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Upregulation of Prostaglandin E_2 and Interleukins in the Central Nervous System and Peripheral Tissue during and after Surgery in Humans

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Background: **The central and peripheral inflammatory response to surgery may influence patient outcomes. This study examines the time course and clinical relevance of changes in prostaglandin E_2 and cytokines in cerebrospinal fluid, local tissue (surgical site), and circulating blood during and after total hip replacement.**

Methods: **Thirty osteoarthritis patients undergoing primary total hip arthroplasty with spinal anesthesia were randomly allocated to three groups (n = 10/group): placebo for 4 days before surgery and on the morning of surgery; placebo for 4 days before surgery and oral rofecoxib 50 mg on the morning of surgery; oral rofecoxib 50 mg for 4 days before surgery and the morning of surgery. Cerebrospinal fluid and plasma were collected before surgery and up to 30 h after incision for measurement of prostaglandin E_2 and interleukins. When hip replacement was complete, a drain was placed in the hip wound and exudates were collected at 3 to 30 h after incision.**

Results: **Cerebrospinal fluid showed an initial increase in interleukin 6 and a later rise in prostaglandin E_2 concentration after surgery; interleukin 1β and tumor necrosis factor α were undetectable. Hip surgical site fluid evidenced an increase in prostaglandin E_2, interleukin 6, interleukin 8, and interleukin 1β; tumor necrosis factor α decreased at 24 and 30 h. Preoperative administration of the cyclooxygenase 2 inhibitor rofecoxib reduced cerebrospinal fluid and surgical site prostaglandin E_2 and cerebrospinal fluid interleukin 6. Cerebrospinal fluid prostaglandin E_2 was positively correlated with postoperative pain and cerebrospinal fluid interleukin 6 with sleep disturbance. Poorer functional recovery was positively correlated with increased surgical site prostaglandin E_2.**

Conclusions: **These results suggest that upregulation of prostaglandin E_2 and interleukin 6 at central sites is an important component of surgery induced inflammatory response in patients and may influence clinical outcome.**

THERE are detrimental effects of surgery that may not be direct consequences of surgical intervention, but rather the result of postoperative pain and biochemical consequences of the endocrine-metabolic response to surgical trauma.[1] Tissue injury associated with surgery initiates a systemic reaction accompanied by increased proinflammatory cytokines. These proinflammatory cytokines can induce peripheral and central nervous system sensitization, leading to hyperalgesia[2] with induction of cyclooxygenase 2 (COX-2) activity.[3]

Prostaglandin E_2 (PGE_2) is the predominant eicosanoid released after surgical trauma and has been associated with inflammation, pain, and fever.[4] Human dental studies using a microdialysis catheter showed that the increase in PGE_2 in peripheral tissue at the molar extraction site is associated with the onset of pain.[5,6] Animal data also have demonstrated an increase in spinal PGE_2 after peripheral inflammation.[7]

Surgery leads to a complex systemic response, with increases in plasma PGE_2 and interleukin 6 (IL-6) despite perioperative neuronal blockade.[8] IL-6 is a sensitive early marker of tissue damage with peak serum levels proportional to the amount of surgical trauma.[9] In addition, IL-6 is produced in substantial quantities at the surgical site as measured from a wound drain[10,11] and has been associated with many pain states.[12]

In inflammatory pain models, COX-2 is upregulated both at the injury site[13] and in the spinal cord.[13–15] Therefore, inhibiting central COX-2 activity may reduce centrally generated inflammatory hypersensitivity.[13] COX-2 inhibitors have little or no effect on coagulation and therefore are attractive for use in the surgical setting.[16] Perioperative oral administration of COX-2 inhibitors reduces postoperative pain[17] and improves postoperative outcome after knee arthroplasty.[18] However, it is not known whether orally administered COX-2 inhibitors produce some of their effect by reducing central COX-2 activity. Issues of cardiovascular safety in the administration of COX-2 inhibitors have arisen (two drugs, including the study drug, have been withdrawn from the market in the United States), and so the long-term therapeutic implications of COX-2 inhibitors remains unknown.

No human study to date has evaluated the time course, relationship, and clinical relevance of changes in PGE_2 and cytokines in the cerebrospinal fluid (CSF) compared with the local tissue site and circulating blood after surgical trauma. Therefore, this study was designed to examine the inflammatory response to surgery both in the central and peripheral compartments and to corre-

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late the PGE_2 and cytokine responses to clinically relevant outcomes, along with attenuation of this inflammatory response by COX-2 inhibitor administered in the perioperative period. The primary objective of this study was to determine whether hip replacement surgery causes an upregulation of PGE_2 in the CSF. The secondary objective was to determine if perioperative oral COX-2 inhibitor administration modulates CSF PGE_2 levels.

