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## RESEARCH ARTICLES

# Postoperative Pain Significantly Influences Postoperative Blood Loss in Patients Undergoing Total Knee Replacement

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**ABSTRACT**

*Background and Objectives.* Although hypertension has long been recognized as a factor that might increase intraoperative blood losses in major orthopedic surgery, the effects of postoperative pain-induced hypertension on blood losses have not so far been evaluated. The aim of this study was to evaluate the effect of pain on perioperative blood losses of patients undergoing primary total knee replacement (TKR).

*Methods.* Data from patients participating in a randomized clinical trial comparing intravenous patient-controlled analgesia (PCA) (N = 20) with PCA plus continuous femoral nerve (three-in-one) block (N = 20) or PCA plus continuous posterior lumbar plexus (psoas compartment) block (N = 20) were prospectively and retrospectively collected. Correlations between relevant variables and measured and calculated blood loss, number of transfused unit, and late (96 hours) postoperative hemoglobin were tested by linear regressions. Stepwise regressions for each of the four above-mentioned goals were constructed using a probability to enter of 0.25 and to leave of 0.1. A $P < 0.05$ was considered significant.

*Results.* At the stepwise regressions there was a significant positive correlation between measured blood losses and morphine consumption from 12 to 18 hours ($P = 0.006$); between calculated blood loss and preoperative mean arterial blood pressure ($P = 0.01$) and preoperative hemoglobin value ($P = 0.02$); and between late postoperative hemoglobin and body weight ($P = 0.047$).

*Conclusion.* In patients undergoing TKR, there is a significant correlation between measured blood loss and morphine consumption from 12 to 18 hours. It is concluded that postoperative pain significantly influences postoperative blood loss in patients undergoing TKR.

*Key Words.* Blood Loss; Surgical; Blood Transfusion; Orthopedic Surgery; Total Knee Replacement; Postoperative Pain

### Introduction

Total knee replacement (TKR) is accompanied by high postoperative blood losses and often requires administration of allogenic red blood cells [1]. Factors that have been reported to increase blood losses are: simultaneous bilateral TKR [2], tourniquet release for hemostasis [3], and postoperative wound drainage [4]. Preoperative exsanguination of the operated limb with an Esmarch bandage [5], tourniquet use [6], hypotensive epidural anesthesia in the absence of tourniquet use [7], and fibrin sealant spray [8] decrease blood losses while temporary clampage of wound drains [9] has no significant effect. Transfusion rate, which varies widely depending on local hospital practices, is increased by low preoperative hemo-

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globin level [10], insertion of a noncemented prosthesis [3], and revised [11] or bilateral simultaneous TKR [2]. The effects of increased age on transfusion rate are controversial [10,12]. Appliance of strict transfusion criteria [13], blood predonation [11], hypotensive epidural technique (in the absence of tourniquet use) [7], fibrin sealant spray [8], postoperative blood salvage and reinfusion [14], erythropoietin [15], and antifibrinolytic agents [16] have all been proposed to reduce allogenic transfusion rate. Although hypertension has long been recognized as a factor that might increase intraoperative blood losses in major orthopedic surgery [17], the effects of postoperative pain-induced hypertension on blood losses have not so far been evaluated. The aim of this study was to evaluate the effect of pain and pain treatment modalities on perioperative blood losses of patients undergoing primary TKR.

