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Effects of intrathecal and intravenous dexamethasone on complications associated with intrathecal morphine after cesarean section: A comparative study

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Abstract:

BACKGROUND: Pain and nausea and vomiting are of serious complications following the use of opiates after surgery, especially cesarean section. Control of postoperative complications is one of the necessities of quality promotion of health-care system. Medications with few side effects such as corticosteroids including dexamethasone can be an appropriate option. In addition, the route of administration can have a significant effect on the effectiveness of the drug. The aim of the present study was to compare the effects of intrathecal with intravenous dexamethasone in reducing the complications associated with intrathecal morphine after cesarean section.

MATERIALS AND METHODS: The study was a double-blind randomized controlled clinical trial and determined the effect of intrathecal and intravenous dexamethasone on the incidence and severity of complications of intrathecal morphine after cesarean section on 120 patients and its relationship with serious complications after surgery. Descriptive and analytical statistics were used to examine the characteristics of the case and control groups, and STATA SPSS software was used to compare the two groups.

RESULTS: There was no significant association between the two groups in terms of baseline characteristics. Pain score in the intrathecal injection group was lower than the intravenous injection group, with a statistically significant difference (P = 0.02). In addition, there was a significant association regarding to the incidence of nausea, vomiting, and itching between intrathecal and intravenous injection groups (P = 0.008).

CONCLUSION: Dexamethasone was effective to reduce opiate complications after cesarean section. Establishing a suitable association between dexamethasone half-life, efficacy, type of use, and time of use can result the best outcomes and promote patients' satisfaction in cesarean section.

Keywords:

Cesarean section, intrathecal dexamethasone, intrathecal morphine, intravenous dexamethasone, nausea pruritus, pain

Introduction

Cesarean section is one of most commonly performed operations all over the world. It has been increasingly popular with spinal anesthesia in the recent years. Currently, regional anesthesia is ongoing as a common anesthetic method in 80% of patients compared to general anesthesia in 20% of cases.[1,2] Spinal anesthesia in comparison to general anesthesia reduces the mortality associated with cesarean

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section by 16 times.[3] The most common causes that prolong the duration of recovery and morbidity in surgical patients are nausea and vomiting, pain, and inability of patient to tolerate oral feeding.[4-6] In fact, the most common postoperative complication is nausea and vomiting,[7,8] which occurs after the use of anesthetic or analgesic drugs.[9-12] Approximately 30% of patients experience nausea and 20% of them have vomiting after the operation.[7,8] Lack of management of nausea and vomiting following anesthesia leads to dehydration and electrolyte imbalances.[9-12] Epidural and intrathecal administration of opioids is very common in controlling postoperative pain.[13] Morphine is a derivative of opium used to relieve postoperative pain, especially those with severe pain. Complications associated with the use of this drug are nausea, vomiting, and itching.[14-17] Accordingly, preventive measures should be performed to control the complications.[14-16,18] One of the preventive interventions to decline postoperative complications of opioids is the use of corticosteroids, which can reduce postoperative pain, nausea, and vomiting.[4-6,19-24] The use of corticosteroid compounds prolongs the duration of anesthesia and analgesia in the peripheral nervous block.[22,24,25]

Some antiemetics are also used to reduce nausea and vomiting induced by intrathecal opioids.[26] Besides nausea and vomiting, itching is another adverse effect of spinal or epidural opioids, with an incidence rate of 60% for neuraxial opioids or 15%–18% due to epidural regional anesthetics or intravenous opioids. Itching is common, while the treatment is easy and is considered clinically less important.[16] Dexamethasone is one of the corticosteroids with anti-inflammatory, immunosuppressant, and antiemetic properties.[27] This inexpensive and available drug is used to control postoperative nausea and vomiting.[9-12,28,29] Dexamethasone has exhibited its antiemetic characteristics in many studies[30] by reducing prostaglandins as a potent stimulant for nausea and vomiting, as well as by decreasing the excretion of serotonin from the gastrointestinal tract.[4,19,23,30-35] In addition, dexamethasone can stimulate the secretion of endorphin, which can lead to happiness and a feeling of well-being in patients.[36]

It reduces the production of 5-hydroxytryptophan in the central nervous system, thereby exerting its anti-inflammatory and analgesic effects,[37] but remains unclear regarding its antiemetic mechanisms.[38] Studies have reported that the effects of this drug are equal to or better than 5-HT3 receptor antagonist[30,39] or approximately comparable to antiemetic drugs.[40] Much research is ongoing to reduce the use of opioids to avoid unintended side effects. In addition, intravenous and oral dexamethasone significantly reduces postoperative pain. Epidural and spinal steroids are used to reduce chronic pain.[33,41] In some studies, intrathecal dexamethasone prolonged the duration of sensory block and postoperative analgesia.[42-44]

Many studies have been conducted to reduce complications after cesarean section under regional anesthesia with opioids. Several studies administrated a single dose of dexamethasone, either intravenously or intrathecally, immediately before the operation to reduce complications, including nausea, vomiting, and pain in patients undergoing cesarean section in both epidural and spinal anesthesia. The present comparative study aimed to evaluate the effects of intravenous and intrathecal dexamethasone to reduce postoperative complications caused by intrathecal morphine.

