose (ketorolac 10 mg repeatable every six hours) consumption was recorded the surgery day. Active and passive ranges of motion were recorded the day before surgery and at days 2, 5, 10, and 21 after surgery. Edema was assessed measuring circumference of the operated limb at the middle of the patella, one-third, two-thirds above and below the patella, at the ankle (the day before surgery, days 5-10-15-21 after surgery). Functional outcome was assessed in the rehabilitation unit until three weeks after surgery using the FAC scale and the Barthel index [23], [24]. FAC scale evaluates specifically the ambulation (kind of surface, necessity of aids, supervision or assistance). Barthel index is an international validated scale for the evaluation of the autonomy in activity of daily living (that can be influenced by pain, limited ROM or complication after TKA).

Statistical analysis

To obtain the correct sample size we used the effect size calculated in a recent review by Marques et al. about local anesthetic infiltration for peri-operative pain control in total hip and knee arthroplasties. The effect size, measured by mean standardized difference, at rest 24 hours after surgery was during activity − 0.85 (95% CI − 1.45, − 0.25; p = 0.006) [19]. The sample size needed to have an alpha error of 0.05 and a power (1-beta) of 0.80 supposing a two tail gaussian distribution was 54 patients. Regarding the minimum difference using the formula 1.96 * standard error of the mean (SEM) * $\sqrt{2}$ we obtained a value of minimal important change of 1.41 regarding group A and 0.85 for group B [25]. The sample size and power measures were calculated with the software G*Power3. Statistical analyses were performed using the GraphPad 4.0 (GraphPad Software, Inc.,

San Diego, CA, USA). Due to the low numerosity of the sample we assumed a non-gaussian distribution of the considered variables. Differences between single variables at different times in each group were evaluated with the one way Friedman analysis of variance (ANOVA) for repeated measure and Dunn's post hoc test. Differences for each variable at each evaluation time among the two groups were evaluated with two way ANOVA and Bonferroni post-hoc test. A type I error level of 0.05 was chosen. A P value lower than 0.05 was considered statistically significant.

Results

A total of 64 patients were enrolled receiving a complete analgesic protocol. Thirty-two patients were assigned to group A and 32 to group B. The day before surgery two patients of the group B quit the study because of opioid related side effects (nausea/vomiting). Adverse events were self limiting after oxicodone interruption. The demographical and anamnestic characteristics of the studied population are resumed in Table 1. No periarticular injection related adverse events and differences in wound healing between the two groups were observed.
No statistical differences at any evaluation were observed regarding pain, edema and ROM among the two groups (Fig. 3, Fig. 4, Fig. 5). The same results were observed throughout the rehabilitation program.

Discussion

The results of this study showed no statistical difference in adding a periarticular anesthesia protocol (ropivacaine 1%, 20 mL) in patients undergoing TKA, regarding post-operative pain reduction and ROM improvement. Moreover, no differences were recorded among the two groups about edema reduction of the operated limb and functional outcome up to three weeks after surgery. Given the expanding number of joint arthroplasties and the severe pain following these procedures, the optimal postoperative management is becoming increasingly important as a public-health concern. The failure to provide adequate analgesia hinders early rehabilitation which is critical to maintain ROM and potentially delay hospital discharge [26]. Meanwhile elderly patients show an increased prevalence of chronic diseases and pharmacological polytherapy with consequent increased chances of drugs side effects and unpredictable interactions. Early pain control

