

Postoperative Analgesic Effects of Continuous Wound Infiltration with Diclofenac after Elective Cesarean Delivery

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Background: **Postoperative pain mostly results from sensitization of afferent fibers at injury sites driving central sensitization. Recently, peripheral processes have gained attention as mechanisms of hyperalgesia, and prostaglandins are among highly sensitizing agents. To date, perioperative administration of a single local dose of nonsteroidal antiinflammatory drugs has shown inconclusive efficacy. Rather than a single bolus, the current study evaluates the postoperative analgesic effect of diclofenac continuous intrawound infusion after elective cesarean delivery.**

Methods: **Ninety-two parturients were randomly allocated to receive a 48-h continuous intrawound infusion with 240 ml containing 300 mg diclofenac, 0.2% ropivacaine, or saline. In the ropivacaine and saline groups, patients also received 75 mg intravenous diclofenac every 12 h for 48 h. Postoperative evaluation included intravenous morphine consumption by patient-controlled analgesia and visual analog pain scores. Punctate mechanical hyperalgesia surrounding the wound and presence of residual pain after 1 and 6 months were also assessed.**

Results: **Continuous diclofenac infusion significantly reduced postoperative morphine consumption (18 mg; 95% confidence interval, 12.7–22.2) in comparison with saline infusion and systemic diclofenac (38 mg; 95% confidence interval, 28.8–43.7) ($P = 0.0009$) without unique adverse effects. Postoperative analgesia produced by local diclofenac infusion was as effective as local ropivacaine infusion with systemic diclofenac.**

Conclusions: **After elective cesarean delivery, continuous intrawound infusion of diclofenac demonstrates a greater opioid-sparing effect and better postoperative analgesia than the same dose administered as an intermittent intravenous bolus.**

THE antinociceptive effect of nonsteroidal antiinflammatory drugs (NSAIDs) mainly results from inhibition of cyclooxygenases involved in prostaglandin production. Analgesia and antihyperalgesia from NSAIDs after tissue injury involves both peripheral and central sites of action.[1] For that reason, cyclooxygenase inhibitors are widely used during the postoperative period[2] and have been the object of many studies. Several clinical trials have compared the analgesic efficacy of NSAIDs given by different systemic routes, concluding that route has minimal effect for systemic administration.[3] In contrast, the antinociceptive effects after local administration of NSAIDs at the site of injury are controversial in postoperative conditions, and specifically, the results from wound infiltration remain inconclusive.[4] However, it is worth noting that most of the trials regarding intrawound infiltration with NSAIDs rely on administration of a single dose despite the fact that current knowledge about perioperative incisional pain emphasizes the need for an effective analgesia covering the entire perioperative period.[5]

Today, cesarean delivery is a common surgical procedure with increasing rate.[6]

Postoperative analgesia is mainly provided by systemic opioids or by NSAIDs, which strongly potentiate opioids and are particularly effective to relieve the visceral component of pain.[7–10] Continuous wound irrigation with a local anesthetic has been used with success to provide effective analgesia after cesarean delivery.[11–13] Local anesthetic injection into the wound is a simple way to relieve pain by direct inhibition of noxious impulses from the site of injury. Another approach to modulate peripheral nociceptive transmission is to reduce the local expression of mediators that sensitize nociceptors on afferent fibers. Among these, prostaglandins are potent sensitizing agents, released after increased cyclooxygenase expression in immune cells and fibroblasts at the site of injury. Furthermore, local administration of NSAIDs minimizes their potential adverse effects by reducing the bioavailability and plasma concentration to 15–20% of those usually resulting from systemic delivery.[14,15]

The primary goal of this study was to assess the analgesic effects of the nonselective cyclooxygenase inhibitor diclofenac, administered into the wound with a continuous infusion covering the first 48 postoperative hours after elective cesarean delivery. Postoperative opioid use, as determined by intravenous patient-controlled analgesia (PCA) morphine, in patients receiving local diclofenac administration by continuous intrawound infusion was compared with the same dose administered systemically by intermittent intravenous bolus and with wound infiltration with the local anesthetic ropivacaine. Further, because the goals of postoperative analgesia include, in addition to effective immediate pain relief and rapid recovery, prevention of central sensitization perhaps leading to subsequent residual pain, a secondary

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goal was to examine the impact of the different analgesic regimens on the persistence of pain at 1 and 6 months after completion of the surgical procedure.

