The use of rectal diclofenac for post-cesarean analgesia

Mumtaz Rashid, *MRCOG,* ***Hanan M. Jaruidi,*** *MBBS.*

ABSTRACT

Objective: To determine whether the prophylactic use of rectal diclofenac sodium produces effective analgesia after cesarean section.

Methods: A randomized single blind controlled trial. The study period was from September 1997 - April 1998. Forty patients undergoing both emergency and elective cesarean section were studied, with 20 patients in each arm. The study group received 100 mg rectal diclofenac immediately after cesarean section followed by 50 mg at 12 hours and 100 mg at 36 hours after the surgery. The control group did not receive any diclofenac suppositories.

Results: The results showed that the visual analogue score for pain in the study group was significantly less at 12, 18 and 24 hours after surgery ($P < 0.05$). The amount of pethidine consumed was also significantly less ($P < 0.05$) with 28 injections consumed in the study group as compared with 52 in the control group (each pethidine injection = 100 mg). The incidence of sedation and constipation was significantly less ($P<0.05$) in the study group. However, the incidence of nausea and post-operative pyrexia was comparable in the 2 groups.

Conclusion: Rectal diclofenac provides effective analgesia when given after cesarean section. It also reduces the patients opioid requirements with a corresponding reduction in the opioid related side-effects.

Keywords: Diclofenac, pethidine, opioid, analgesia, cesarean section, pain score.

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Cesarean section is commonly associated with post-operative pain. This post-operative pain relief is usually achieved by giving centrally acting drugs such as morphine or its derivatives. Central nervous and peripheral side-effects of opioids restrict their use.[1] Most important of these side-effects are a reduced level of consciousness, nausea and vomiting, depression of respiratory centre with a risk of respiratory failure and a decrease in smooth muscle tone that leads to delayed intestinal passage and an increased risk of prolonged postoperative bowel paralysis. Early mobilization after obstetric surgery is essential to avoid complications and aid post-operative recovery. The addition of supplementary analgesics that could reduce a patients opioid requirements and thus reduce opioid related side-effects would therefore be of considerable importance in post-operative recovery. Diclofenac is a potent non-steroidal anti-inflammatory agent (NSAID) which has both analgesic and anti-inflammatory properties. It has been shown to provide effective pain relief in severe conditions such as primary dysmenorrhoea[2] and renal colic.[3] It has also been shown to reduce opioid requirement after orthopedic,[4] abdominal[5] and gynecological[6] surgery. Previous work on the use of diclofenac following cesarean section has shown that the addition of a single 100 mg rectal diclofenac increased the mean time to first analgesia by more than 5 hours.[7] However, this was not accompanied by a reduction in the amount of analgesia given in the first 48 hours after operation or significantly

From the Department of Obstetrics & Gynecology, Security Forces Hospital, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. M. Rashid, Consultant Obstetrics & Gynecology, Security Forces Hospital, PO Box 3643, Riyadh 11481, Kingdom of Saudi Arabia. Tel. +00966 (1) 4774480. Fax. +00966 (1) 4764757.

lower pain scores. In a related study a single intramuscular dose of 75 mg of diclofenac given after cesarean section was found to lower opioid requirement and reduce the subjective pain score and observed sedation.[8] The purpose of our study was to evaluate prospectively, the efficacy of using more than one rectal diclofenac sodium in the management of post-cesarean pain and to establish whether prophylactic rectal diclofenac, as an adjunct to parenteral pethidine, provides better analgesia after cesarean section. In addition, it was hoped to determine whether it reduces the amount of opioid used in the post-operative period, whether or not its use reduces the incidence of opioid related side effects such as sedation, nausea, vomiting and constipation.

Methods. The trial was conducted over an 8 month period from September 1997 - April 1998 at the Security Forces Hospital, Riyadh, Kingdom of Saudi Arabia. Patients undergoing both elective and emergency lower segment cesarean section under general anesthesia were recruited into the study. Verbal consent was obtained from all the patients. Patients recruited had no contraindication to the use of non-steroidal anti-inflammatory drugs. There were 40 patients studied with 20 patients in each arm. The patients were allocated randomly to the 2 groups. One group received 100 mg of rectal diclofenac immediately after cesarean section followed by 50 mg at 12 hours and 100 mg at 36 hours. The control group did not receive any rectal diclofenac. Both groups received 100 mg of pethidine through intramuscular injection at 4-6 hourly intervals on request. The women entered into the trial were not offered other non-steroidal anti-inflammatory agents until at least 12 hours after administration of the last dose of diclofenac suppositories. A random number table was used to code both the diclofenac and control groups using a block containing odd and even numbers in equal proportion. The assessor was kept blind to the randomization process. Before the operation, all the patients were shown a visual analogue score (VAS) and were instructed to place a mark, at 6 hour intervals, on a 10 cm line to indicate the degree of their pain. Visual analogue scores were completed at 6, 12, 18 and 24 hours after the operation. Nausea and vomiting score were assessed at 6, 12 and 24 hours after the surgery by using a 3 point rating score (0 = none, 1 = nausea and 2 = vomiting). Sedation was assessed at 6, 12 and 24 hours after the surgery also by using a 3 point rating score (1 = awake, 2 = drowsy and 3 = asleep). The time and amount of pethidine consumed in the first 24 hours and second 24 hours after the surgery was recorded in order to assess the total pethidine consumption in the 2 groups. Incidence of post-operative pyrexia was also analyzed in the 2 groups. The amount of lochia loss was assessed by the nurse and documented. Students t-test was used for comparing mean values. Wilcoxon's rank-sum test was used for the VAS data and the Chi square test for the sedation and nausea data and for the comparison of other frequencies. A P value of ≤ 0.05 was considered to be significant.

