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Antiinflammatory Effect of Peripheral Nerve Blocks after Knee Surgery

Clinical and Biologic Evaluation

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Background: **Nerve blocks provide analgesia after surgery. The authors tested whether nerve blocks have antiinflammatory effects.**

Methods: **Patients had combined sciatic (single-shot) and continuous femoral block (48 h) (block group) or morphine patient-controlled analgesia after total knee arthroplasty. Pain at rest and upon movement was monitored at 1 (D1), 4 (D4), and 7 days (D7) and 1 (M1) and 3 months (M3) after surgery. Knee inflammation was evaluated (skin temperature, knee circumference) before surgery and at D1, D4, D7, M1, and M3. Plasma cytokine concentrations (interleukin [IL]-6, IL-1β, tumor necrosis factor [TNF], IL-10, soluble receptor 1 of TNF [sTNF-R1]) were measured before surgery and at 4 h, D1, D4, and D7 after surgery. Capsule and synovial membrane cytokines were measured (IL-6, TNF, IL-1, IL-10). Knee flexion was evaluated before surgery and at D1, D4, D7, M1, and M3. Morphine use and recovery time to autonomy were monitored.**

Results: **Pain at rest and upon movement was lower in the block group than in patient-controlled analgesia patients between D1 and D7 (analysis of variance, $P < 0.005$). Knee flexion was improved in the block group for D1 to M1 (analysis of variance, $P < 0.0001$). Block group patients recovered nonassisted mobilization (*t* test, $P = 0.04$) and toilet use (*t* test, $P = 0.03$) more rapidly. Knee circumference and skin temperature were lower in the block group between D1 and D7 (analysis of variance, $P < 0.05$). Synovial membrane IL-1 ($P < 0.05$) and IL-10 ($P < 0.01$) increased, and plasma IL-6 and sTNF-R1 peaked at 24 h, with no difference between groups.**

Conclusion: **Nerve blocks inhibited clinical inflammation after total knee arthroplasty, with no change in tissue and plasma cytokine concentrations.**

REGIONAL anesthetic techniques provide efficient postoperative analgesia.[1,2] In particular, continuous femoral nerve block after total knee arthroplasty provides efficient postoperative analgesia and prolonged functional improvement.[3,4]

Postoperative pain is mainly caused by tissue inflammation. Mediators of inflammation include bradykinin, serotonin, prostaglandins, histamine, leukotrienes, and cytokines.[5] Cytokines are important mediators of local and systemic inflammatory response after surgery.[5–7] In addition, cytokines are involved in nociception and development of hyperalgesia.[8–11]

Recent studies suggest that the measurement of proinflammatory (tumor necrosis factor [TNF], interleukin [IL]-6, IL1-β, IL-2) and antiinflammatory (IL-10, soluble receptor 1 of TNF [sTNF-R1]) cytokine concentration in plasma may help to quantify the systemic inflammatory response after surgery.[6,11–13] Specifically, plasma IL-6 concentration is correlated with the severity of surgery[14,15] and may be predictive of postoperative recovery.[16,17]

Several animal experiments show that C-fiber blockade may limit the development of peripheral inflammation in the corresponding innervated zone. This effect has been shown after nerve transection[18] or after direct application of vanilloid receptor agonist,[19] tetrototoxine,[20] or local anesthetic[18,20] on the nerve trunk. Contradictory findings have been obtained for local anesthetic: Inflammation was inhibited in carrageenan-injected rats after prolonged sciatic block with bupivacaine[18] or ipsilateral and contralateral single-shot bupivacaine sciatic block,[20] and no effect was observed with tonicaine sciatic and saphenous nerve blocks.[21] Prolonged duration of C-fiber block seems to be involved in this inhibition of inflammation.[18] This inhibiting effect of nerve block on peripheral inflammation has been reproduced in humans with lidocaine nerve block in a model of superficial burn injury[22] but not for capsaicin-induced inflammation.[23] In addition, lidocaine and bupivacaine seem to have a systemic antiinflammatory effect,[24] and bupivacaine can reduce cytokine production through a local and systemic effect *ex vivo*.[25] The systemic antiinflammatory effect of lidocaine has been also observed in capsaicine-,[26,27] heat-,[28] histamine-,[29] or burn-induced[30] inflammation models in humans. Overall, these findings, obtained in acute inflammatory pain models in animals and humans, suggest that peripheral nerve block using local anesthetics can reduce neurogenic inflammation. However, the precise mechanism is still debated.

