Effect of a Continuous Peripheral Nerve Block on the Inflammatory Response in Knee Arthroplasty

Hema Bagry, M.D., Juan Carlos de la Cuadra Fontaine, M.D., Juan Francisco Asenjo, M.D., David Bracco, M.D., and Franco Carli, M.D., M.Phil.

Background and Objectives: Experimental nerve block in animals inhibits the inflammatory response. The purpose of this study was to determine to what extent a 48-hour local anesthetic block of all afferent and efferent nerve fibers of the knee area has an impact on postoperative inflammatory response.

Methods: Twelve patients scheduled for primary total knee arthroplasty received spinal anesthesia, and then were randomly allocated to either patient-controlled analgesia with morphine (n = 6) or a combination of continuous lumbar plexus and sciatic nerve blocks (continuous peripheral nerve block; CPNB) with ropivacaine 0.2% for 48 hours. Blood samples were collected before surgery and at 3, 8, 24, and 48 hours after surgical incision to measure plasma glucose, serum insulin and cortisol, C-reactive protein, interleukin-6, and leukocyte count. Pain visual analog scale at rest and on knee flexion were recorded and complications classified.

Results: Visual analog scale was lower in the CPNB group at rest and on knee flexion on postoperative days 1 and 2 ($P < .05$). There were no differences in circulating levels of glucose, insulin, and cortisol. C-reactive protein and leukocyte count were lower in the CPNB group ($P < .05$). There was a positive correlation between the peak leukocyte count and the inflammatory markers ($P < .03$). Three patients in the patient-controlled analgesia group and one in the CPNB group had complications requiring conservative management.

Conclusions: Continuous lumbar plexus and sciatic nerve blocks with ropivacaine contribute to the attenuation of the postoperative inflammatory response. *Reg Anesth Pain Med 2008;33:17-23.*

Key Words: Knee arthroplasty, PCA, CRP, IL-6, Inflammatory response.

Surgery induces a complex neuroendocrine, inflammatory, and coagulation cascade response.[1] The release of neurogenic substances from the surgical area into the innervated tissues contribute to the establishment of peripheral inflammation.[2] This can be accompanied by a marked systemic inflammatory response which, with time, impairs normal host defenses against infection thus delaying wound healing.[3]

Total knee arthroplasty represents a major surgical stress, and is associated with a significant increase in the postoperative circulating levels of plasma hormones and inflammatory markers.[4] The postoperative changes in interleukin-6 (IL-6) and C-reactive protein (CRP) have been described over a 7-day period, and while IL-6 concentration starts to rise within the first 6 hours after the surgical incision and reaches a peak at 24 hours, CRP concentration increases 24 hours after surgery and its peak is between 48 and 72 hours.[4,5]

Previous studies have shown that the neurogenic inflammatory response can be attenuated by experimental nerve section and nerve block, however the latter has to be prolonged enough to minimize the formation of edema in the area affected.[6] Prevention of late hyperalgesia can be provided not only by the preinjury block, but also by the postinjury block.[7] Despite these promising animal data, previous human studies on the effect of neuraxial blockade with local anesthetics on postoperative inflammatory response yielded negative results.[8]

From the Department of Anesthesia, McGill University Health Centre, Montreal, Quebec, Canada.

Accepted for publication June 25, 2007.

Dr. J.C. de la Cuadra Fontaine was a recipient of the McGill University Health Centre Foundation Fellowship in Regional Anesthesia.

This work was supported by a grant from the McGill University Health Centre to F. Carli.

This work was presented in part at the annual meeting of the American Society of Regional Anesthesia, Vancouver, Canada, April 18-21, 2007.

