A RANDOMIZED CONTROLLED STUDY COMPARING SUBCUTANEOUS PETHIDINE WITH ORAL DICLOFENAC FOR PAIN RELIEF AFTER CAESAREAN SECTION

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ABSTRACT:

It is important to provide effective postoperative analgesia following a Caesarean section because mothers wish to be pain-free, mobile and alert while caring for their babies. The role of regular oral diclofenac as postoperative analgesia was evaluated in a randomized controlled study and it was compared to the established method of parenteral pethidine. Forty healthy women scheduled for elective Caesarean section under spinal anaesthesia with 2-2.5 mg of heavy bupivacaine 0.5% were randomized to receive either 75 mg of oral diclofenac twice daily or 1 mg/kg of subcutaneous pethidine every 8 hourly. Efficacy of pain relief (visual analogue score), patients' satisfaction and side effects such as sedation, nausea and vomiting were recorded for three days. The demographic variables were similar in both groups. Pain relief was adequate and comparable in both groups with similar mean visual analogue score during the second and third day of the study period. However, on the first postoperative day, 60% of the diclofenac group population required rescue medication consisting of subcutaneous pethidine in order to achieve the same pain scores as those in the pethidine group who did not require any rescue medications. Women who received oral diclofenac reported lower sedation and higher overall satisfaction. The incidence of nausea and vomiting was similar in both groups. This concluded that although oral diclofenac 75mg twice daily may not be superior to the traditional method of subcutaneous pethidine for pain relief following caesarean section, it can still be used alone as an alternative, as it has other benefits of a non-opioid analgesia. *(JUMMEC 2009; 12 (2): 63-69)*

KEYWORDS: *diclofenac, caesarean section, pethidine, postoperative analgesia*

Introduction

Various modes of analgesia can be used to provide postoperative pain relief. However, mothers who have had a Caesarean section are different from other postoperative patients because of their need and desire to be mobile as soon as possible in order to minimize postoperative complications and to allow for the care of their newborn.

Parenteral administration of opioids, usually by the intramuscular or subcutaneous route, together with antiemetics has been used as the predominant method of pain relief following Caesarean section in most parts of the world. More recently, newer techniques have become available. These include intrathecal opiods, continuous epidural analgesia, patient-controlled analgesia and patient-controlled epidural analgesia (PCEA). Although these techniques have been shown to produce better pain relief, they can have many adverse effects requiring close observation of the women. They are also often expensive, require trained personnel and special equipment or monitoring and may restrict women from free and safe access to their babies, thus interfering with good early mother-child interaction.

The University of Malaya Medical Centre (UMMC) is a large public hospital with limited resources and staff, who cater to a large number of patients. There is a high turnover of mothers in the lower income

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group who are often left with minimal nursing care, expected to recover expeditiously to care for their newborns within a few hours following the operation, and who need to get back to their normal lives at home as soon as possible. It is not feasible to provide the majority of these mothers with more sophisticated methods of pain relief following Caesarean section. Subcutaneous pethidine has been used as the standard method of pain relief in the postnatal wards. However, they can cause sedation, drowsiness, nausea and vomiting and may affect the mother's ability and desire to breastfeed.

Breastfeeding is now encouraged worldwide and UMMC is in the process of becoming a baby-friendly hospital with 100% of mothers breastfeeding in the postnatal wards. It is therefore becoming even more important that inadequate pain relief or excessive sedation, nausea and vomiting does not become a barrier to these breastfeeding mothers. It is our observation that most mothers prefer oral analgesia that does not cause any drowsiness, sedation or nausea and vomiting. They are often willing to put up with some mild discomfort in exchange for alertness and mobility in order to care for their newborn. A few studies have shown that oral medications such as paracetamol, aspirin, morphine and ibuprofen, either on its own or as a combination, can be used either individually or in combination to provide effective analgesic therapy for women following Caesarean section (1-3). However, none of these studies compared the oral analgesia to the traditional regimen of parenteral opiods. In this prospective, randomized control trial we aimed to evaluate the efficacy of oral diclofenac, 75 mg twice daily, as the postCaesarean analgesia and compare it to subcutaneous pethidine, 1 mg/kg, every 8 hourly.

Materials and Methods

This study was approved by the UMMC ethics committee. After written consent was obtained, the study was conducted on 40 healthy women with a single fetus scheduled for elective Caesarean section under spinal anaesthesia. Exclusion criteria included those aged under 18 years and with known contraindications to the use of non steroidal anti-inflammatory drugs (NSAIDS) such as hypersensitivity, renal impairment, bleeding disorders, gastric problems and asthmatics.