In postoperative patients, local anesthetic epidural block limits *ex vivo* cytokine production after visceral

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surgery,[13] and peripheral nerve blocks limit C-reactive protein increase after knee surgery.[31] We tested the hypothesis that combined sciatic (single-shot) and femoral (continuous for 48 h after surgery) peripheral nerve blocks, used to treat postoperative pain after total knee arthroplasty, have an antiinflammatory effect, reflected by a reduction of both postoperative plasma and tissue cytokine concentrations and clinical indices of inflammation. Our study involved a 3-month follow-up after total knee arthroplasty, to assess pain control, functional recovery, and biologic (plasma and tissue cytokine concentration) and clinical indices (circumference and skin temperature) of operative knee inflammation.

Materials and Methods

Patients

Our study was approved for the two institutions by an ethics committee (Comité de Protection des Personnes, Boulogne Billancourt, France), and all patients gave written informed consent. We recruited consecutive patients scheduled to undergo total knee arthroplasty, regardless of age. Patient inclusion criteria were an indication for total knee arthroplasty due to knee arthritis and surgery performed during general anesthesia. Exclusion criteria were previous surgery or trauma of the knee or preoperative use of corticosteroids. Nonsteroidal antiinflammatory drugs were discontinued 48 h before surgery for all patients and substituted with acetaminophen. The main outcome measure was IL-6 plasma concentration 24 h after surgery. Based on previous reports,[13,15] 20 patients were needed in each group to detect a 50% reduction in IL-6 plasma concentration at 24 h after surgery with a power of 80% and an α risk of 5%. Secondary clinical outcome measures for inflammation were knee circumference and temperature.

Anesthesia, Surgery, and Postoperative Pain Relief

All patients were given 100 mg hydroxyzine before surgery. Surgery was performed during balanced general anesthesia combining propofol, sufentanil, a muscle relaxant, and sevoflurane. The same surgeon (P.P.) performed all operations. Postoperative pain was controlled for all patients by intravenous morphine patient-controlled analgesia (PCA) in combination with intravenous acetaminophen (1 g every 6 h; Perfalgan®; BMS Laboratory, Rueil Malmaison, France). PCA delivered a 1-mg morphine bolus with a 5-min lockout time. In cases of poor pain control by the patient, the PCA bolus was increased to 2 mg. PCA analgesia was discontinued 72 h after surgery. A randomization list was generated, and patients were assigned consecutively to two groups: The PCA group was treated by patient-controlled morphine and the block group was treated with combined sciatic (single-shot) and femoral (continuous for 48 h after surgery) peripheral nerve blocks. Femoral block was performed preoperatively according to the technique of Capdevila *et al.*,[4] with an initial 20-ml bolus of 0.75% ropivacaine (Naropein®; Astra Zeneca, Rueil Malmaison, France) followed by a continuous infusion of 0.2% ropivacaine, $0.15 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for 48 h. The sciatic block was performed preoperatively according to the technique of Winnie with 20 ml ropivacaine, 0.75%.[32] The absence of sensory response to cold tested before surgery in the area of the femoral and sciatic nerves confirmed that the nerve blocks were effective. Patients failing this test were excluded.

Study Design

Clinical Evaluation. Clinical evaluations were performed before surgery (D0) and at 1 (D1), 4 (D4), and 7 days (D7) and 1 (M1) and 3 months (M3) after surgery. Evaluations were performed on the mornings of D1, D4, and D7 and when the patient came back for follow-up surgical consultation at M1 and M3. During clinical evaluation, the patient was in the supine position in a quiet room, at a constant temperature (22°C), with the lower limb in neutral position. The circumference and skin temperature of the operated knee and contralateral knee were monitored at each follow-up visit. Skin temperature was measured in the center of the patella with a Thermopoint device (Protechnique, Quebec, Canada). The temperature was recorded as the mean of two successive measures. The knee circumference was measured by a thread, to the nearest half centimeter, along a horizontal line crossing the middle of the patella. All circumference and skin temperature measurements were performed by the same investigator (D.F.). Knee circumference and skin temperature were measured after surgery, after removal of all dressings. Pain was evaluated at rest and when moving (flexion/extension of the knee during physical therapy) by a 100-mm visual analog scale graduated from 0 (no pain) to 100 mm (worst imaginable pain). Pain scores and duration of preoperative pain were recorded the day before surgery. Pain scores were then monitored at D1, D4, D7, M1, and M3 and during all physical therapy sessions. Cumulative doses of PCA morphine were recorded at 24, 48, and 72 h. Physical therapy was started 24 h after surgery with passive and active mobilization of the operated knee. The active angle of flexion was recorded during hospitalization and at the follow-up visits at M1 and M3 by a physical therapist not involved in the study. Functional recovery was evaluated by recording the delay for first mobilization out of the bed and first use of the toilet with and without assistance.