Reprint requests: Franco Carli, M.D., M.Phil., Department of Anesthesia, McGill University Health Centre, 1650 Cedar Ave, Room D10.144, Montreal, Quebec H3G 1A4 Canada. E-mail: franco.carli@mcgill.ca

1098-7339/08/3301-0001$34.00/0
doi:10.1016/j.rapm.2007.06.398

Continuous block of the nerve fibers supplying the knee area with local anesthetics has been shown to provide excellent analgesia and accelerate the recovery process after knee arthroplasty.[9,10] It is not known whether these benefits might be explained by the modulatory effect of the anesthetic block on the inflammatory response. With this in mind, the present physiological study was designed to characterize the postoperative endocrine and inflammatory response in knee arthroplasty patients receiving a peripheral nerve block of 48 hours duration versus that in patients receiving intravenous analgesia. Based on the results of animal investigations, this study's hypothesis is that an anesthetic block of all afferent and efferent nerve fibers surrounding the knee attenuates the inflammatory response.

Methods

Patients

This prospective randomized study was conducted between October 2005 and July 2006. After study approval by the McGill University Health Centre Ethics Board, a written consent was obtained from all patients. Twelve patients suffering from osteoarthritis and scheduled for primary unilateral total knee arthroplasty were identified at the preoperative clinic. Patients with an American Society of Anesthesiologists physical status classification of I or II, and older than 18 years, were included in the study. Exclusion criteria were: history of local anesthetic or morphine drug allergy, contraindication to the use of patient-controlled analgesia (PCA) or peripheral nerve block (skin infection at puncture site, bleeding disorders), morbid obesity (body mass index >40), neurological disease, chronic systemic inflammatory disease, diabetes mellitus, and chronic use of corticosteroids, nonsteroidal anti-inflammatory drugs, or opioids. In the preoperative clinic all patients were instructed in the use of a visual analog pain scale (VAS; 0-10 cm) with 0 representing no pain at all and 10 the worst imaginable pain.

Anesthesia

Standard monitoring (pulse oximeter, electrocardiogram, noninvasive blood pressure) was applied to all patients on their arrival in the anesthetic room. A 20-gauge intravenous cannula was inserted in the antecubital fossa and exclusively used for blood sampling. Another 16-gauge cannula was inserted in the opposite arm and used for intravenous fluid therapy and administration of perioperative medications. Premedication was with intravenous midazolam 0.03 mg/kg. After intravenous preload with 500 mL normal saline, the spinal block was performed in the sitting position with either a 25- or 27-gauge Whitacre spinal needle at the L2-3 or L3-4 intervertebral space. After clear free flow of cerebrospinal fluid, 12.5 mg of isobaric racemic bupivacaine 0.5% was administered to achieve sensory block (to cold and pinprick) at or above T10 dermatones. During surgery, sedation, if necessary, was achieved with a continuous infusion of propofol. Intravenous normal saline (0.9% NaCl) was administered during surgery at a rate of 6 to 8 mL/kg per hour, and intraoperative normothermia (36.0°C) was maintained with warming blankets.

Surgical Care

Surgery was performed during the morning hours to avoid circadian endocrine variations. All total knee standard replacements were performed by the same surgeon. Intravenous cefazolin 2 g was administered 20 minutes before surgery. A pneumatic tourniquet was positioned on the thigh before surgery and inflated up to 275 mm Hg. An intra-articular drain was positioned by the surgeon in the knee joint and removed on the first postoperative day.

Experimental Protocol

Upon arrival in the operating room, patients were randomly allocated to PCA or peripheral continuous nerve block (CPNB) using sealed envelopes.

PCA group. Upon arrival in the recovery room, patients were connected to the PCA machine set up to deliver incremental doses of 1 mg of morphine, with a lockout of 7 minutes and no background infusion.

Continuous peripheral nerve block (CPNB) group. Before spinal anesthesia, stimulating catheters (Stimucath Arrow International, Reading, PA) were placed adjacent to the lumbar plexus by the posterior approach and sciatic nerve by the infragluteal approach. The lumbar plexus[11] and the sciatic nerve[12] were identified with nerve stimulation according to previously published landmarks. Respectively, quadriceps contraction and foot motor responses below 0.8 mA were elicited to ascertain correct positioning of the stimulating catheters. The combination of nerve blockade was aimed at providing complete sensory blockade of all aspects of the knee area. Upon surgery completion, a loading dose of lidocaine 2% with epinephrine 2.5 μg/mL, 0.5 mL/kg, was administered half in each catheter. For continuous postoperative analgesia, ropivacaine 0.2% was administered at a rate of 8 mL/h

(lumbar plexus) and 5 mL/h (sciatic nerve) for 48 hours.

