

# Pain relief after cesarean section: Oral methadone vs. intramuscular pethidine

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**Background:** Appropriate pain management is needed during the post-partum hospitalization period for preventing cesarean section (CS) related complications. Protocols of post-partum pain management should be planned based on the facilities of each center or region. The aim of current study was to compare the analgesic efficacy of oral methadone and intra muscular (IM) pethidine which the latter was routinely used in our center in post cesarean pain treatment. **Materials and Methods:** In this prospective double-blind clinical trial, women who were candidate for cesarean section were selected and randomized into two groups. All patients routinely received a single IM pethidine dose (50 mg) after CS in the recovery room. One group of patients received 0.7 mg/kg pethidine every 6 hour IM, and another group received 0.07 mg/kg oral methadone every 6 hour. Severity of pain assessed using visual analogue scale (VAS) score in 6, 12, 18 and 24 hour after surgery. **Results:** Pain severity in methadone group at 6, 12, 18 and 24 hour post operation were  $6.4 \pm 0.9$ ,  $3.4 \pm 0.8$ ,  $1.9 \pm 1.1$ ,  $0.5 \pm 0.5$  ( $p < 0.05$ ) and for patients in pethidine group were  $6.6 \pm 0.8$ ,  $3.4 \pm 0.9$ ,  $2.1 \pm 1.0$  and  $0.5 \pm 0.5$  ( $p < 0.05$ ), respectively (Mean  $\pm$  SD). Between groups differences in each follow up time were not statistically significant. There was no difference between groups in terms of complications and supplementary analgesic use. **Conclusion:** Considering the similar analgesic effects of methadone and pethidine, satisfaction of patients and nursing system with methadone use and the cost benefit of methadone, it can be recommended to use methadone for post operative pain relieving.

**Key words:** Cesarean Section, Methadone, Pethidine, Pain.

## INTRODUCTION

Postoperative pain management is considered as an important issue in clinical practice. Though different approaches have been introduced for proper pain relief, but these multimodal approaches are still inadequate and unsatisfactory in many patients.<sup>1</sup>

Cesarean section is one of the most common operations. Patients who undergo cesarean delivery should achieve more postoperative pain relief than other surgical patients because of different factors related to the operation complications as well as maternal and neonatal wellbeing.

Immobility due to inadequate pain control could result in thromboembolic events, inappropriate neonatal care and delay in discharge which consequently increase the cost of this common procedure both for patients and health care system.

Thus, it seems that postoperative pain management in this group of patients is more challenging than other surgical patients.<sup>2,3</sup>

Several studies have investigated different protocols of post-partum pain management in women undergoing cesarean section and some new

technologies of postoperative pain treatment have been also reported.<sup>4,5</sup> On the other hand, the protocols of post-partum pain management in this group of patients are not similar in different region and it seems that it would be planned regarding the facilities of each center or region.

Among pain relieving agents, opioids have an important role in postoperative analgesia which most commonly are administered systemically or neuraxially.<sup>6</sup> Moreover, recent studies have reported the beneficial effects of oral analgesics. However, oral analgesia not only could provide appropriate pain relief but also they have some advantages such as easy administration and low cost.<sup>7</sup> One of the opioids which could be used as oral analgesia is methadone. Though the use of methadone is not common due to its long plasma half-life, but evidences suggested that it could be used in hospitalized patients as the opioid of first choice because of its analgesic properties and marked safety profile.<sup>8</sup>

Providing an appropriate pain management is needed during the post-partum hospitalization period for preventing cesarean section related complications. Considering the fact that the protocols of post-partum pain

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management should be planned based on the facilities of each center or region, the aim of current research was to compare the analgesic efficacy of oral methadone and IM pethidine which the latter is routinely used in our center in post cesarean pain treatment.

## MATERIALS AND METHODS

In this prospective double-blind clinical trial, primiparous pregnant women who were candidate for elective cesarean section and referred to Shahid Beheshti Hospital in Isfahan during February and March 2009 were enrolled. The protocol was approved by the Institutional Review Board and Medical Ethics Committee of Isfahan University of Medical Sciences (Research project number 386356). Written consent was obtained from the parents of patients.

Non addict women with spinal anesthesia during cesarean section without history of surgery and chronic disease and with American Society of Anesthesiologists (ASA) score of I and II were enrolled.<sup>9</sup> Demographic characteristics and variables related to cesarean section in methadone and pethidine groups such as age, weight, height, operation time, anesthesia time and hospitalization time were recorded.