Biologic Evaluation. Cytokine concentrations were measured in plasma before surgery (H0), four hours after completion of surgery (H4), and at day one (D1), day four (D4) and day seven (D7) after surgery. Cytokines concentrations in the capsule (C1 and C2 respectively) and synovial membrane (S1 and S2 respectively) of the operated knee were also measured at the beginning and at the end of surgery. We measured the proinflammatory cytokines, TNF-α and sTNF-R1, IL-1β and IL-6, and the antiinflammatory cytokine IL-10, in plasma; in tissue, we measured TNF-α, IL-1 β, IL-6, and IL-10. Cytokines were assayed using enzyme-linked immunosorbent assay kits (DuoSet®; R&D Systems, Lille, France). The lower limits for quantification were 15.6 pg/ml for TNF-α, 12.5 pg/ml for sTNF-R1, 3.9 pg/ml for IL-1β, 9.4 pg/ml for IL-6, and 31.2 pg/ml for IL-10.

Statistical Analysis

The analysis used Statview 5.0 software (SAS, Paris, France). The primary outcome was systemic IL-6 concentration at D1. The secondary outcomes were knee circumference and temperature, tissue and plasma cytokine concentrations, pain scores, and functional scores. Clinical and biologic data were compared between groups and over time using two-way analysis of variance (ANOVA; one way for repeated measures). We used unpaired and paired *t* tests with a Bonferroni adjustment for multiple comparisons. Data are expressed as mean ± SEM. $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

Forty patients were included in the study. Two patients in the PCA group were excluded immediately at the beginning of the study because of absence of a preoperative blood sample for cytokine concentration measurement. A total of 20 patients in the block group and 18 patients in the PCA group were analyzed. Patient characteristics were similar in both groups, with prolonged period of pain before surgery and intense pain when moving (table 1).

Postoperative Analgesia

Morphine use was significantly lower in the block group than in the PCA group in the postanesthesia care unit (4 ± 1.8 *vs.* 21 ± 2 mg; $P = 0.0001$) and at D1 (12 ± 2.3 *vs.* 25 ± 2.7; $P = 0.001$). Morphine PCA use per day was also lower in the block group than in the PCA group on the second (18 ± 4 *vs.* 24 ± 4 mg; $P = 0.43$) and third postoperative days (10 ± 2.7 *vs.* 18 ± 6.5; $P = 0.23$), but it did not reach significance. Pain at rest was lower in the block group for D1 to D7 (ANOVA, group effect, $P = 0.005$; fig. 1A). *Post hoc* analysis showed significant differences between the two groups at D4 (*t* test, $P = 0.01$) and D7 (*t* test, $P = 0.002$). Pain when moving was lower in the block group than in the PCA group for D1 to D7 (ANOVA, group effect, $P = 0.0005$; fig. 1B). *Post hoc* analysis showed significant differences between the two groups at D1 (*t* test, $P = 0.003$), D4 (*t* test, $P = 0.002$), and D7 (*t* test, $P = 0.001$). We did not observe a significant difference in pain score at M1 or M3 between the patient groups (figs. 1A and B).

Table 1. Patient Characteristics

	Block Group	PCA Group
Age, yr	67 ± 2	70 ± 2
Sex, men/total	6/20	4/18
Weight, kg	75 ± 3	73 ± 4
Duration of preoperative pain, mo	99 ± 28	101 ± 25
Preoperative pain intensity at rest, VAS	18 ± 5	18 ± 5
Preoperative pain intensity when moving, VAS	62 ± 5	68 ± 5

Values are expressed as mean ± SEM.