Postoperative Care

Both groups received oral acetaminophen 650 mg every 6 hours, while nonsteroidal anti-inflammatory drugs were withheld during the study period of 48 hours. Analgesia was adjusted to maintain a VAS below 3 at rest: In the PCA group, the bolus dose was increased to 1.5 mg each 7 minutes, if necessary. In the CPNB group, according to block testing by cold, additional top-up boluses of 4 mL ropivacaine 0.2% were given and the rate of the infusion was increased up to a maximal of 20 mL per hour for the total of the 2 catheters combined. Patients were mobilized out of bed starting the day after surgery, and the degree of knee flexion was assessed daily by a physiotherapist. The CPNB and PCA were discontinued after 48 hours and oral medications, consisting of long-acting oxycodone, oxycodone, and acetaminophen, were prescribed.

Data Collection

Data collection and blood sampling were started before surgery and continued thereafter at 3, 8, 24, and 48 hours after surgical incision for the measurement of plasma glucose, serum insulin and cortisol, CRP, IL-6, and white cell count. Tourniquet time, length of surgery, 24-hour intra-articular drain output, and length of hospital stay were recorded for each patient. Postoperative morphine consumption was recorded only in the PCA group. A research assistant and a physiotherapist unaware of the study hypothesis assessed VAS at rest and on knee flexion at 3, 8, 24, 48, 72, and 96 hours from time of incision. Postoperative complications were followed up to postoperative day 30 using the classification proposed by Dindo et al.[13]

Analysis of Blood Samples

The blood samples were centrifuged within 30 minutes of collection, and plasma and serum were separated and stored at −70°C for further analysis. Plasma glucose was measured by glucose oxidase enzymatic method, coefficient of variation 1.8% at 6.83 mmol/L and 1.9% at 13.8 mmol/L. Serum insulin was measured by solid-phase, 2-site chemiluminescent immunometric assay, coefficient of variation 6.4% at 7.39 μIU/mL and 5.3% at 300 μIU/mL. Serum cortisol was measured by electrochemiluminescence immunoassay, coefficient of variation 1.3% at 208 nmol/L and 1.1% at 1,268 nmol/L. C-reactive protein (CRP) was measured by immunoturbidimetric assay, coefficient of variation 2.5% at 5.76 mg/L and 0.76% at 150.1 mg/L. Samples of IL-6 were analyzed using a commercial ELISA system, working range 3 to 300 pg/mL, coefficient of variation 6.4% at 17.2 pg/mL and 3.8% at 191 pg/mL. Leukocyte counts were determined by routine hematological methods.

Statistical Analysis

Area under the curve for CRP and IL-6 were calculated using the trapezoid method. Data were analyzed using SAS software (SAS Institute, Cary, NC). Due to the small sample size and nonnormal distribution of most of the parameters, nonparametrical tests were applied in all comparisons. Continuous parameters were compared across groups using the 2-sided Wilcoxon Kruskal-Wallis test. Nominal data or ordinal data (VAS scores) were compared using the χ^2 analysis. A P value of less than .05 was considered statistically significant. Data are expressed as median and interquartile range (IQ). The power calculation was based on a previous prospective evaluation of the kinetic of CRP after total knee arthroplasty.[14] The peak CRP at 24 postoperative hours was 120 mg/L with a standard deviation of 20 mg/L. The study was aimed to detect a 30% blunting of this CRP reaction with a power of 0.8 assuming the same sigma with no additional confounding parameters. The total number to enroll was 12 (i.e., 6 patients in each group) to achieve the desired statistical power.