Materials and Methods

Patient Selection

After approval of the Institutional Review Board of Rush University Medical Center, Chicago, Illinois, consecutive osteoarthritis patients between the ages of 55 and 75 yr scheduled to undergo elective primary total hip arthroplasty by a single orthopedic surgeon were contacted and assessed for study eligibility with a screening medical history. A study consent form was sent to patients who agreed to participate in the clinical study. After obtaining consent, the patient was allocated a study number and the study drug was dispensed to each participant. Using a random number table, patients were allocated to one of three groups, without stratification by demographic characteristics: group 1 (n = 10; control) received a placebo each morning for 4 days before surgery and on the day of surgery; group 2 (n = 10; 1-day COX-2 inhibitor) received placebo each morning for 4 days before surgery and on the day of surgery received oral rofecoxib 50 mg; group 3 (n = 10; 5-day COX-2 inhibitor) received oral rofecoxib 50 mg each morning for 4 days before surgery and on the day of surgery. Study drug administration on the day of surgery was timed to precede surgical incision by 90 ± 30 min. All prior nonsteroidal antiinflammatory drug therapy was discontinued 14 days before surgery.

Protocol

The physicians and nurses managing the patient during surgery and in the recovery room, the personnel involved with postoperative pain assessment and management of the intrathecal infusion, and the study patients were blinded to group assignments. Treatment assignment codes were not available to the investigators until all patients completed the study. A global pain score using the visual analog scale (VAS) with 0 corresponding to no pain and 10 to the worst imaginable pain for the patient was obtained before surgery.[5] In the operating room, patients were sedated with midazolam (0.05 $mg \cdot kg^{-1}$ titrated to effect) and an intrathecal catheter was placed in the sitting position, at the L3–L4 or L4–L5 vertebral level to deliver spinal anesthesia with bupivacaine 0.5% (7.5 mg) and fentanyl 25 μg. Before administering spinal anesthesia, 0.5 ml CSF was removed with simultaneous sampling of venous blood (5 ml) for the analysis of PGE_2 and cytokines. Patients were maintained at normothermia in the operating room.[19] A sensory analgesic level of T10 was obtained before commencement of surgery. At completion of surgery an intrathecal infusion of fentanyl 0.5 $\mu g \cdot ml^{-1}$ and bupivacaine 0.1 mg ml^{-1} was initiated[16] using a continuous basal infusion with superimposed patient controlled intrathecal analgesia bolus doses. Initial infusion rates were 4 $ml \cdot h^{-1}$ basal intrathecal infusion plus patient controlled intrathecal analgesia of 1 ml every 12 min with a 4-h lockout of 40 ml. The patients were instructed before surgery to use patient-controlled intrathecal analgesia at their discretion to maintain the VAS pain score of less than 4, following a previously applied protocol.[18] A standardized surgical technique of noncemented hip arthroplasty performed through a mini-incision (<10 cm long) anterolateral approach was used in all patients.

Biochemical Sampling

The intrathecal catheter was left in place for 30 h after surgery to provide analgesia. CSF (0.5 ml) and blood (5 ml in plasma collection tubes) were collected at the time of intrathecal catheter placement and also at surgical incision for baseline measurements (to act as control for intrathecal anesthesia). In addition, CSF and blood were collected at: 1, 3, 9, 24, and 30 h after incision for measurements of PGE_2, interleukin 1β (IL-1β), IL-6, interleukin 8 (IL-8), and tumor necrosis factor α (TNF-α). In a preliminary study, CSF interleukin 10 was undetectable during the postoperative period, and that cytokine therefore was excluded from the assays. When the hip replacement was complete, a drain was placed in the hip wound and the exudates were collected in a Snyder 400-ml capacity reservoir. Samples from the hip drain exudate system were collected at 3, 9, 24, and 30 h after incision. One hour before scheduled collection time, the hip drain reservoir was emptied and the exudate was collected over the next 60 min. Drain fluids and blood were centrifuged and the supernatant removed. These fluids and CSF were frozen at −80°C for subsequent assay.

Biochemical Analysis

Prostaglandin E_2 and cytokine concentrations in samples of plasma, hip drain supernatant, and CSF were measured by sandwich enzyme-linked immunosorbent assay in 96-well microtitration plates following the manufacturer's protocols. Enzyme-linked immunosorbent assay kits were obtained from Assay Designs (Ann Arbor, MI) for PGE_2 and R&D Systems (Minneapolis, MN) for the cytokines IL-6, IL-8, IL-1β, and TNF-α. All samples were assayed in duplicate. The detection limits for the assays in $pg \cdot ml^{-1}$ were: PGE_2, 13.4; IL-6, 9.4; IL-8, 25.0; IL-1β, 3.9; and TNF-α, 15.6. For all assays, the intraday

and interday coefficients of variation were both less than 10%.

