A randomized study of the effects of preoperative ketorolac on general anaesthesia for caesarean section

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Background: Ketorolac may attenuate the maternal stress response to tracheal intubation, while avoiding opioid-induced neonatal depression. We aimed to evaluate the haemodynamic and hormonal effects of prophylactic ketorolac on surgical stress and analgesia after caesarean delivery.

Methods: After ethical approval, 90 patients scheduled for elective caesarean delivery were randomly allocated to receive either ketorolac 15 mg i.v. bolus 20 min before induction, followed by an infusion of 7.5 mg/h (n = 45), or saline placebo (n = 45). Anaesthesia was maintained with 50% nitrous oxide in oxygen with 0.5% isoflurane. Haemodynamic variables, plasma cortisol concentrations, uterine relaxation, need for supplementary doses of oxytocin, peri-operative blood loss, haematocrit, Apgar scores at 1 and 5 min, postoperative pain scores at rest and movement, and tramadol consumption were recorded.

Results: After induction, patients receiving ketorolac had a smaller increase in heart rate, systolic and mean arterial blood pressure (P < 0.001) and lower plasma cortisol concentrations, (32.2 ± 7.61 vs. 45 ± 15.1 μg/dL, P < 0.05), lower pain scores at rest and movement for the first two postoperative hours (P < 0.001) and a longer time to first request for analgesia. Fewer patients in the ketorolac group received tramadol in the four hours after surgery (7 (15.6%) vs. 14 (31.1%), P = 0.004). There were no differences between groups in peri-operative blood loss, vomiting or Apgar scores. There was no echocardiographic evidence of premature closure of the ductus arteriosus in the newborns.

Conclusion: Prophylactic ketorolac is safe and effective in attenuating the maternal stress response to intubation and improves the quality of analgesia after caesarean delivery.

Keywords: Anaesthesia; Caesarean section; Stress response; Ketorolac

INTRODUCTION

Effective analgesia after caesarean delivery results in early mobilization and enhances bonding between mother and baby. Increased sympathetic nervous system activity and plasma concentrations of catecholamines after tracheal intubation, in women undergoing caesarean delivery, may decrease placental perfusion and uterine blood flow by 20-35%. Opioids provide a high level of patient satisfaction, but are usually omitted at the induction of general anaesthesia for caesarean delivery because of concerns about placental transfer resulting in neonatal respiratory depression. The use of non-steroidal anti-inflammatory drugs (NSAIDs) significantly reduces the need for opioids after caesarean delivery minimising opioid-induced side-effects. The use of intravenous tenoxicam before induction of general anaesthesia significantly reduces haemodynamic variability during surgery and postoperative opioid consumption without increasing side effects. Ketorolac given intravenously has been suggested to be as effective as morphine in the management of surgical pain, but with fewer side effects. The U.S. Food and Drug Administration currently does not approve the use of ketorolac in breastfeeding women, even though the American Academy of Pediatrics has found ketorolac to be compatible with breastfeeding.
We postulated that the use of ketorolac before induction of anaesthesia for uncomplicated caesarean delivery would reduce both maternal stress response and postoperative analgesic consumption, without harmful effects on either mother or baby. Therefore, the present study was designed to evaluate the effects of ketorolac on surgical stress and analgesic consumption after caesarean delivery.

METHODS

This randomised double-blinded placebo-controlled study was carried out from March 2005 to October 2006 after approval of the Institutional Ethical Committee of Mansoura University Hospitals. After written informed consent was obtained, we studied 90 ASA I & II women aged 20-35 years, with uncomplicated, singleton pregnancies of at least 36 weeks’ gestation, undergoing elective caesarean delivery, via a Pfannenstiel incision, under general anaesthesia. Indications for caesarean delivery were breech presentation, cephalopelvic disproportion or previous caesarean delivery. Women with a history of allergy to non-steroidal anti-inflammatory agents, bleeding tendency, bronchial asthma, peptic ulcer, liver or kidney diseases or those with inflammatory agents, bleeding tendency, bronchial asthma were excluded from the study. All operations were performed by the same surgeon. Before surgery, all subjects were given instruction on the visual analogue scale (VAS) to be used in their assessment.

