Obstetrical and Pediatric Anesthesia

Intravenous acetaminophen *vs* oral ibuprofen in combination with morphine PCIA after Cesarean delivery

[L'acétaminophène intraveineux vs l'ibuprofène par voie orale comme adjuvant de la morphine AICP après une césarienne]

Jamal A. Alhashemi MBBS MSc FRCPC FCCP, Qamar A. Alotaibi MBBS, Manal S. Mashaat MBBS, Tarek M. Kaid MBChB MD, Razaz H. Mujallid MBBS, Abdullah M. Kaki MBBS FRCPC

Purpose: To compare the effects of *iv* acetaminophen with those of oral ibuprofen with respect to postoperative pain control and morphine requirements in patients receiving morphine patient-controlled *iv* analgesia (PCIA) after Cesarean delivery.

Methods: Forty-five term patients scheduled for Cesarean delivery were randomized to receive acetaminophen 1 g *iv* every six hours plus oral placebo (group A) or ibuprofen 400 mg *po* every six hours plus *iv* placebo (group I); the first dose of study drug was given 30 min preoperatively. Postoperatively, all patients received PCIA for 48 hr using morphine bolus dose 2 mg *iv*, lockout interval ten minutes, and no basal infusion. Visual analogue scale (VAS; 0 to 10) at rest and morphine requirements were recorded every hour for four hours then every four hours for a total of 48 hr postoperatively. Patient satisfaction was recorded on a ten-point scale (from 1 to 10) 48 hr postoperatively.

Results: Visual analogue scale scores decreased similarly in both groups over time, however, there were no differences between groups at any time during the study period (estimated marginal means: 1.4 ± SEM 0.2 *vs* 1.9 ± SEM 0.2 for groups A and I, respectively, $P = 0.124$). Cumulative doses of postoperative morphine were 98 ± 37 *vs* 93 ± 33 mg for groups A and I, respectively ($P = 0.628$). Patient satisfaction with analgesia was high in both groups (9 ± 1 *vs* 9 ± 1, $P = 0.93$).

Conclusion: Intravenous acetaminophen is a reasonable alternative to oral ibuprofen as an adjunct to morphine patient-controlled analgesia after Cesarean delivery.

***Objectif** : Comparer les effets de l'acétaminophène iv à ceux de l'ibuprofène par voie orale quant au soulagement de la douleur et à la consommation de morphine chez les patientes recevant de la morphine dans le cadre d'une analgésie iv contrôlée par le patient (AICP) après une césarienne.*

***Méthode** : Quarante-quatre patientes se présentant pour une césarienne ont reçu, de façon aléatoire, soit de l'acétaminophène 1 g iv toutes les six heures plus un placebo (groupe A), soit de l'ibuprofène 400 mg po toutes les six heures plus un placebo iv (groupe I), la première dose étant donnée 30 min avant la chirurgie. Après la chirurgie, toutes les patientes ont bénéficié d'une AICP avec morphine pendant 48 h, à la dose de 2 mg iv, avec un intervalle d'interdiction de dix minutes et aucune perfusion continue. On a noté les échelles visuelles-analogiques de douleur (EVA ; 0 à 10) au repos et les besoins en morphine toutes les heures pendant quatre heures, puis toutes les quatre heures pour un total de 48 h suivant la chirurgie. La satisfaction des patientes a été évaluée selon une échelle à dix niveaux (de 1 à 10) après 48 h.*

***Résultats** : Les scores d'EVA ont diminué avec le temps de façon semblable dans les deux groupes. Toutefois, on n'a retrouvé de différences significatives entre les groupes à aucun moment (moyenne marginale estimée : 1,4 ± ETM 0,2 vs 1,9 ± ETM 0,2 pour les groupes A et I, respectivement, $P = 0,124$). Les doses cumulatives de morphine étaient de 98 ± 37 vs 93 ± 33 mg pour les groupes A and I, respectivement ($P = 0,628$). Le niveau de satisfaction était élevé dans les deux groupes (9 ± 1 vs 9 ± 1, $P = 0,93$).*

***Conclusion** : L'acétaminophène par voie iv est une alternative acceptable à l'ibuprofène par voie orale comme adjuvant dans le cadre d'une analgésie à la morphine contrôlée par le patient.*

From the Department of Anesthesia & Critical Care, King Abdulaziz University, King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

Address correspondence to: Dr. Jamal A. Alhashemi, Department of Anesthesia & Critical Care, P.O. Box 31648, Jeddah 21418, Saudi Arabia. Fax: +966 2 6408015; E-mail: jalhashemi@kau.edu.sa

Supported by Departmental Research Fund and, in part, by Bristol Meyers Squibb, Saudi Arabia (supplier of the study drug).

