Original Article

Evaluation of the analgesic effect of subcutaneous methadone after cesarean section

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Abstract

Background: Inadequate pain control has a significant role in maternal and neonatal health in early post-partum period which interferes with breastfeeding and has a negative influence on child normal growth. The aim of this study is evaluation of subcutaneous methadone effectiveness on post-operative pain control.

Materials and Methods: Double blind randomized prospective clinical trial involving 60 term pregnancy patients through 2008 to 2009 Undergo cesarean. Inclusion criteria: Prime gravid candidate of elective cesarean and spinal anesthesia class 1 or 2. Known case of drug allergy and methadone interaction, addiction, uncontrolled medical disease excluded. Case group injected 10 mg of subcutaneous methadone in the site of incision before final suture. Morphine was a pain reliever in follow up examination. Data include mean of pain, nausea and vomiting, MAP, etc., collected and analyzed by independent-*T* test and Man Whitney test.

Results: Although mean usage of morphine between groups was not significant statistically but the mean pain severity (P value < 0.05) and mean satisfactory (P value = 0.02) was statistically significant between groups. Other parameters were not statistically significant.

Conclusion: We suggest subcutaneous methadone as a safe pain reliever in post cesarean section patients.

Key Words: Cesarean, morphine, pain control, subcutaneous methadone

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INTRODUCTION

According to International association of pain definition, pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. It is also a defense mechanism to inform the body of the problem.

In the past few decades progress in knowledge of pathophysiology of pain has led to the new pain control methods based on these mechanisms.

Pain is the result of either direct or inflammation mediated stimulation of neural terminal ends.

Labor and delivery is a painful process. Delivery and surgical procedures result in peripheral pain receptors activation through tissue damage receptors (for examples: Such as A-mechano-thermal and c-polymodal fibers), and Chemical mediators released from tissue during surgery, signal pain through

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neural pathways. (For Examples: Mediators such as histamine, bradykinin, serotonin, hydroxitriptophan, *p* substance and prostaglandins).[1]

Body in response to pain will show some reflexes such as increased tonicity of skeletal muscles, increased oxygen consumption and lactic acidosis.[2]

These reflexes themselves result in increased heart rate and cardiac output through autonomic neural pathways.

Postoperative pain may result in some complications such as lung dysfunction due to restriction of lung expansion secondary to increased pain, cardiovascular complications, increased risk of cardiac ischemic events, increased risk of Deep Vein Thrombosis and pulmonary emboli due to immobilization, psychological complications such as nervousness and finally prolonged hospitalization.[1]

The effective relief of pain is of paramount important in all patients. Recent data show that ineffective pain control after surgery can delay rehabilitation and patient discharge up to four days.[2]

Uncontrolled pain may result in complications such as thromboemboli, ileus and pneumonia.

Cesarean is the most common surgery in America, so limiting cesarean surgery complications is of paramount important.[2]

Different methods and drugs have been used to control pain and research to define a pain relieving method with the least adverse effect is important.

Patient- control pain by intravenous, spinal or epidural pumps, local anesthetic methods, glucocorticoids, NSAIDS and cryoanalgesia are some of methods in use.

Studies showed opioids analgesic effect by peripheral nociceptors methadone stimulates spinal and CNS opioid receptors and change the pain response.[3]

Methadone is a synthetic opioid agonist with a prolonged half-time. it has been used since 1960 in treatment of opioid dependence,[4,5] but it is used in chronic pain control and is a strong pain reliever in patients with cancer.[5,6]

Methadone is the second line opioid in the treatment of patients suffering pain and is safe in those with long-time hospitalization.[7]

Also methadone is used in opioid-dependent pregnant women to decrease complications such as LBW and prematurity.[3]

Effectiveness of methadone in controlling acute or chronic pain either in the form of oral or epidural both in adults or children has been shown.[7]

Because of minimal transfer of methadone into human milk, breastfeeding is safe.[8]

Besides, as it has no active metabolite and because of its low price; methadone can be a good replacement for other pain relievers.[9]

Subcutaneous injection of methadone can make the same blood level of drug that IV infusion will. And there is no data that cachectic or hypertensive patients have problem in absorption of subcutaneous methadone.[10] For postoperative pain management for acute pain equianalgesic dose of methadone is 10 mg IV/IM route.[11]

Some studies have shown efficacy of subcutaneous methadone in relieving acute pain (Alberto University in Canada).

