ATTENUATION OF THE PRESSOR RESPONSE TO TRACHEAL INTUBATION IN PREGNANT PATIENTS BY KETOROLAC DURING CAESAREAN SECTION

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ABSTRACT

Objectives: ketorolac may attenuate maternal stress response to tracheal intubation, without subsequent dangers of opioid-induced neonatal depression. The objective of this study is to evaluate the haemodynamic and hormonal effects of pre-emptive ketorolac on surgical stress and the postoperative analgesic consumption, after Caesarean delivery.

Study Design: A prospective randomized double-blinded placebo-controlled study.

Methods: After ethical approval, 90 patients scheduled for elective Caesarean deliveries were randomly allocated to the ketorolac group (n=45); received IV ketorolac 15 mg bolus, followed by an infusion of 7.5 $mg.h^{-1}$,and the saline for placebo group (n=45). Anaesthesia was maintained with 50% nitrous oxide, 0.5% isoflurane, and vecuronium. The haemodynamic variables and the levels of plasma cortisol were recorded before and after induction, and after delivery. The graded uterine relaxation, the need for supplementary doses of oxytocin, the peri-operative blood loss, bleeding time, and Apgar scores at 1 and 5 minutes, postoperative pain scores at rest and with movement, and tramadol consumptions were assessed.

Results: After intubation, parturients receiving ketorolac had a smaller increase in heart rate, systolic and mean arterial blood pressure (P< 0.001) and lower plasma cortisol concentrations, (45± 15.1 vs. 32.2 ± 7.61 $\mu g.\ dl^{-1}$, P<0.05). Therefore, they had lower VAS pain scores at rest and on movement, for the first 2 post-operative hours (P<0.001), later time to first request for analgesia and less tramadol consumption for the first 4 post-operative hours [0 (0-100) mg vs. 100 (0-100) mg, P = 0.004]. There were no differences between groups with regard to peri-operative blood loss, bleeding time, transfusion requirements, nausea, vomiting or Apgar scores, with no evidence of premature closure of the ductus arteriosus of the newborns.

Conclusion: Pre-emptive ketorolac is safe and effective in attenuating the maternal stress response with improved quality of post-operative analgesia in Caesarean delivery patients.

Key words: Anaesthesia, Caesarean section, stress response, ketorolac.

INTRODUCTION

Pain relief of good quality after Caesarean section results in early mobilization and good early mother-child interaction. Increased sympathetic nervous system activity and plasma concentrations of catecholamines after tracheal intubation, in women having Caesarean delivery, may decrease placental perfusion and uterine blood flow by 20%-35%[1]. Opioid analgesia gives a very high level of patient satisfaction. Opioids are routinely omitted at the induction of general anaesthesia for Caesarean

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delivery because of concerns about the placental transfer of drugs resulting in neonatal respiratory depression[2]. The use of non-steroidal anti-inflammatory drugs [NSAIDs] reduces the need for opioids significantly after Caesarean section with reduced risk of negative side-effects[3]. Therefore, intravenous pre-emptive tenoxicam significantly reduces the haemodynamic variability of light general anaesthesia at induction-delivery and twenty-four hours postoperative opioid consumption in patients undergoing Caesarean delivery without increasing side effects[4]. Ketorolac given intravenously is as effective as morphine in the management of surgical pain, and it has fewer side effects[5]. The U.S. Food and Drug Administration currently does not approve the use of ketorolac in breastfeeding patients, even though the American Academy of Pediatrics has found ketorolac to be compatible with breastfeeding[6].

We postulated that the use of ketorolac before the induction of anaesthesia for uncomplicated Caesarean section would reduce the maternal stress response after tracheal intubation and the postoperative analgesic consumption, without subsequent harmful effects to both the mother and the neonate. Therefore, the present study was designed to evaluate the effects of ketorolac on surgical stress and the postoperative analgesic consumption, after Caesarean delivery.

MATERIALS & METHODS

Patients:

This prospective randomized 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 ninety ASA I & II women aged 20-35 years, with uncomplicated, singleton pregnancies of at least 36 weeks gestation, undergoing elective lower segment Caesarean section [LSCS], with Pfannenstiel incision, under general anaesthesia. The indications for Caesarean delivery were breech presentation, cephalo-pelvic disproportion, or previous Caesarean delivery. Patients with a history of allergy to non-steroidal anti-inflammatory agents, bleeding tendency, bronchial asthma, peptic ulcer, liver, or kidney diseases or patients who had obstetric complications such as pregnancy induced hypertension, placenta praevia, abruptio placenta, or with any evidence of intrauterine growth retardation or other fetal abnormality were excluded from the study. All operations were performed by the same surgeon. The anaesthesiologist administering the general anaesthesia was not involved with subsequent post-operative patient assessment.