The women were randomized into two groups—Group P and Group D—of 20 patients each by the drawing of shuffled coded envelopes. All patients fasted overnight and received premedication with 150 mg of oral ranitidine the night before the operation, another 150 mg the morning of the operation, and 30 ml of sodium citrate on arrival to the operating theatre. All received 0.5% heavy bupivacaine 2-2.5 ml. No other analgesia was given intraoperatively. All were monitored with a standard ECG, non-invasive blood pressure monitor and oximeter. On the basis of usual departmental guidelines, 20 ml of plain bupivacaine 0.5% was infiltrated locally by the obstetrician and 50 mg of diclofenac suppository was administered rectally to all patients immediately after surgery, while still on the operating table.

Women in Group P received subcutaneous pethidine 1 mg/kg before they were discharged from the recovery room. They continued to receive 1 mg/kg of pethidine subcutaneously with 10 mg of metoclopromide intramuscularly every 8 hours in the postnatal ward for three days. Women in Group D received oral diclofenac sodium 75 mg twice daily. The first dose of the oral diclofenac was given on the evening of the operation day (Day 1 p.m.).

Each woman was made aware that a dose of pethidine (1 mg/kg subcutaneously 3 hourly PRN) was available on request should the existing regular pain regimen did not provide adequate pain relief. Patients indicated their Visual Analogue Score (VAS) for pain at rest, nausea and vomiting and patient satisfaction twice a day, in the morning and evening, from the first to the third evening of the operation (a total of five recordings per patient), prior to receiving the oral diclofenac or subcutaneous pethidine. VAS were assessed by measurement on a 100-mm visual analogue scale ranging from zero for "no pain" and "no nausea" to 100 for "the worst pain imaginable", and "severe, intractable vomiting". VAS for patient satisfaction was evaluated using the same scale but ranging from 100 for "very satisfactory" to zero for "not satisfactory at all".

Patients were asked to slide a mark along a scale that indicated the level of pain, nausea and vomiting and satisfaction. The level of sedation was evaluated once a day in the afternoon by the same independent observer who was blinded to the analgesia received, using a

scale of 0 to 3 (0: awake, 1: somnolent, but responsive to verbal stimuli, 2: responsive to touch, and 3: deeply asleep).

The total amount and number of times when pethidine was requested and given was recorded.

Using Atlman's nomogram (4), it was estimated that a sample size of 40 patients would detect a 30% difference in the satisfaction score with 80% power and type I error of 0.05. Data analysis was performed with the Statistical Package for Social Sciences (SPSS) version 10.0 software. Data is presented as mean (SD) or median (25th, 75th percentile). VAS pain, nausea and vomiting, and satisfaction scores were analyzed using an analysis of variance (ANOVA) for repeated measurements and independent sample *t test*. The sedation score was analyzed using the Mann-Whitney U test. A *p* value of less than 0.05 was considered statistically significant.

Results

Forty patients were enrolled in the study: 20 in Group P and 20 in Group D. One patient from Group D was discharged on the third morning of the operation and did not complete the last section of the evaluation (Day 3 p.m.), but her other data was included in the analysis. Age, weight and parity were similar in the two groups (Table 1). There was no significant difference between the two groups in the mean VAS pain score (Figure 1) and the mean VAS nausea and vomiting score for all three days following the Caesarean section.

Table 1: *Demographic Data.*

	Group P	Group D	P Value
Age (years)	30.4 (4.4)	31.4 (5.6)	NS
Parity	20 (1.00 , 2.75)	2.5 (1.25, 3.75)	NS
Weight (kg)	68.6 (6.7)	68.2 (6.9)	NS

Values are means (SD)