Results

There were no differences in anthropometric characteristics and clinical data between the two groups (Table 1). Postoperative knee drainage during the first 24 hours was 595 mL (IQ 400-766 mL)

Table 1. Demographic Characteristics and Clinical Data of the 2 Groups Studied

	PCA (n = 6)	CPNB (n = 6)
Gender (female/male)	2/4	3/3
Age (y)	74 (65-75)	69 (60-80)
Weight (kg)	74 (67-101)	74 (63-83)
Height (cm)	169 (165-173)	169 (164-178)
BMI	27 (24-34)	26 (21-29)
Surgery duration (h)	2.3 (1.5-3)	1.5 (1.4-1.6)
Duration tourniquet (min)	70 (49-85)	62 (46-74)
Postoperative morphine consumption (mg)	54 (38-101)	0
Length of hospital stay (days)	7 (7-9)	8 (6-8)

NOTE. Data are presented as median (interquartile range) and n.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CPNB, continuous peripheral nerve block; PCA, patient controlled analgesia.

Table 2. Pain Visual Analog Scale of the 2 Groups Studied

	Day	PCA (n = 6)	CPNB (n = 6)	*P*
VAS at rest				
	1	2 (1-6)	1 (0-2)	NS
	2	5 (3-6)	2 (2-3)	<0.05
	3	3 (3-4)	2 (2-4)	NS
	4	3 (2-4)	2 (2-4)	NS
VAS on knee flexion				
	1	4 (2-7)	1 (1-2)	<0.02
	2	7 (6-7)	4 (3-6)	<0.05
	3	5 (5-6)	5 (4-6)	NS
	4	5 (4-6)	4 (3-7)	NS

NOTE. Data are presented as median (interquartile range).
Abbreviations: CPNB, continuous peripheral nerve block; NS, not significant; PCA, patient-controlled analgesia; VAS, visual analog scale.

in the PCA group, and 688 mL (IQ 591-712 mL) in the CPNB group. No patient required blood transfusion. Pain scores at rest and during knee flexion are shown in Table 2. Pain relief was better on days 1 and 2 in the CPNB group.

Biochemical and Physiological Data

Markers of the neuroendocrine response to surgery such as plasma glucose levels, serum cortisol and insulin, heart rate, and body temperature were comparable in both groups (Table 3). Although a lower white blood cell count in the CPNB group was not significant (Table 3), the average white cell count during the plateau phase was 13.6 g/dL (IQ 10.5-17.3) in the PCA group versus 9.0 g/dL (IQ 8.3-10.1) in the CPNB group ($P < .03$). There was a significant correlation between insulin concentration and IL-6 levels ($r = 0.63$, $P < .05$).

Baseline CRP and IL-6 were comparable in both groups (Fig 1). Two patients in the PCA group had baseline CRP values greater than 20 mg/L resulting in large variability. CRP concentration in both PCA and CPNB groups was raised at 24 and 48 hours after surgery, with a lower increase in the CPNB group. The area under the curve of the CRP levels was lower in the CPNB group, 2,363 mg · h/L (IQ 2,009-2,914) versus 4,716 mg · h/L (IQ 3,129-6,588) in the PCA group ($P < .005$). Although IL-6 was not significantly different between the two groups, there was a tendency to lower IL-6 levels in the CPNB group at postoperative 8, 24, and 48 hours. There was significant correlation between the peak leukocyte count and peak IL-6 and peak CRP (Fig 2).

Postoperative Complications

Three patients from the PCA group and one patient from the CPNB group developed postoperative complications during the first 30 postoperative days (not significant). Two of these were directly related to surgery (superficial wound infection and local effusion), both of which responded to conservative management. Urinary tract infection and deep vein thrombosis were the other complications reported.