Before surgery, all patients were instructed about the visual analogue scale (VAS) to be used in their assessment.

All women were given oral ranitidine 150 mg [Zantac, Glaxo SmithKline, Egypt] the night before and on the morning of surgery, with 0.3 mol.l-1 sodium citrate (30 ml) given 15 minutes before operation. In the operating theatre, the women were positioned supine on the operating table with 15° firm rubber wedge under the right hip to effect left uterine displacement. A 20 gauge cannula was inserted into a forearm vein, and a slow intravenous infusion of 500 ml lactated Ringer's solution was given over the first 20 minutes.

Study design:

Patients were allocated randomly to two groups by drawing of sequentially numbered sealed opaque envelopes that each contained a computer-generated randomization code. Placebo group (n=45) received an IV bolus of 20 ml of normal saline 0.9% followed by a constant infusion (10 $ml.hr^{-1}$). Ketorolac group (n=45) received an IV loading dose of 20 ml of

ketorolac tromethamine [Toradol, MUP, Syntex Pharm AG] (0.75 $mg.ml^{-1}$), 20 minutes before induction of anaesthesia, followed by a constant infusion (10 $ml.hr^{-1}$) of the same solution until the end of surgery. Both placebo and the ketorolac solution looked the same. The test solution was prepared by one anaesthesiologist, just before induction of anaesthesia, and another anaesthesiologist who was blinded to the solution performed anaesthesia. All the staff in the operating room remained unaware of the randomization code of the patients.

Monitoring:

The standard monitoring [five leads electrocardiography, non-invasive blood pressure monitoring, pulse oximetry (SpO_2), and end-tidal carbon dioxide concentration ($EtCO_2$)] was commenced with Capnomac Ultima monitor (Datex-Ohmeda, Instrumentarium Corp., Helsinki, Finland).

Anaesthesia:

After 5 minutes of pre-oxygenation, rapid-sequence induction of anaesthesia was performed with thiopental 4-6 $mg.kg^{1}$ followed by administration of suxamethonium 1.5 $mg.kg^{-1}$, after loss of verbal response, to achieve muscle relaxation. 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-minute arterial pressure recording, and tracheal intubation was completed before the 2-minute reading. Maintenance of anaesthesia was achieved by a mixture of 0.5% isoflurane and nitrous oxide 50% in oxygen. Neuromuscular block was maintained with vecuronium 0.06 mg kg^{-1}. The lungs were ventilated [with Ohmeda 7000 ventilator] with a tidal volume of 8 $ml.kg^{-1}$, an inspiration-expiration ratio of 1:2, and at a respiratory rate necessary to maintain normocapnia, confirmed by measuring the $EtCO_2$. An infusion of lactated Ringer's solution 800 ml was given throughout the procedure. Induction to delivery (I-D) times was recorded by using a stopwatch.

After the umbilical cord was clamped, an infusion of oxytocin 10 i.u. in 500 ml of 5% glucose was started. Midazolam 0.05 $mg.kg^{-1}$ and fentanyl 1.0 $\mu g.kg^{-1}$ were given IV and nitrous oxide was increased to 70%. Isoflurane was discontinued at the start of skin closure and nitrous oxide and study drug infusion was discontinued after the last skin suture was applied. At the end of the surgery, residual neuromuscular block was antagonized with neostigmine 50 $\mu g.kg^{-1}$ and atropine 20 $\mu g.kg^{-1}$.

Measurements:

Heart rate (HR), systolic arterial blood pressure (SBP), and mean arterial blood pressure (MAP) were measured immediately before and at 1, 2, 3, 5, 6, 10 minutes after intubation, and at 15, 30 minutes after delivery; and after extubation.

The obstetrician assessed uterine tone by palpation and rated the degree of uterine contraction on an unmarked 10-cm visual analogue scale: 0 indicated none and 10 severe relaxation. If uterine tone remained unsatisfactory at 3 minutes, an additional bolus of oxytocin 5 i.u was administered upon the obstetrician's request. The intra-operative blood loss was assessed by measuring blood in the suction bottle minus liquor, weighing wet swabs and estimating blood on drapes and on the floor. The postoperative transfusion requirements and blood loss were estimated from nursing inspection of the perineal pad, was graded as (0) small, (1) moderate, or (2) large. Skin Ivy bleeding time (BT) was determined pre-operatively and 1 hour post-operatively.