Materials and Methods

Study design and setting

The present study was randomized, double-blind controlled clinical trial on patients referred to Imam Khomeini Hospital in Sari (Iran) from January 1 up to May 30, 2016, to determine the effect of intrathecal and intravenous dexamethasone on the incidence and severity of complications of intrathecal morphine after selective cesarean section.

Study participants and sampling

This study was conducted on 120 patients of Imam Khomeini Hospital in Sari (Iran), using $N= ([Z1-\alpha/2+z\beta]2\ s2)/(\mu1-\mu2)\ 2$ formula.

Data collection tool and technique and the research procedure

The patients who met the inclusion criteria were divided into two intervention groups of A and B using block randomization method. Prior to the operation, adequate explanations were provided to patients to properly indicate postoperative nausea and vomiting using the visual analog scale (VAS). After transferring patients to the operating room, 5 mL/kg of ringer lactate solution was infused for all patients. A standard monitoring (including measurement of noninvasive blood pressure, electrocardiography, and arterial oxygen saturation) was performed using a monitoring device (Saadat/Alborz B9). Then, spinal anesthesia was performed in a sitting position with 25-gauge Quincke spinal needle (Dr. Japanco. Ltd., China) in L3-L4 or L4-L5 space with 10 mg of Marcaine 0.5% (10 mg in 2 mL) and 0.2 mg of intrathecal morphine for the both groups.

The first group also received 8 mg of intrathecal dexamethasone injected in the same space (2 mL, Iran Hormone Co.). However, the second group received 8 mg of intravenous dexamethasone in addition to 2 mL of intrathecal distilled-water in the same space.

Immediately after spinal injection, the patients were placed in supine position and received oxygen at a rate of 5-–6 l/min by mask.

The intensity and incidence of nausea, vomiting, itching, and pain based on VAS were asked and recorded in recovery room after the operation and then at 1, 6, 12, and 24 h after discharge from recovery by a trained nurse or an anesthesiology resident who were unaware of the study protocol.

If nausea and vomiting VAS scores were >4, 4 mg of ondansetron was prescribed and recorded in a questionnaire. The primary outcome of the study was to compare the intensity and incidence of nausea and vomiting in patients, and the secondary outcome was to measure the intensity of itching and pain in patients based on VAS. At baseline, weight (kg) and height (cm) were measured and body mass index (BMI) was calculated by dividing the weight (kg) by height squared (m). This information was recorded in the relevant sheet, along with specifications such as age, educational level, duration of the operation and anesthesia, presence or absence of postoperative nausea and vomiting history, and total ondansetron dosage in 24 h after the operation.

The study time was performed in 8 postoperative time intervals, including recovery (T1), and 30 min (T2), 60 min (T3), 90 min (T4), 120 min (T5), 6 h (T6), 12 h (T7), and 24 h (T8) after the operation.

According to previous studies (Mahmoud Abdel-Aleem and Jhi-Joung Wang) and the difference in nausea and vomiting between intravenous dexamethasone and placebo groups (39%) and the difference in nausea and vomiting between the intrathecal dexamethasone and placebo groups (16%), as well as considering Type I error of 0.05 and test power of 80%, the sample size was calculated as 57 in each group. Finally, 60 patients were considered in each group considering a possible dropout.[22,24] Descriptive statistics were used to examine the characteristics of the case and control groups, such as frequency distribution, mean, and standard deviation, and for analytical statistics using STATA SPSS software to compare the two groups using Chi-square, Fisher's exact tests, and *t*-test. After collecting data with using descriptive statistics and using SPSS v16 statistical software, the frequency of variables was calculated with 95% confidence interval. In Comparison of primary and secondary Quantitative variables of the two groups, t-test and in the absence of normal distribution, Mann–Whitney test were used. Chi-square test or Fisher's exact test was used to compare nominal and ordinal qualitative variables between the two groups. Incidence of nausea and vomiting, itching, and pain was measured by general linear model. The time of evaluation was calculated based on the type of injection (intrathecal and intravenous) as a confounding factor.