The method of spinal anesthesia and cesarean section was similar in two groups. All patients received a single IM pethidine dose (50 mg) routinely after CS in recovery room. The patients were randomly divided into two groups using generated random digits by the Open EPI random program. Then, one group of patients received 0.7 mg/kg pethidine every 6 hour IM, and another group received 0.07 mg/kg methadone every 6 hour orally.<sup>10</sup> The drugs were prepared and coded by Vice-Chancellery for Treatment and brought to hospitals (Blinding). Nurses administrated the drugs according to their randomized number. The pain score and nausea questionnaire was completed by interns. None of the nurses and interns was aware of the differences in treatments.

In cases of requesting additional analgesia, diclofenac suppositories (100 mg) were administrated if visual analog

scale (VAS) > 3 and its consumption was recorded for each patients. The consumption of metoclopramide was recorded too. Metoclopramide was administrated at VAS for nausea > 5-6 with a dose of 0.1 mg/kg.

Severity of pain and nausea assessed using VAS at 6, 12, 18 and 24 hour after surgery. All women were trained for recording their pain and nausea severity by this scale. Complications of the administrated drugs including nausea, respiratory depression, constipation, urinary retention, tachycardia and pruritus were recorded in each groups of women using questionnaire. Patients and nurses satisfaction about rout of administration was also recorded using a questionnaire.

Neonates in two groups were followed up for 72 hours in hospital regarding poor feeding, distress and any other abnormal sign and symptoms reported by nurses and the intern. The vital signs were recorded every 4 hours by nurses.

Between groups comparisons for quantitative variables were done using Student's t-test when distribution was normal, and Mann-Whitney test if distribution was not normal. For analyzing qualitative variables, chi-square or Fisher exact test were used. SPSS software ver. 15 (Chicago, Illinois, USA) was used for Statistical analysis.

## RESULTS

No In this study, 102 pregnant women was recruited and randomized into two groups (pethidine and methadone, 51 subjects in each group). Demographic characteristics and variables related to cesarean section in two groups are presented in table 1. ASA classification, post operative complications, vomiting and the patients and nurses satisfaction about route administration in two groups are presented in table 2. VAS for pain and nausea, as well as findings about antiemetic and analgesic consumption are presented in table 3. No complication was reported in neonates of two groups during the 72 hours of follow-up period.

**Table 1. Demographic characteristics and variables related to cesarean section in methadone and pethidine groups**

	Methadone group (Mean ± SD)	Pethidine group (Mean ± SD)	P-value
Age(yr)	28.4 ± 4.3	27.3 ± 4.7	0.2
Height(cm)	161.4 ± 6.8	161.0 ± 8.1	0.7
Weight(kg)	75.8 ± 8.0	77.5 ± 6.9	0.2
Operation time(min)	35.9 ± 4.3	36.5 ± 4.5	0.4
Anesthesia time(min)	39.8 ± 3.0	39.5 ± 4.5	0.4
Hospitalization time(days)	2.86 ± 0.57	2.96 ± 0.6	0.4