Stress response was determined by changes in plasma cortisol concentrations. Maternal venous blood samples (10 ml) were collected at three time intervals: preoperatively; 5 minutes after intubation, and 1 hour after delivery. These times were based on likely physiological responses over time and economic limitations. The blood samples were centrifuged, and serum was drawn off and stored at 4C°until assayed within 2 weeks of collection. Plasma cortisol levels were determined using a radioimmunoassay technique (Gamma Coat® Cortisol 125 IRIA). The sensitivity was 0.2 $\mu g. dl^{-1}$ (0.6 $nmol. dl^{-1}$) and coefficient of variation was 9%.

All neonates were assessed by a single paediatrician who was unaware of the analgesic drug given. Apgar scores were recorded at 1 and 5 minutes. The paediatrician examined each newborn immediately after delivery, after 8, 12, 24 hours in hospital, and 7 days later for any evidence of premature closure of the ductus arteriosus or pulmonary hypertension. The newborns were observed with monitoring of arterial blood pressure, heart rate, temperature and arterial oxygen saturation (SpO_2).

From the time of extubation, we assessed the severity of post-operative pain on a 10-cm visual analogue scale at rest and with movement, which ranged from 0 for no pain to 10 for the worst pain imaginable, at 0, 1, 2, 4, 6, 8, 10 and 12 hours after surgery. After operation, tramadol (Tramal) 100 mg IV was prescribed when visual analogue scale scores were 5 or more at rest, and 7 or more with movement or if the patient requested additional analgesia. The time to first request for analgesia and the total analgesic consumption for the first 12 post-operative hours were recorded.

The patients scored the presence and intensity of postoperative side effects as follows: sedation [four-point verbal rating scores (VRS): awake, drowsy, rousable or deep sleep], nausea and vomiting [(0) no nausea, (1) mild-moderate nausea, (2) mild vomiting (once per observation period) with severe nausea, (3) moderate vomiting (twice per observation period), (4) severe vomiting (3-4 times per observation period), or (5) persistent vomiting that needed treatment with an anti-emetic agent] at 0, 1, 2, 4, 6, 8, 10 and 12 hours after surgery, and intra-operative recall.

Statistical analysis

Statistical analysis was performed using Statistica '99 software (StatSoft, Tulsa, Okla.). Data were tested for normality using Kolmogorov-Smirnov test. Un-paired Student's t test was performed 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 repeated 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 a sufficiently large sample size to be adequate to detect a 20% reduction in post- induction blood pressures values, with a type-I error of 0.05 and a power of approximately 90%.

RESULTS

Maternal Data:

All 90 patients completed the study period: 45 patients in the placebo group, and 45 in the ketorolac group. Maternal age, weight, height, gestational age, I-D time, anaesthesia time, and estimated weight of

the fetus, did not significantly differ between the groups [Table (I)].

Baseline HR, SBP and MAP were similar between the two groups [Figures (1, 2, 3)]. The changes in HR from baseline values after tracheal intubation (at 2, 3, 4, 5, 6, and 10 minutes), and at 15 minutes after delivery were significantly greater in the placebo group than in the ketorolac group (P<0.001) [Figure (1)].

The changes in SBP and MAP from baseline values after tracheal intubation (at 1, 2, 3, 4, 5, 6, and 10 minutes), and at 15 minutes after delivery were significantly greater in the placebo group than in the ketorolac group (P < 0.001) [Figures (2, 3)]. HR, SBP, and MAP increased after intubation and returned to baseline levels by 3-4minutes in both groups (P < 0.01) [Figures (1, 2, 3)].

The placebo group had a significantly higher pain scores [VAS] at rest and on movement, than did the ketorolac group for the first 2 hours following surgery (P < 0.001) [Table (II)]. The time to first tramadol request in the ketorolac group [3.0±1.45 hours] was significantly longer than in the placebo group [1.2±0.994 hours] (P=0.001) [Table (III)]. Additionally, the median doses of tramadol consumption for the first 4 hours after surgery were significantly higher in the placebo group than in the ketorolac group (P=0.004) [Table (III)]. VRS scores for sedation were similar in the two groups [Table (III)].

Baseline maternal cortisol concentrations in the placebo group, 28.2 ± 11.4 μg. dl^{-1}, were similar to those in the ketorolac group, 27.8 ± 11.25 μg. dl^{-1},. Five-minutes after intubation and 1 hour after delivery, cortisol concentrations were significantly greater in the placebo group [45 ± 15.1 μg. dl^{-1} and 43 ± 13.3 μg. dl^{-1}, respectively], compared with the ketorolac group [32.2 ± 7.61 μg. dl^{-1}, and 32.33 ± 10.3 μg. dl^{-1}, respectively], (P= 0.032 and 0.014, respectively) [Figure (4)].