Accepted for publication August 29, 2006.

Revision accepted September 25, 2006.

Competing interests: None declared.

MULTIMODAL analgesia is commonly used in the management of postoperative pain after Cesarean delivery[1] where opioids are often combined with nonsteroidal anti-inflammatory drugs to decrease the amount of opioids administered and their potential adverse effects, and also to improve the quality of postoperative analgesia.[1,2] However, nonsteroidal anti-inflammatory drugs have been associated with adverse effects such as peptic ulceration, gastritis, and renal impairment. In addition, these drugs are excreted in mother's milk albeit in small amounts.[3,4] In contrast, acetaminophen (paracetamol) is a non-opioid analgesic that is devoid of these adverse effects and is regarded as being safe in breast-feeding mothers.[5] However, the analgesic efficacy of acetaminophen has been limited by the delayed absorption and sub-therapeutic plasma concentration of its enteral formulation, which have been attributed in part to under-dosing of the drug and in part to variable drug absorption with a coefficient of variance ranging from 40–93% despite adequate dosing.[6,7] Recently, an *iv* formulation of acetaminophen has been introduced and its pharmacokinetic properties have been characterized.[8] Although *iv* acetaminophen solves the bioavailability issue of its enteral formulation, there are no studies that compare the analgesic effects of *iv* acetaminophen with that of nonsteroidal anti-inflammatory drugs in the management of postoperative pain after Cesarean delivery.

Accordingly, this randomized, double-blind clinical trial was undertaken to compare the postoperative analgesic effects of *iv* acetaminophen with those of oral ibuprofen in patients receiving morphine patient-controlled *iv* analgesia (PCIA) after Cesarean delivery.

Methods

After institutional Ethics Committee approval, 45 pregnant women gave written informed consent to participate in this randomized double-blind clinical trial, which spanned from July 1 to December 31, 2005. Patients were included in the study if they were ≥ 37 weeks pregnant and scheduled for elective Cesarean delivery under spinal anesthesia. They were excluded from the study if they had any of the following: 1) abnormally lying placenta; 2) prenatally diagnosed fetal abnormalities; 3) intra-uterine fetal death; 4) hypertensive diseases of pregnancy; 5) renal impairment (serum creatinine ≥ 200 $\mu mol \cdot L^{-1}$); 6) any contraindication to spinal anesthesia; 7) a language barrier or mental disorder that would prevent the patient from understanding how to operate a PCIA device; or 8) any allergy and/or contraindication to any of the study medications. Using a computer-generated randomization schedule and opaque, sealed, and serially numbered envelopes, patients were randomized to receive either *iv* acetaminophen (group A) or oral ibuprofen (group I). Randomization was performed by the hospital's pharmacy and the study drugs were delivered as infusion bags and coated tablets in blister packages not allowing identification of content to ensure blinding. Patients, nursing staff, physicians, and the data collector were all blinded to patient group assignment.

Preoperatively, each patient received appropriately detailed instructions regarding proper use of a PCIA device (I-pump™, Baxter Healthcare Corp., Deerfield, IL, USA). Group acetaminophen patients received acetaminophen (Perfalgan®, UPSA Laboratories, Agen, France) 1g (100 mL) *iv* over 15 min and one placebo tablet *po*, each given every six hours for 48 hr, whereas those in group ibuprofen received ibuprofen 400 mg *po* and normal saline (placebo) 100 mL *iv* over 15 min, each given every six hours for 48 hr; the first dose of the study drug in both groups was administered 30 min before surgery. In the operating room, Ringer's lactate 500 mL *iv* bolus infusion was administered for hydration, standard monitors were applied, oxygen was administered via nasal prongs at 2 $L \cdot min^{-1}$ until delivery of the baby, and spinal anesthesia was performed in all patients in the sitting position at the L3-4 or L4-5 interspace using a 27-G Whitacre needle and 2.5 mL of 0.5% hyperbaric bupivacaine mixed with fentanyl 10 µg. Cesarean delivery was performed using a horizontal lower segment uterine incision in all patients. Intraoperative pain, if any, was treated with fentanyl 50 µg *iv prn*, and no sedative drugs were allowed in the perioperative period and for 72 hr postoperatively. Intraoperative and postoperative nausea and vomiting were treated with metoclopramide 10 mg *iv* every six hours *prn*.