Clinical Outcomes

Visual analog scores beginning at 3, 9, 24, and 30 h after surgical incision and total intrathecal medication consumption were recorded. Patients rated sleep disturbance during the night after surgery (0 = no sleep disturbance to 10 = greatest sleep disturbance).[18] Functional outcome was assessed by the time to ambulate 10 and 25 m with standardized walking aids,[20] time to achieve milestones such as transfer unassisted in and out of bed, ability to ambulate with a walker unassisted on a level surface, and the ability to ascend and descend four steps using a railing.[21] Tympanic temperature was monitored before surgery and at each blood and CSF measurement time point after surgical incision.

Statistical Analysis

A sample size of 16 patients per group was required to provide 90% power to detect differences over time between groups with respect to changes in CSF PGE_2 at an $\alpha = 0.05$. The trial was terminated prematurely when the study drug was withdrawn from the market. However, 30 patients completed the study protocol (10 per group). One patient from each group subsequently was dropped from the study because of consistent inability to sample CSF. Analyses were performed using repeated measures analysis with preplanned contrasts for both trend and between-subject factors. For statistical analysis, all assay results that were below the level of detection were replaced by the level of detection. Maximum-likelihood estimates and corresponding *P* values were generated using the mixed regression procedure in the Statistical Analysis System package version 8.2 (SAS, Cary, NC). The Dunnett-Hsu procedure was used to control for type I family-wise error rate for multiple comparisons. In particular, in analyzing changes in variables over time (*e.g.*, CSF PGE_2), later time-point concentrations were compared with the 0-h baseline; and in comparing differences among groups in the COX-2 modulation study, each COX-2 dose group was compared with placebo. All tests were two-sided, and an α value of 0.05 was chosen as the threshold for significance. Continuous descriptive measures are reported as mean and standard deviation. Demographic measures were tested for between-group differences using one-way ANOVAs or chi-square tests, depending on the scale of the measure. Correlations between variables were performed by Pearson correlation coefficient of area under the curve (AUC) up to 30 h. An autoregressive time series model was used to evaluate relationships over time. Concentration-time slopes were calculated as changes in concentration divided by change in time. Regression coefficients (slopes) were estimated using the mixed regression procedure, and family-wise error rate was controlled using the stepdown Bonferroni procedure.

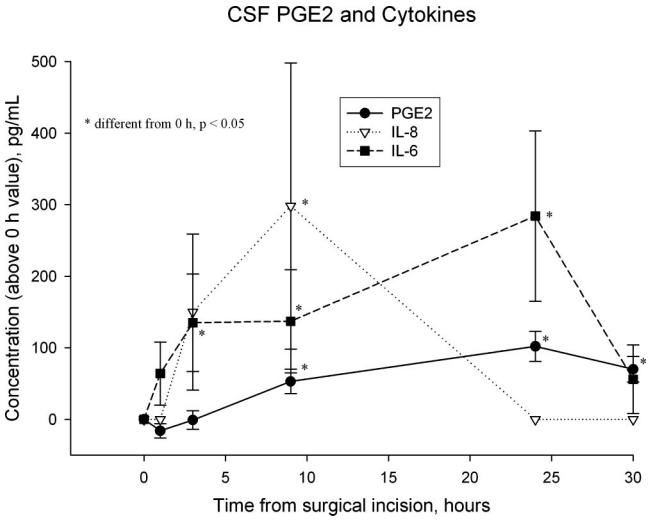

Fig. 1. Graph showing the cerebrospinal fluid (CSF) time course of prostaglandin E_2 (PGE_2), interleukin 6 (IL-6), and interleukin 8 (IL-8) concentration in control hip surgery patients. Baseline values just before surgical incision (0 h value) were 40.0, 0.0, and 0.6 pg·ml^{-1}, respectively. Asterisks indicate significant difference ($P < 0.05$) from baseline. Note: PGE_2 values at 1 and 3 hour (h) and IL-8 values at 1, 24, and 30 hours are below the detection limit.

Results

Upregulation of PGE_2 and Cytokines

In control (placebo) patients, PGE_2 was increased in CSF at all measurement points from 9 through 30 h from the start of surgery (fig. 1). There was also an increase in CSF IL-6 that was measured at 3 h and persisted through 30 h. CSF IL-8 was increased only at the 9-h measurement. CSF IL-1β and TNF-α concentrations were below the detection limit of the assay at baseline and during the postoperative period. Differences in the time course of the CSF PGE_2 and cytokine levels were characterized by significance of the CSF concentration-time slopes (table 1). Over the 0- to 3-h period, only IL-6 had a significant positive concentration-time slope. At 3 to 9 h and 9 to 24 h, only PGE_2 showed significant positive CSF concentration-time slope estimates.