Discussion

The present findings show that continuous lumbar plexus and sciatic nerve blocks with local anesthetics significantly attenuated the postoperative

Table 3. Clinical, Metabolite, and Hormone Data of the 2 Groups Studied Before and After Surgery

	Group	Before Surgery	After Surgery			
			3 h	8 h	24 h	48 h
White cell count (10^9/L)						
	PCA	6.8 (5.1-8.4)	9.0 (6.6-12.2)	18.0 (11.8-24.7)	11.1 (8.2-18)	9.0 (8.1-15.0)
	CPNB	6.7 (6.8-7.4)	8.2 (7.1-8.2)	8.1 (7.8-10.1)	8.4 (8.2-9.9)	7.0 (6.1-9.5)
Heart rate (beats/min)						
	PCA	67 (62-70)	64 (56-87)	63 (56-93)	74 (66-102)	79 (70-93)
	CPNB	75 (63-81)	63 (58-74)	53 (53-78)	60 (59-80)	76 (60-87)
Body temperature (°C)						
	PCA	36.2 (36-36.5)	35.3 (35-36.1)	36.4 (36.3-36.6)	37 (36.7-38)	37 (37-38.1)
	CPNB	36.5 (36-36.9)	35.5 (34.3-36)	36.4 (36.3-36.8)	36.9 (36.5-37)	36.8 (36.7-37)
Glucose (mmol/L)						
	PCA	6.0 (4.8-7.8)	6.4 (5.9-7.1)	6.6 (5.6-9.4)	6.8 (5.4-8.9)	6.4 (5.6-8.7)
	CPNB	5.6 (4.7-7.0)	5.4 (5.0-6.3)	6.8 (5.4-7.5)	7.1 (6.7-7.1)	6.1 (5.4-6.7)
Insulin (μU/L)						
	PCA	34 (27-40)	32 (16-83)	43 (14-76)	114 (70-187)	121 (74-226)
	CPNB	37 (20-73)	29 (14-83)	55 (31-79)	117 (50-424)	51 (29-128)
Cortisol (nmol/L)						
	PCA	339 (221-675)	449 (171-777)	547 (409-700)	606 (400-90)	394 (317-535)
	CPNB	530 (404-621)	297 (237-581)	758 (310-1000)	484 (203-678)	505 (227-728)

NOTE. Data are presented as median (interquartile range).
Abbreviations as in Table 2.

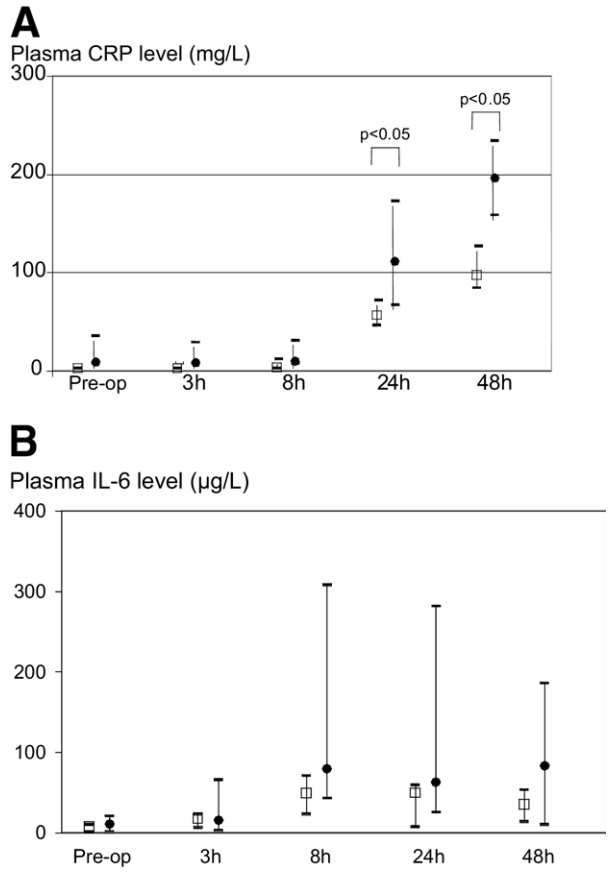

Fig 1. Concentrations of (A) C-reactive protein (CRP) and (B) interleukin-6 (IL-6), preoperatively (Pre-op), and postoperatively, at 3, 8, 24, and 48 hours, in the 2 groups studied. Error bars represent interquartile range. Black circles = PCA group; unfilled squares = CPNB group.

plasma levels of CRP when compared with systemic opioids. In contrast, no difference was found in the endocrine response between the 2 groups.