Block group = patients treated by combined sciatic (single-shot) and femoral (continuous for 48 h after surgery) nerve blocks; PCA group = patients treated by morphine patient-controlled analgesia; VAS = visual analog scale.

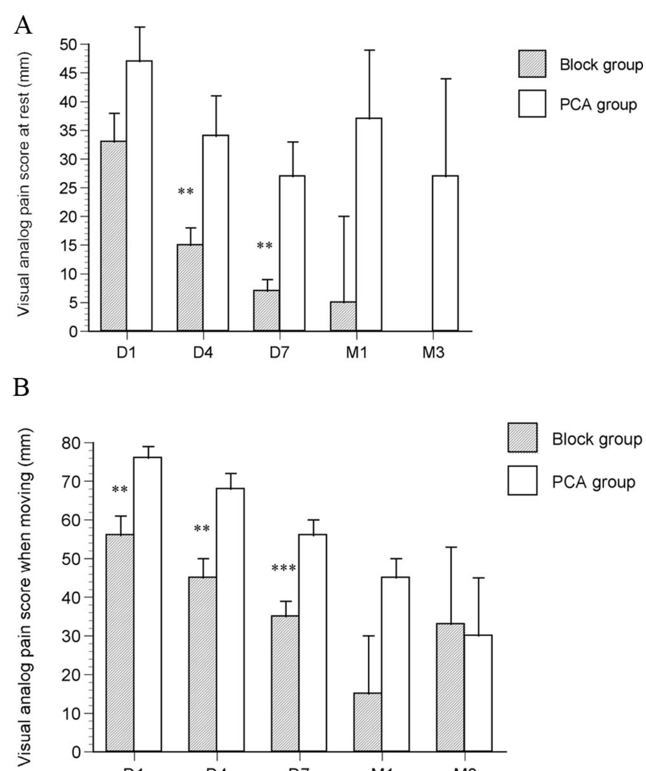

Fig. 1. Time course of visual analog pain score. Visual analog pain scores at rest (*A*) and when moving (*B*) at 1 (D1), 4 (D4), and 7 days (D7) and 1 (M1) and 3 months (M3) after surgery. Values are expressed as mean ± SEM. Block group = patients treated by combined sciatic (single-shot) and femoral (continuous for 48 h after surgery) nerve blocks; PCA group = patients treated by morphine patient-controlled analgesia. Pain was reduced in patients from the block group between D1 and D7 at rest (analysis of variance, group effect, $P = 0.005$). *Post hoc* analysis showed significant differences at D4 (*t* test, $P = 0.01$) and D7 (*t* test, $P = 0.002$) between the two patient groups. Pain when moving was reduced in the block group between D1 and D7 (analysis of variance, group effect, $P = 0.0005$; *B*). *Post hoc* analysis showed significant differences at D1 (*t* test, $P = 0.003$), D4 (*t* test, $P = 0.002$), and D7 (*t* test, $P = 0.001$) between patient groups. ** *t* test, $P < 0.01$. * *t* test, $P < 0.001$.**

Postoperative Function Recovery

Patients in the block group had a more rapid recovery of operative knee flexion, between D1 and M1, than PCA patients (ANOVA, group effect, $P = 0.0001$; fig. 2A). *Post hoc* analysis showed significant differences between the two groups at D1 (*t* test, $P = 0.0001$), D4 (*t* test, $P = 0.0004$), D7 (*t* test, $P = 0.009$), and M1 (*t* test, $P = 0.01$). There was no difference in functional recovery between block and PCA groups at M3. Patient in the block group recovered more rapidly than PCA patients, as assessed by autonomy criteria for nonassisted mobilization (*t* test, $P = 0.04$) and toilet use (*t* test, $P = 0.03$; fig. 2B).