Table 1. Analysis of Cerebrospinal Fluid Concentration Time Slopes for IL-6, PGE_2, and IL-8

	0–3 h		3–9 h		9–24 h	
	Slope*	*P* Value†	Slope*	*P* Value†	Slope*	*P* Value†
IL-6	42.87	0.0174‡	7.92	0.5562	6.82	0.2904
PGE_2	4.33	0.1933	10.11	0.0033‡	3.50	0.0339‡
IL-8	28.89	0.1192	33.70	0.2988	−19.86	0.3223

* Slope in pg·ml^{-1}·h^{-1}. † Stepdown Bonferroni adjusted *P* values. ‡ $P < 0.05$.

IL-6 = interleukin 6; IL-8 = interleukin 8; PGE_2 = prostaglandin E_2.

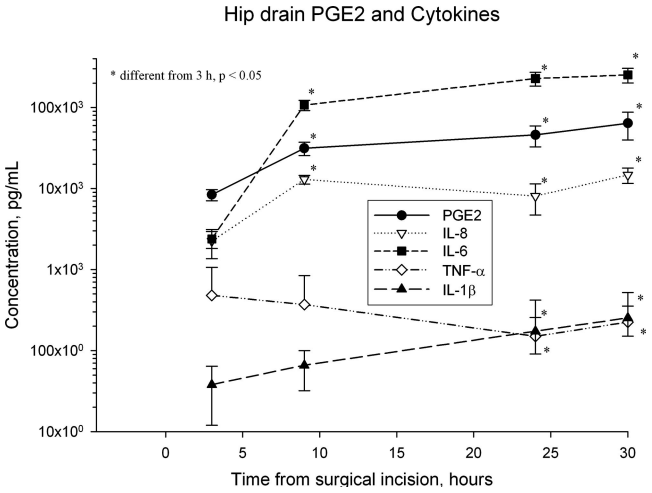

Fig. 2. Graph showing the hip drain fluid time course of prostaglandin E_2 (PGE_2), interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor α (TNF-α), and interleukin 1β (IL-1β) concentration in control hip surgery patients. Asterisks indicate significant difference ($P < 0.05$) from 3-h sample.

In control patients, local tissue (surgical site hip drain) PGE_2, IL-6, and IL-8 were increased from the 3-h initial sampling time at all measurement points from 9 through 30 h (fig. 2). Hip drain IL-1β increased at 24 and 30 h measurement points. However, the local tissue TNF-α was decreased at 24 and 30 h. In plasma, the only changes in concentration were an increase in PGE_2 at 1 h and a late increase in IL-6 at 24 and 30 h (fig. 3). Plasma IL-1β and TNF-α concentrations were below the detection limit at baseline and during the postoperative period. The hip drain concentrations of PGE_2, IL-6, IL-8, and IL-1β were greater than the plasma concentrations at

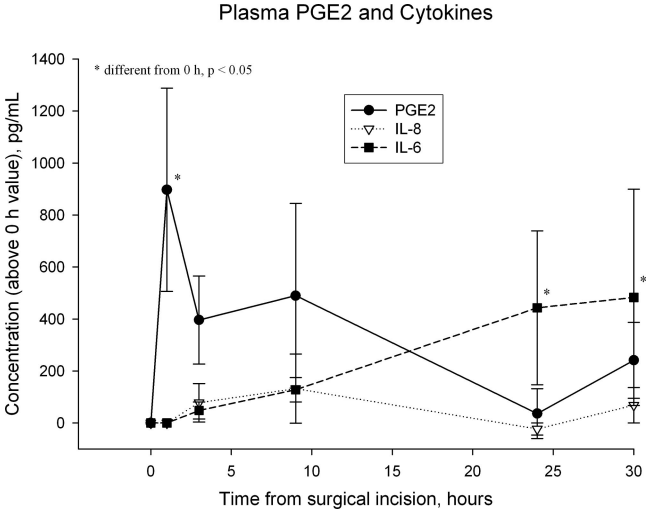

Fig. 3. Graph showing the plasma time course of prostaglandin E_2 (PGE_2), interleukin 6 (IL-6), and interleukin 8 (IL-8) concentration in control hip surgery patients. Baseline value just before surgical incision (0 h value) were 446.4, 12.2, 0.0 pg·ml^{-1}, respectively. Asterisks indicate significant difference ($P < 0.05$) from baseline. Note: IL-6 values at 1 h and IL-8 values at 1 and 24 hours are below the detection limit.