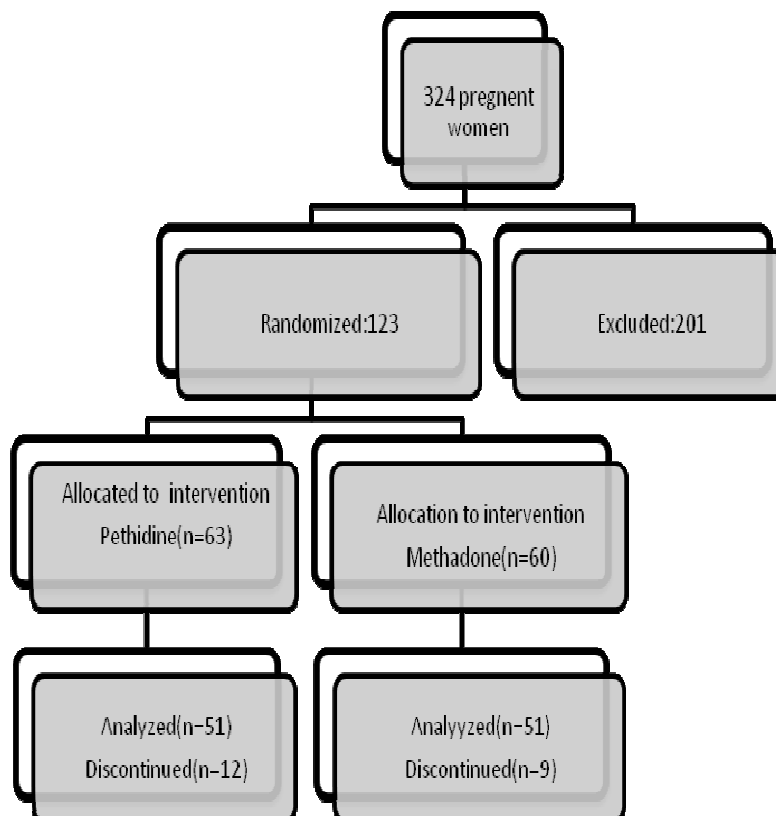


Figure 1. Clinical trial profile

Table 2. American Society of Anesthesiologists (ASA) score classification, post operative complications and the patients and nurses satisfaction about route administration in methadone and pethidine groups after cesarean section

		Methadone group n(%)	Pethidine group n(%)	P-value
ASA	Class I	47(92)	49(96)	0.4
	Class II	4(8)	2(4)	
Complications	Pruritus	1(2)	0(0)	0.317
	Urinary retention	20(39)	27(53)	0.166
	Constipation	29(57)	39(75)	0.037
	Tachycardia	3(6)	3(6)	1.00
Severity of nausea after 6 hours	Mild	28(55)	21(41)	0.167
	Moderate	21(41)	27(53)	
	Severe	2(4)	3(6)	
Severity of nausea after 12 hours	Mild	42(82)	36(70)	0.185
	Moderate	6(12)	11(22)	
	Severe	3(6)	4(8)	
Severity of nausea after 18 hours	Mild	47(92)	47(92)	1.00
	Moderate	4(8)	4(8)	
	Severe	0(0)	0(0)	
Severity of nausea after 24 hours	Mild	36(70)	9(18)	0.749
	Moderate	9(18)	6(12)	
	Severe	6(12)	36(70)	
Patients satisfaction	Yes	42(86)	41(80)	0.428
	No	7(14)	10(20)	
Nurses' satisfaction	Yes	38(74)	29(57)	0.062
	No	13(26)	22(43)	

**Table 3. Visual analogue scale for pain and nausea, analgesic and metoclopramide consumption in methadone and pethidine groups after cesarean section**

	Hours after cesarean section	Methadone group Mean $\pm$ SD	Pethidine group Mean $\pm$ SD	P-value
VAS (pain)	6 hours	6.4 $\pm$ 0.9	6.6 $\pm$ 0.8	0.413
	12 hours	3.4 $\pm$ 0.8	3.4 $\pm$ 0.9	0.643
	18 hours	1.9 $\pm$ 1.1	2.1 $\pm$ 1.0	0.249
	24 hours	0.5 $\pm$ 0.5	0.5 $\pm$ 0.5	0.557
Analgesic consumption	6 hours	0.3 $\pm$ 0.5	0.3 $\pm$ 0.5	0.678
	12 hours	0.04 $\pm$ 0.2	0.06 $\pm$ 0.2	0.650
	18 hours	0	0	1.00
	24 hours	0	0	1.00
	Total (24 hours)	0.5 $\pm$ 0.5	0.5 $\pm$ 0.6	0.392
VAS (nausea)	6 hours	0.3 $\pm$ 0.6	0.3 $\pm$ 0.7	0.649
	12 hours	0.2 $\pm$ 0.7	0.3 $\pm$ 0.8	0.516
	18 hours	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	1.00
	24 hours	0.6 $\pm$ 0.8	0.5 $\pm$ 0.8	0.908
Metoclopramide consumption	6 hours	0.06 $\pm$ 0.2	0.1 $\pm$ 0.3	0.466
	12 hours	0.04 $\pm$ 0.2	0.08 $\pm$ 0.3	0.405
	18 hours	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	1.00
	24 hours	0.2 $\pm$ 0.4	0.2 $\pm$ 0.4	0.653

VAS: Visual analogue scale

## DISCUSSION

Inappropriate postoperative pain control in women undergoing cesarean section can significantly affect on the well being of both mothers and newborns during postpartum period. It could result in respiratory, dietary intake and ambulation impairment which consequently lead to complications such as thromboembolism, ileus, atelectasis, and pneumonia. Moreover, it could result in normal development impairment in neonates due to affecting their feeding.<sup>11</sup> In accordance with advances in the understanding of the pain pathophysiology and improvement of mechanism-based pain relief approaches, different protocols for pain managements was investigated. In this study, we evaluated the two different methods of opioid administration, oral methadone and IM pethidine, in post cesarean pain relief. Our findings indicated that both of them have similar effect in this regard with non significant differences in related complications.