Oral ranitidine 150 mg (Zantac, Glaxo SmithKline, Egypt) was given the night before and on the morning of surgery, with 0.3 mol/L sodium citrate (30 mL) given 15 min before induction. In the operating theatre women were positioned supine on the operating table with a 15° firm rubber wedge under the right hip to effect left uterine displacement. A slow 500-mL i.v. infusion of lactated Ringer’s solution was given to all subjects over 20 min.

Subjects were allocated randomly to two groups by drawing sequentially numbered sealed opaque envelopes containing a computer-generated randomisation code. The placebo group \( (n = 45) \) received a 20-mL i.v. bolus of 0.9% saline 20 min before induction of anaesthesia followed by a constant infusion at 10 mL/h. The ketorolac group \( (n = 45) \) received a 20-mL i.v. loading dose of ketorolac tromethamine (Toradol, MUP, Syntex Pharm AG) (0.75 mg/mL), 20 min before induction of anaesthesia, followed by a constant infusion at 10 mL/h of the same solution continued until the end of surgery. Both placebo and ketorolac solutions looked identical. The test solution was prepared by one anaesthesiologist immediately before induction of anaesthesia. Another anaesthesiologist who was blinded to the study solution gave the anaesthetic, and a third performed the assessments. All staff in the operating room were unaware of the randomization code.

Subjects were monitored with electrocardiography, non-invasive blood pressure, pulse oximetry (SpO\(_2\)), and end-tidal carbon dioxide concentration (EtCO\(_2\)). After pre-oxygenation for 5 min, rapid-sequence induction was performed with thiopental 4-6 mg/kg followed by suxamethonium 1.5 mg/kg after loss of verbal response. Cricoid pressure was applied after loss of consciousness and was released after correct placement of the tracheal tube had been confirmed. Laryngoscopy was performed after the 1-min blood pressure recording, and tracheal intubation was completed before the 2-min reading. Anaesthesia was maintained with a mixture of 0.5% isoflurane and 50% nitrous oxide in oxygen. Neuromuscular block was maintained with vecuronium 0.06 mg/kg. The lungs were ventilated using a tidal volume of 8 mL/kg, an inspiration-expiration ratio of 1:2, and at a respiratory rate necessary to maintain an EtCO\(_2\) of 4-4.6 kPa. An infusion of lactated Ringer’s solution 800 mL was given to all subjects during the procedure. Induction to delivery (I-D) time was recorded using a stopwatch.

After the umbilical cord was clamped, a 10-unit infusion of oxytocin in 500 mL of 5% glucose was started. Intravenous midazolam 0.05 mg/kg and fentanyl 1.0 μg/kg were given and nitrous oxide was increased to 70%. Isoflurane was discontinued at the start of skin closure and nitrous oxide and the study drug infusion were discontinued after the last skin suture was applied. At the end of surgery, residual neuromuscular block was antagonised with neostigmine 50 μg/kg and atropine 20 μg/kg.

Heart rate, systolic pressure and mean arterial pressure (MAP) were recorded immediately before and at 1, 2, 3, 5, 6, 10 min after intubation, and 15 and 30 min after delivery and after extubation. The obstetrician assessed uterine tone by palpation every minute after delivery of the placenta and rated the degree of uterine relaxation on a 10-cm VAS (0: well contracted; 10: completely relaxed). If uterine tone remained unsatisfactory after 3 min, an additional 5-unit bolus of oxytocin was administered. Intra-operative blood loss was assessed by measuring blood in the suction bottle minus the sonographically estimated amniotic fluid volume, visual estimate of blood on drapes and floor and weighing swabs after use. Postoperative transfusion requirements and blood loss were estimated as previously reported by Huang et al.\(^8\) from inspection of the perineal pad (0: small; 1: moderate; 2: large). Haematocrit values were recorded before and 48 h after surgery. Bleeding time was determined by the Ivy
method preoperatively and 1 h postoperatively by an experienced technician.