can influence its subsequent evolution avoiding long term neuronal remodeling and sensitization [27]. The administration of analgesic drugs before the noxious stimuli onset (pre-emptive analgesia) has an important role to prevent sensitization of the central nervous system throughout the perioperative period [28]. To date there are several analgesic strategies but there is no gold standard protocol for patients undergoing total joint replacements [29]. In light of these considerations, periarticular injections from various drugs combinations (like adrenaline, anesthetics, NSAIDs, opioids and CCS) are an effective way to reduce oral drug consumption and side effects occurrence 17., 18.. However available studies have not determined whether each of these drugs alone achieves similar improvements in pain management. Defining the effectiveness of each drug alone could encourage the development of a standardized PMDI protocol, avoiding the use of expensive and noneffective drugs. Our study demonstrates that periarticular anesthetic injection (ropivacaine 1%, 20 mL), in association with a multimodal oral and intravenous analgesia (oxicodone/naloxone, methylprednisolone, etoricoxib) is not superior to the multimodal oral and intravenous analgesia alone in terms of pain control, edema reduction and functional outcome until three weeks after surgery. In particular we observed no significant differences in NRS scores and analgesic drug consumption on the day of surgery. Our data are somehow in line with other previous studies performed about periarticular anesthetic injection regarding pain perception after arthroplasty, however previous evidence about multimodal analgesia protocols after TKA is scarce and contrasting. Yuenyongviwat et al [21] showed that periarticular 20 mL of 0.25% bupivacaine administration is able to reduce morphine consumption on the surgery day; on the other hand no differences were found in visual analogical scale (VAS) at any time after surgery between case and control group. Lastly, they administered a different multimodal analgesic protocol compared to the one used in this study. Murphy et al [20] performed a periarticular anesthetic injection with 150 mg levobupivacaine in 60 mL 0.9% saline in patients undergoing total hip arthroplasty reporting similar pain scores (VAS and McGill pain score) for treatment and control groups in the postoperative period and less mean morphine consumption in the levobupivacaine group. However, they observed no differences in the frequency of postoperative nausea and vomiting or urinary retention in these patients. This work has some limitations: first the sample is relatively small compared to similar studies. Second this was a monocentric study, thus our results could have been biased and the inclusion of other centers may have strengthened the generalizability of the results. Moreover, to evaluate patients functional outcome, we

choose outcome questionnaires widely used to assess disability in hospitalized patients but not specifically validated for TKA. Finally, the results of our study are related only to patients undergoing spinal anesthesia and could not be generalized for general anesthesia procedures.

In conclusion, our data suggest that additive periarticular anesthetic protocol with ropivacaine 1% 20 mL (200 mg) is not superior to an analgesic multimodal oral and endovenous protocol alone in patients undergoing TKA, regarding post-operative pain control, operated limb edema reduction and post-operative mobility improvement. While multimodal analgesic protocols are a safe and effective way to reduce pain after joint arthroplasties, the role of any single drug remains still unclear. Thus, further research is needed to investigate the single contribution of each drug commonly used in multimodal periarticular analgesia in post surgical pain management.