Materials and Methods

After approval by the institutional human ethics committee (St. Luc Hospital, Université Catholique de Louvain, Brussels, Belgium) and written informed consent were obtained, 92 healthy parturients who had American Society of Anesthesiologists physical status I or II and were scheduled to undergo elective cesarean delivery were included in the study according to a randomized, prospective, blinded protocol. The patient, the person in charge of perioperative management, and the staff involved in data collection were not aware of the patient group assignment. Patients were instructed regarding the analgesic system they would use after surgery, the continuous wound instillation device, the PCA pump, and how to use the visual analog scale (VAS; 0 = none and 100 = maximal). Finally, they received instructions on answering the postoperative pain questionnaire. The parturients were then randomly assigned using computer-generated random numbers to one of the three following groups to receive after cesarean delivery a continuous wound instillation with 0.2% ropivacaine (ropivacaine group), 300 mg diclofenac in 240 ml (diclofenac group), or saline (saline group). A local infusion of saline was included as a control to test whether perfusion of the injured area by itself might reduce pain by diluting or flushing locally released mediators. Exclusion criteria for the study included refusal to participate, American Society of Anesthesiologists physical status III or higher, asthma or cardiovascular problems, allergy to diclofenac or NSAIDs, and more than one previous cesarean delivery.

Intraoperative Procedure

All parturients were premedicated with 50 mg intravenous ranitidine; 10 mg metoclopramide; and 30 ml oral sodium citrate, 0.3 M. After a 500-ml intravenous preload with balanced salt solution, a standardized intrathecal injection was performed in all parturients. With the patient in the sitting position, a 25-gauge pencil-point spinal needle was inserted at the L3–L4 interspace, and 1.8–2 ml of a mixture of 0.5% hyperbaric bupivacaine with sufentanil (final dilution: 4 mg/ml bupivacaine and 1 μg/ml sufentanil) was injected. Thereafter, patients were placed in supine position, and all cesarean procedures were performed similarly through a classic Pfannenstiel incision and peritoneal closure. On completion of surgery, under aseptic conditions, the surgeon inserted a multihole 20-gauge catheter (Pain Buster®; I-Flow Corporation, Lake Forest, CA) superficial to the fascia. The catheter was then connected to an elastomeric pump set to deliver 5 ml/h for 48 h. The elastomeric pump was filled with saline, 0.2% ropivacaine, or 300 mg diclofenac in 240 ml isotonic saline. In both the saline and ropivacaine groups, 75 mg intravenous diclofenac diluted in 50 ml saline was administered every 12 h as a brief infusion over 20 min, whereas in the diclofenac group, a similar brief infusion of 50 ml saline was provided. Intravenous administration of either diclofenac or saline was initiated in the recovery room. The NSAID dose was chosen based on the doses of diclofenac currently used for postoperative analgesia after cesarean delivery.[7,8,10]

Immediately after recovery from spinal analgesia, an intravenous PCA device was begun, set to deliver 1 mg morphine per demand with a 5-min lockout time and a maximum allowed dose of 25 mg per 4 h. If necessary, patients were allowed to receive 1 g acetaminophen per 6 h. Analgesic regimens, continuous wound instillation, and PCA devices were supplied during the first 48 postoperative hours.

Outcome Assessment

Early postoperative pain and wound hyperalgesia were assessed using the following parameters: cumulative dose of morphine consumption (PCA use) and paracetamol needs at 12, 24, and 48 h; VAS pain scores for parietal pain (wound pain) at rest and at mobilization (with sitting on the edge of the bed) as well as for visceral pain (global VAS assessment of pain from uterine cramping) at 12, 24, and 48 h.

The area of hyperalgesia for punctate mechanical stimuli around the surgical incision was measured at 24 and 48 h according to the method previously described.[16,17] Stimulation with a von Frey hair (396 mN) was started from outside the hyperalgesic area where no pain sensation was experienced toward the incision until the patient reported a distinct change in perception. The first point where a painful, sore, or sharp feeling appeared was marked, and the distance to the incision was measured. The area of hyperalgesia was determined by testing along radial lines separated by 5 cm around the incision. The observations were translated onto graph paper, and the surface was calculated. All of the postoperative data were collected by an anesthesiologist who was not involved with intraoperative patient care and was blinded to the group assignment.