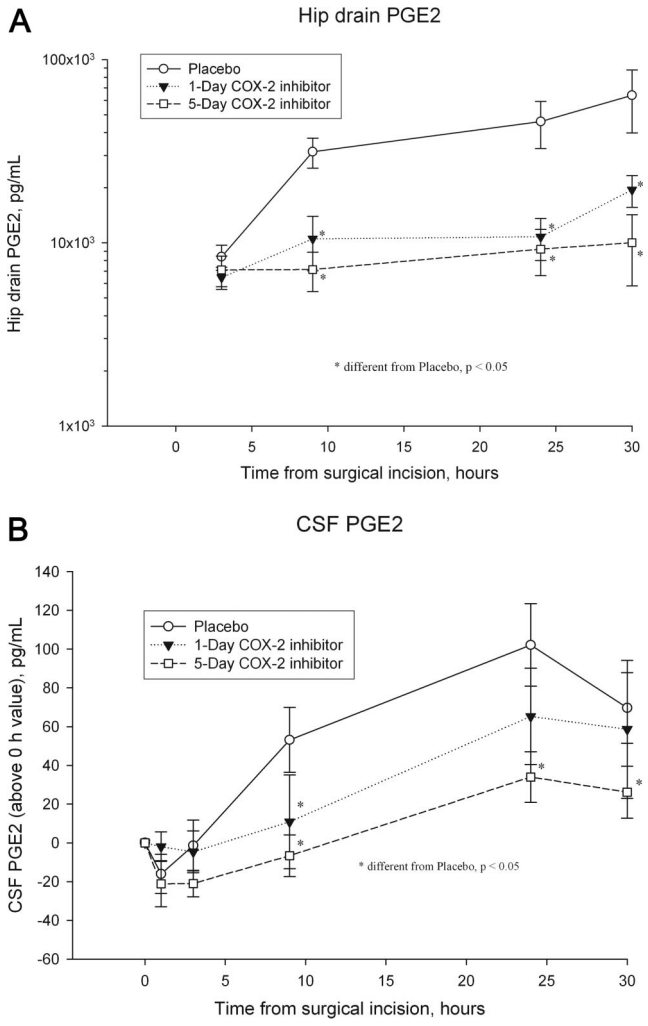

Fig. 4. Graph showing the time course of prostaglandin E_2 (PGE_2) concentration in three groups of patients: placebo (control), 1-day preoperative cyclooxygenase-2 (COX-2) inhibitor, 5-day preoperative COX-2 inhibitor. (*A*) Cerebrospinal fluid (CSF) concentrations (relative to 0 h value). Baseline values did not differ between groups. (*B*) Hip drain concentrations. Asterisks indicate significant difference ($P < 0.05$) from placebo group. Note: PGE_2 values at 1 and 3 h for the placebo group and at 1, 3, and 9 h for the two drug groups are below the detection limit.

9 h and at all subsequent measurement points. Hip drain TNF-α was greater than plasma TNF-α at 3 and 9 h.

Effect of COX-2 Inhibition on PGE_2 and Cytokines

When three groups of patients are considered, there is a reduction of CSF PGE_2 by the COX-2 inhibitor with either dose regimen (fig. 4A). The 5-day dosing decreased CSF PGE_2 levels at 9, 24, and 30 h compared with the placebo patients, whereas the single dose reduced the PGE_2 level at the 9-h measurement. Surgical site PGE_2 also was reduced by either dosing regimen of COX-2 inhibitor (fig. 4B), but there was no COX-2 inhibitor modulation of plasma PGE_2.

CSF IL-6 concentration was reduced at the 3, 9, and 24 h measurement points by 5-day dosing of COX-2

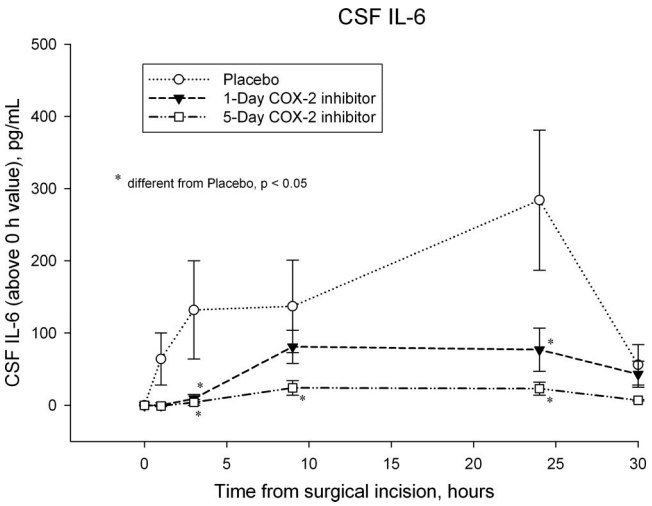

Fig. 5. Graph showing the time course of cerebrospinal fluid (CSF) interleukin 6 (IL-6) concentration in three groups of patients: placebo (control), 1-day preoperative cyclooxygenase-2 (COX-2) inhibitor, 5-day preoperative COX-2 inhibitor. Baseline values did not differ between groups. Asterisks indicate significant difference ($P < 0.05$) from placebo group. Note: IL-6 values at 1 and 3 h for the 1-day drug group and at 1, 3, and 24 h for the 5-day group are below the detection limit.