Results. Of the 42 women entered into the trial, 40 completed the questionnaires which were available for analysis (Figure 1). Two women were excluded from the study; one developed wound infection and had post operative pyrexia lasting several days whilst the other developed pulmonary embolism with a prolonged protracted post-operative period. Out of the 40 women, there were 20 patients in each arm. The entry characteristics of the 2 groups in the trial were comparable to each other (Table 1). There were no reports of local irritation or discomfort from the suppositories and no patient expressed an objection to the route of administration. There were no adverse comments about the suppositories. No side-effects in particular bleeding disorder or gastrointestinal problems were reported. The pain scores obtained at each assessment are shown in Table 3. There was a difference in the median visual analogue pain score in the 2 groups at 6 hours but it did not reach statistical significance. However, the median linear analogue score for the pain in the study group was significantly low ($P < 0.05$) at 12, 18 and 24 hours after the surgery. The amount of pethidine consumption in the first 24 hours and second 24 hours after surgery is shown in Table 3. The difference is statistically significant ($P<0.05$). Total pethidine consumed during 48 hours after surgery is 280 mg in the study group compared to 520 mg in the control group ($P <0.05$). The incidence of sedation was significantly different at all times in the 2 groups

Figure 1 - Flow chart showing recruitment of patients into the study.

Table 1 - Demographic features of patients in each group (Mean ± SD).

	DICLOFENAC	CONTROL
Age (years)	28.0 (4.3)	26.8 (5.4)
Height (cm)	157.1 (9.0)	158.0 (6.3)
Gestation (weeks)	37.2 (2.9)	36.9 (3.5)
Weight (kg)	72.0 (12.1)	69.2 (9.1)

Table 2 - Incidence of post operative complications and other factors.

Side effects and other factors	No. of patients		P value
	Study group	Control group	
Constipation	15	15	<0.05
No. of glycerine suppositories used	10	28	<0.05
Post-op pyrexia	4	5	>0.05
Excessive lochia	0	0	-
Hospital stay	4.5 days	5 days	>0.05

Table 3 - Visual analogue score (VAS) for pain and pethidine consumption after surgery. P* < 0.05.

VAS (cm)		Pethidine consumption (mg)	
Diclofenac	Control	Diclofenac	Control
6 hour 5.9	6.5	-	-
12 hour 2.3*	3.9	-	-
18 hour 2.0*	3.6	-	-
24 hour 1.3*	3.2	280*	420
48 hour -	-	280*	520

Table 4 - Assessment of severity of sedation and nausea (number of patients per category) P* < 0.05.

Sedation						
	6 hour		12 hour		24 hour	
	Diclofenac	Control	Diclofenac	Control	Diclofenac	Control
Awake	14*	2	16*	8	20*	14
Sleepy	6*	18	4*	12	0*	6
Nausea						
	6 hour		12 hour		24 hour	
	Diclofenac	Control	Diclofenac	Control	Diclofenac	Control
None	10	12	11	14	16	17
Nausea	6	5	5	3	3	2
Vomiting	4	3	4	3	1	1

(Table 4). At 6 hours, 18 patients were asleep in the control group as compared with 6 in the study group. Similarly at 12 hours 12 patients were asleep in the control as compared with 4 in the study group and at 24 hours after surgery 6 patients were still sleepy in the control group compared with none in the study group. There was no difference between the nausea scores at any time between the 2 groups (Table 4). The incidence of constipation and subsequent use of glycerine suppositories was significantly different in the groups (Table 2). Fifteen patients suffered from constipation in the control group as compared with only 5 in the study group. Subsequently 28 glycerine suppositories were used in the control group as compared to 10 in the study group. Two patients in the control group had enema for the relief of constipation. There was no difference in the incidence of post-operative pyrexia (Table 2). There were 5 patients in the control group and 4 patients in the study who had post-operative pyrexia. Post-operative pyrexia was defined as a temperature of 37.5° or more lasting for more than 48 hours after the surgery without any evidence of infection. There was no incidence of post-partum hemorrhage. The overall hospital stay in the 2 groups was comparable (Table 2).