Ethical consideration

An approval was obtained from the Ethics Committee of Mazandaran University of Medical Sciences with ethical code of IR. MAZUMS. REC.94-1753A. After explaining the research procedure, informed consent was obtained with RCT code of IRCT2.16112631095N1 from all patients. Totally, 120 patients were selected who were candidates for elective cesarean section.

Inclusion and exclusion criteria

Inclusion criteria were Class I and II American Society Anesthesiologists, willingness of the patient to participate in the study and signing an informed consent, undergoing for elective cesarean section, and age range between 18 and 35 years old. The exclusion criteria were unwillingness to participate in the study, smoking, height <150 cm, mental disorders, corticosteroid use, alcohol consumption and drug abuse, contraindication to receive regional anesthesia, allergy to drugs used in the study, allergy to drugs used in the study, diabetes, hypertension, receiving antiemetic medications 24 h prior to the operation, receiving antiemetic medications 24 h prior to the operation, and history of any other surgery.

Results

In this study, 120 candidates for cesarean section were studied, 60 of them received intravenous injection and 60 others received intrathecal injection of dexamethasone. The mean age of samples was 29.58 years. the mean surgical time was 66.93 min, and the mean education level in two groups was 43.5% ($P = 0.3$). There was no significant association between the two groups in terms of baseline characteristics. Only there were more obese participants in the intravenous injection group than the intrathecal injection group ($P < 0.001$) [Table 1].

The mean incidence rate of preoperative and postoperative nausea in the both groups was not significant in terms of time trend. Regardless of the study time, the incidence of nausea was lower in the intravenous injection group than the intrathecal injection, which was statistically significant ($P = 0.04$). The incidence trend of nausea was slowed down over time, but the incidence at the baseline was higher in the intrathecal group than the intravenous injection [Table 2]. This also applied to itching, so that the incidence rate of itching was different between the intravenous injection group and the intrathecal injection group, which was statistically significant ($P = 0.07$). The incidence rate of itching in both groups was insignificant compared to other factors and decreased over time [Table 3].

Table 1: Basic demographic and clinical characteristics of patients in both groups

	Group		*P*
	Intravenous (*n*=60), *n* (%)	Intrathecal (*n*=60), *n* (%)	
Age (year), mean (SD)	29.09 (5.51)	30.07 (5.1)	0.33
BMI			
Thin	0	0	<0.001
Normal	5 (8.5)	16 (28.6)	
Over weight	21 (35.6)	32 (57.1)	
Obese	33 (55.9)	8 (14.3)	
Education			
Low	0	1 (1.7)	0.3
Middle	31 (54.4)	25 (42.4)	
High	26 (45.6)	33 (55.9)	
Surgery time (min), mean (SD)	67.86 (22.82)	66 (20.64)	0.67
Anesthesia time (min), mean (SD)	82.77 (26.35)	80.28 (23.23)	0.73
History of nausea after surgery	1 (1.7)	5 (8.3)	0.21
History of pruritus after surgery	0	1 (1.7)	>0.99
Antiemetic drug use after surgery	10 (16.7)	6 (10)	0.28

SD=Standard deviation, BMI=Body mass index

Table 2: Mean (standard deviation) of nausea scores at T1–T8 follow-up times in both groups

score	Group	
	Intravenous (*n*=60)	Intrathecal (*n*=60)
T1	0.41 (0.81)	1.25 (1.83)
T2	0.53 (0.93)	0.73 (1.16)
T3	0.37 (0.74)	0.44 (0.83)
T4	0.08 (0.28)	0.36 (0.80)
T5	0.08 (0.34)	0.18 (0.47)
T6	0.08 (0.39)	0.04 (0.19)
T7	0.05 (0.22)	0.13 (0.58)
T8	0.00 (0.00)	0.02 (0.13)
F statistics (*P*)		
Time effect	1.57 (0.141)	
Group effect	4.19 (0.04)	
Interaction effect	2.77 (0.008)	

Table 3: Mean (standard deviation) of pruritus scores at T1-T8 follow-up times in both groups

score	Group	
	Intravenous (*n*=60)	Intrathecal (*n*=60)
T1	0.22 (0.70)	0.59 (1.29)
T2	0.40 (1.04)	0.46 (1.09)
T3	0.36 (0.931)	0.29 (1.04)
T4	0.16 (0.62)	0.21 (0.80)
T5	0.12 (0.46)	0.14 (0.48)
T6	0.09 (0.43)	0.18 (0.54)
T7	0.09 (0.39)	0.13 (0.38)
T8	0.05 (0.29)	0.11 (0.37)
F statistics		
Time effect	0.54 (0.81)	
Group effect	0.32 (0.57)	
Interaction effect	1.17 (0.32)	

Regardless of the time of pain evaluation, the incidence rate of pain was less in the intrathecal injection group compared to the intravenous injection group, which was statistically significant ($P = 0.02$). In addition, the process of pain incidence in the intravenous injection group was different from the intrathecal injection group [Table 4].