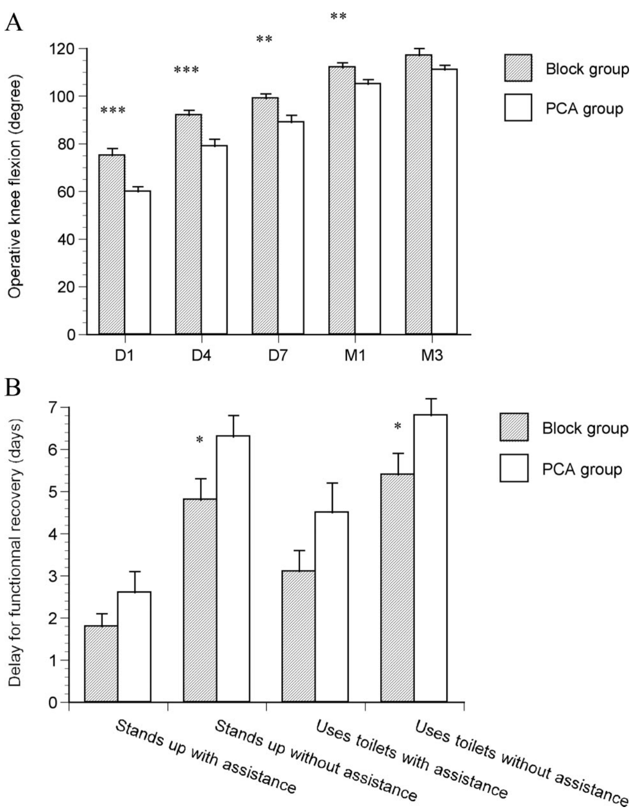

Fig. 2. Time course of knee flexion and patient autonomy. Postoperative knee flexion (degrees) at 1 (D1), 4 (D4), and 7 days (D7) and 1 (M1) and 3 months (M3) after surgery (*A*). Patient autonomy as assessed by time taken (days after surgery) to stand up with assistance, stand up without assistance, use the toilet with assistance, and use the toilet without assistance (*B*). Block group = patients treated by combined sciatic (single-shot) and femoral (continuous for 48 h after surgery) nerve blocks; PCA group = patients treated by morphine patient-controlled analgesia. Block group patients had a more rapid recovery in terms of operative knee flexion between D1 and M1 (analysis of variance, group effect, $P = 0.0001$; *A*). *Post hoc* analysis showed significant differences at D1 (*t* test, $P = 0.0001$), D4 (*t* test, $P = 0.0004$), D7 (*t* test, $P = 0.009$), and M1 (*t* test, $P = 0.01$). ** *t* test, $P < 0.01$. * *t* test, $P < 0.001$. Patients in the block group gained autonomy in terms of non assisted mobilization and use of the toilet more rapidly than patients from the PCA group. * *t* test $P < 0.05$.**

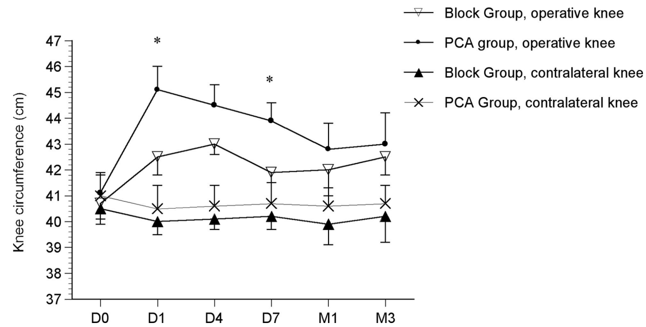

Fig. 3. Time course of operative knee circumference. Knee circumference was measured by a thread, to the nearest half centimeter, at the middle of the patella, before surgery (D0) and at 1 (D1), 4 (D4), and 7 days (D7) and 1 (M1) and 3 months (M3) after surgery. Block group = patients treated by combined sciatic (single-shot) and femoral (continuous for 48 h after surgery) nerve blocks; PCA group = patients treated by morphine patient-controlled analgesia. The increase in circumference of the operated knee, for D1 to D7, was significantly smaller for the block group than for the PCA group (analysis of variance, interaction between group × time, $P = 0.01$). *Post hoc* analysis showed significant differences at D1 (*t* test, $P = 0.02$) and D7 (*t* test, $P = 0.02$). There was no change in knee circumference for the contralateral knee. Values are expressed as mean ± SEM. * *t* test, $P < 0.05$.

Clinical Signs of Inflammation

The postoperative circumference of the operated knee increased after surgery. This increase was significantly smaller for block group patients than for PCA group patients between D1 and D7 (ANOVA, interaction between group and time, $P = 0.01$; fig. 3). *Post hoc* analysis showed significant differences at D1 (*t* test, $P = 0.02$) and D7 (*t* test, $P = 0.02$). There was no significant difference in postoperative knee circumference increase between the two groups at M1 or M3 (fig. 3).