Upon arrival to the postanesthesia care unit (PACU), all patients received morphine 0.05 $mg \cdot kg^{-1}$ *iv* bolus and were started on a PCIA device [I-pump™, Baxter Healthcare Corp., Deerfield, IL, USA] with the following settings; morphine bolus dose 2 mg *iv*, lockout interval ten minutes, and no basal infusion.

Measurements

Intraoperatively, newborn's Apgar scores at one and five minutes were determined. Postoperatively, pain at rest was assessed every hour for the first four hours, and every four hours thereafter for a total of 48 hr using the visual analogue scale (VAS) with two anchor points; 0 being no pain and 10 being the worst pain

the patient had ever experienced. Furthermore, the amount of morphine required, the number of PCIA attempts made, and patient level of sedation (1 = wide awake; 2 = sleepy but easily aroused; 3 = sleepy and difficult to arouse) were documented at the same time intervals postoperatively. Patients who had a VAS score ≥ 5 received rescue morphine 5 mg *iv* bolus every four hours *prn*. Forty-eight hours after surgery, morphine PCIA was discontinued and patients were prescribed tramadol 1 $mg \cdot kg^{-1}$ *im* every four hours, as needed. When morphine PCIA was discontinued, patients were asked to rate their satisfaction with postoperative analgesia on a ten-point scale; 1 being extremely dissatisfied and 10 being extremely satisfied. Postoperative adverse events including, but not limited to, nausea, vomiting, pruritus, respiratory depression (respiratory rate ≤ 10 $breaths \cdot min^{-1}$), and/or oxygen desaturation (SpO_2 ≤ 92%) were recorded by the bedside nurse who was also blinded to patient group assignment. The occurrence or lack thereof of adverse events was evaluated at the same four-hour time intervals as the other assessments, and was recorded as "occurred/did not occur".

Statistical analysis

Based on a two-sided alpha of 0.05, 90% power, a clinically relevant difference in VAS score of 2,[9] and a population variance of 2, a total of 44 patients were required for the conduct of the study. All analyses were performed on an intention-to-treat basis. Repeated measures analysis of variance was used to analyze the effects of drug therapy on the time course of VAS score, sedation score, and the amount of morphine administered postoperatively. Apgar scores and patient satisfaction data were analyzed using unpaired *t* tests. The number of PCIA attempts were analyzed with the Mann-Whitney-U test. Postoperative adverse effects were compared using Fisher's exact test. All statistical procedures were performed using SPSS® statistical package (SPSS Inc., Chicago, IL, USA), version 13.0 for Windows® except for sample size calculation which was performed using PS Power and Sample Size Calculations Program®, version 2.1.31 (Copyright © 1997 by WD Dupont and WD Plummer).[10] Results are presented as mean ± SD, unless otherwise indicated, and statistical significance was defined as $P < 0.05$.

Results

Fifty consecutive patients were assessed for eligibility for inclusion in the study; two were excluded because of language barrier and three refused to participate in the trial. Forty-five patients gave written informed consent to participate in the study, were randomized (22 patients to group acetaminophen and 23 to group ibuprofen), completed the study without protocol violations, and were analyzed in the group to which they were randomized. Baseline characteristics (Table I) and newborn's Apgar scores at one and five minutes (Table II) were similar between groups. None of the patients in either group required rescue fentanyl intraoperatively. Visual analogue scale

TABLE I Patients characteristics

Variable	*Group A (n = 22)*	*Group I (n = 23)*
Age (yr)	33 ± 5	32 ± 5
Weight (kg)	81 ± 16	78 ± 15
ASA physical class, I/II (*n*)	12/10	12/11
Gestational age (weeks)	38 ± 1	38 ± 1
Parity	3 ± 2	3 ± 2
Gravidity	4 ± 2	4 ± 2
Co-morbidities:		
Diabetes (*n*)	0	1
Hypertension (*n*)	1	0
Anesthesia to delivery time (min)	20 ± 8	20 ± 7
Surgery time (min)	66 ± 16	61 ± 16
Intraoperative rescue fentanyl (*n*)	0	0

A = acetaminophen; I = ibuprofen; ASA = American Society of Anesthesiologists. Data are presented as mean ± SD or absolute numbers.