Surgical trauma induces an inflammatory state characterized by the release of both pro- and anti-inflammatory proteins. Proinflammatory cytokines induce not only a local inflammation at the site of injury, but also systemic responses such as tachycardia, tachypnea, leukocytosis, and pyrexia.[5] Tissue injury also induces a neuroendocrine stress response involving primarily the hypothalamic pituitary axis, adrenomedullary axis, and the parasympathetic nervous system along with synthesis of acute phase proteins in the liver.[3] Attenuation of the inflammatory response can reduce injury-induced immunosuppression and is linked to functional recovery.[15] Persistently elevated concentrations of CRP and IL-6 following hip arthroplasty were found to be associated with poor mobilization and rehabilitation.[15]

The surgical area of the knee receives nerve fibers from the lumbar plexus and sciatic nerve, with the femoral nerve, the obturator nerve, and the lateral femoral cutaneous nerve supplying the anterior, medial, and lateral areas of the knee, respectively, and the sciatic nerve the posterior part. Continuous nerve deafferentation of the surgical area was achieved with local anesthetics for a period of 48 hours, accompanied by sensory block of the lower limb. The pain intensity at rest and with movement during the study time showed that the surgical area was adequately blocked.

Intraplantar injection of carrageenan in rats has been used as a model of localized inflammatory pain with an evolution similar to the time course of postoperative pain.[16] The release of neurogenic substances such as substance P and neurokinin A, have been shown to facilitate the initial development of peripheral inflammation, which triggers systemic inflammation. The administration of local anesthetics either directly in the nerve fibers or in tissues adjacent to the inflamed area attenuates the formation of edema. Gentili et al. reported that a sciatic nerve block with local anesthetics of at least 6 hours duration in rats was associated with marked

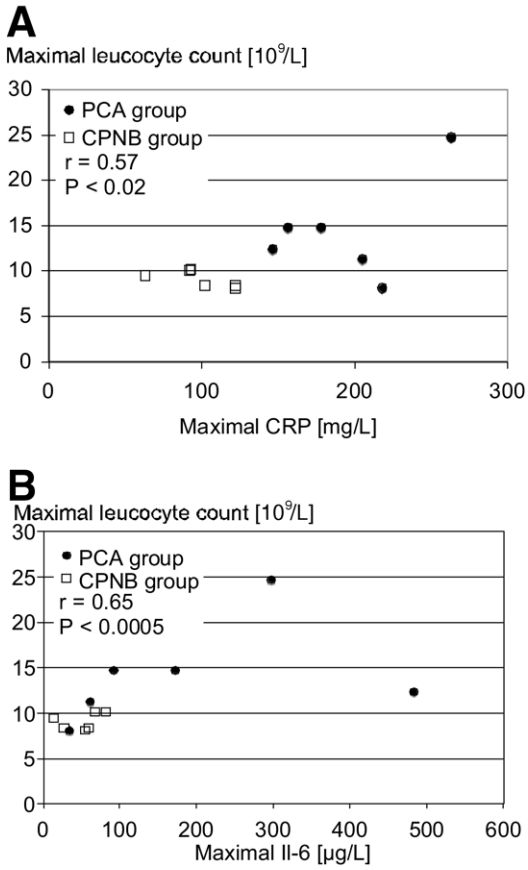

Fig 2. Relationship between peak leukocytes, and (A) peak C-reactive protein (CRP), and (B) peak interleukin-6 (Il-6).

reduction in inflammation and edema.[17] This might be explained by the prolonged interruption of neuronal afferent activity, which is responsible for prolonged analgesia, and efferent activity, regulating the liberation of neurogenic substances. Using the same model of intraplantar injection of carrageenan, a neurolytic nerve block of prolonged duration demonstrated an attenuation of the systemic inflammatory response.[6] Although we cannot strictly compare the effect caused by an inflammogen injection in the skin with the surgical model used in this study, it is plausible to expect an equivalent humoral and neurogenic inflammatory response.