Stress response was determined by changes in plasma cortisol concentrations. Maternal venous blood samples were collected at three times: preoperatively, 5 min after intubation and 1 h after delivery. These times were based on likely physiological responses over time and local economic limitations. The blood samples were centrifuged and serum was drawn off and stored at 4°C until assayed within 2 weeks of collection. Plasma cortisol levels were determined using a radioimmunoassay technique (Gamma Coat® Cortisol 125IRIA). The sensitivity was 0.2 μg/dL (0.6 nmol/dL) and the coefficient of variation 9%.

All neonates were assessed by a single paediatrician unaware of the mothers’ randomisation. Apgar scores were recorded at 1 and 5 min. The paediatrician examined each newborn immediately after delivery, after 8, 12, 24 h, and 7 days later for evidence of premature closure of the ductus arteriosus or pulmonary hypertension. Newborns were observed by monitoring arterial blood pressure, heart rate, temperature and arterial oxygen saturation. A 2D transthoracic echocardiograph (TOSHIBA® SSH-140-A ultrasound machine with 5 and 7.5 MHz electronic sector transducer) with colour Doppler flow mapping allowed assessment of patency and diameter of the ductus arteriosus and direction of the shunt 8, 12, 24 h after delivery.

The severity of postoperative pain was assessed on a 10-cm VAS at rest and on movement (0: no pain; 10: worst pain imaginable) 0, 1, 2, 4, 6, 8, 10 and 12 h after surgery. For postoperative pain relief intravenous tramadol (Tramal, Janssen-Cilag Pharmaceutica Ltd) 100 mg was prescribed when VAS scores were 5 or more at rest, or 7 or more on movement, or if the patient requested additional analgesia. The time to first request for analgesia and the number of subjects receiving tramadol during the first 12 h were recorded.

The presence and intensity of side effects were scored as follows: sedation (four-point verbal rating scores (VRS): awake, drowsy, rousable or deep sleep); nausea and vomiting (0: no nausea; 1: nausea no vomiting; 2: nausea and vomiting) 0, 1, 2, 4, 6, 8, 10 and 12 h after surgery, and the presence of intra-operative recall.

Statistical analysis

Data were analysed using Statistica ’99 software (StatSoft, Tulsa, Okla.). Data were tested for normality using the Kolmogorov-Smirnov test. An unpaired Student’s t test was used to compare the parametric values of the two groups; Mann-Whitney U test was performed to compare the non-parametric values of the two groups. Serial changes in haemodynamic and cortisol data at induction were analyzed with repeat measures analysis of variance. Data were expressed as frequency, mean ± SD, percentage or median (range). A value of P < 0.05 was considered to represent statistical significance. Based upon our preliminary data, a prior power analysis indicated that 45 patients in each group would be sufficient to detect a 20% reduction in post-induction blood pressure values, with a type-I error of 0.05 and a power of approximately 90%.

RESULTS

All 90 patients completed the study: 45 patients in the placebo group and 45 in the ketorolac group. Maternal age, weight, height, gestational age, I-D time, duration of anaesthesia, and birth weight did not significantly differ between the groups (Table 1).

Baseline heart rate, systolic pressure and MAP were similar in the two groups (Figs. 1–3). Changes in heart rate from baseline were significantly greater in the placebo group than in the ketorolac group at 2, 3, 5, 6, 10 min after induction, and 15 min after delivery ($P < 0.001$) (Fig. 1). Similarly changes in systolic pressure and MAP from baseline were significantly greater

<table>
<thead>
<tr>
<th>Table 1. Patient data</th>
<th>Placebo group ($n = 45$)</th>
<th>Ketorolac group ($n = 45$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.1 ± 4.18</td>
<td>26.2 ± 5.10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.6 ± 7.96</td>
<td>77.7 ± 10.78</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162 ± 3.35</td>
<td>160 ± 2.25</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.9 ± 1.51</td>
<td>39.3 ± 1.71</td>
</tr>
<tr>
<td>Induction to delivery time (min)</td>
<td>11.4 ± 1.76</td>
<td>10.8 ± 1.47</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>39.7 ± 5.26</td>
<td>41.8 ± 5.63</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.3 ± 0.26</td>
<td>3.2 ± 0.19</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

![Fig. 1 Peri-operative heart rate. Data are mean± SD. *P < 0.05 compared with the placebo group.](image-url)
In the placebo group than in the ketorolac group 1, 2, 3, 4, 5, 6, and 10 min after induction, and 15 min after delivery \((P < 0.001)\) (Figs. 2 and 3).