TABLE II Secondary outcomes and postoperative adverse events

Variable	*Group A (n = 22)*	*Group I (n = 23)*
Newborn's Apgar score at 1 min	8 ± 1	7 ± 2
Newborn's Apgar score at 5 min	9 ± 1	9 ± 2
PCIA attempts (*n*)		
0-24 hr postoperatively	61 (42, 104)	85 (29, 165)
24-48 hr postoperatively	33 (19, 52)	29 (20, 57)
Patients receiving rescue morphine (*n*)	1	2
Patient satisfaction with analgesia	9 ± 1	9 ± 1
Nausea (*n*)		
- Postanesthesia care unit	4	2
- Ward (up to 48 hr postoperatively)	12	8
Vomiting (*n*)		
- Postanesthesia care unit	4	0
- Ward (up to 48 hr postoperatively)	3	1
Pruritus (*n*)	10*	19
Respiratory depression (*n*)	0	0
Oxygen desaturation (*n*)	0	0

A = acetaminophen; I = ibuprofen; PCIA = patient-controlled *iv* analgesia. Adverse events were assessed during the first 48 hr postoperatively. Data are presented as mean ± SD, median (Q1, Q3), or absolute numbers. * $P = 0.013$, Fisher's exact test.

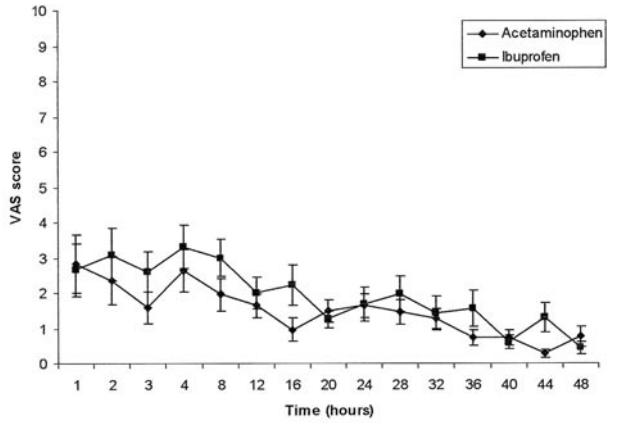

FIGURE 1 Postoperative changes in visual analogue scale during the first 48 hr postoperatively. Data are presented as mean ± SEM. Visual analogue scale scores decreased within each group over time during the assessment period, but there were no differences between the two study groups (P = 0.143 for the overall F-test of between-subjects effects).

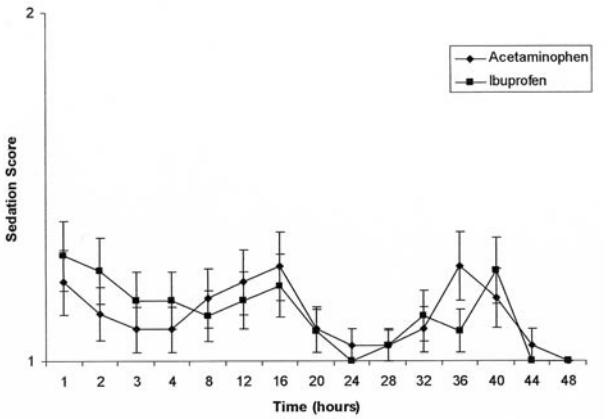

FIGURE 3 Sedation score during the first 48 hr postoperatively. Data are presented as mean ± SEM. There were no differences between groups with regard to sedation score during the study period (P = 0.465 for the overall F-test of between-subjects effects).