The incidence of postoperative residual pain or discomfort was evaluated at 1 and 6 months after surgery. Patients where asked to answer the following questions:

1. Do you feel any pain at the scar area?
   If yes: Do you take medication to alleviate it?
   Do you take analgesics everyday or occasionally (at least two times per week)? Which one(s)?
   If no: Do you have any particular sensations from the scar area? Itching, burning, sensitivity . . .

2. Do you feel pain at any other place?
   If yes: Where? Do you take analgesics?
3. Which unpleasant manifestations have you experienced since your operation?

This inquiry was performed by a research nurse by telephone call and confirmed by mail.

Adverse Effects of Treatments and Other Outcome Parameters

Perioperative complications such as hypotension, nausea, or vomiting were recorded. Close attention was paid to the wound healing by both the surgeons and the nurses involved in the postoperative cares to detect any excessive inflammatory reaction or infection. Postoperative blood loss was recorded. Time for recovery in terms of hours before the patient was able to stand up and return to bowel function and days of hospital stay were recorded.

Statistical Analysis

Statistical analysis was performed with Statistica for Windows (version 5; Statsoft, Tulsa, OK). Statistical power calculations ($\alpha = 5\%$, $\beta = 10\%$) based on preliminary data suggested that a group size of 30 should detect a difference of at least 30% in postoperative morphine consumption between subcutaneous saline and subcutaneous ropivacaine or diclofenac groups. Data were analyzed using analysis of variance and analysis of variance for repeated measures (demographic data, postoperative morphine use, and VAS scores) or using Kruskal-Wallis analysis of variance on ranks (area of hyperalgesia). The normal distribution of the data was assessed according to the Kolmogorov-Smirnov test. *Post hoc* comparisons were made using the Tukey honest significant difference test. Comparison of the observed proportions were performed using chi-square analysis and the Fisher exact test with Yates correction if appropriate. Results are expressed as mean ± SD or otherwise specified. A probability (*P*) value of less than 0.05 was considered to be statistically significant.

Results

Ninety-two patients were enrolled, and 90 completed the study; one patient was excluded because spinal anesthesia failed and was converted to general anesthesia, and another was excluded after early disconnection of the subcutaneous device. Demographic data as well as intraoperative parameters were similar among the three groups (table 1). Sensory level of spinal anesthesia reached the T4–T6 level in all the parturients included in the study, allowing surgery without pain. The duration of the surgical procedure and the duration of spinal anesthesia did not differ among groups.

Local administration of diclofenac significantly reduced the postoperative consumption of morphine by PCA compared with a similar dose of diclofenac administered systemically ($P < 0.05$ compared with saline group at 12, 24, and 48 h after surgery) (fig. 1). Total PCA morphine requirement was 38 mg (95% confidence interval, 28.8–43.7) in the saline group receiving intravenous diclofenac, 28 mg (95% confidence interval, 18.2–32) in the ropivacaine group with intravenous diclofenac, and 18 mg (95% confidence interval, 12.7–22.2) in the diclofenac group (analysis of variance test significant between the groups $P = 0.0012$, $F = 7.24$; $P = 0.0009$ compared with saline with systemic diclofenac administration).

Table 1. Demographic Data

	Saline Group	Ropivacaine Group	Diclofenac Group
n	30	30	30
Age, yr	31 ± 6	33 ± 5	31 ± 5
Parity, n	2.4 ± 2	2.4 ± 1	2.6 ± 2
Previous cesarean delivery, %	41	31	37
Weight, kg	75 ± 14	69 ± 9	71 ± 16
Duration of surgery, min	57 ± 8	52 ± 6	48 ± 9
Duration of spinal analgesia, min	109 ± 30	112 ± 29	107 ± 22

Data are expressed as mean ± SD. Treatment groups: saline group receiving continuous wound infiltration with saline and 75 mg intravenous diclofenac every 12 h for 48 h; ropivacaine group receiving continuous wound infiltration with 0.2% ropivacaine and 75 mg intravenous diclofenac every 12 h for 48 h; diclofenac group receiving continuous wound infiltration with 300 mg diclofenac/48 h and intravenous saline every 12 h for 48 h.