There was no significant difference between the two groups in the surgical assessment of uterine tone or in the need for supplementary oxytocin (Table 2). Additionally, perioperative blood loss was similar in the two groups and no patient required blood transfusion. Preoperative and postoperative bleeding times did not change significantly in either group.

The placebo group had significantly higher VAS scores for pain at rest and on movement than did the ketorolac group for the first 2 h following surgery \((P < 0.001)\) (Table 3). The time to first tramadol request was significantly longer in the ketorolac group than in the placebo group (Table 4). Additionally, the number of patients receiving tramadol during the first 4 h after surgery was significantly higher in the placebo group than in the ketorolac group \((P = 0.004)\).

Baseline maternal cortisol concentrations in the placebo group \((28.2 \pm 11.4 \mu g/dL)\), were similar to those in the ketorolac group \((27.8 \pm 11.25 \mu g/dL)\). Five minutes after intubation and 1 h after delivery, cortisol concentrations were significantly greater in the placebo group than in the ketorolac group \((P = 0.032\) and 0.014, respectively) (Fig. 4).

There were no reported serious side effects during the study. There were no differences between groups in the

**Table 2. Peri-operative data**

<table>
<thead>
<tr>
<th></th>
<th>Placebo group ((n = 45))</th>
<th>Ketorolac group ((n = 45))</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS assessment of uterine relaxation</td>
<td>3 (0-3)</td>
<td>3 (0-3)</td>
</tr>
<tr>
<td>Patients needing supplementary oxytocin</td>
<td>5 (11.1%)</td>
<td>7 (15.6%)</td>
</tr>
<tr>
<td>Haematocrit (%) pre-op</td>
<td>35.7 ± 2.14</td>
<td>36.4 ± 1.59</td>
</tr>
<tr>
<td>48 h post-op</td>
<td>33.6 ± 1.92</td>
<td>34.2 ± 2.04</td>
</tr>
<tr>
<td>Intra-operative blood loss (mL)</td>
<td>279 ± 88.97</td>
<td>298 ± 89.95</td>
</tr>
<tr>
<td>Postoperative blood loss (mL)</td>
<td>0 (0-2)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td>Bleeding time (min pre-op)</td>
<td>3.6 ± 1.24</td>
<td>3.4 ± 1.18</td>
</tr>
<tr>
<td>1 h post-op</td>
<td>3.7 ± 1.05</td>
<td>3.7 ± 0.96</td>
</tr>
<tr>
<td>Patients experiencing nausea and vomiting</td>
<td>5 (11.1%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Apgar score 1 min</td>
<td>8 (5-10)</td>
<td>7 (4-10)</td>
</tr>
<tr>
<td>5 min</td>
<td>10 (9-10)</td>
<td>10 (9-10)</td>
</tr>
</tbody>
</table>

Data are median (range), \(n (\%)\) or mean ± SD.