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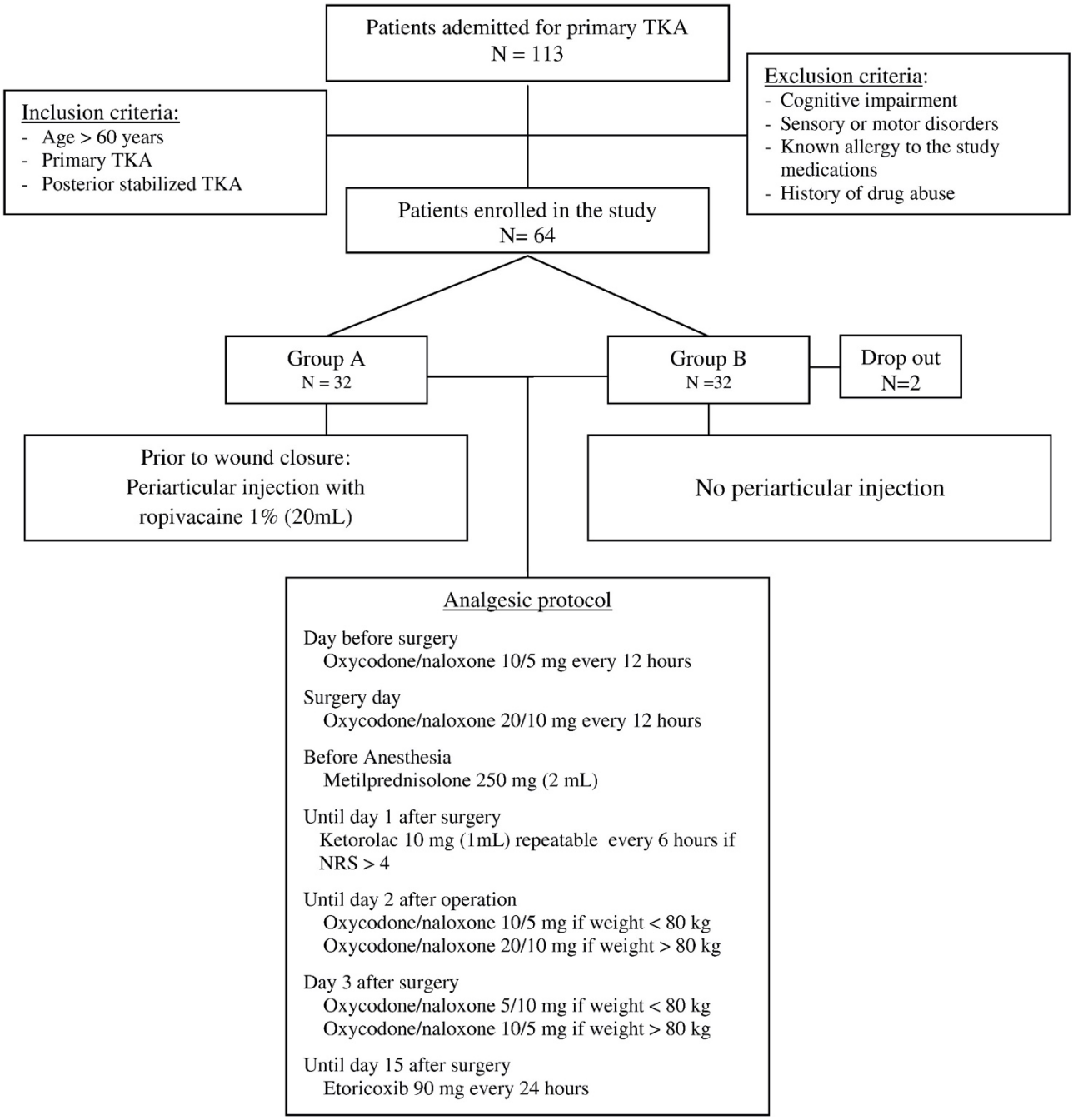

Figure 1. Study flow chart.

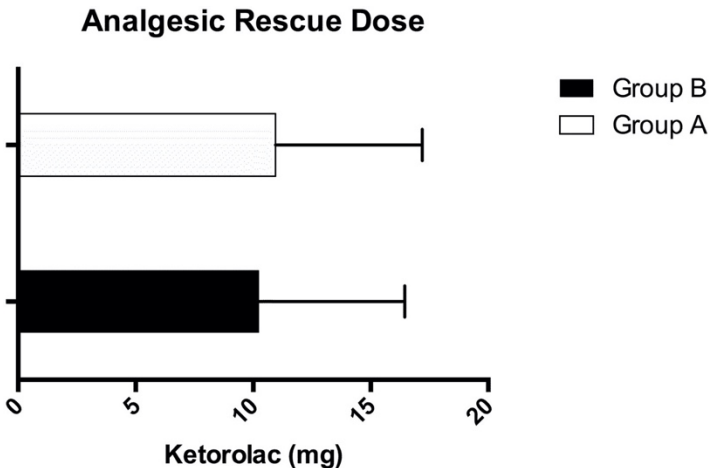

Figure 2. Ketorolac consumption as rescue dose on surgery day.