In subcutaneous route, the dose is lower and so price will be.[12]

Besides, risk of bacteremia and infection in subcutaneous route is less than IV route. Finally in patients unable to eat such as end-stage patients subcutaneous injection is suitable.[13]

Opioids in injecting form are strong and rapid acting analgesics. Morphine is one of the most common opioids used in post cesarean section patients.

Histamine release after morphine injection may cause flushing, tachycardia, hypotension, itching and bronchospasm.[14]

According to fewer contraindication of methadone compared to morphine and more prolonged half-time of methadone and less dose adjustment requirements[15] of it and because of lack of data about effectiveness of subcutaneous methadone in controlling post cesarean section pain, we decided to design this study.

MATERIALS AND METHODS

60 prime gravide who were cesarean section candidate in educational hospital of Shahid Beheshti in Isfahan medical university were selected through October 2008 to October 2009.

All had ASA class 1 or 2. After receiving consent form

from them we suit them in two groups, case and control accidentally.

Inclusion criteria

Prime gravid candidate of elective cesarean section surgery and class 1 or 2 undergo spinal anesthesia.

Exclusion criteria

1. History of drug sensitivity 2. Being drug dependent. 3. History of gastrointestinal disease. 4. Any uncontrolled disease. 5. Taking drugs in interaction with methadone: Amitriptyline, antihistamin, chloralhydrate, clomipramine, gluthetimide, methocarbamol, MAO inhibitors, nortriptyline, ascorbic acid, phenytoin, phosphate, rifampin, phenothiazine, cimetidine, protease inhibitors, diuretics, hydroxyzine, loperamide, naloxan, naltroxan, neuromuscular blocker stranquilizers, sedative hypnotics paregoric. 6. Operation time more than one hour after randomized 60 patient sampling, which divided to two equal groups of 30.

Before anesthesia induction, all patients received 500cc ringer lactate. Method of anesthesia was the same. Spinal anesthesia in 12-13 or 13-14 in sitting position with 25G needles with 2.5cc bupivacaine 5%, then patient changed to supine position with the bed tilted to left.

In case group 10 mg methadone (5cc) was injected to incision site before suturing it by gynecology resident; and control group had no incision site injection. Also she did not know about the drug. Nurses and other stuff involved in data collection did not know about group of patients, neither case, nor control.

In hours 0, 0.25, 0.5, 1, 2, 4, 6, 12, 18, 24 post operation, we evaluated mean pain, mean arterial pressure, frequency distribution of nausea and vomiting and drug complication and mean metoclopromide injected, mean heart rate and mean respiratory rate.

To estimate severity of pain we used VAS method by asking patient to show it in a 10 cm ruler. 0: no pain, 10: the most severe pain has ever experienced.

In estimating nausea and vomiting we used 0: nothing, 1: nausea and 2: vomiting. To treat vomiting we used 10 mg metoclopramide in IV form.

Mean recovery time was evaluated according to Modified Aldrete score criteria.[16] Sedation was estimated by 0: completeconscious 1: drowsiness 2: drowsiness but get awake easy 3: asleep but awake able 4: asleep and unawake able post operation evaluation of patients was done by a person who did not know about patients group. If patients suffered pain would call anesthesiologist and received 0.05 mg/kg bullous morphine to reach VAS 3.

Number of nausea and vomiting episodes in different times (0, 0.25, 0.5, 1, 2, 4, 6, 12, 18, 24 hours) evaluated and if it was sever 0.15 mg/kg metoclopromide was injected.