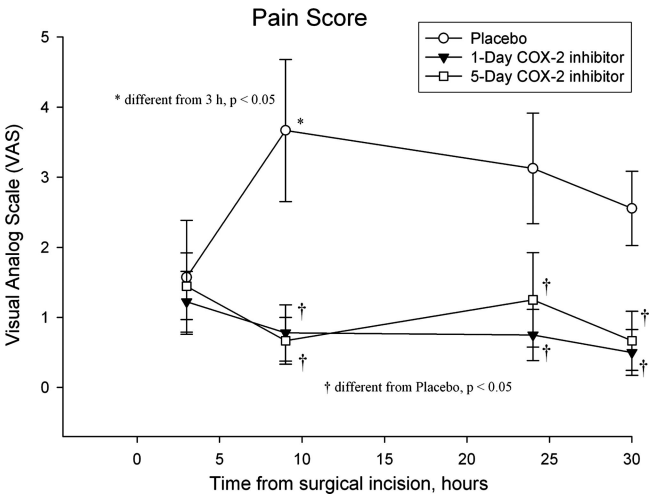

Fig. 6. Graph showing the time course of visual analog scale (VAS) pain score beginning at 3 h from the start of surgery in three groups of hip surgery patients. Asterisks indicate significant difference ($P < 0.05$) from 3-h score within that group; † significant difference ($P < 0.05$) from placebo group. COX-2 = cyclooxygenase 2.

inhibitor, and at 3 and 24 h with the 1-day dose (fig. 5). Surgical site IL-6 was not reduced by either dose of COX-2 inhibitor, nor was plasma IL-6. IL-8 concentrations were not modulated by COX-2 inhibitor in the CSF, hip drain, or in the plasma, and IL-1β and TNF-α hip drain concentrations were not COX-2 inhibitor modulated.

Clinical Outcomes

Demographic characteristics did not differ among the three groups of patients (table 2) and none of the patients received blood transfusion during the time of the study. COX-2 inhibitor administration, with either dosing regimen, reduced postoperative pain at 9-, 24-, and 30-h assessment points (fig. 6). In addition, 24 h from the start of surgery, intrathecal drug consumption for postoperative pain was reduced in the 5-day COX-2 inhibitor group (79.1 ± 18.5 ml) *versus* the placebo groups (106.9 ± 16.5 ml), although the 1-day COX-2 inhibitor group (98.9 ± 12.3 ml) was not different from placebo.

The VAS for pain was not significantly correlated with any of the PGE_2 or cytokine levels in the placebo patients. However, when all the three groups were combined, over the 30-h postoperative time period, VAS was positively correlated with CSF PGE_2 level ($P = 0.0043$). Similarly, CSF IL-6 concentration was correlated positively with VAS ($P = 0.0057$). CSF IL-6 also was correlated positively with postoperative day 1 sleep disturbance, both for the placebo group ($P = 0.0482$) and all three groups combined ($P = 0.0270$). CSF IL-8 also was correlated positively with sleep disturbance, but only for the three combined groups ($P = 0.0330$).

There was a positive correlation between poorer functional recovery and increased surgical site PGE_2 concentration measured at the 30-h time point. The decreased performance during physical therapy included increased time to ambulate 10 and 25 m ($P < 0.01$), to get out of bed ($P = 0.03$), and to walk up steps ($P = 0.0003$). Finally, there was no correlation of body temperature with any measured variable, including CSF PGE_2. All patients' body temperatures were less than 37.1°C before surgery and 37.2°C after surgery.

Table 2. Patient Characteristics

	Control (Placebo)	1-day COX-2 Inhibitor	5-day COX-2 Inhibitor
Age (yr)	70.8 (5.9)	70.6 (3.5)	68.1 (4.4)
Weight (kg)	151.0 (44.9)	143.6 (60.8)	155.1 (65.0)
Height (cm)	169.1 (8.7)	171.7 (9.9)	170.2 (9.4)
Female (%)	36	29	36
Intraoperative IV fluids (ml)	2818 (1011)	2667 (557)	2240 (959)
Intraoperative blood loss (ml)	456 (208)	439 (145)	350 (117)
Duration of surgery (min)	104 (16)	103 (17)	109 (23)

Data are presented as mean (standard deviation).

COX-2 = cyclooxygenase 2; IV = intravenous.