Operative knee temperature increased after surgery. The increase was significantly smaller in the block group than in the PCA group between D1 and D7 (ANOVA, interaction between group and time, $P = 0.03$; fig. 4). *Post hoc* analysis showed significant differences at D4 (*t* test, $P = 0.01$) and D7 (*t* test, $P = 0.02$). There were no significant differences between the two groups at M1 or M3 (fig. 4).

The skin temperature and circumference of the contralateral knee were stable throughout the study period (figs. 3 and 4).

Cytokine Levels

Plasma concentrations of IL-1, TNF, and IL-10 were below the detection limit for almost all samples and therefore were not analyzed. There was a maximal increase of plasma IL-6 and sTNF-R1 concentration at D1 in both treatment groups, with this increase persisting until D7 for sTNF-R1 (fig. 5), but this increase was not significantly different between the block and PCA groups.

The overall tissue cytokine concentration increased during surgery. This increase was significant for IL-1 (72 ± 136%; paired *t* test, $P < 0.05$) and IL-10 (128 ±

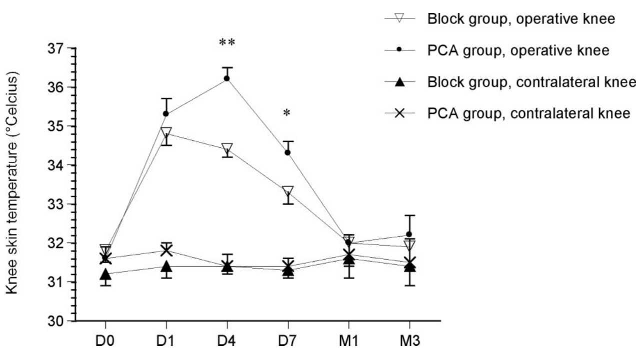

Fig. 4. Time course of operative knee skin temperature. Skin temperature of the operated knee was measured with a Thermopoint device (Protechnique, Quebec, Canada) (in degrees Celsius) at the middle of the patella before surgery (D0) and at 1 (D1), 4 (D4), and 7 days (D7) and 1 (M1) and 3 months (M3) after surgery. Block group = patients treated by combined sciatic (single-shot) and femoral (continuous for 48 h after surgery) nerve blocks; PCA group = patients treated by morphine patient-controlled analgesia. The increase in temperature of the operated knee, for D1 to D7, was significantly smaller in the block group than in the PCA group (analysis of variance, interaction between group and time, $P = 0.03$). *Post hoc* analysis showed significant differences at D4 (*t* test, $P = 0.01$) and D7 (*t* test, $P = 0.02$). There was no significant change in skin temperature of the contralateral knee. Values are expressed as mean ± SEM. * *t* test, $P < 0.05$. ** *t* test, $P < 0.01$.

224%; paired *t* test, $P < 0.01$) in the synovial membrane sample, but there was no significant difference between the two treatment groups (table 2).

Discussion

This study demonstrates a clinical antiinflammatory effect of peripheral nerve blocks after surgery. This effect was supported by a reduction in both operative knee circumference and temperature but was not associated with a reduction of tissue or plasma proinflammatory cytokine concentration.

Continuous postoperative nerve blocks, regardless of catheter location, provide improved postoperative analgesia and fewer opioid-related side effects than opioid analgesia.[1] Our study suggests that this analgesic effect may be related to both reduced nociceptive inputs and a local antiinflammatory effect. Interestingly, our study is consistent with previous data showing the beneficial effects of postoperative nerve blocks on knee function.[4] Patients with peripheral nerve block had an improved postoperative knee flexion and more rapid recovery of functional autonomy. As previously observed,[4] this effect on function persisted after discontinuation of peripheral nerve block: Patients with nerve block had improved operative knee flexion 1 month after surgery. This persistent improvement of function cannot be explained by the pharmacologic effect of ropivacaine. It may be related to the prolonged combined analgesic and antiinflammatory effect of peripheral nerve blocks. In our study, the effect on postoperative pain, knee edema,