Drug complications such as headache, nausea, vomiting, itching, urinary retention, hypotension and decreased respiratory drive were evaluated. At time 24 hrs patient opinion about quality of pain relieving was asked and registered as excellent, very good, good, weak, and bad.

If operation time was prolonged, or sever hemorrhage result in transfusion or hysterectomy occurred or if it was needed to use more dosage of anesthetic drugs or any sensitivity to drug happened the patient was excluded from study.

RESULTS

Mean age in year, was 24.7 ± 3.9 in first group, second one was 23.8 ± 4.2; Independent *T*-test did not show significant difference (*P* value = 0.43). Mean weight in Kg, in first group was 73.8 ± 9.7 and in second group was 70.96 ± 9.2 (*P* value = 0.266). Mean recovery time in minute, in first group was 53.8 ± 10.3 and in second group was 52.7 ± 10.4.

Independent *T*-test showed mean of age, weight, and recovery time had no significant statistically difference (*P* value > 0.05) [Table 1].

Independent *T*-test showed significant difference in VAS in 0, 15 min, 30 min, 4 hrs and 24 hrs after operation between groups. In the other times there

Table 1: Mean of age, weight, and recovery time

Mean	First group	Second group	*P* value
Age	24.7±3.9	23.8±4.2	0.431
Weight	73.8±9.7	70.9±9.2	0.266
Recovery time	53.8±10.3	52.7±10.4	0.686

Significant difference: *P*<0.05

Table 2: Mean pain score by VAS system

Time	First group		Second group		*P* value
	Mean	SD	Mean	SD	
0	0.4	1	1.3	0.9	0.001
15 min	0.9	1.2	2.6	1.5	0.000
30 min	2.7	2.07	3.9	2.1	0.033
1 hour	2.1	1.6	2.3	1.7	0.748
2 hour	1.7	1.5	2.24	1.66	0.192
4 hour	1.3	1.2	1.9	1.08	0.042
6 hour	2.2	1.9	2.7	1.8	0.313
12 hour	1.56	1.3	2.03	1.52	0.218
18 hour	1.9	1.5	1.7	1.03	0.609
24 hour	2.3	1.9	4.06	1.3	0.000

Significant difference: *P*<0.05

were no significant differences between VAS of groups (P value < 0.05) [Table 2].

Mean opioid usage (morphine) in first group was 7.2 mg and in the second group was 9 mg, which had no significant statistically difference.

Mean of nausea episodes in first group was 0.3 and in second group was 0.24, which had no significant statistically difference (P value = 0.44).

Mean of metoclopromide usage in first group was 0.3 and in second group was 0.24, which had no significant statistically difference (P value = 0.44).

Mann-Whitney test showed there is no statistically difference in mean of sedation score between groups (sig >0.05) [Table 3].

ANOVA test showed no statistically difference between Mean of blood pressure groups (P value > 0.05).

ANOVA test showed significant statistically difference between respiratory rates of groups in times 0 (P value = 0.007) and two hour (P value = 0.044), but in other times there were no difference.

ANOVA test showed significant statistically difference between heart rate of groups just in time 0 (P value = 0.000) [Table 4].

There was no drug side effect after operation.

Mann-Whitney test showed mean of satisfaction in first group had a significant statistically difference (P value = 0.02) [Table 5].

Table 3: Mean sedation score in times

Time	0	0.25	0.5	1	2	4	6	12	18	24
First group	0	0.2	0.2	0	0	0	0.06	0	0	0
Second group	0.03	0.2	0.06	0	0	0	0	0	0	0
P-value	0.309	0.787	0.145	1	1	1	0.161	1	1	1

Significant difference: *P*<0.05

Frequency distribution of needle insertion site in first group were 0 (0%) in L_2-L_3, 23 (76.7%) in L_3-L_4, 7 (23.3%) in L_4-L_5 and in the second group were 2 (6.66%) in L_2-L_3, 15 (50%) in L_3-L_4, 13 (53.44%) in L_4-L_5.