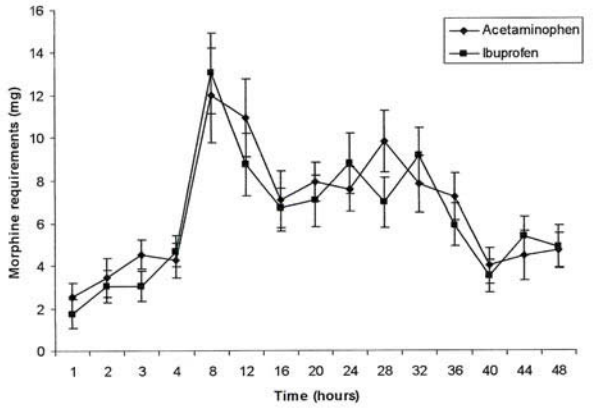

FIGURE 2 Postoperative morphine requirement during the first 48 hr postoperatively. Data are presented as mean ± SEM. There were no differences between groups with regard to postoperative morphine requirements during the study period (P = 0.562 for the overall F-test of between-subjects effects).

scores within each group decreased over time during the postoperative period (P = 0.001 for the overall F-test of within-subjects effects; Figure 1), however, there were no significant differences in VAS scores between those who received *iv* acetaminophen and those who received oral ibuprofen (P = 0.143 for the overall F-test of between-subjects effects; Figure 1). Similarly, there were no differences in postoperative morphine requirements between study groups during the assessment period (P = 0.562 for the overall F-test of between-subjects effects; Figure 2). One (4.5%) patient in group acetaminophen and two (8.7%) in group ibuprofen required a single dose of rescue morphine on the first postoperative day (P = 1.0, Fisher's exact test). The median number of PCIA attempts made was comparable between groups (P = 0.71 and 0.99 for days one and two, respectively; Table II). Postoperative sedation was minimal and not different between the study groups (P = 0.465 for the overall F-test of between-subjects effects; Figure 3). Patient satisfaction with postoperative analgesia was high in both treatment groups (P = 0.93; Table II). There were no episodes of desaturation or respiratory depression in either group, and no major adverse events were observed in the study. In contrast, nausea and vomiting were observed postoperatively but none of the patients in either study group experienced nausea or vomiting intraoperatively. In the PACU, nausea occurred in four (18.2%) patients in group acetaminophen and two (8.7%) in group ibuprofen (P = 0.41, Table II). In contrast, four (18.2%) group acetaminophen patients vomited in the PACU compared with none in group ibuprofen (P = 0.05, Table II). On the ward, three out of the four acet-

aminophen patients who experienced vomiting in the PACU had one more episode of vomiting 28 hr postoperatively compared with only one (4.3%) patient in group ibuprofen whose vomiting occurred 32 hr after surgery ($P = 0.35$, Table II). Postoperative pruritus was reported more frequently among patients who received ibuprofen compared with those who received acetaminophen ($P = 0.031$; Table II). With the exception of two (8.7%) patients in group acetaminophen and one (4.3%) in group ibuprofen who had pruritus in the PACU, this adverse effect was observed at 12 hr after surgery and continued until the end of the study period amongst those who received it in both study groups.

Discussion

This study compared the analgesic effects of *iv* acetaminophen with those of oral ibuprofen in patients receiving morphine PCIA after Cesarean delivery. The study did not demonstrate a significant difference between groups with regard to VAS scores or morphine requirements during the first 48 hr postoperatively. Furthermore, postoperative pain was adequately controlled in all patients as indicated by the fact that VAS scores were less than 4[11] throughout the assessment period in both study groups (Figure 1), and only one patient in group acetaminophen and two in group ibuprofen required a single dose of rescue morphine postoperatively. *Post hoc* power analysis indicated that the study had a 34% power to detect the clinically minor difference in VAS scores between groups and that a total of 160 patients were required to demonstrate statistical significance. Based on the findings of Farrar *et al.*[12] who demonstrated that the best cut-off point for a patient-determined clinically important analgesic response is a change of ≥ 2 on a 0–10 numeric rating pain scale, there was no consideration to extend the trial to recruit the re-calculated sample size.