## Methods

Data from patients participating to a randomized study (block randomization of six patients with two of each treatment group) comparing three methods of postoperative analgesia for patients undergoing TKR were prospectively and retrospectively (blood pressures and the use of β-blockers) collected [18]. The local ethics committee approved this study and a written informed consent was obtained for all patients. Sixty American Society of Anesthesiologists (ASA) I to III patients aged 20–80 years scheduled for a primary cemented TKR for osteoarthritis were included in the study and received: intravenous (IV) morphine patient-controlled analgesia (PCA) alone (N = 20) or IV PCA plus a continuous femoral (three-in-one) nerve block (CFNB) (N = 20) with 30 mL of ropivacaine 0.5% (Naropin® AstraZeneca, Mississauga, Ontario, Canada) with freshly added epinephrine 1:200,000 followed by an infusion of plain ropivacaine 0.2% at 12 mL/h for 48 hours (N = 20) or a continuous posterior lumbar plexus (psoas compartment) nerve block (CPNB) with the same amount of the same solutions of local anesthetics. All blocks were performed in a regional anesthetic induction room by either a staff anesthesiologists familiar with the technique or a fellow in regional anesthesia according to the techniques described by Winnie et al. [19]. Catheters were systematically withdrawn at 48 hours.

Patients allergic to one of the substances used or with a congenital or acquired coagulopathy (including taking a medication with known effects on hemostasis or coagulation within the last 7 days) were excluded from the study.

The surgery was performed under normotensive spinal anesthesia with 12.5–15 mg of isobaric 0.5% bupivacaine (Marcaine®, Hospira, Montreal, Quebec, Canada) and fentanyl 10–15 μg. All patients had a cemented prosthesis inserted through a classic medial parapatellar arthrotomy and a tourniquet settled at 150 mm Hg over the systolic blood pressure was applied until skin closure. Fibrin sealant was not used and a compressive splint was installed at the end of the surgery. A negative pressure wound drain (hemovac) was inserted and kept for 24 hours after the surgery. There was no perioperative blood reinfusion. Passive knee motion was started on postoperative day one.

Intraoperative blood losses were obtained by weighing sponges and measured blood recovered in suction canisters. Postoperative blood losses were obtained by measuring volume of blood recovered in suction drains. Total blood losses were also estimated with the following formula:

$$\{[(\text{Initial Hb} - \text{Final Hb})/(\text{Mean Hb})] \times \text{EBV}\} + \text{TBV}$$

where Initial Hb, Final Hb, Mean Hb, EBV, and TBV are defined as:

- Initial Hb: preoperative hemoglobin measured the morning of the surgery
- Final Hb: final hemoglobin measured at 96 hours after the surgery
- Mean Hb: (Initial Hb + Final Hb)/2
- EBV: estimated blood volume calculated as 65 mL/kg body weight for men and 60 mL/kg for women
- TBV: transfused blood volume calculated as 500 mL for each unit of diluted packed red blood cells or autologous whole blood administered.

Hemoglobin levels were measured preoperatively, in the recovery room, and at 24, 48, and 96 hours after the surgery. Blood losses were replaced with Ringer Lactate (three volume for one volume) or colloids (Pentaspan®, Bristol-Myers Squibb, Ontario, Canada) until the hemoglobin reached a predefined minimal acceptable value defined as 9.0 g/dL in women over 65 years of age and men over 60 years of age or patients with a known history of coronary heart disease or instable intra- or postoperative vital signs and 7.0 g/dL for all others.

Rectal temperature at the arrival at the postanesthesia care unit (PACU) was noted. Sodium indomethacin suppository (Indocid®, Ratiopharm, Mississauga, Ontario, Canada) 100 mg twice a day for a 48-hour period was also added to the postoperative analgesic regimen unless contraindicated (previous history of upper gastrointestinal tract ulcers or bleeding, evidence of renal insufficiency (creatinine blood level higher than 150 μmol/L). Postoperatively, patients were routinely seen twice a day or more if needed by a trained nurse under the supervision of an anesthesiologist to make sure that pain was appropriately controlled. Thromboembolic prophylaxis was ensured by enoxaparin 30 mg administered subcutaneously twice a day started on postoperative day one. Systolic (SP) and diastolic blood pressure (DP) before surgery, at the end of surgery (after tourniquet release) at the arrival at PACU, at 6, 24, and 48 hours, and during physiotherapy on postoperative day one and two were retrospectively retrieved from the charts. Mean arterial blood pressure (MAP) was calculated by the formula MAP = P + [(SP − P)/3].