The surgeon's VAS assessment of uterine relaxation indicated that there was no significant difference between the two groups [Table (IV)]. 15.6% of patients [7/45] in the ketorolac group and 11.1% of patients [5/45] in the placebo group required supplementary doses of oxytocin, but this difference was not significant [Table (IV)]. Additionally, the peri-operative blood loss was similar in both groups and no patient required blood transfusion [Table (IV)]. Pre-operative and post-operative bleeding times did not change significantly in both groups [Table (IV)].

There were no reported serious side effects during this study. There were no differences between groups with respect to the frequency and severity of nausea and vomiting [Table (IV)]. None of the mothers complained of intra-operative recall.

Neonatal Data:

The Apgar scores at 1 and 5 minutes were similar in ketorolac and placebo groups [Table (IV)]. Additionally, there were no reported postoperative differences in the follow-up examination of the cardiovascular status, evidence of premature closure of the ductus arteriosus or pulmonary hypertension of the newborns in both groups.

DISCUSSION

The sympathetic responses [hypertension and tachycardia] to laryngoscopy and tracheal intubation and their pharmacological modifications have been well documented. The present study demonstrates that administration of ketorolac prior to Caesarean delivery resulted in lower increases in HR, SBP, MAP, and cortisol levels, in response to endotracheal intubation, 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 ("stress") response to tracheal intubation[7], and may provide preemptive analgesia to reduce postoperative pain[8]. However, maternally administered opioids may cross the placenta and adversely affect the neonate[9].

The analgesic effects of NSAIDs have been investigated in patients after Caesarean section[3,4,6]. No studies have investigated the effects of pre-emptive ketorolac after Cesarean delivery.

The intra-operative lower values of HR, SBP, MAP, and cortisol levels, after intubation, in our ketorolac group were similar to those reported in previous studies. El-Hakim and coworkers found that pre-emptive tenoxicam is an effective pretreatment to minimize the haemodynamic variability of light general anaesthesia at induction-delivery and in improvement of post-operative analgesia, with slight increase in bleeding time in Cesarean delivery patients[4,10]. Moreover, rectal Ibuprofen (500 mg) pre-treatment in peri-operative course is able to reduce the endocrine response and cytokine release[11].

NSAIDs act by anti-inflammation. They inhibit the production of prostaglandins and they decrease pain by inhibiting phosphodiesterase enzyme which increase cyclic AMP in the white blood cells, so white blood cells decrease the release of prostaglandins, leukotrienes, bradykinin, serotonin and histamine which will decrease pain at the periphery[12].

The present study showed improved analgesia and decreased tramadol consumption with a lower incidence of sedation for the first 4 post-operative hours by using ketorolac after Caesarean section, which may coincide with the duration of action of the drug infusion. Previous studies have administered IM ketorolac after Caesarean delivery and found that ketorolac has similar efficacy to IM meperidine, but ketorolac produced fewer side effects[13]. In addition, Ketorolac proved to have morphine sparing effect, improve analgesia, reduce opioid requirements, and also reduced the incidence of the pruritus, nausea, vomiting, constipation, sedation or respiratory depression commonly associated with opioids[14]. Therefore, ketorolac had the potential to replace opioids in the treatment of severe pain.

Platelet inhibition with altered haemostasis i among the list of adverse effects associated with the administration of ketorolac. In addition, others concluded that haemostasis was significantly more difficult to achieve in patients receiving ketorolac [15-16]. In the present study, we found no evidence of increased peri-operative blood loss in those receiving ketorolac. Similarly, El-Hakim and others' concluded that during Caesarean delivery IV tenoxicam causes a slight increase in bleeding time with no significant changes in platelet marker levels, and the extent of uterine relaxation or bleeding[4,10]. In addition, others reported that platelet function, by Ivy bleeding time, platelet aggregometry, and thromboelastography, was not inhibited after IV ketorolac despite near complete abolition of serum thromboxane B_2 (TxB_2) production[17]. 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[18]. Several studies have used simple, but clinically relevant, assessments of vaginal blood loss or the need for oxytocics either intra- or postoperatively and reported no significant effect in patients receiving NSAIDs[4,19-22].

NSAIDs are known to induce premature closure of the patent ductus arteriosus when given in large doses to mothers before delivery. In the current study, there was no reported evidence of premature closure of the ductus arteriosus or pulmonary hypertension of the newborns in both groups. Similarly, several studies reported no difference in neonatal outcome, as determined by Apgar scores and blood gas analyses with the pre-operative use of IV tenoxicam or postoperative Caesarean delivery pain relief[23]. Vermillion and others' reported that in 61 cases in which the pregnant women were treated for preterm labor with indomethacin (25 mg orally every 6 hours), a dramatic yet reversible increase in the incidence of indomethacin-induced ductal constriction occurs at 31 weeks' gestation. However, after discontinuation of indomethacin therapy, all follow-up echocardiograms demonstrated a return to non-constricted ductal flow velocities, with no significant adverse neonatal outcomes[24]. Moreover, the transfer of ketorolac into breast milk has been quantified, and it is considered to be safe for use during lactation[25]. Thus, a possible explanation could be that, we used relatively small doses of ketorolac for limited periods of continuous IV infusion.