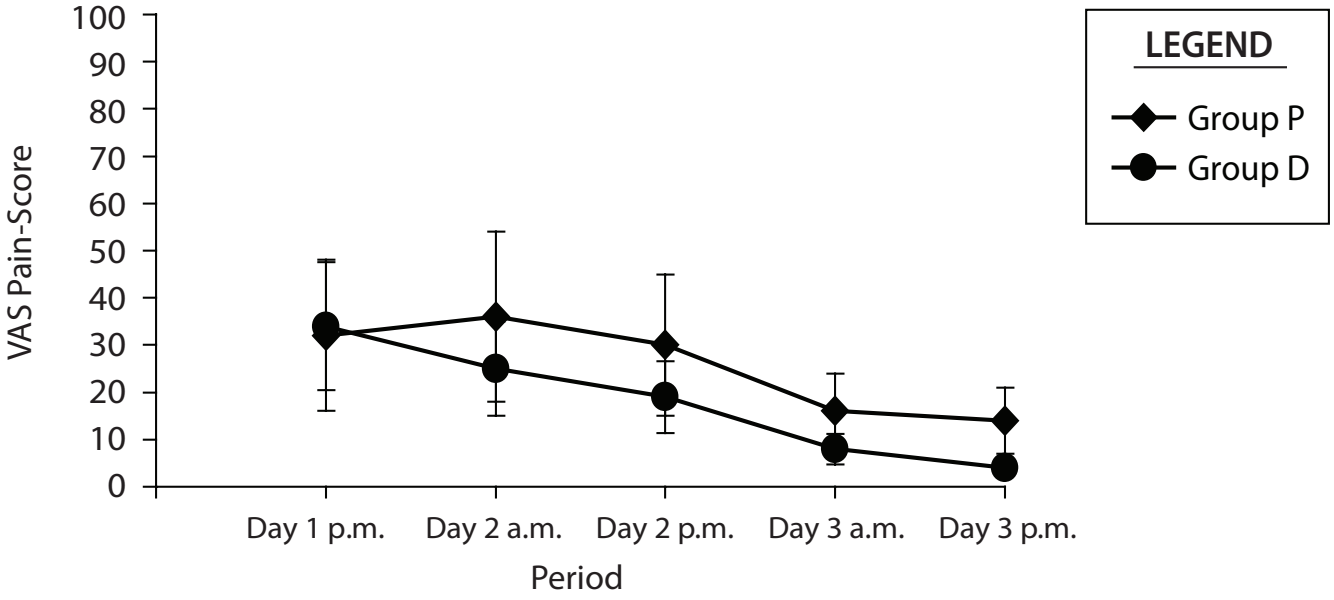
NS: not significant

Table 2: *Median Sedation Score (25th, 75th percentile) in Group P and Group D on 3 days Following Surgery.*

	Group P	Group D	P Value
Day 1	2 (2, 2)	0 (0, 2)	0.000
Day 2	1 (1, 2)	0 (0, 0)	0.000
Day 3	0 (0, 1)	0 (0, 0)	0.024

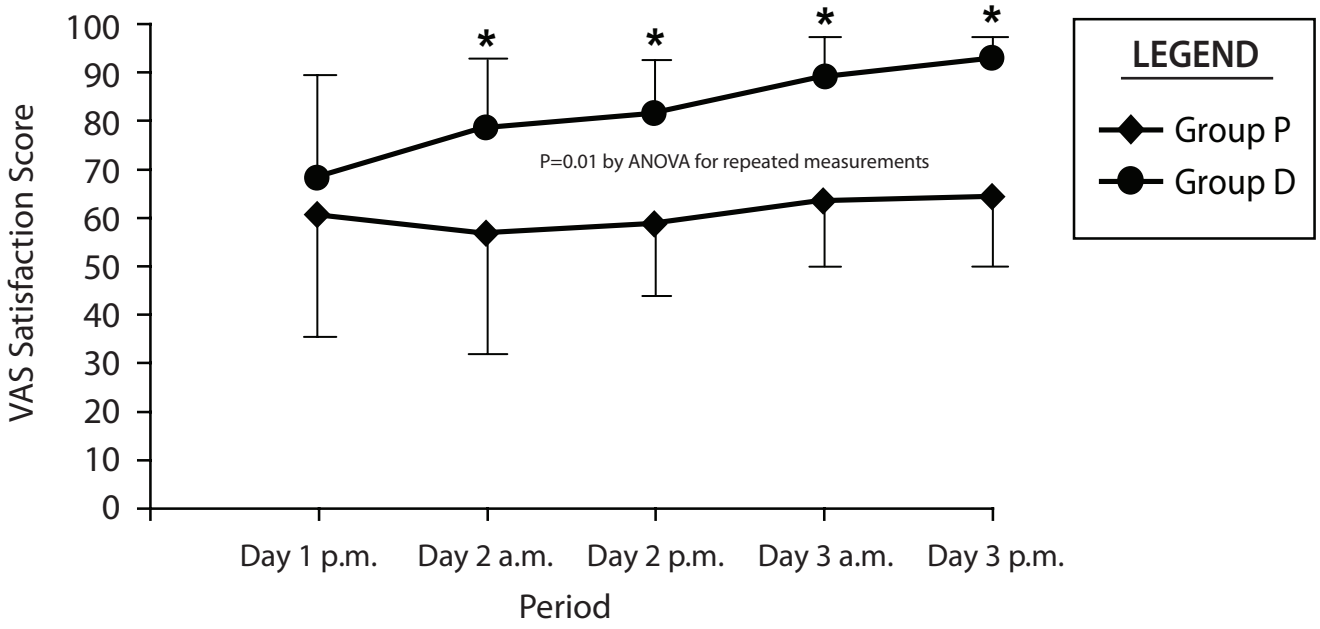
by Mann-Whitney U test

Only two women in Group P reported mild nausea with a score of 10 and 25 respectively. Women in Group P were significantly more sedated than those in Group D (Table 2) on all three days following surgery. The satisfaction score was not significantly