Data were analyzed with the JMP 5.0.1, Professional Edition (SAS Campus Drive, Cary, NC, USA, 2002) and Prism 4.0 (GraphPad Software Inc, San Diego, CA, USA, 2003). Differences between the three study groups were compared by Chi-square tests, Kruskal–Wallis analysis, ANOVA, or repeated measures ANOVA (followed by the Student–Newmann–Keuls or the Scheffe test where needed). The effects of age, weight, height, estimated blood volume, preoperative and final (96 hours) hemoglobin values, length of surgery, verbal analogical pain (VAS) scores at rest at 6, 24, and 48 hours and at motion on postoperative day one and two, of morphine consumption by 6-hour intervals from 0 to 48 hours and of total morphine consumption (0–48 hours), of rectal temperature at arrival in PACU, and of mean arterial blood pressure before the surgery and at the end of surgery (after tourniquet release), at arrival in PACU, at rest at 6, 24, and 48 hours and during automated passive knee mobilization on postoperative day one and two on measured, calculated, and transfused blood losses and on final (96 hours) postoperative hemoglobin values were first tested with linear regressions. Data with a $P$ value <0.25 were used for the stepwise regression analysis (probability to enter of 0.25 and to leave of 0.1). Comparisons of mean measured blood losses between patients who received sodium indomethacin or β-blockers or not were performed with Student's *t*-tests.

## Results

One patient had to be switched to subcutaneous (SC) hydromorphone because of poor understanding of the PCA device. Equivalence was made from SC hydromorphone to IV morphine for his morphine consumption (ratio of 5 to 1) and the patient's data were treated on an intention-to-treat basis. General data for each of the three study groups are provided in Table 1. VAS scores at rest

**Table 1** General data

| | IV PCA (N = 20) | CFNB (N = 20) | CPNB (N = 20) | *P* |
|---|---|---|---|---|
| Age (year) | 69.5 (4.9) | 66.7 (12.1) | 69.9 (6.9) | 0.80 |
| Sex (female/male) | 13/7 | 12/8 | 13/7 | 0.67 |
| Use of β-blockers (yes/no) | 3/17 | 6/14 | 6/14 | 0.43 |
| Length of surgery (min) | 102.0 (16.6) | 108.9 (16.9) | 117.1 (24.3) | 0.06 |
| Sodium indomethacin (yes/no) | 16/4 | 19/1 | 18/2 | 0.32 |
| Hemoglobin values (g/dL) | | | | 0.32 |
| Preoperative | 13.2 (1.2) | 13.7 (1.7) | 13.0 (1.5) | |
| Postoperative (96 hours) | 9.4 (1.1) | 9.4 (1.1) | 9.2 (1.1) | |
| Measured blood loss (mL) | 765.3 (432.6) | 743.4 (356.3) | 733.0 (409.5) | 0.97 |
| Calculated blood loss (mL) | 2,287.0 (1,075.0) | 2,752.4 (1,175.6) | 2,606.5 (330.1) | 0.49 |
| Number of units transfused | 0 (0–2) | 0 (0–2) | 0 (0–2) | 0.97 |
| Mean arterial blood pressure at rest (mm Hg) | | | | 0.85 |
| Preoperative | 105.1 (12.6) | 106.2 (14.9) | 107.9 (13.5) | |
| Intraoperative | 91.7 (12.0) | 88.3 (15.6) | 88.3 (12.2) | |
| Postanesthesia care unit | 95.2 (11.4) | 90.8 (10.5) | 92.7 (11.8) | |
| At 6 hours | 91.8 (13.1) | 95.3 (11.5) | 92.0 (9.9) | |
| At 24 hours | 89.0 (11.3 | 87.7 (11.3) | 90.1 (10.4) | |
| At 48 hours | 89.4 (12.0) | 91.0 (11.9) | 92.0 (9.3) | |
| Mean arterial blood pressure during physiotherapy (mm Hg) | | | | 0.14 |
| POD one | 89.3 (12.1) | 92 (3.6) | 93.3 (4.2) | |
| POD two | 83.0 (8.3) | 89.3 (8.1) | 93.5 (11.0) | |

IV PCA = intravenous patient-controlled analgesia with morphine alone; CFNB = continuous three-in-one femoral nerve blockade for 48 hours plus IV PCA; CPNB = continuous posterior lumbar plexus (psoas compartment) block for 48 hours plus IV PCA; POD = postoperative day. Data are given as mean (±SD) for continuous variables with normal distribution and as median (interquartiles 25th–75th) for other variables.