In conclusion, in this study pre-emptive IV ketorolac is safe and effective in attenuating the maternal stress response with improved the quality of post-operative analgesia in Caesarean delivery patients, with no adverse neonatal outcome.

Limitations to our study:

Further multi-center studies are needed to define the efficacy and the safety of the use of pre-operative ketorolac in pregnant patients undergoing Caesarean delivery for the attenuation of the stress response and evaluate the neonatal outcome.

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Table I : Demographic data of the patients in ketorolac group and placebo group. Data are expressed as [mean ± SD].

	Second group (n = 72)	P value
Age (Years)	27.1 ± 4.18	26.2 ± 5.10
Weight (Kg)	78.6 ± 7.96	77.7 ± 10.78
Height (cm)	162 ± 3.35	160 ± 2.23
Gestational age (weeks)	38.9 ± 1.51	39.3 ± 1.71
I-D time (minutes)	11.4 ± 1.76	10.8 ± 1.47
Anaesthesia time (minutes)	39.7 ± 5.26	41.8 ± 5.63
Birth weight (Kg)	3.3 ± 0.26	3.2 ± 0.19

I-D time = Induction to delivery time (minutes)

* Significant when P < 0.05.

Table II : Visual analogue scale (VAS) assessment of post-operative pain, at rest and with movement in the studied groups. Data are expressed as [median (range)].

	Placebo group (n = 45)		Ketorolac group (n = 45)	
	At rest	On movement	At rest	On movement
post-extubation	4 (1 - 8)	7 (4 - 10)	2 (0 - 6)*	5 (3 - 9)*
1 hour	6 (2 - 7)	9 (5 - 10)	2 (1 - 6)*	5 (4 - 9)*
2 hours	4 (3 -7)	7 (6 -10)	2 (0 - 6)*	5 (3 - 9)*
4 hours	3 (1 - 6)	6 (7 - 9)	5 (0 - 7)	8 (3 - 10)
6 hours	2 (0 - 4)	5 (3 - 7)	2 (0 - 6)	5 (3 - 9)
8 hours	1 (0 - 8)	1 (0 - 8)	3 (0 - 6)	3 (0 - 6)
10 hours	2 (0 - 6)	5 (3 - 9)	2 (0 - 7)	5 (3 - 10)
12 hours	2 (0 - 9)	5 (3 -10)	1 (0 - 8)	4 (3 - 10)

* P < 0.05 Significatn when compared with the placebo group.

Table III : The time to first request for analgesia, the post-operative hourly tramadol consumption, and verbal rating score (VRS) for sedation in the studied groups. Data are expressed as [mean ± SD or median (range)] .

	Placebo group (n = 45)	Ketorolac group (n = 45)	P value
The time to first request for analgesia (hours)	1.2 ± 0.94	3.0 ± 1.45	0.001*
The postoperative hourly tramadol consumption (mg)			
0 - 4 hours	100 (0 - 100)	0 (0 - 100)	0.004*
4 - 8 hours	100 (0 - 200)	100 (0 - 300)	1.000
8 - 12 hours	100 (0 - 200)	100 (0 - 200)	0.724
The verbal rating score (VRS) for sedation			
0 hours	2 (2 - 3)	1 (0 - 3)	0.206
1 hours	0 (0 - 1)	0 (0 - 1)	0.534
2 hours	0 (0 - 0)	0 (0 - 0)	1.000
4 hours	0 (0 - 0)	0 (0 - 0)	1.000
6 hours	0 (0 - 0)	0 (0 - 0)	1.000
8 hours	0 (0 - 0)	0 (0 - 0)	1.000
10 hours	0 (0 - 0)	0 (0 - 0)	1.000
12 hours	0 (0 - 0)	0 (0 - 0)	1.000

* P < 0.05 Significatn when compared with the placebo group.

Table VI : The Peri-operative data. Data are expressed as [median (range), percentage% (numbers) or mean ± SD].