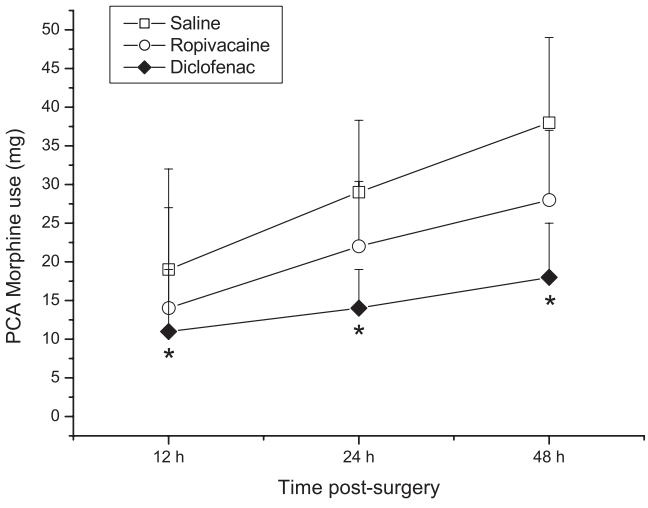

Fig. 1. Postoperative use for intravenous patient-controlled analgesia (PCA). Cumulative doses of morphine delivered by PCA device at 12, 24, and 48 h after surgery. * $P < 0.05$ with saline group. Data are expressed as mean ± SD. Treatment groups: saline group receiving continuous wound infiltration with saline and 75 mg intravenous diclofenac every 12 h for 48 h; ropivacaine group receiving continuous wound infiltration with 0.2% ropivacaine and 75 mg intravenous diclofenac every 12 h for 48 h; diclofenac group receiving continuous wound infiltration with 300 mg diclofenac/48 h and intravenous saline every 12 h for 48 h.

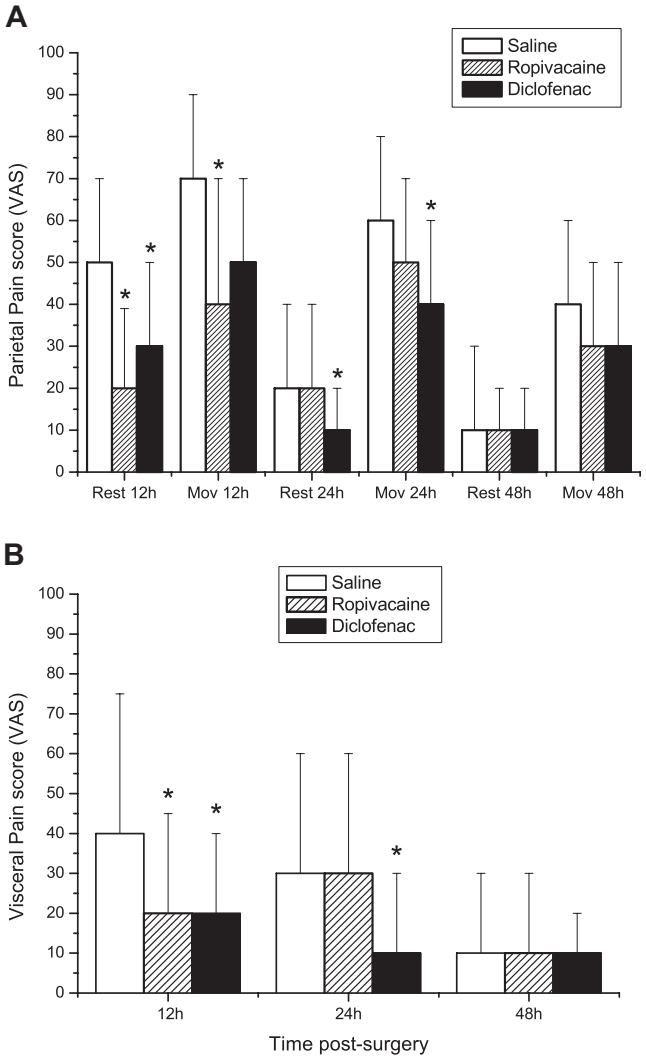

Fig. 2. (*A*) Evaluation of postoperative somatic (parietal) pain. Visual analog scale (VAS) pain scores from 0 (no pain) to 100 (maximal pain), at rest (Rest) and at movement (Mov), assessed at 12, 24, and 48 h after surgery. (*B*) Evaluation of postoperative visceral (uterine cramping) pain. VAS pain scores from 0 (no pain) to 100 (maximal pain), assessed at 12, 24, and 48 h after surgery. * $P < 0.05$ with saline group. Data are expressed as mean ± SD. Treatment groups: saline group receiving continuous wound infiltration with saline and 75 mg intravenous diclofenac every 12 h for 48 h; ropivacaine group receiving continuous wound infiltration with 0.2% ropivacaine and 75 mg intravenous diclofenac every 12 h for 48 h; diclofenac group receiving continuous wound infiltration with 300 mg diclofenac/48 h and intravenous saline every 12 h for 48 h.