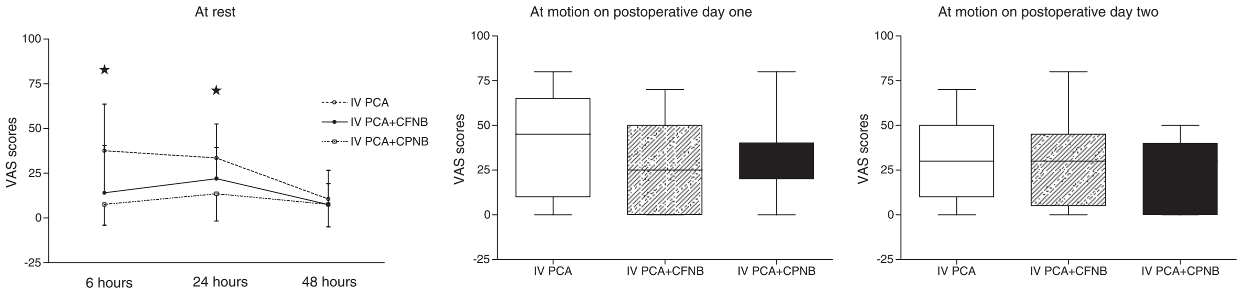


**Figure 1** Effect of analgesia technique on VAS scores at rest and at motion on postoperative day one and day two in patients undergoing total knee replacement. VAS scores at rest were significantly higher at 6 and 24 hours for the group with IV PCA than the two other groups ($P < 0.0001$), which did not differ between them. VAS scores at motion on postoperative day one and two were comparable among the three groups. VAS = verbal analogical pain scores; IV PCA = IV morphine patient-controlled analgesia alone; IV PCA+CFNB = IV PCA plus continuous femoral nerve block; IV PCA+CPNB = IV PCA plus continuous posterior lumbar (psoas compartment) nerve block.

and at motion, measured blood loss and morphine consumption according to the analgesic technique are given in Figures 1–3. Data who showed a statistically significant correlation ($P < 0.05$) with measured blood loss (up to 24 hours) were: mean arterial blood pressure during physiotherapy on postoperative day two ($P = 0.02$; negative) and morphine consumption from 12 to 18 hours ($P = 0.02$; positive; Figure 4A) and from 18 to 24 hours ($P = 0.03$; positive; Figure 4B). There was a significant correlation between calculated blood loss (total blood loss) and preoperative hemoglobin value ($P = 0.0001$; positive), morphine consumption from 6 to 12 hours ($P = 0.02$; positive; Figure 4C) and from 0 to 48 hours ($P = 0.047$; positive; Figure 4D), and preoperative mean arterial blood pressure ($P = 0.044$; positive). Final (96 hours) postoperative hemoglobin value was correlated to weight ($P = 0.04$; positive).