Not significantly different by ANOVA for repeated measurements

Figure 1: *Mean (SD) VAS pain score*



* P < 0.01 by independent sample t test

Figure 2: *Mean (SD) VAS satisfaction score*

different in both groups on the first day but it became significantly higher in Group D on Day 2 and Day 3 of surgery (Figure 2). Twelve patients (60%) from Group P had refused one or more doses of subcutaneous pethidine. Twelve patients (60%) requested for rescue subcutaneous pethidine in Group D and none of the patients in Group P requested for any rescue medicine. Out of these twelve patients, nine requested for it once and three requested for it twice, all on Day 1 of surgery.

Discussion

Diclofenac is a benzene-acetic acid derivative that works like other NSAIDS by inhibiting the cyclo-oxygenase isoforms to mediate the body's production of the prostaglandins implicated in pain and inflammation. A central anti-nociceptive effect has also been postulated (5-6). It has been widely used as part of the multimodal pain therapy for postsurgical analgesia. Several studies have shown that diclofenac suppository is opioid-sparing, reducing the opiod consumption between 35-40%, following Caesarean section (7-10). It has also been shown to reduce the PCEA requirement (11). Our study showed that while the sole use of oral diclofenac may not be adequate for analgesia on the first postoperative day when administered at regular interval, it may be used as the sole analgesia on the second and third day following Caesarean section.

Ideal pain treatment following Caesarean section should guarantee the mothers' comfort, avoid side effects, allow for early ambulation and optimal interaction between the mother and her baby. Such a perfect technique of analgesia is not yet available. The traditional and most widely used method of parenteral opiods as well as the newer technologies such as patient-controlled analgesia, continuous epidural analgesia, patient-controlled epidural analgesia and intrathecal administration of various analgesics fall short of being the ideal pain treatment.

Oral analgesia is a relatively uncommon and underreported mode of postoperative pain therapy. Surgeons are reluctant to use oral analgesia immediately following abdominal surgery because of reduced gastrointestinal motility, decreased absorption of medications, nausea and vomiting and drowsiness from general anaesthesia. However, a Caesarean section is mainly done under regional anaesthesia and there is usually no handling of the intestine during the operation. Oral opiods have been used to treat post-Caesarean section pain, but, like parenteral opiods, it can cause excessive sedation (2,12). In a previous study, as many as twenty percent of the women treated with oral morphine chose to switch to another oral analgesic mainly because of complaints of sleepiness and drowsiness (2). On the contrary, our study and one previous study (3)

showed that oral non-narcotic drugs did not cause sedation while they provided adequate pain relief and high patient satisfaction when administered at fixed intervals.

In this study, the degree of pain was measured by using the 100-mm visual analog score. Work performed by Collins *et al* helped in the interpretation of VAS scores for pain (13). Their work suggests that patients with moderate pain (scored on a scale of none, slight, moderate, or severe) would score moderate pain on the VAS as >30mm (mean, 49 mm) and would score severe pain starting approximately 54 mm (mean, 75 mm). In our study, the VAS pain score was not significantly different in both groups. Most women experienced mild to moderate pain, implying that both diclofenac and pethidine provide equally good pain relief.

Neither oral diclofenac nor subcutaneous pethedine alone was likely to abolish post-Caesarean section pain totally. However, despite experiencing a similar level of pain, the women in the diclofenac group expressed higher overall satisfaction. Two factors may explain this finding:

1. these women were much less sedated than those in the pethidine group and thus felt more able to care for their newborns, which increased their level of satisfaction. This is reflected by the high number of women in the pethidine group (60%) who refused one or more doses of subcutaneous pethidine, citing drowsiness as unpleasant and undesirable, and

2. Diclofenac was shown to increase plasma concentration of endorphin and thus may improve patients' sense of well being (14).