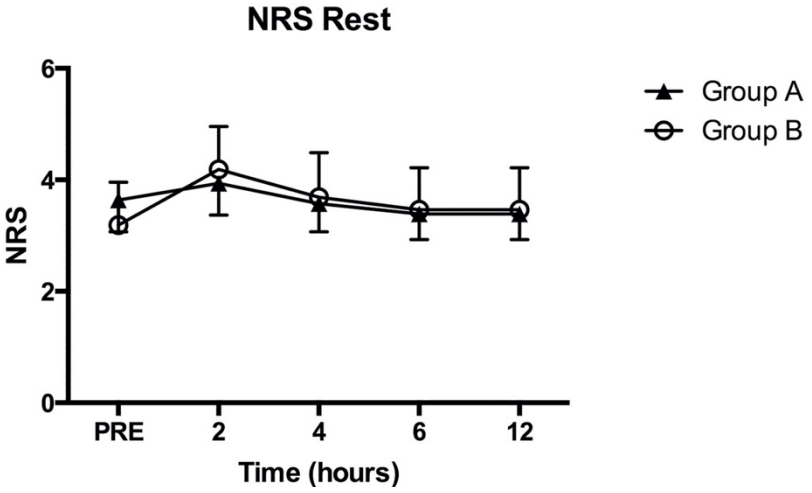

Figure 3. NRS at rest on surgery day.

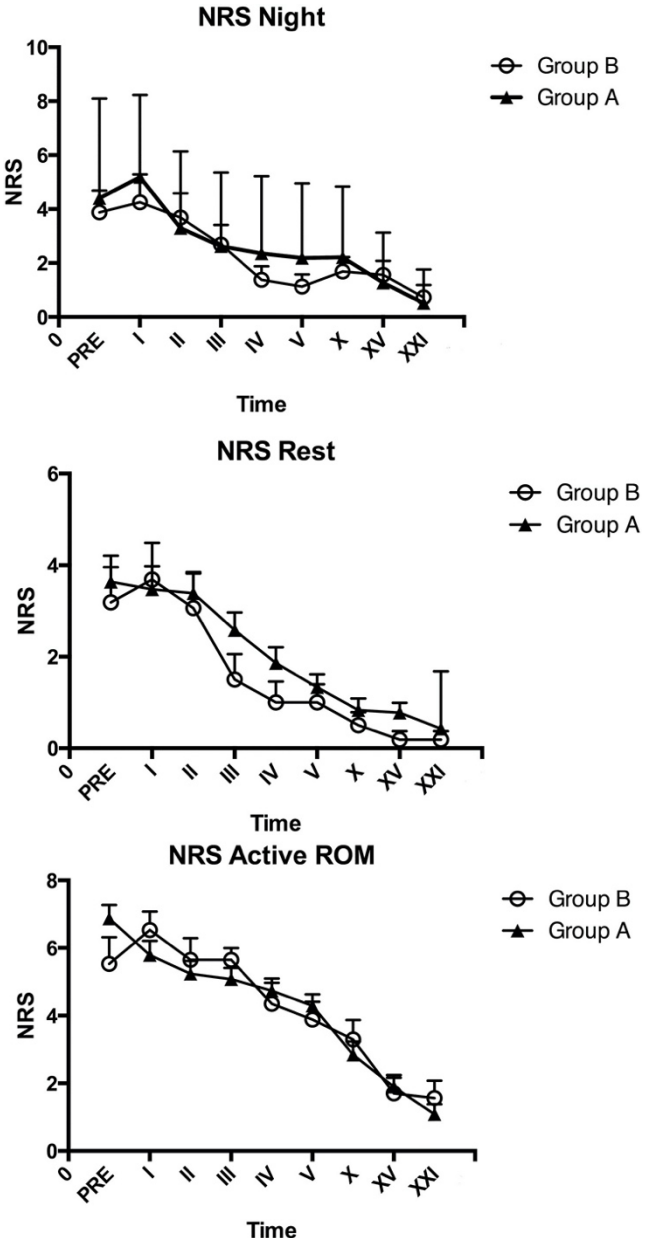

Figure 4. NRS at rest, at night and during active motion from day 1 to day 21 after surgery.