Data with a $P$ value <0.25 (used for the stepwise regressions) were: for measured blood loss: age, morphine consumption from 12 to 18 hours, from 18 to 24 hours, and from 0 to 48 hours, VAS scores during physiotherapy on postoperative day one and two, preoperative mean arterial blood pres-

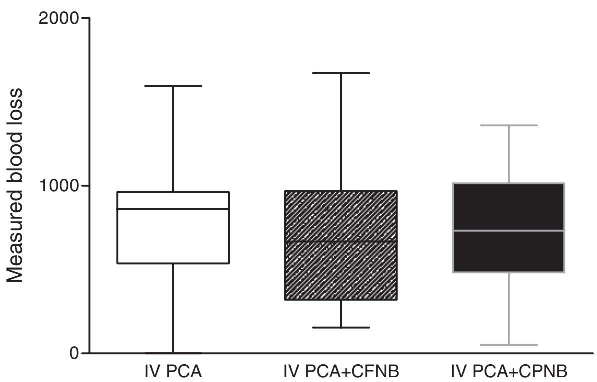


**Figure 2** Effect of the type of analgesia technique on blood loss of patients undergoing total knee replacement. Whisker boxes are constructed with the median and interquartiles (25th–75th) values. Measured blood loss was comparable for the three groups. IV PCA = IV morphine patient-controlled analgesia alone; IV PCA+CFNB = IV PCA plus continuous femoral nerve block; IV PCA+CPNB = IV PCA plus continuous posterior lumbar (psoas compartment) nerve block.

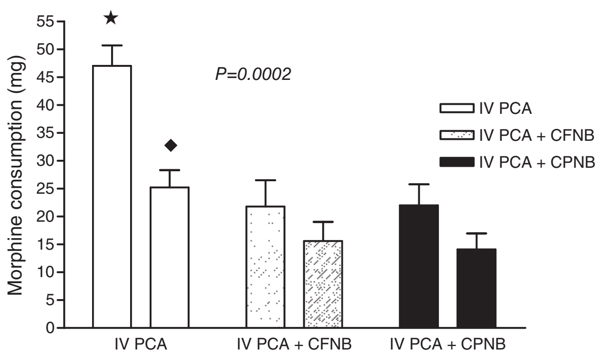


**Figure 3** Effect of the type of analgesia technique on morphine consumption of patients undergoing total knee replacement. The two groups with continuous peripheral nerve blocks required significantly less IV morphine than the group with IV PCA alone ($P = 0.0002$; repeated measures ANOVA). Post hoc tests (Scheffe) revealed that the IV PCA group required significantly more IV morphine than the continuous femoral nerve block (CFNB) group ($P = 0.0003$) and the continuous psoas compartment nerve block (CPNB) ($P = 0.0003$) for either the first (left bar of each set) or the second 24-hour period (right bar of each set) ($P = 0.046$ and 0.03, respectively). The two groups with continuous nerve blocks did not differ one from another. IV PCA = IV morphine patient-controlled analgesia alone; IV PCA+CFNB = IV PCA plus continuous femoral nerve block; IV PCA+CPNB = IV PCA plus continuous posterior lumbar (psoas compartment) nerve block. Bars indicate mean and SD.