Discussion

The upregulation of PGE_2 in CSF, documented at 9 through 30 h after the start of hip replacement surgery, is similar to findings in animal models of peripheral inflammation. In rats with unilateral hind paw inflammation, CSF PGE_2 increased beginning at 6 h and peaked at 12 h after injection of complete Freund's adjuvant.[13] After intraarticular injections of kaolin and carrageenan in the rat knee, there was a pronounced intraspinal release of PGE_2 at 7 to 9 h after injection.[7] In both animal models, the increase in PGE_2 was accompanied by an upregulation of spinal COX-2 protein. CSF IL-6 was increased at 3 h from the start of hip surgery and remained elevated at 24 h. This is similar to another hip replacement study in which a single CSF IL-6 level obtained on postoperative day 1 was increased.[22] The increase in CSF IL-6 at 24 h in our study was 283 $pg \cdot ml^{-1}$, whereas in the latter study, the CSF IL-6 increase was approximately 150 $pg \cdot ml^{-1}$, both under spinal anesthesia. In that study, CSF IL-10 did not change at the single measured time point, which matches our preliminary findings (see Materials and Methods). CSF IL-8 increased in our study, although it was only at the 9-h measurement. CSF IL-8 has also been shown to be increased after major surgery, such as thoracoabdominal aortic reconstruction.[23] Surprisingly, CSF levels of IL-1β and TNF-α did not increase above the detection limits in our patients throughout the postoperative period. These IL-1β results are different from a study in rats with peripheral inflammation, in which there was a large upregulation of CSF IL-1β, starting at 2 h after insult.[13] In patients undergoing lower-extremity revascularization under spinal anesthesia, the immediate postoperative CSF TNF-α level increased only slightly.[24] However, after thoracoabdominal aortic surgery under general anesthesia, there was no increase in CSF levels of IL-1β, TNF-α, or IL-6.[23] The latter results may be the result of suppression of central inflammatory responses by general anesthesia. However, different types of surgery may generate different central nervous system inflammatory responses. In this hip surgery study, an analysis of concentration-time slopes suggests that in the CSF there is an initial increase in IL-6 that is followed by an increase in PGE_2. Topical IL-6 application has been shown to increase PGE_2 production in the central nervous system both *in vivo*[25] and in tissue culture.[26,27]

After hip replacement surgery, hip drain fluid evidenced a postoperative increase in PGE_2 after 3 h from the time of surgical incision. In dental patients, PGE_2 at the surgical site increased starting 1 to 2 h after molar extraction.[5,6] In our study, hip drain IL-6, IL-8, and IL-1β levels also increased after 3 h, but TNF-α decreased. This is similar to a previous hip replacement study under spinal anesthesia in which hip drain IL-6 and IL-1 increased during the postoperative period, but TNF-α did not.[10] After reduction mammoplasty in patients, wound fluid IL-6 increased after surgery and there was a trend toward increased IL-8 levels.[11] Because the first hip drain samples were obtained 3 h from the surgical incision in this study, we are unable to conclude definitively whether upregulation of any of the cytokines preceded the increase in local PGE_2 production.

The only changes we observed in the plasma levels were an initial increase in PGE_2 and a late increase in IL-6. Several studies have shown an increase in blood IL-6 levels after hip surgery.[9,10,22,28–30] Some of these studies also measured blood levels of IL-1β and TNF-α[10,29] and showed no increase, which is consistent with our study. Our circulating concentrations of PGE_2, IL-6, IL-8, and IL-1β were all less than the hip drain levels at 9, 24, and 30 h after surgery, and the plasma level of TNF-α was less than the hip drain at 3 and 9 h. At the 24-h measurement, hip drain levels were approximately two orders of magnitude more than the corresponding plasma levels of PGE_2, IL-6, or IL-8. In a similar hip surgery study, it was also noted that concentrations of cytokines were higher in wound drainage fluid than in the systemic circulation.[10] This suggests that hip drain fluid levels are not plasma derived but instead represent a local inflammatory response. Thus, it is not clear what role circulating cytokines, except possibly IL-6, play in the systemic response to hip replacement surgery. This is unlike the human response to endotoxin injection, where circulating levels of TNF-α, and then IL-6 and IL-8, rapidly increase.[31] The plasma levels of PGE_2, IL-6, and IL-8 were not correlated with the corresponding CSF levels that were measured in our patients, and so there is no indication that the CSF levels represent diffusion from the blood. This is consistent with animal studies showing that PGE_2 and IL-6 cross the blood–brain barrier poorly.[32,33] Mechanisms have been proposed by which circulating cytokines can trigger brain endothelial cells to produce PGE_2, which then can diffuse into the central nervous system.[34] Thus, the rise in blood IL-6 levels observed at 24 and 30 h may have contributed to the persistent increase in CSF PGE_2 at those times.

Animal models of peripheral inflammation have demonstrated an upregulation of spinal cord COX-2[7,13–15] and subsequent increase in central PGE_2 levels.[7,13] Surgical incision also can increase COX-2 protein levels in the rat spinal cord.[35] An upregulation of both CSF and surgical site PGE_2 was observed in the current study, and the question arises whether those levels can be reduced by COX-inhibitors. Because of the risk of increased bleeding during surgery, nonsteroidal antiinflammatory drugs, which are primarily COX-1 inhibitors, were not tested. Rofecoxib, the COX-2 inhibitor used in the present study, has good penetration into the central nervous system after oral dosing,[36] and that may allow direct central COX-2 inhibition, in addition to the expected peripheral COX-2 inhibition.