As mentioned, the use of oral opioids for pain management among postpartum patients is increasing in spite of their limitations such as slow gastric emptying after lower abdominal surgery and/or postoperative nausea and vomiting. In our study, all patients received a single IM pethidine dose (50 mg) after CS in recovery room, so we have not reported any of GI complications. Jakobi et al. reported the satisfactory pain relief effect of oral analgesia in post cesarean section pain and the

advantages of oral analgesia such as easy administration and less costly alternative.<sup>12</sup>

Though short-acting oral opioids are the first choice, but we study the effect of methadone, a long acting opioid. Methadone has long-acting nature (15-60 hours) and highly variable clearance rate in comparison with pethidine (2-6 hours) which considered as one of its limitations for pain management in this group of patients especially for neonates.<sup>13</sup>

Although pethidine is considered as an effective analgesic for treating acute pain, but its use is limited due to its relatively long-acting behavioral and neurological effects in the newborn and its slow elimination. Previous studies indicated that it could delay breastfeeding and disturb the mother-infant interaction. It has negative effect on the suckling infant which limit its routine administration in this context.<sup>14</sup>

The use of methadone in pain management has increased rapidly over the past decade and there are controversial reports regarding the use of methadone for pain relief. Trafton et al. in USA reported that considering the special properties of methadone and its better clinical outcomes, it could be used for pain management by considering its related recommended precautionary prescribing and monitoring practices.<sup>8</sup> However, Terpening et al. recommended that it should not be used as first-choice drug for pain managements.<sup>15</sup>

In this study, no adverse effect was reported during the 72

hours follow-up period of neonates and their mothers after cesarean section. In terms of safety of using methadone for breast-feeding neonates after cesarean delivery, it was shown that methadone level in breast milk was very low, and therefore breastfeeding seems to be safe. Some studies indicated that methadone concentrations in breast milk were unrelated to maternal methadone dose.<sup>16-18</sup>

In this study the severity of pain in two studied groups reduced significantly during administration of two drugs and there were not significant differences between two groups. In addition, the patients requesting additional use of other analgesics (diclofenac) was not significantly different in the two groups.

Adverse effects of drugs and post operative complications were not significantly different in the two groups except for constipation which was higher in pethidine group. Regarding patients' and nurses satisfactions, though it was not significantly higher but it had a trend to be higher in methadone group specially for nurses.

In literature review, there was not similar study but there were studies which investigated the utility of methadone in this field. Beeby et al. compared the pain relief effect of methadone, morphine and bupivacaine epidural for post cesarean section pain and showed that methadone was the most effective agent with few side effects.<sup>19</sup> Richlin and colleagues compared the effect of methadone and morphine for postoperative pain treatment following lower abdominal surgery and indicated that IV methadone use for mentioned purpose is effective with low toxicity and side effects and the severity of pain was lower in methadone group evaluated by VAS.<sup>20</sup> Shir et al. studied the efficacy of orally and epidurally administrated methadone for severe pain and showed that more than 85% of patients reported adequate pain relief and those treated with oral methadone did not report any serious side effects.<sup>21</sup>

The limitation of our study was that we did not evaluate the post cesarean pain after 24 hours which would be helpful for more accurate results and we did not evaluated the neonates after 72 hours, although according to previous studies methadone use during breast feeding is safe.

In conclusion, considering the mentioned studies and similar analgesic effects of methadone and pethidine, and satisfaction of patients and nursing system for methadone use, in addition to cost benefit of methadone, it could be used as an appropriate pain relieving analgesia for postoperative pain treatment following cesarean section. But it seems that to achieve more conclusive results in this field and considering that recent approaches consisted of a balanced combination of nonopioids and opioid analgesics,<sup>22</sup> further studies should be planned for studying the use of oral methadone with a non-opioid analgesic agent in this regard.

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