Chi-square test showed frequency distribution of needle insertion had no significant statistically difference (P value = 0.09).

DISCUSSION

Methadone has no active metabolite and it should absorb well either oral or rectal. It has low price and a long half-life. Because of its long half-life, pain control was superior in patients taking methadone and morphine compared to patients taking morphine.

There is large variation interindividually in the methadone pharmacokinetics. It has a rapid and extrusive distribution phase (half-life 2-3 hrs) followed by a slow elimination phase (beta half-life 15-60 hrs).

Mercadante *et al*., in a prospective study compared effect of methadone and morphine in patients with cancer. 20 patients received methadone orally and 20 patients received sustained release morphine. Patients were taking drug 2-3 times per day as need. Pain control and side effects were th e same in two groups. In patients receiving methadone, more stable analgesia overtime was seen.[17]

In our study there was no significant difference statistically in mean morphine consumption, but mean pain severity was higher in group treated with morphine alone. In other word, in patients treated with morphine and methadone pain control was better. There was no significant difference in mean episodes of nausea, mean metoclopramide consumption frequency, mean sedation score and mean arterial pressure statistically.

Subcutaneous rout of methadone taking is valuable but there are some reports of local skin reactions, such as swelling and erythem following its administration.

Table 4: Mean of blood pressure respiratory rates and heart rate in times after operation

Time	0	0.25	0.5	1	2	4	6	12	18	24
First group BP	85.66	85.72	85.33	81.72	82.38	83.55	81.22	79.66	80.05	81.11
Second group BP	85.71	87.79	84.82	83.92	84.10	82.20	81.96	80.53	80.95	82.67
P value between groups	0.979	0.241	0.707	0.085	0.234	0.369	0.644	0.587	0.552	0.272
First group RR	21.36	21.30	20.66	20.40	20.06	20.53	19.93	19.76	19.86	20.00
Second group RR	19.90	21.03	20.71	20.64	20.89	20.78	20.07	19.71	19.71	20.00
P value between groups	0.007	0.585	0.909	0.561	0.044	0.543	0.721	0.889	0.724	1
First group HR	92	88.23	88.1	86.7	86.56	84.53	85.63	86.00	84.33	84.40
Second group HR	83.9	85.35	84.82	85.10	84.46	84.7	84.50	84.7	83.64	83.75
P value between groups	0.000	0.106	0.074	0.318	0.166	0.864	0.364	0.741	0.642	0.590

Significant difference: *P*<0.05

Table 5: Mean of satisfaction after operation

Satisfactory	First group (%)	Second group (%)
Good	0	6.66
Very good	53.3	70
Excellent	46.7	23.3

These side effects are preventable by changing the site of injection and co-administration of dexamethason or hyaloronidase.

In a case series study methadone was used successfully by using dexamethasone infusion and rotating its injection site.[18]

In our study there was just one injection and there was no need to rotate injection site.

In all together in our study mean satisfaction was higher in group receiving methadone and morphine vs. those receiving morphine alone.

In Yoram Shir study on 3954 patients with severe pain, methadone was used in oral form or by epidural route. There was no significant side effect in those received oral form and in those received methadone epidurally three cases of respiratory depression was reported that it was because of pump failure.

CONCLUSION

The result showed that methadone has a significant immune profile and can be used in hospitalized patients as an effective analgesia.[19]

Tolerance is lower in methadone compared to other opioid. On the other hand, some studies suggest that constipation occurs later in patients taking methadone compared to other opioids.[20]

According to unpredictable complications of morphine such as conjunctivitis, amblyopia, ocular pain, leucopenia and it's so many contraindications[15] it's so valuable that subcutaneous methadone can relief pain successfully and so we can use it instead of morphine. Regardless of its use in our study, we can use methadone in other situations such as in cancers and in especially interminably ill patients in which consciousness is not full and so oral route is difficult or it can be used instead of rectal rout which is aggressive.

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