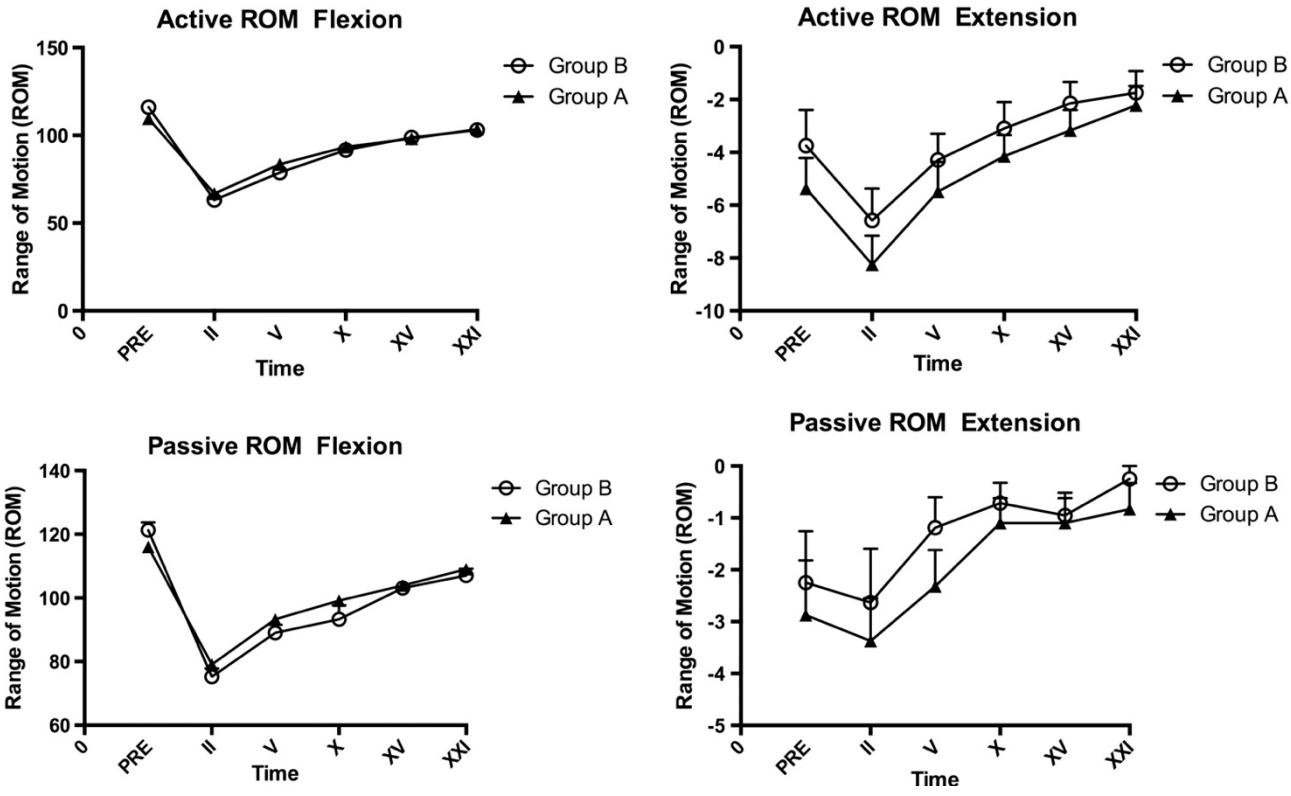

Figure 5. Active and passive ranges of motion of the operated knee from day 1 to day 21 after surgery.

	Group A (n = 32)	Group B (n = 32)
Gender (F/M)	2:1	2:1
Mean age	70.6 ± 8.4	71.24 ± 7.5
Drop out	0	2
BMI ≥ 30	6 (18.75%)	7 (23.33%)
Hypertension	15 (46.87%)	17 (56.66%)
Dyslipidemia	10 (31.25%)	10 (30%)
Diabetes	5 (15.62%)	1 (3.33%)
Disthyroidism	4 (12,5%)	0
Anxiety-depressive disorder	4 (12.5%)	3 (10%)
Contralateral TKA	8 (25%)	6 (20%)

TKA = total knee arthroplasty; BMI = body mass index.

Table 1. The Demographical and Anamnestic Characteristics of the Studied Population.