**Table 3. VAS score for postoperative pain at rest and with movement in the two groups**

<table>
<thead>
<tr>
<th></th>
<th>Placebo group ((n = 45))</th>
<th>Ketorolac group ((n = 45))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-extubation</td>
<td>4 (1-8)</td>
<td>2 (0-6)*</td>
</tr>
<tr>
<td>At rest</td>
<td>6 (2-7)</td>
<td>2 (1-6)*</td>
</tr>
<tr>
<td>2 h</td>
<td>4 (3-7)</td>
<td>2 (0-6)*</td>
</tr>
<tr>
<td>4 h</td>
<td>3 (1-6)</td>
<td>5 (0-7)*</td>
</tr>
<tr>
<td>6 h</td>
<td>2 (0-4)</td>
<td>5 (0-7)*</td>
</tr>
<tr>
<td>8 h</td>
<td>1 (0-8)</td>
<td>3 (0-6)*</td>
</tr>
<tr>
<td>10 h</td>
<td>2 (0-6)</td>
<td>2 (0-7)*</td>
</tr>
<tr>
<td>12 h</td>
<td>2 (0-9)</td>
<td>1 (0-8)</td>
</tr>
<tr>
<td>At rest</td>
<td>7 (4-10)</td>
<td>5 (3-9)*</td>
</tr>
<tr>
<td>1 h</td>
<td>9 (5-10)</td>
<td>5 (4-9)*</td>
</tr>
<tr>
<td>2 h</td>
<td>7 (6-10)</td>
<td>5 (3-9)*</td>
</tr>
<tr>
<td>4 h</td>
<td>7 (6-10)</td>
<td>8 (3-10)</td>
</tr>
<tr>
<td>6 h</td>
<td>6 (3-7)</td>
<td>5 (3-9)*</td>
</tr>
<tr>
<td>8 h</td>
<td>1 (0-8)</td>
<td>3 (0-6)*</td>
</tr>
<tr>
<td>10 h</td>
<td>5 (3-9)</td>
<td>5 (3-10)</td>
</tr>
<tr>
<td>12 h</td>
<td>5 (3-10)</td>
<td>4 (3-10)</td>
</tr>
</tbody>
</table>

Data are median (range). \(^*P < 0.05\) significant compared with the placebo group.
frequency and severity of sedation or nausea and vomiting. No woman reported intra-operative recall.

Apgar scores at 1 and 5 min were similar in the two groups (Table 2). Additionally, there were no reported differences in neonatal cardiovascular status, evidence of premature closure of the ductus arteriosus or pulmonary hypertension between the groups.

DISCUSSION

The sympathetic response to laryngoscopy, tracheal intubation and surgical stimulation and its pharmacological modification have been well documented. The present study demonstrated that administration of ketorolac before caesarean delivery resulted in lower increases in heart rate, systolic pressure, MAP and cortisol levels in response to tracheal intubation and surgical stimulation, and better postoperative analgesia without adverse neonatal outcome.

Opioids are an integral component of general anaesthetic techniques for major surgery. They attenuate the haemodynamic and catecholamine responses to tracheal intubation and surgical stimulation,9 and may provide pre-emptive analgesia to reduce postoperative pain.10 However, administration opioids to the mother before delivery risks adverse effects on the neonate.11 The analgesic effects of NSAIDs after caesarean delivery have previously been investigated,3,4,6 although no studies have investigated the effects of ketorolac given before induction, which could potentially lead to premature closure of the ductus arteriosus.12

The increase in heart rate, systolic pressure, MAP and cortisol levels associated with tracheal intubation and surgical stimulation may be blunted with NSAIDs as has been demonstrated in previous studies. El-Hakim and colleagues found that pre-emptive tenoxicam reduced haemodynamic variability at induction whilst improving postoperative analgesia, but slightly increased bleeding time in women undergoing caesarean delivery.4,12 Moreover, pre-treatment with rectal ibuprofen (500 mg) reduces the endocrine response and cytokine release associated with surgery.13 NSAIDs inhibit the production of prostaglandins and decrease pain by inhibiting the phosphodiesterase enzyme. The resulting increase in cyclic AMP in white blood cells inhibits the release of prostaglandins, leukotrienes, bradykinin, serotonin and histamine, thereby decreasing pain.14 The present study showed improved analgesia with reduced tramadol consumption for the first four postoperative hours in those women receiving ketorolac, which may coincide with the duration of action of the drug. In a previous study of post-caesarean pain relief, intramuscular ketorolac 30 mg had similar efficacy to pethidine 75 mg, but with fewer side effects.15 In another study, ketorolac proved to have a morphine-sparing effect, provided better analgesia than morphine and also reduced the incidence of pruritus, nausea, vomiting, constipation, sedation and respiratory depression.16