Although there was no between-group difference, VAS scores within each group decreased over time during the postoperative period. This was paralleled with a decrease in the amount of morphine required postoperatively (Figure 2), although there was an initial increase in the early postoperative period. The initial gradual increase in morphine requirement during the first four hours after surgery could be explained by the gradual recession of the spinal anesthetic during this time period, while the peak in morphine consumption at eight hours postoperatively was likely due to patient ambulation at that time. Nevertheless, there was no increase in VAS scores in either group during these time periods (Figure 1). These results are consistent with those reported by other investigators when *iv* propacetamol (a pro-drug of *iv* paracetamol) was compared with *iv* keterolac.[13] In the current investigation, however, *iv* acetaminophen was compared with an oral rather than with an *iv* nonsteroidal anti-inflammatory drug since the parenteral formulations of these drugs are not available in Saudi Arabia. Although the comparison of two drugs with different routes of administration could bias the results in favour of the *iv* agent due to higher bioavailability, postoperative VAS scores and morphine requirements were similar among patients who received *iv* propacetamol and those who received *iv* keterolac[13] and were comparable to those reported in the current study. The observed alertness of all study patients was not unexpected given that neither acetaminophen nor ibuprofen possesses any sedative properties. Furthermore, the concomitant administration of morphine PCIA did not appear to have an effect on patients' level of sedation, which is in keeping with previous reports.[14]

Patient satisfaction scores with postoperative analgesia were high in all study patients which suggests improved quality of postoperative analgesia in both study groups. These results are consistent with those reported by Varrassi *et al.*[13] but are in direct contrast with those of Beaussier *et al.*[15] who have reported decreased patient satisfaction with *iv* propacetamol when compared with *iv* parecoxib. One possible explanation for this is the fact that postoperative supplementary analgesia in the current study was provided with *iv* morphine PCIA as opposed to nurse-administered oral and/or *sc* morphine in Beaussier's study.[15]

Postoperative adverse events were common but minor in this study and consisted mainly of nausea, vomiting, and pruritus. The nausea and vomiting were likely due to postoperative morphine PCIA and the fact that anti-emetic medication was only administered on demand and not prophylactically. In support of this interpretation is the occurrence of this adverse effect in the PACU where a morphine loading dose was administered at the start of PCIA, and the recurrence of vomiting in the acetaminophen group 28 hr postoperatively when the second peak in morphine consumption was observed in this group (Figure 2). Based on the fact that only one patient in group ibuprofen experienced postoperative vomiting (32 hr after surgery), it is unlikely that this adverse effect had biased the outcome of this study by limiting the absorption of oral ibuprofen in this group. The late occurrence (12 hr postoperatively) of pruritus in the majority of study patients suggests that it was secondary to morphine PCIA. However, the

additional contribution of intrathecal fentanyl administration to the occurrence of pruritus in patients who received the medication early in the PACU cannot be excluded. Nevertheless, the incidence of pruritus was consistent with that reported by other investigators.[16] An interesting and unexpected observation was the lower incidence of pruritus among patients who received *iv* acetaminophen compared with those who received oral ibuprofen (Table II). This was not related to patient level of sedation as all patients were alert throughout the study (Figure 3). Since cyclooxygenases are involved in the regulation of several central nervous system processes,[17] it is possible that acetaminophen acted through the inhibition of one of these processes to decrease the occurrence of pruritus. It is also possible that the central serotonergic effect of acetaminophen[18] might have affected the occurrence of pruritus; however, the exact mechanism remains to be elucidated.

Study limitations

One limitation of the study design is the lack of a placebo group. However, the efficacy of both nonsteroidal anti-inflammatory drugs and acetaminophen, when compared with placebo, has already been established.[1,2,19] In addition, the use of morphine PCIA alone negates the contemporary practice of multimodal analgesia in the postoperative period which has been demonstrated to be superior to morphine alone.[1,20] Although "typical" multi-modal analgesia includes intrathecal morphine administration, preservative-free morphine is not available in our country and hence it was not used as part of the multi-modal analgesia protocol in this study. This, in turn, limits the generalizability of the study results when applied to patients who receive intrathecal morphine as part of their routine intraoperative care. Another potential criticism is the lack of dose-response curves for the study drugs. However, the maximum allowable dose for *iv* acetaminophen was used in this study, and the efficacy of the dose of ibuprofen used has been demonstrated previously.[20,21] In addition, Hahn *et al.*[8] suggest that acetaminophen may have a ceiling effect at a dose of 5 $mg \cdot kg^{-1}$ which is well below the dose administered in this study (approximately 12.5 $mg \cdot kg^{-1}$, calculated based on the average body weight of the study patients).

In conclusion, *iv* acetaminophen provides comparable analgesia to oral ibuprofen, as an adjunct to morphine PCIA, in patients undergoing Cesarean delivery under spinal anesthesia. Accordingly, *iv* acetaminophen is a reasonable option for multi-modal post-Cesarean analgesia in women who have a contraindication to the use of nonsteroidal anti-inflammatory drugs.