The present study demonstrates that COX-2 inhibition

reduces CSF PGE_2 over the 9- to 30-h period from start of surgery, and the effect was more pronounced with multiple (5-day) dosing *versus* a single dose. Our previous clinical, pharmacokinetic analysis showed that such multiple daily dosing doubles both the plasma and CSF levels of rofecoxib compared with a single dose.[36] Hip drain PGE_2 was suppressed by COX-2 inhibition and the single dose was as effective as multiple dosing. In an oral surgery model, pretreatment with another COX-2 inhibitor, celecoxib, suppressed local tissue PGE_2 at 80 to 240 min from the end of surgery.[37] Interestingly, the COX-2 inhibitor also decreased postoperative CSF IL-6 levels in our hip surgery patients. PGE_2 has been demonstrated to stimulate IL-6 production in various *in vitro* studies: mouse macrophages,[38] rat leukocytes,[39] human astrocytoma,[40] osteoblast-like cells,[41] and rat astrocytes.[42] In human astrocytoma cells, PGE_2 stimulation increased IL-6 mRNA levels at 30 min, and maximal mRNA levels were achieved 60 min after PGE_2 stimulation.[40] In mouse macrophages, a cause-and-effect relationship (60-min delay) was shown between increased PGE_2 and IL-6 production, and indomethacin inhibited IL-6 mRNA expression.[38] Therefore, a plausible explanation for the reduced CSF IL-6 levels seen with administration of a COX-2 inhibitor is by reduction of CSF PGE_2 and less subsequent stimulation of central IL-6 production.

In the present study, COX-2 inhibition with single or multiple doses reduced postoperative pain, an observation noted in an earlier knee replacement surgery study.[18] In the current study, we demonstrate a correlation between CSF PGE_2 and VAS over the 30-h monitoring period. Peripheral PGE_2 sensitizes nerve endings and contributes to pain,[43] intrathecal PGE_2 is directly nociceptive in rodents,[44] and PGE_2 applied to spinal cord slices depolarizes spinal neurons.[45] When our three study groups are combined, the VAS was correlated positively with CSF IL-6 levels. CSF IL-6 concentration correlated with sleep disturbance, both for the control patients and all groups combined. Experiments in rats with central IL-6 administration have shown an initial enhancement of nonrapid eye movement sleep, after which sleep was suppressed.[46]

Increase in surgical site PGE_2 was correlated with poorer functional recovery, including increased time to begin ambulating, get out of bed, walk up steps, and walk 10 and 25 m. This is consistent with our previously published study in patients undergoing total knee replacement: when COX-2 inhibitor was administered before surgery, there was an improvement in the functional outcome.[18] There was suppression of the hip drain PGE_2 with COX-2 inhibition in the present study, with improved outcome. We did not find a correlation between plasma IL-6 and functional recovery unlike another hip surgery study.[20] Fever has been related directly to brain levels of PGE_2.[47] In our study, there was no correlation between CSF PGE_2 and body temperature. However, no patient had a temperature of more than 37.2°C. After total knee arthroplasty, patients who were febrile had higher knee drain and serum IL-6 levels than afebrile patients.[48] Because we did not have any febrile patients, it is not surprising that there was no correlation of body temperature with any of the biochemical measures in our study.

In addition to the consideration that other types of major surgery may evoke a different spectrum of inflammatory responses than hip replacement surgery, there is another factor that may limit generalization of our results. All of our patients received spinal anesthesia with an indwelling intrathecal catheter. In a similar hip surgery study, with patients receiving general or spinal anesthesia, CSF IL-6 levels on postoperative day 1 were more variable in the latter group, raising the possibility that spinal anesthesia led to neuroaxial irritation.[22] However, we did not observe an acute change in any of our CSF measures, in the interval between placement of the spinal catheter and the initial surgical incision. Still, some of our measures may be secondary to the local anesthetic dosing. In rodents, general anesthesia can suppress the initial CSF PGE_2 inflammatory response to surgery,[49] and if this effect is also demonstrated in humans, that may explain anesthesia-related differences in CSF IL-6.[22,23]

The primary conclusion of our study is that hip replacement surgery is associated with postoperative upregulation of PGE_2, IL-6, and IL-8, both centrally and at the surgical site. CSF PGE_2 is associated with postoperative pain, and tissue PGE_2 is associated with functional recovery. Preoperative administration of a COX-2 inhibitor reduces both CSF and surgical site PGE_2 levels as well as CSF IL-6 levels.

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