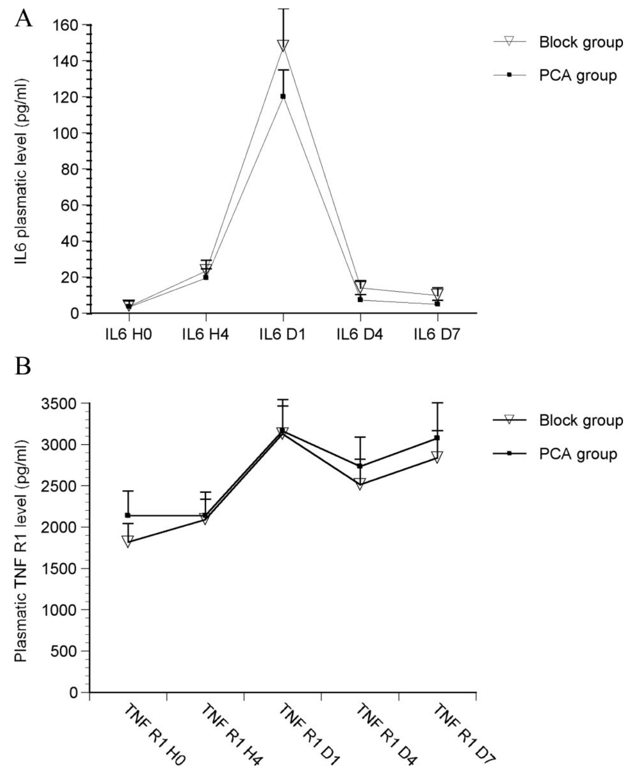

Fig. 5. Time course of plasma interleukin (IL)-6 and soluble receptor 1 of tumor necrosis factor (sTNF-R1) levels. IL-6 (*A*) and sTNF-R1 (*B*) plasma levels before surgery (D0) and at 4 h (H4) and 1 (D1), 4 (D4), and 7 days (D7) after surgery. Values are expressed as mean ± SEM. Block group = patients treated by combined sciatic (single-shot) and femoral (continuous for 48 h after surgery) nerve blocks; PCA group = patients treated by morphine patient-controlled analgesia; pg/ml = picograms of cytokine per milliliter of plasma. We did not observe significant differences between the groups.

and temperature was significant after discontinuation of postoperative nerve block (*i.e.*, after 2 days). Previous animal[21] or human[22,33,34] experiments suggest that nerve block may exert significant effects beyond its pharmacologic action on both nociception and inflammation. Our clinical findings extend these previous results by describing the prolonged effect of peripheral nerve block on nociception, inflammation, and postoperative functional recovery.

Peripheral nerve blocks reduced edema and temperature increase in our patients after surgery. This is the first study testing the effect of peripheral nerve block on clinical inflammation after surgery. One limitation of our study is caused by the fact that we could not perform a blinded study because of the sensory effects of the block and the visibility of the catheter during postoperative evaluation. As in a previous clinical study on knee surgery,[35] we used the combination of circumference and temperature measurements to evaluate clinical inflammation. Previous experimental studies in humans have used similar clinical criteria (*i.e.*, flare, erythema, temperature) to evaluate inflammation.[22,23,26,28–30,36] The precise mechanisms underlying the observed antiedema-

Table 2. Tissue Cytokine Concentrations

	Block Group		PCA Group	
	Sample 1	Sample 2	Sample 1	Sample 2
IL-6 level in the capsule, pg/g	150 ± 35	186 ± 37	170 ± 34	234 ± 56
IL-6 level in the synovial membrane, pg/g	159 ± 35	265 ± 52	183 ± 56	190 ± 31
IL-10 level in the capsule, pg/g	301 ± 53	420 ± 102	359 ± 75	592 ± 169
IL-10 level in the synovial membrane, pg/g†	275 ± 83	545 ± 142	266 ± 59	411 ± 110
IL-1 level in the capsule, pg/g	43 ± 7	50 ± 12	65 ± 20	64 ± 12
IL-1 level in the synovial membrane, pg/g*	42 ± 12	66 ± 13	35 ± 7	45 ± 7
TNF level in the capsule, pg/g	190 ± 81	170 ± 41	125 ± 37	149 ± 52
TNF level in the synovial membrane, pg/g	153 ± 70	277 ± 102	69 ± 16	157 ± 46

Values are expressed as mean ± SEM.

* $P < 0.05$, † $P < 0.01$ (paired t test); significant increase between the first and second samples for global analysis.