	Placebo group (n = 45)	Ketorolac group (n = 45)	P value
VAS assessment of uterine relaxation	3 (0 - 3)	3 (0 - 3)	0.851
Percentage of the patients needed supplementary doses of oxytocin (i.u)	11.1% (5/45)	15.6 (7/45)	0.772
The intra-operative blood loss (ml)	279 ± 88.97	298 ± 89.95	0.557
The postoperative blood loss	0 (0 - 2)	0 (0 - 3)	1.000
BT (minutes): Pre-operative	3.6 ± 1.24	3.4 ± 1.18	0.655
Post-operative	3.7 ± 1.05	3.7 ± 0.96	0.857
Percentage of the patients suffered from nausea and vomiting	11.1% (5/45)	6.7% (3/45)	1.000
The post-operative score for nausea and vomiting			
0 hours	0 (0 -3)	0 (0 -1)	1.000
1 hours	0 (0 - 1)	0 (0 - 3)	1.000
2 hours	0 (0 - 1)	0 (0 - 1)	1.000
4 hours	0 (0 - 3)	0 (0 - 1)	1.000
6 hours	0 (0 - 1)	0 (0 - 1)	1.000
8 hours	0 (0 - 1)	0 (0 - 1)	1.000
10 hours	0 (0 - 1)	0 (0 - 0)	1.000
12 hours	0 (0 - 1)	0 (0 - 1)	1.000
Apgar score: 1 minutes	8 (5 - 10)	7 (4 - 10)	1.000
5 minutes	10 (9 - 10)	10 (9 - 10)	1.000

* P < 0.05 Significatn when compared with the placebo group.

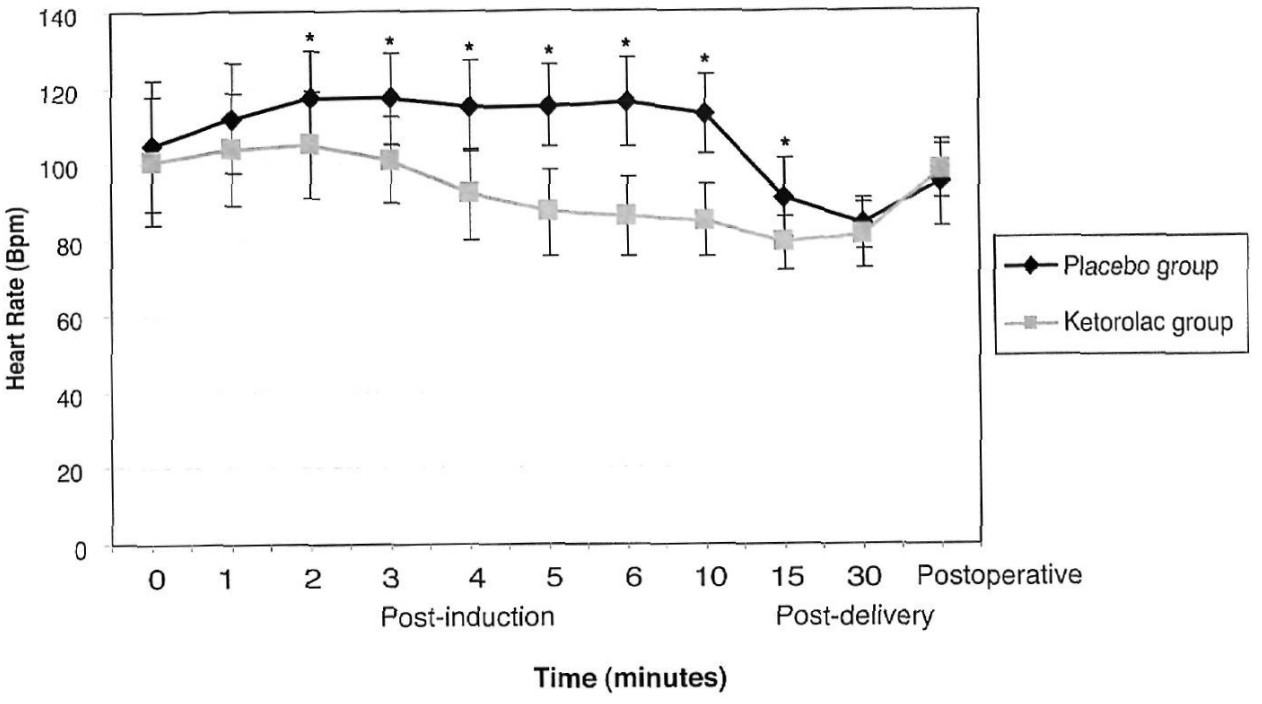


Figure (1) : Perioperative heart rate [Bpm] changes in the studied group [mean ± SD].