For the first 12 h after surgery, patients receiving a subcutaneous infusion of ropivacaine reported lower VAS pain scores at rest and during movement than those receiving local saline infusion (fig. 2A). Patients who received a continuous local infusion of diclofenac also reported lower VAS pain scores than those receiving saline infusion and systemic diclofenac with rest at 12 and 24 h and with movement at 24 h after surgery (fig. 2A). Visceral pain related to postdelivery uterine cramping was significantly reduced during the first 24 h by the subcutaneous infusion of diclofenac in comparison with local saline infusion combined with systemic administration of diclofenac (fig. 2B). Wound infiltration with ropivacaine was also more effective than saline to relieve visceral pain at 12 h after surgery. As was the case for somatic pain (fig. 2A), the analgesic benefits of either subcutaneous ropivacaine or diclofenac infusion on the visceral pain component did not extend beyond 24 h after the surgical procedure (fig. 2B).

Acetaminophen needs and total dose at 48 h did not differ among the groups: 2 ± 2 g in the saline group, 2 ± 1.5 g in the ropivacaine group, and 2 ± 1.7 g in the diclofenac group.

The area of punctate hyperalgesia around the wound did not differ among groups. The percentages of patients presenting with postoperative mechanical hyperalgesia at 24 and 48 h after surgery were 33% and 27%, respectively, in the local diclofenac group, 46% and 25% in the local ropivacaine group, and 47% and 43% in the local saline group. When present, the areas of punctate hyperalgesia (expressed as mean ± SD and extreme values) were 6.9 ± 5.5 (1–18) and 4.4 ± 3.1 (1–10) cm^2 in the saline group at 24 and 48 h after surgery, respectively, whereas the areas were 7.7 ± 4.2 (3–15) and 5.7 ± 3.8 (4–12) cm^2 in the ropivacaine group and 5.1 ± 2.5 (1–10) and 3.1 ± 1.6 (1–5) cm^2 in the local diclofenac group.

Groups did not differ in adverse effects in the immediate postoperative period. Blood loss collected in the drainage system was 47 ± 33 and 46 ± 39 ml, respectively, in the saline and the ropivacaine groups receiving systemic diclofenac administration and 48 ± 22 ml in the diclofenac group ($P > 0.05$). Time before return to bowel function and to first oral intake as well as hospital stay did not differ between groups. Finally, neither scar infection nor delay in wound repair occurred in patients in the study.

All patients completed the study and answered questionnaires regarding residual pain either by phone call or by mail. At both 1 and 6 months after cesarean delivery, groups did not differ in residual pain located at the scar. When assessing the presence of chronic postsurgical pain at 6 months after completion of surgery, only 1 patient (3%) in the diclofenac group reported persistent pain, whereas 7 patients (23%) in the saline group and 3 patients (10%) in the ropivacaine group still reported pain (P = not significant). At 6 months, the incidence of unpleasant sensations not defined as pain (*i.e.*, hypoesthesia, mechanical allodynia), did not differ among groups: 1 patient in the diclofenac group, 1 patient in the ropivacaine group, and 4 patients in the saline group. Only 1 patient in the saline group needed regular analgesics, *i.e.*, acetaminophen with codeine and NSAID, to alleviate her residual pain.

Discussion

Although different nociceptive mechanisms participate in incisional pain,[5,18] acute postoperative pain re-

sults in part from sensitization of primary afferent nociceptors at the site of injury, which in turn drives pain and enhanced responsiveness of central neurons.[19]

The current results show that postoperative continuous intrawound infusion of the NSAID diclofenac displays a significant morphine-sparing effect at 12, 24, and 48 h after cesarean delivery when compared with the same dose administered systemically (intermittent infusions of 75 mg every 12 h). After cesarean delivery, systemic administration of diclofenac (150- to 300-mg daily dose) reduces opioid needs by 39–46%.[7,8,20] Using a continuous wound infiltration has allowed a further decrease in morphine use. In the postoperative context, specifically in obstetrics, where women want to recover quickly to take care of their baby, an opioid-sparing effect, which reduces nausea and vomiting as well as sedation, might be beneficial and hasten recovery.[21,22] These results contrast with most of those already published on intrawound infiltration with NSAIDs.[4,15] Although none of those clinical trials involved caesarean delivery or hysterectomy, they all reported the effect from a single dose of NSAID either before or immediately after completion of the surgical procedure. In contrast, our patients benefited from 48-h continuous postoperative wound irrigation. Experiments in human volunteers[23] and in preclinical animal models[24] argue for a continuous postoperative administration of local analgesics. Effectively, for incisional pain, sensitization of central neurons and postoperative pain are initiated and maintained by continuous ongoing afferent inputs from the lesioned tissues. That is, when the effect from a single application of analgesic treatment abates, the surgical wound reinitiates sensitization and regenerates pain.[5]