Block group = patients treated by combined sciatic (single-shot) and femoral (continuous for 48 h after surgery) nerve blocks; IL = interleukin; PCA group = patients treated by morphine patient-controlled analgesia; pg/g = picograms per gram of tissue; TNF = tumor necrosis factor.

tous effect of peripheral nerve block is unknown. First, in the absence of a change in markers of inflammation, one cannot exclude that the reduction of edema may have been due, at least in part, to other factors such as improved function and greater mobility of the operated leg. However, this antiedematous effect was combined with a reduction of skin temperature, suggesting an antiinflammatory effect. Second, the design of our study (*i.e.*, no systemic administration of ropivacaine) cannot rule out a systemic effect of ropivacaine on edema because we used high doses of ropivacaine and did not measure the plasma concentration of ropivacaine in patients. Systemic lidocaine reduces erythema and flare in acute inflammation models in humans,[26–30] whereas systemic bupivacaine does not reduce edema in carrageenan-injected rats[20]; however, the effect of systemic ropivacaine on edema has not been tested in humans or animals. Therefore, although a systemic effect of ropivacaine on edema cannot be ruled out, it seems unlikely. Third, peripheral nerve block may reduce inflammation. Contradictory findings have been obtained in human studies, with a positive effect of lidocaine nerve block in a model of superficial burn injury[22] but no effect observed for capsaicin-induced inflammation.[23] Contradictory findings have also been obtained in animal models, with decreased local edema in carrageenan-injected rats after sciatic nerve infusion of bupivacaine[18] or ipsilateral and contralateral bupivacaine sciatic nerve block[20] and no effect observed after a tonicaine nerve block.[21] Overall, these findings from human and animal studies suggest that local anesthetic can reduce peripheral inflammation through a sodium channel–dependent segmental effect; we consider this the most likely mechanism of the antiedematous effect of peripheral nerve blocks observed in our study.

The dissociation between the clinical and biologic markers of inflammation observed in our study also deserves discussion. Peripheral nerve blocks had no detectable effect on the increase of plasma cytokine levels. Our findings are in line with a recent study using a combined continuous lumbar plexus and sciatic nerve blocks with ropivacaine after knee surgery. The authors did not detect a change in IL-6 plasma level associated with a blunted increase in C-reactive protein.[31] This absence of a detectable effect on plasma IL-6 levels by peripheral nerve blocks may be explained by limited sensitivity of enzyme-linked immunosorbent assay to measure plasma cytokine concentration, as compared with an *ex vivo* cytokine assay. However, this technique has been used in previous studies to detect changes in cytokine profiles of surgical patients[37] or patients with fibromyalgia and painful neuropathy.[38,39] Alternatively, it is possible that plasma cytokine levels do not reflect the clinical antiinflammatory effect observed on the operated knee. Indeed, this clinical antiinflammatory effect of peripheral nerve block is probably related to inhibition of neurogenic inflammation with reduced peripheral release of substances such as substance P and calcitonin gene–related peptide. The effect on neurogenic inflammation may be independent of plasma cytokine levels. It is also possible that tissue damage and inflammation related to total knee arthroplasty may overcome the effects of nerve block on inflammatory response. Other clinical studies using more extensive nerve blocks, such as epidural analgesia, have demonstrated attenuated proinflammatory cytokine production after visceral surgery.[13,37,40] Therefore, the effects of nerve blocks on biologic indicators of inflammation seem to depend on several factors, including the type of marker (*i.e.*, C-reactive protein or IL-6), the technique of regional anesthesia (*i.e.*, peripheral nerve block or epidural analgesia), the assay used to measure of cytokine concentration (*i.e.*, *in vivo* or *ex vivo* assays), and probably the type of surgery.

We did not observe any effect of peripheral nerve block on tissue cytokine concentration, consistent with the absence of significant effects on plasma cytokine levels in patients receiving peripheral nerve block. Cytokine levels in operative area have not been previously studied. Our study demonstrated an overall increase in tissue cytokine concentration during surgery; we detected a significant increase in IL-10 and IL-1 levels in the synovial membrane. We did not find a correlation between preoperative pain or postoperative pain intensity and tissue cytokine concentration.

In conclusion, our study suggests that peripheral nerve block used for postoperative analgesia also exerts a prolonged antiinflammatory effect; the combination of these effects probably participates in the observed improved functional recovery.

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