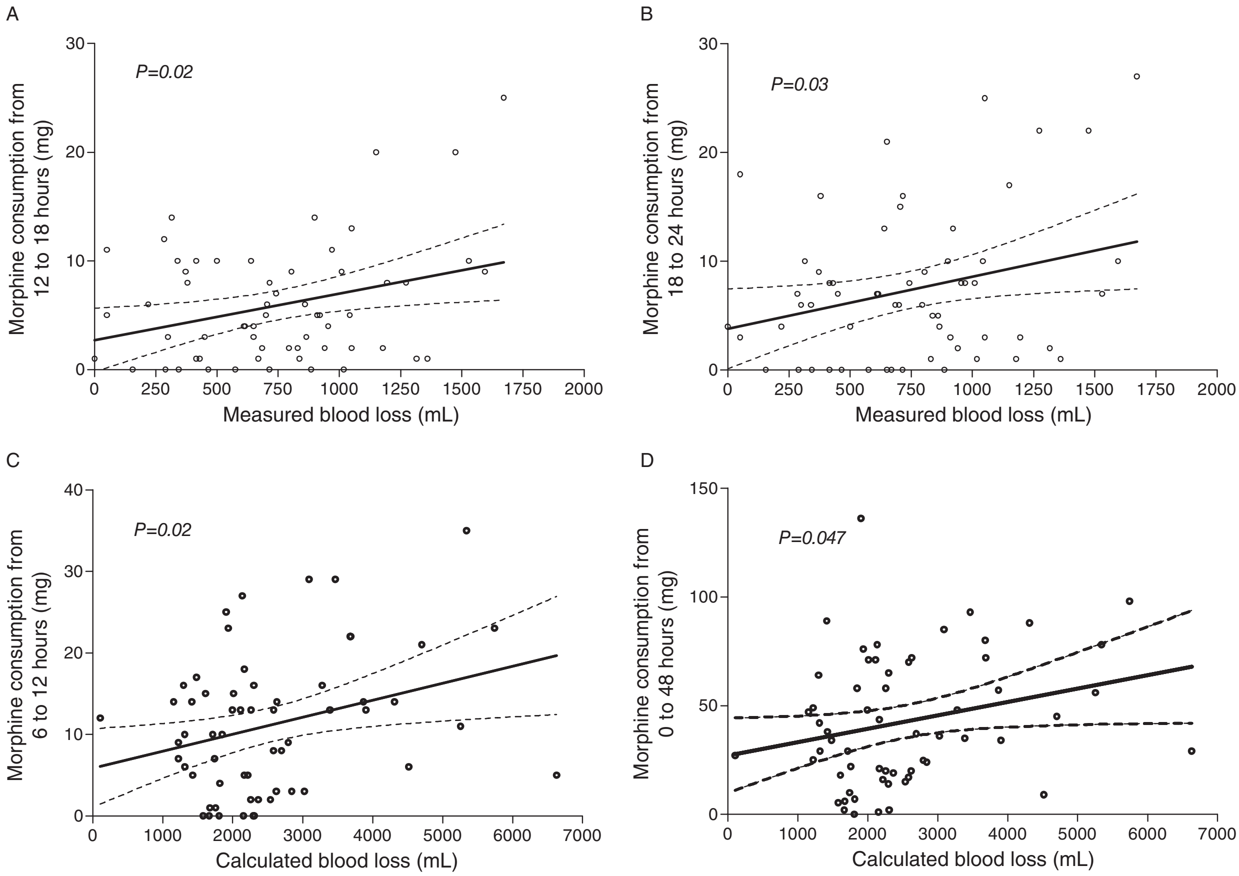


**Figure 4** Effect of postoperative pain as measured by an indirect assesor (morphine consumption) on blood loss of patients undergoing total knee replacement. Dotted lines indicate the 95% confidence intervals of the fits. There were statistically significant positive correlations between measured (up to 24 hours) blood loss and morphine consumption from 12 to 18 hours and from 18 to 24 hours. Calculated (total) blood loss was correlated to morphine consumption from 6 to 12 hours and from 0 to 48 hours.

sure, mean arterial blood pressures at 24 and 48 hours, and mean arterial blood pressure during physiotherapy on postoperative day two; for calculated blood loss: weight, preoperative hemoglobin, morphine consumption from 6 to 12 hours, from 0 to 48 hours, preoperative mean arterial blood pressure, and mean arterial blood pressure during physiotherapy on postoperative day two; for the number of transfused units: weight, preoperative hemoglobin value, preoperative mean arterial blood pressure, mean arterial blood pressure at 6 hours after the surgery and during physiotherapy on postoperative day two; and for the 96 hours postoperative hemoglobin value: weight, central core temperature measured at the arrival in PACU, and preoperative mean arterial blood pressure. Factors that remained statistically significant ($P < 0.05$) at the stepwise regressions for measured and calculated blood loss, for the number of transfused units, and for postoperative hemoglobin values are given in Table 2. The correlations between VAS scores at motion on postoperative day one and two and mean arterial blood pressure measured at the same times were not statistically