Discussion. Morphine, or its derivatives have been extensively used to treat post-operative pain. However, due to a high incidence of side effects associated with opioids, better drugs for the relief of post-operative pain are needed. The mechanism behind the post-operative pain is not completely understood but it is thought that prostaglandin release and local edema caused by the surgical procedure are involved as causative factors. Prostaglandin E2 increases the sensitivity of the sensory nerve ends to pain stimulants.[9] This effect could be counteracted by the anti-prostaglandin action of non-steroidal anti inflammatory agents. Uterine cramps, another source of postpartum pain, occurs as a result of prostaglandin action on the myometrium which stimulates contractions. This pain may also be reduced by the use of NSAIDs. Diclofenac is a derivative of a phenylacetic acid and has potent anti-inflammatory, analgesic and anti-pyretic properties. It is contraindicated in women with peptic ulceration or gastro-intestinal bleeding and those with a history of allergy to non-steroidal anti-inflammatory agents including aspirin. Patients considered at risk were carefully screened and excluded from the study.

Our results suggest that diclofenac is an effective post-operative analgesic. It provided better analgesia at 12, 18 and 24 hours after the surgery. The duration of the therapeutic effect of diclofenac is 3-4 times longer than its half life in the plasma and release of pain mediating prostaglandins are inhibited and remain so despite the decrease of the drug's plasma

concentration. On the other hand, the analgesic effect of morphine is dependent on continuous stimulation of the opiate receptors and the effect of a single injection generally persists for only 4-6 hours. These results are consistent with the previous work which demonstrated that diclofenac reduces opioid requirement after abdominal surgery,[5] hysterectomy[6] and perineal repair.[10] However, our finding of low pain scores is not in agreement with other reported results where a single dose of 100 mg of rectal diclofenac[7] after cesarean section gave no pain relief. Diclofenac has a longer duration of action (12-24 hours) and in our study opioid-sparing effect persisted up to 48 hours after the surgery. Indeed none of the patients in the study group received any pethidine injection in the 2nd 24 hour post-operative period whereas 10 pethidine injections were consumed by the control group in the 2nd 24 hour post-operative period. The 3rd dose of diclofenac was administered 36 hours after surgery so that its benefits could be assessed in the 2nd half of our study. There was no reduction in the nausea score in the study group despite reduced opioid consumption. This is not unexpected because it is a routine in our unit to give 25 mg of intramuscular phenergan injection along with 100 mg of pethidine injection to counteract the opioid side effects of nausea and vomiting. Moreover, many other factors have been shown to influence the incidence of post-operative nausea and vomiting in addition to peri-operative opioids.[11] The observed sedation was also markedly less at all the times in the study group. This helps in early mobilization of the patients which itself leads to early post-operative recovery thus reducing the risk of deep venous thrombosis. In addition, a faster post-operative recovery means early establishment of breast feeding which helps in establishing materno-infant bonding. Opioids have a depressant effect on the large bowel peristalsis and a stimulant effect on the anal sphincter tone that lead to intestinal paralysis. Post-operative intestinal paralysis is often a problem to the patient as well as constant source of anxiety for the surgeon. The incidence of observed constipation was significantly less in the study group due to less opioid consumption, early mobilization of the patient and early resumption to normal diet. It is an advantage that diclofenac does not interact with anesthetics; for example it does not cause respiratory depression and it has been suggested that giving NSAIDs before surgery begins may minimize the initiation of pain in the peripheral tissues and enhance their effectiveness as analgesics.[12] However, we did not give diclofenac until after delivery because NSAIDs are known to induce premature closure of the ductus arteriosus when given in large doses to the mother before delivery. There was no reported incidence of post-partum hemorrhage in the patients studied in spite of a theoretical possibility due to diclofenac having tocolytic[13] and thrombocytopenic properties.[14] Diclofenac also offers, therefore, an attractive possibility of combining post-operative pain relief with thrombosis prophylaxis. In addition, rectal administration of diclofenac has the advantage that absorption is rapid and analgesia can be delivered irrespective of vomiting which commonly occurs in the post-operative period. Diclofenac is antipyretic due to its direct depressant effect on the heat regulatory centre of brain. In spite of this antipyretic property there was no difference in the incidence of post-operative pyrexia between the study and control groups. Diclofenac is licensed for use during lactation. When given on a regular basis active substances have been detected in breast milk, but in such small quantities that no undesirable effects are likely.[8] Inflammation in tissues injured by surgery may result in post-operative adhesions. Antiphlogistic drugs are sometimes used in an attempt to prevent the development of adhesions after tubal surgery. A positive effect of NSAIDs has been demonstrated in animals[15] and diclofenac may exhibit such an effect in humans. Large randomized controlled studies are needed to compare diclofenac to other analgesics but this study shows that diclofenac is an effective analgesic when given after cesarean section and has significant opioid sparing effects.

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