An attempt to attenuate the markers of the inflammatory response using continuous intense epidural blockade with local anesthetics has not been successful,[8] implying that neuraxial deafferentation is insufficient to prevent the development of peripheral and systemic inflammation. This is in contrast with the present study where the nerve block significantly inhibited CRP and IL-6. Such difference might be explained by the fact that in the present study all afferent and efferent fibers innervating the surgical area were blocked. This prevents primary and secondary hyperalgesia, while epidural blockade could not provide adequate deafferentation. Therefore, neurogenic mediators liberated at tissue level may have contributed to the development of peripheral and systemic inflammation. Although one might propose that the dense block caused by the spinal local anesthetic would have an effect on the inflammatory markers, it is unlikely because the spinal block is of a short duration, and insufficient to attenuate the establishment of hyperalgesia.

There has been some emphasis in explaining the present findings on a neurogenic basis, but a systemic effect of local anesthetic cannot be excluded; in fact there is good evidence that local anesthetics administered either systemically or locally modulate the inflammatory response in animals.[18] Tetrodotoxin-resistant sodium and other nonsodium channels have been shown to mediate this effect.[19] Lidocaine protects vascular and endothelial smooth muscle against cytokine-induced injury via lidocaine action on adenosine triphosphate-sensitive potassium channels.[20] Sinclair et al. found that local anesthetics suppressed metabolic activation and secretory function of leukocytes in a dose-dependent manner.[21]

After surgery, leukocytes are mobilized into the circulation under the influence of acute phase proteins. These leukocytes accumulate at the inflamed local site enhancing the local antimicrobial defense. Leukocyte counts increased after surgery in both groups with peak at 8 hours. There was a trend to a higher leukocyte count in the PCA group, with a significant correlation between the peak postoperative leukocyte count and peak serum IL-6 and CRP. The rise in leukocyte count was not accompanied by high body temperature, and this might be due to the use of acetaminophen, an antipyretic.

Perioperative inflammation and metabolic stress are closely interlinked and give rise to a state of insulin resistance, resulting in an exaggerated proinflammatory and prothrombotic state. We observed a significant rise in serum insulin levels following surgery in both the groups that paralleled IL-6 levels, with significant correlation between peak levels of serum insulin and IL-6, as previously described,[22] indicating the importance of serum insulin as a marker of both inflammation and metabolic stress.[22]

As there appears to be an association between inflammatory response and postoperative morbidity,[9,10] it was decided to observe postoperative complications during the first 30 postoperative days by using the classification of Clavien.[13] which has been validated in a large population (over 6,000 patients). There were 3 patients in the PCA group with postoperative complications (wound infection, wound hematoma, and urinary tract infection) and 1 in the CPNB group (deep vein thrombosis). The severity of all of them were classified as Clavien 1 or 2 and responded to conservative management.

It is recognized that the small number of patients represents a limitation of this study; nevertheless it illustrates the importance of establishing an association between inflammatory response and postoperative outcome as measured by morbidity and not by length of hospital stay. The latter, commonly used as a measure of outcome is influenced by the health care system, the administrative culture, patients' expectations, and availability of family and community support.

In conclusion, the results of this physiologic study confirm that knee arthroplasty induces a distinct inflammatory response, which can be attenuated by a prolonged block of all the nerve fibers supplying the knee area. There is a need to determine in a large population whether this anesthetic technique impacts on postoperative morbidity and accelerates functional recovery.

Acknowledgments

The authors thank Dr. E. Lenczner, orthopedic surgeon, for his assistance with this project.

References

1. Weissman C. The metabolic response to stress: an overview and update. *Anesthesiology* 1990;73:308-327.
2. Jancso N, Jancso-Gabor A, Szolcsanyi J. Direct evidence for neurogenic inflammation and its preven-