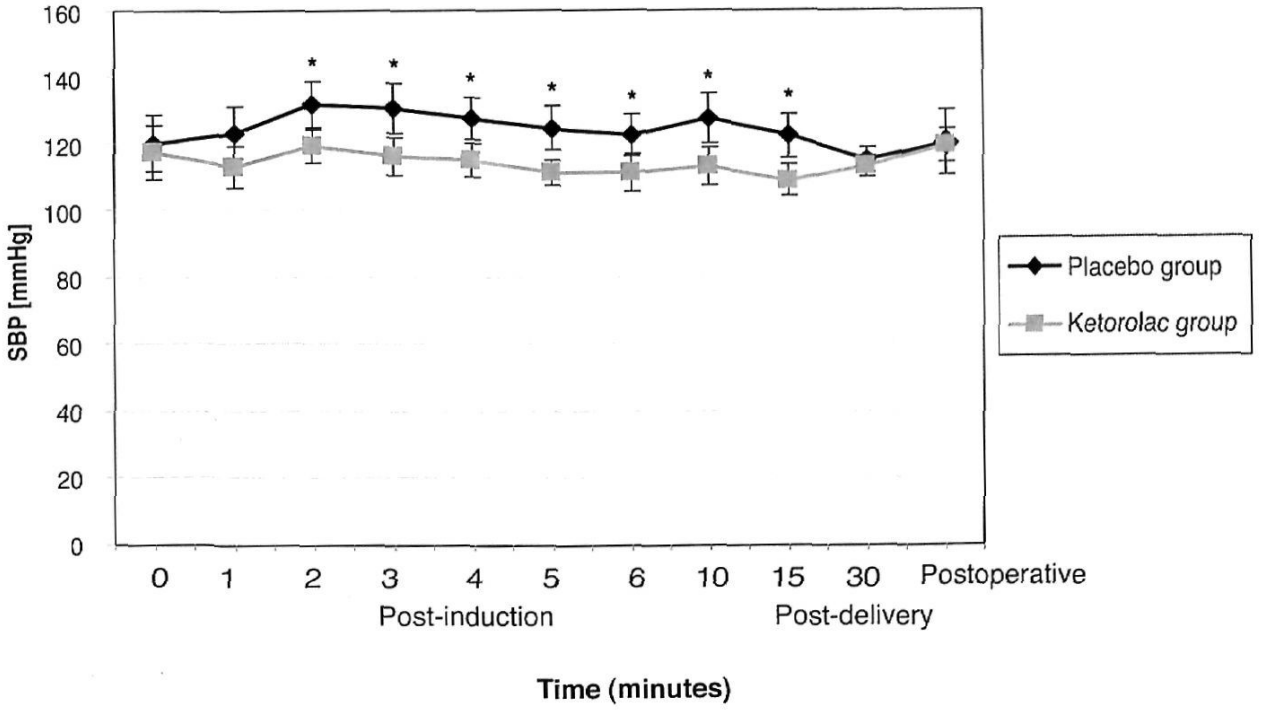
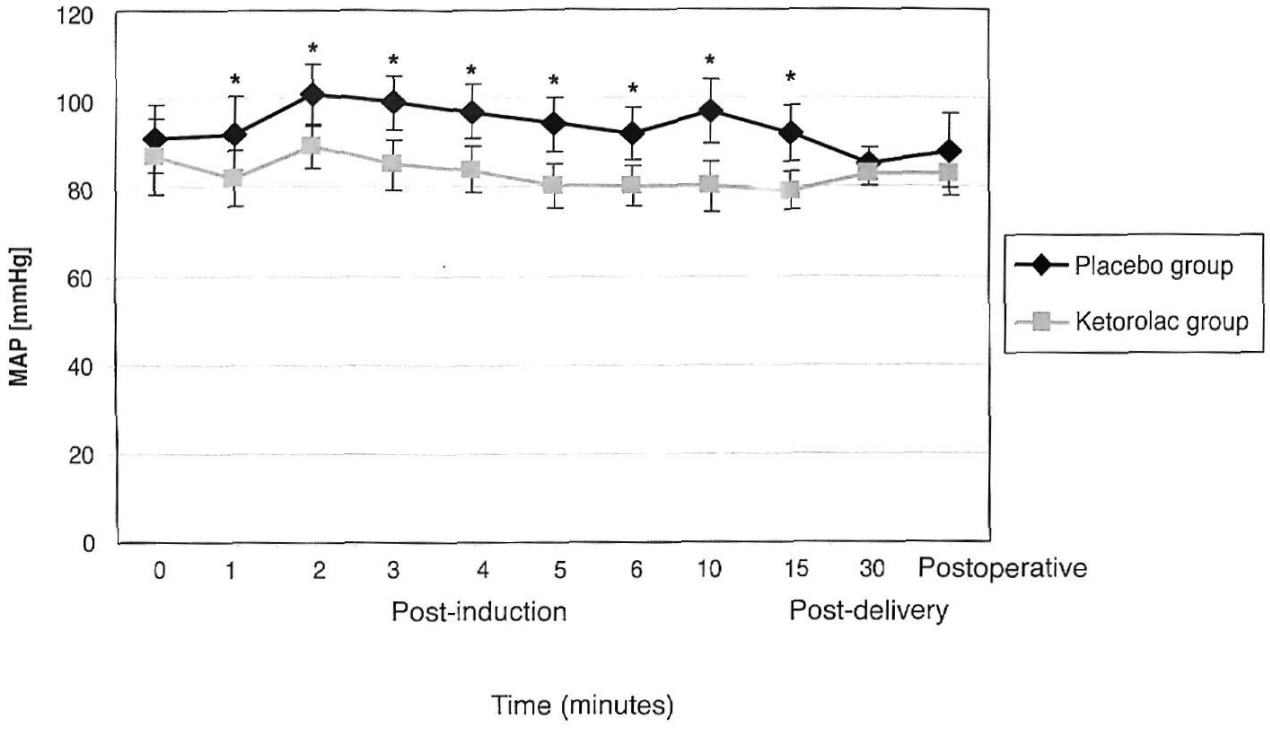
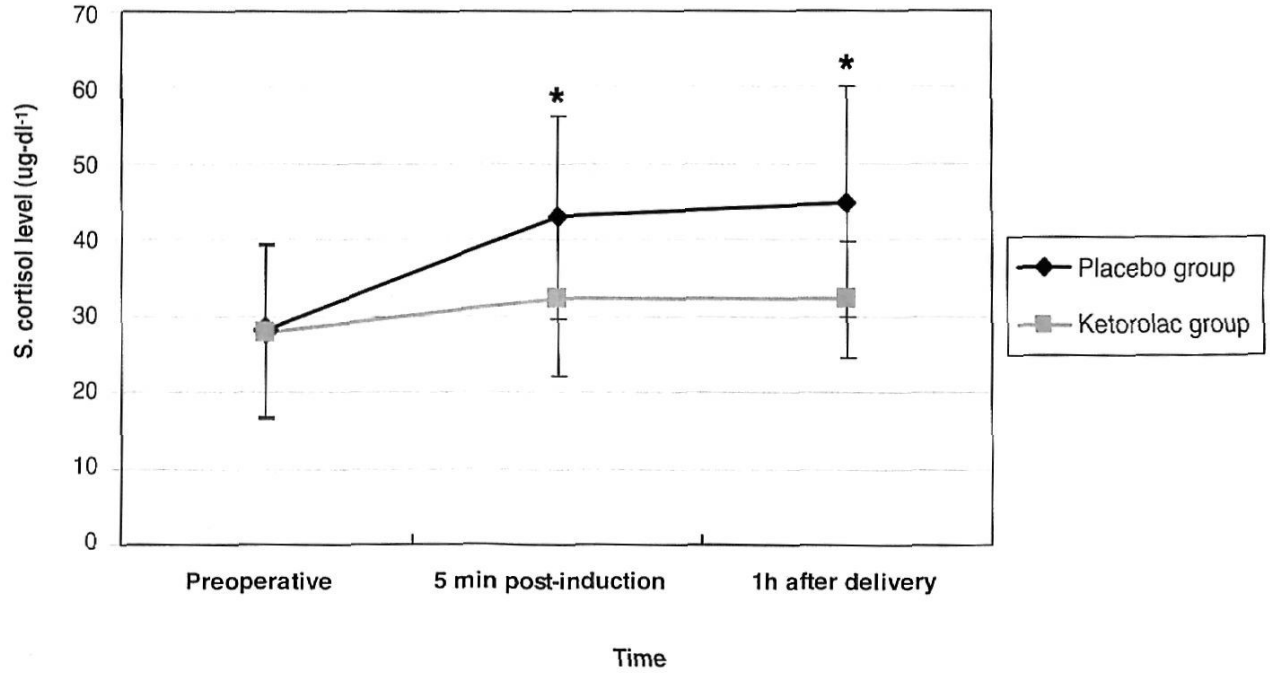


Fig. 2. Perioperative systolic arterial blood pressure (SBP) [mmHg] changes in the studied groups [mean ± SD].



* P< 0.05 when compared with placebo group.

Figure (3) : Perioperative mean arterial blood pressure (MAP) [mmHg] changes in the studied groups [mean ± SD].



* P< 0.05 when compared with placebo group.

Fig. 4. Serum cortisol level changes in the studied groups. Data are expressed as [mean ±SD].