Ketorolac inhibits platelet function and alters haemostasis. Some studies have concluded that haemostasis was significantly more difficult to achieve in patients receiving ketorolac.17,18 We found no evidence of increased perioperative blood loss in those receiving ketorolac. El-Hakim et al. demonstrated that intravenous tenoxicam caused a slight increase in bleeding time with no significant change in platelet marker levels, uterine relaxation or bleeding.12 In addition, others have reported that platelet function, assessed by Ivy bleeding time, platelet aggregometry and thromboelastography, was not inhibited after intravenous ketorolac despite near complete abolition of serum thromboxane B2 production.19 Extensive post-marketing surveillance indicates a very small risk of gastrointestinal or operative site bleeding, with no significant increase compared with opioids, when appropriate doses are used in young adult populations for less than five days.20 Several studies have used simple but clinically relevant assessments of vaginal blood loss and the need for oxytocics either intra- or postoperatively and report no significant adverse

![Fig. 4 Serum cortisol concentrations. Data are mean ± SD. *P < 0.05 compared with the placebo group.](image-url)

<table>
<thead>
<tr>
<th>Time to first request for analgesia (h)</th>
<th>Placebo group (n = 45)</th>
<th>Ketorolac group (n = 45)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 h</td>
<td>1.2 ± 0.94</td>
<td>3.0 ± 1.45</td>
<td>0.001</td>
</tr>
<tr>
<td>4-8 h</td>
<td>14 (31.1%)</td>
<td>7 (15.6%)</td>
<td>0.004</td>
</tr>
<tr>
<td>8-12 h</td>
<td>10 (22.2%)</td>
<td>10 (22.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>8 (17.8%)</td>
<td>9 (20%)</td>
<td>0.724</td>
</tr>
</tbody>
</table>

Data are mean ± SD or n (%).

![Table 4. Postoperative analgesia](image-url)
effect in patients receiving NSAIDs.4,21–23 Blood loss is
difficult to measure during caesarean delivery due to the
unknown volume of amniotic fluid. Visual estimates of
blood loss are known to be imprecise and often under-
estimated.24 In the current study, this inaccuracy is
reflected in the estimates of minimal intraoperative
blood loss. Therefore, measurement of haematocrit, before and 48 h after surgery, provides a more reliable
method of assessing blood loss.25

NSAIDs are known to induce premature closure of
the patent ductus arteriosus when given in large doses
to mothers before delivery. We found no echocardi-
ographic evidence of premature closure of the ductus
arteriosus or pulmonary hypertension in the new borns
in either group. No difference in neonatal outcome, as
assessed by Apgar scores and blood gas analyses has
previously been shown with the preoperative use of intra-
venous tenoxicam.26 Vermillion and colleagues reported
that in 61 cases in which pregnant women were treated
for preterm labour with indomethacin (25 mg orally
every 6 h), a dramatic yet reversible increase in the inci-
dence of indomethacin-induced ductal constriction
occurred at 31 weeks’ gestation. However, after discon-
tinuation of indomethacin, all follow-up echocar-
diograms demonstrated a return to non-constricted duc-
tal flow velocities, with no significant adverse effect on
neonatal outcome.27 Moreover, the transfer of ketorolac
into breast milk has been quantified and it is considered
to be safe for use during lactation.28

Umbilical arterial blood gases can help assess the
degree of perinatal asphyxia, placental insufficiency and
premature closure of ductus arteriosus. We did not
measure cord gases, as 5-min Apgar scores were >8 in both
groups, and none of the mothers showed intraoperative
haemodynamic instability. Clinical diagnosis of a
haemodynamically significant patent ductus arteriosus
is imprecise. Therefore, echocardiographic evaluation
has become essential in assessing the patency of the
ductus arteriosus, direction and degree of shunting at
ductal level, and estimate of pulmonary artery pressure.29

The use of patient-controlled analgesia might have
been more helpful in the assessment of postoperative
pain. Rescue analgesia was given by staff at the request
of the patient. A subjective assessment of pain relief and
more accurate measure of analgesic requirement is pos-
sible with PCA. However, it does so at a relatively high
cost.

In conclusion, in this study intravenous ketorolac
given pre-induction was found to be safe and effective
in attenuating the maternal stress response in women
undergoing elective caesarean delivery. K etorolac im-
proved the quality of postoperative analgesia and had
no adverse effects on neonatal outcome. Further studies
are needed to define the efficacy and safety of preoper-
ative ketorolac in caesarean delivery.

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Preoperative ketorolac and caesarean section 219