**Table 2** Factors influencing measured and calculated blood loss, number of transfused blood units, and postoperative hemoglobin values: stepwise regressions

| | *P* value | Slope |
|---|---|---|
| Measured blood loss | | |
| Morphine consumption from 12 to 18 hours | 0.006 | + |
| Calculated blood loss | | |
| Preoperative mean arterial blood pressure | 0.01 | + |
| Preoperative hemoglobin value | 0.02 | + |
| Number of unit transfused | | |
| Mean arterial blood pressure at 6 hours after the surgery | 0.02 | – |
| Postoperative hemoglobin value (96 hours) | | |
| Body weight | 0.047 | + |
| Preoperative mean arterial blood pressure | 0.037 | – |

+ indicates positive correlation; – indicates negative correlation.

significant ($P = 0.23$; $r^2 = 0.12$; positive slope and $P = 0.76$; $r^2 = 0.002$; positive slope, respectively). Fifteen patients were using β-blockers; their measured blood loss was not different from the rest of the patients: 732.9 ± 365.7 mL vs 752.0 ± 407.0 mL ($P = 0.87$). Seven patients did not receive indomethacin; their blood loss was statistically lower than the rest of the patients (710.3 ± 359.9 vs 1127.9 ± 390.6 mL; $P = 0.006$).

## Discussion

In the present study, there was a significant positive correlation between measured blood loss and an objective indirect (morphine consumption) pain indicator. This might be explained in several ways. First, through histaminic liberation, morphine might have induced peripheral venodilation and increase blood loss through this mechanism. However, the fact that morphine consumption was twice as high when PCA alone was used for postoperative analgesia (72.2 ± 26.6 vs 37.3 ± 34.7, and 36.1 ± 25.8 mg) (mean ± SD) and that blood loss was not increased in that treatment group do not favor that mechanism [18]. Second, through sympathetic stimulation, pain may increase arterial blood pressure and hence surgical blood losses. This might be particularly true in major orthopedic surgery where hypotensive anesthetic techniques have been used to decrease intraoperative blood losses [20]. In knee surgery, hypotensive anesthetic techniques may help to decrease intraoperative blood losses and transfusion rate in patients who are operated without a tourniquet [7]. For those who are operated with a tourniquet, bleeding occurs mainly after the surgery: 50% within the first 3 hours and 80% within the first 24 hours [7,21]. In the present study, it was not possible to establish statistically significant correlations between VAS scores at motion and mean arterial blood pressures measured at the same time, but mean arterial blood pressures were calculated from data retrospectively collected from the charts. Finally, even if the pain is not severe enough to significantly increase the mean systemic arterial blood pressure during physiotherapy, a patient experiencing pain might contract the moving leg and raise the venous blood pressure of that limb and increase its blood loss that way.

Knee surgery is associated with high pain scores at rest and during rehabilitation physiotherapy [22]. Plexus blocks have been claimed to reduce postoperative pain and to facilitate rehabilitation after knee surgery [22]. In hip surgery, a single shot lumbar plexus block decreases intraoperative mean arterial pressure and has a modest effect on intra- and postoperative blood losses [23]. In our study, the three modes of analgesia provided reasonably good postoperative analgesia at rest although the two groups with continuous peripheral nerve blocks had lower VAS scores at 6 and 24 hours after the surgery [18]. All the three modes of analgesia, however, were quite disappointing when used for the treatment of pain during physiotherapy as 22 patients out of 60 had VAS score of 50 or higher (scale 0–100; IV PCA = 9, CFNB = 7, and CPNB = 6) on at least one of two evaluations performed on postoperative day one and two during physiotheray and this despite a high rate of deep femoral nerve block (90% and 100% of motor blockade for the CFNB and the CPNB groups, respectively) [18]. Other authors have recently pointed out the ineffectiveness of a continuous femoral nerve block alone to adequately treat postoperative pain after TKR and suggested that the addition of a continuous sciatic nerve block might be useful in over 80% of the patients [24]. The effects of this block combination on postoperative blood loss after TKR will need further evaluation.

In summary, in patients undergoing TKR, postoperative pain significantly contributes to postoperative bleeding.

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