To date, the modulation of peripheral pain transduction has usually been accomplished by wound infiltration with long-lasting local anesthetics,[25,26] and only a few studies report the use of continuous infiltration. After caesarean delivery,[11–13] such local anesthetic infusion provides a mild and short-lasting decrease in pain scores and a significant reduction in postoperative opioid requirements. Our findings show a short-lasting (12-h) reduction in pain scores but no significant decrease in opioid needs with continuous intrawound ropivacaine when compared with local saline infusion. It is possible that the concomitant use of systemic diclofenac blunted the opioid-sparing effect afforded by the intrawound infusion of local anesthetic in our patients.

The current results suggest that continuous local infiltration of diclofenac allows a better management of postoperative pain than the usual systemic route using intermittent administration of the drug. Therefore, these findings question the relative contribution of central and peripheral mechanisms involved in the postoperative antinociceptive effect of NSAIDs. In an experimental human model, the central antihyperalgesic effect accounts for 40% of the total analgesic effect of systemic diclofenac.[27] Systemic administration of therapeutic doses of cyclooxygenase inhibitors is associated with a significant reduction in prostaglandin E2 levels both locally at the site of injury and centrally in the cerebrospinal fluid.[28,29] Consequently, the reduction of both local and spinal prostaglandin E2 concentrations is associated with a decrease in postoperative pain.[28,29] The continuous peripheral administration of diclofenac in our patients involved an infusion rate of 6.25 mg/h (300 mg over 48 h), which some would consider a clinically subtherapeutic dose when administered by the intravenous route. Systemic absorption may have partly accounted for the beneficial effect observed on visceral pain. In a previous clinical trial,[29] small doses of either local or systemic ketorolac, surprisingly, demonstrated delayed but comparable analgesic effect to that of a therapeutic dose. The authors also reported that the analgesic effect of the systemic and the local subtherapeutic doses of ketorolac was not associated with a detectable effect on peripheral prostaglandin E2 levels at the site of injury.[29] These observations suggest not only a central site of action for NSAID analgesia, which is highly sensitive to the effects of NSAIDs and which mediates central hypersensitivity after tissue injury is present, but also that NSAID analgesia might be mediated through local mechanisms unrelated to peripheral prostaglandin suppression.

Finally, in addition to the different routes of diclofenac administration, the design of our study, which compared continuous wound infiltration with diclofenac to intermittent systemic administration, did not allow us to exclude an impact of the timing of NSAID administration on the observed analgesic effects. It is possible that circulating subtherapeutic doses of diclofenac administered at a constant rate from the continuous intrawound infusion reduced postoperative neuronal sensitization more than systemic intermittent therapeutic doses.

Beyond the sensitization of damaged tissue, surgical incision also induces central neuronal sensitization and probably the development of residual pain after surgery.[30] Recent studies mention cesarean delivery as a cause of chronic pain,[31] representing a significant problem in 6–12% of patients 10 months after the procedure.[32] Among the established risk factors for development of chronic pain after surgery, the severity of acute postoperative pain is one of the most striking.[30,32] Although this study was not powered to evaluate the incidence and severity of residual pain after cesarean delivery, our results are in agreement with the risk for development of persistent pain after cesarean delivery (an average incidence for the three groups of 14% residual pain at 6 months).

In summary, our results demonstrate that the continuous intrawound infusion of the nonselective cyclooxygenase inhibitor diclofenac affords better postoperative

pain management after elective cesarean delivery (greater morphine-sparing effect and decreased early VAS scores) without adverse effects than the same dose administered systemically by intermittent intravenous injections. The current results suggest the presence of peripheral analgesic properties of diclofenac apart from the systemic effect, mediated either through cyclooxygenase inhibition and decrease of prostaglandin production or through other local mechanisms.

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