References

1 *Elia N, Lysakowski C, Tramer MR.* Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005; 103: 1296–304.

2 *Angle PJ, Halpern SH, Leighton BL, Szalai JP, Gnanendran K, Kronberg JE.* A randomized controlled trial examining the effect of naproxen on analgesia during the second day after cesarean delivery. Anesth Analg 2002; 95: 741–5.

3 *Hale TW, McDonald R, Boger J.* Transfer of celecoxib into human milk. J Hum Lact 2004; 20: 397–403.

4 *Beaulac-Baillargeon L, Allard G.* Distribution of indomethacin in human milk and estimation of its milk to plasma ratio in vitro. Br J Clin Pharmacol 1993; 36: 413–6.

5 *Spigset O, Hagg S.* Analgesics and breast-feeding: safety considerations. Paediatr Drugs 2000; 2: 223–38.

6 *Nielsen JC, Bjerring P, Arendt-Nielsen L, Petterson KJ.* Analgesic efficacy of immediate and sustained release paracetamol and plasma concentration of paracetamol. Double blind, placebo-controlled evaluation using painful laser stimulation. Eur J Clin Pharmacol 1992; 42: 261–4.

7 *Anderson BJ, Woolard GA, Holford NH.* Pharmacokinetics of rectal paracetamol after major surgery in children. Paediatr Anaesth 1995; 5: 237–42.

8 *Hahn TW, Mogensen T, Lund C, et al.* Analgesic effect of i.v. paracetamol: possible ceiling effect of paracetamol in postoperative pain. Acta Anaesthesiol Scand 2003; 47: 138–45.

9 *Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL.* Defining the clinically important difference in pain outcome measures. Pain 2000; 88: 287–94.

10 *Dupont WD, Plummer WD Jr.* Power and sample size calculations for studies involving linear regression. Control Clin Trials 1998; 19: 589–601.

11 *Yost NP, Bloom SL, Sibley MK, Lo JY, McIntire DD, Leveno KJ.* A hospital-sponsored quality improvement study of pain management after cesarean delivery. Am J Obstet Gynecol 2004; 190: 1341–6.

12 *Farrar JT, Berlin JA, Strom BL.* Clinically important changes in acute pain outcome measures: a validation study. J Pain Symptom Manage 2003; 25: 406-11.

13 *Varrassi G, Marinangeli F, Agro F, et al.* A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gyneco-

logic surgery. Anesth Analg 1999; 88: 611–6.
14 *Cobby TF, Crighton IM, Kyriakides K, Hobbs GJ.* Rectal paracetamol has a significant morphine-sparing effect after hysterectomy. Br J Anaesth 1999; 83: 253–6.
15 *Beaussier M, Weickmans H, Paugam C, et al.* A randomized, double-blind comparison between parecoxib sodium and propacetamol for parenteral postoperative analgesia after inguinal hernia repair in adult patients. Anesth Analg 2005; 100: 1309–15.
16 *Jain K, Grover VK, Mahajan R, Batra YK.* Effect of varying doses of fentanyl with low dose spinal bupivacaine for caesarean delivery in patients with pregnancy-induced hypertension. Int J Obstet Anesth 2004; 13: 215–20.
17 *Yermakova A, O'Banion MK.* Cyclooxygenases in the central nervous system: implications for treatment of neurological disorders. Curr Pharm Des 2000; 6: 1755–76.
18 *Pickering G, Loriot MA, Libert F, Eschalier A, Beaune P, Dubray C.* Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. Clin Pharmacol Ther 2006; 79: 371–8.
19 *Zhou TJ, Tang J, White PF.* Propacetamol versus ketorolac for treatment of acute postoperative pain after total hip or knee replacement. Anesth Analg 2001; 92: 1569–75.
20 *Rosaeg OP, Lui AC, Cicutti NJ, Bragg PR, Crossan ML, Krepski B.* Peri-operative multimodal pain therapy for caesarean section: analgesia and fitness for discharge. Can J Anaesth 1997; 44: 803–9.
21 *Sunshine A, Olson NZ, O'Neill E, Ramos I, Doyle R.* Analgesic efficacy of a hydrocodone with ibuprofen combination compared with ibuprofen alone for the treatment of acute postoperative pain. J Clin Pharmacol 1997; 37: 908–15.