tion by denervation and by pretreatment with capsaicin. *Br J Pharmacol Chemother* 1967;31:138-151.
3. Munford RS, Pugin J. Normal responses to injury prevent systemic inflammation and can be immunosuppressive. *Am J Respir Crit Care Med* 2001;163:316-321.
4. Hall GM, Peerbhoy D, Shenkin A, Parker CJ, Salmon P. Hip and knee arthroplasty: a comparison and the endocrine, metabolic and inflammatory responses. *Clin Sci (Lond)* 2000;98:71-79.
5. Andres BM, Taub DD, Gurkan I, Wenz JF. Postoperative fever after total knee arthroplasty: the role of cytokines. *Clin Orthop Relat Res* 2003:221-231.
6. Pham-Marcou TA, Gentili M, Asehnoune K, Fletcher D, Mazoit JX. Effect of neurolytic nerve block on systemic carrageenan-induced inflammatory response in mice. *Br J Anaesth* 2005;95:243-246.
7. Kissin I, Lee SS, Bradley EL Jr. Effect of prolonged nerve block on inflammatory hyperalgesia in rats: prevention of late hyperalgesia. *Anesthesiology* 1998; 88:224-232.
8. Moore CM, Desborough JP, Powell H, Burrin JM, Hall GM. Effects of extradural anaesthesia on interleukin-6 and acute phase response to surgery. *Br J Anaesth* 1994;72:272-279.
9. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999;91:8-15.
10. Chelly JE, Greger J, Gebhard R, Coupe K, Clyburn TA, Buckle R, Criswell A. Continuous femoral blocks improve recovery and outcome of patients undergoing total knee arthroplasty. *J Arthroplasty* 2001;16: 436-445.
11. Capdevila X, Macaire P, Dadure C, Choquet O, Biboulet P, Ryckwaert Y, D'Athis F. Continuous psoas compartment block for postoperative analgesia after total hip arthroplasty: new landmarks, technical guidelines, and clinical evaluation. *Anesth Analg* 2002; 94:1606-1613, table of contents.
12. di Benedetto P, Bertini L, Casati A, Borghi B, Albertin A, Fanelli G. A new posterior approach to the sciatic nerve block: a prospective, randomized comparison with the classic posterior approach. *Anesth Analg* 2001;93:1040-1044.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205-213.
14. Wirtz DC, Heller KD, Miltner O, Zilkens KW, Wolff JM. Interleukin-6: a potential inflammatory marker after total joint replacement. *Int Orthop* 2000;24:194-196.
15. Hall GM, Peerbhoy D, Shenkin A, Parker CJ, Salmon P. Relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses. *Br J Anaesth* 2001;87:537-542.
16. Fletcher D, Kayser V, Guilbaud G. Influence of timing of administration on the analgesic effect of bupivacaine infiltration in carrageenin-injected rats. *Anesthesiology* 1996;84:1129-1137.
17. Gentili ME, Mazoit JX, Samii KK, Fletcher D. The effect of a sciatic nerve block on the development of inflammation in carrageenan injected rats. *Anesth Analg* 1999;89:979-984.
18. Beloeil H, Asehnoune K, Moine P, Benhamou D, Mazoit JX. Bupivacaine's action on the carrageenan-induced inflammatory response in mice: cytokine production by leukocytes after ex-vivo stimulation. *Anesth Analg* 2005;100:1081-1086.
19. Beloeil H, Ababneh Z, Chung R, Zurakowski D, Mulkern RV, Berde CB. Effects of bupivacaine and tetrodotoxin on carrageenan-induced hind paw inflammation in rats (Part 1): hyperalgesia, edema, and systemic cytokines. *Anesthesiology* 2006;105:128-138.
20. de Klaver MJ, Buckingham MG, Rich GF. Lidocaine attenuates cytokine-induced cell injury in endothelial and vascular smooth muscle cells. *Anesth Analg* 2003;97:465-470, table of contents.
21. Sinclair R, Eriksson AS, Gretzer C, Cassuto J, Thomsen P. Inhibitory effects of amide local anaesthetics on stimulus-induced human leukocyte metabolic activation, LTB4 release and IL-1 secretion in vitro. *Acta Anaesthesiol Scand* 1993;37:159-165.
22. Thorell A, Loftenius A, Andersson B, Ljungqvist O. Postoperative insulin resistance and circulating concentrations of stress hormones and cytokines. *Clin Nutr* 1996;15:75-79.