Patient satisfaction is an essential component of quality of care. However, pain control may be only one of the variables affecting patient satisfaction. The levels of satisfaction with pain control did not correlate with the actual pain level. We believe that assessment of patient satisfaction should be used as a mode to monitor the quality of care in hospital settings rather than concentrating on measuring the pain level alone.

Sixty percent of the women in the diclofenac group requested for subcutaneous pethidine as rescue medicine on the first day of surgery, implying somewhat inadequate pain relief with oral diclofenac alone. It is thought that pain after Caesarean section could be related to at least two components—a somatic one, which is the postoperative pain from the surgical wound; and a visceral one, due to uterine contraction. It is possible that the pain from the surgical wound was the predominant type of pain soon after the surgery and NSAIDs were less effective than opiods in relieving this somatic pain. This might explain the slightly lower satisfaction score on Day 1. By combining analgesic drugs with different modes of action, i.e. opiods with good effect on the somatic component and NSAIDS against the visceral pain, pain treatment after Caesarean section may become more efficacious.

Surprisingly, our study showed that mothers experiencing nausea and vomiting were not a significant finding in either group. This is contrary to the common belief that pethidine, an opiod, causes significant nausea and vomiting. Five factors may explain this finding. Firstly, the structure of pethidine is similar to atropine and local anaesthetics. Drugs with anticholinergic activity can reduce the incidence of nausea and vomiting. Also, the capacity of pethidine to produce nerve blockade could also contribute to a lower incidence of nausea and vomiting.

Secondly, pethidine was given via the subcutaneous route in our study. The maximal opiod plasma concentration could be lower with the subcutaneous route as compared to the intravenous group. Unlike the high "opiod peak level" produced by the intravenous route, the lower "opiod peak level" in the subcutaneous route might be insufficient to stimulate the chemoreceptor trigger zone, producing nausea and vomiting. Indeed a previous study has shown that patients in the pethidine group exhibited a lower incidence of nausea and vomiting than the patients in morphine group, and the incidence increased with increasing dose and with intravenous route (15).

Thirdly, we routinely gave metoclopramide together with pethidine, and this might have reduced the incidence of nausea and vomiting.

Fourthly, the reported incidence of nausea and vomiting may be lower in Asian women. Cepeda *et al* showed that black subjects had lower odds of nausea and vomiting than white subjects (15).

In humans, different races have distinctive pharmacokinetic and pharmacodynamic responses when exposed to medications or even cigarettes and alcohol. Existing knowledge about race differences in response to opiods is contradictory and requires further study.

Fifthly, the sample size of this study may be too small to detect the difference in the incidence and severity of nausea and vomiting between the two groups.

This study did not evaluate the effects of analgesia on the newborns in nusing mothers, but it is well known that morphine and other opiods enter breast milk rapidly with parallel concentration time curves for opiods in maternal plasma and breast milk. On the contrary, NSAIDs, being weak acids are not readily distributed to breast milk as they are readily ionized in the range of pH of breast milk. Therefore, they are not a concern for breastfeeding mothers. Neonates are affected negatively by opiods given to the mother (16). Depressed neurobehavourial scores due to accumulation of opiods and their major metabolites in colostrums and breast milk were found when opiods was given after partus using PCA technique (17). Such effects might also have negative impacts on the interaction between infant and mother as well as on the newborns' feeding behaviour during the first few days (18).

Our findings suggest that oral diclofenac is easily administered, is very cheap and provide satisfactory analgesia following Caesarean section with minimal side effects. It is superior to the traditional method of parenteral opiods. It is conceivable that newer techniques may provide more profound analgesia, this may be at the expense of increased side-effects, limitation of mobility and increased need for technology. Presumably this better analgesia provided by the more sophisticated technologies for postCaesarean pain treatment may offer even more satisfaction than oral diclofenac, but the expected small increase in satisfaction from a score which is already high makes the cost-effectiveness of these new technologies questionable.

Conclusion

In this study of elective Caesarean section under spinal anaesthesia, we found that the use of regular oral diclofenac 75 mg twice daily may not provide comparable pain relief on the first post-operative day, but it provided superior patient satisfaction as compared to the traditional method of subcutaneous pethidine 1 mg/kg. Although offering less than perfect analgesia, oral diclofenac provided comfort to the patients with few side effects and can be monitored on the ward. The use of oral diclofenac 150 mg daily did not seem to have any significant side effects in this group of healthy parturient. Therefore, it is still acceptable to use diclofenac alone as an alternative pain relief following Caesarean section, in view of the other benefits of a non-opioid analgesics and especially in places where newer techniques are neither possible nor practical. However this is only a pilot study, a bigger sample size would be needed to confirm the findings.

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