The present study showed that the pain incidence varied from T1 to T8, so that the postoperative pain intensity in the intrathecal injection group from T1 to T2 was higher than the intravenous injection group and then the pain level in the intravenous injection group was higher than the intrathecal injection group. The pain intensity between the two groups was the highest at T4 (1.37), with a low difference in the early postoperative period and T8 and the pain level reported to be the same in the middle of the study period [Table 4].

Discussion

The incidence of nausea and vomiting after receiving morphine in the intrathecal dexamethasone group was not significantly different from that of the intravenous dexamethasone group. Similarly, the study of Terrence *et al*. performed a systematic review to assess the efficacy of dexamethasone in reducing postoperative nausea, vomiting, pruritus, and enhancing postoperative analgesia in patients receiving neuraxial anesthesia with neuraxial morphine, and they found that dexamethasone reduced the incidence of postoperative nausea (relative risk, [RR] 95% confidence interval, [CI] 0.57 [0.45, 0.72]) and vomiting (RR [95% CI] 0.56 [0.43, 0.72]), Liu *et al*. examined 60 patients with major surgeries and showed that the use of dexamethasone reduced the incidence rate of nausea and vomiting from 63.3% in the control group to 20% in the case group.[4] A study in Italy also found that dexamethasone was able to reduce the incidence rate of nausea and vomiting after chemotherapy by 70%.[39] The antiemetic effect has also been studied for epidural dexamethasone showing success in controlling vomiting

Table 4: Mean (standard deviation) of pain scores at T1-T8 follow-up times in both groups

score	Group	
	Intravenous (*n*=60)	Intrathecal (*n*=60)
T1	0.75 (1.11)	1.17 (1.88)
T2	1.36 (1.57)	1.41 (1.69)
T3	2.69 (2.01)	1.39 (1.25)
T4	2.76 (2.04)	1.39 (1.37)
T5	2.25 (1.84)	1.67 (1.87)
T6	1.98 (2.26)	1.13 (1.18)
T7	1.91 (1.96)	1.17 (1.13)
T8	1.45 (1.36)	1.15 (0.96)
F statistics		
Time effect	4.04 (<0.001)	
Group effect	5.33 (0.02)	
Interaction effect	3.73 (<0.001)	

and nausea caused by morphine.[40] Comparing the antiemetic effect of dexamethasone, ondansetron, and the combination of these two drugs in patients receiving intracranial morphine for orthopedic surgeries showed that the dexamethasone has a significant effect on the prevention of morphine-induced vomiting.[33]

Banihashem *et al*. in 2011 showed that 8 mg of ondansetron and 8 mg of dexamethasone reduced the incidence of nausea and vomiting caused by intrathecal meperidine to a same extent.[41] In the study of Movaffagh *et al*., 8 mg of intravenous and intrathecal dexamethasone reduced the incidence rate of nausea and vomiting caused by epidural morphine in cesarean section.[42] Tzeng *et al*. also obtained a similar result to the above studies.[43] Several other studies also noted the effect of dexamethasone on the prevention of nausea and vomiting.[23,34,43,44] However, Nortcliffe *et al*. showed that dexamethasone was ineffective in preventing nausea and vomiting induced by intrathecal morphine,[44] consistent with the findings of Wu *et al*.[45] Coloma *et al*. studied 80 patients with anorectal surgery and found no significant reduction in the incidence rate of nausea and vomiting.[31]

In addition, many studies have introduced dexamethasone as an antiemetic drug effective on epidural morphine.[40] Wu *et al*. concluded that the dexamethasone alone was unsuccessful in controlling vomiting following intracranial injection of morphine.[30]

Besides nausea and vomiting, itching is one of the most common complications of intrathecal opiates, which should be monitored and controlled after use of morphine. The present study showed that the incidence of itching was also significantly decreased with intrathecal injection over a longer period and this rate was different from intravenous injection. While the effectiveness of dexamethasone has been proven, there is no study on the difference between intravenous injection and intrathecal injection. Szarvas *et al*. showed that intrathecal dexamethasone is effective in preventing itching induced by intrathecal morphine as ondansetron.[46] Banihashem *et al*. also reported the results similar to Szarvas *et al*.[41]

Postoperative pain is a complex physiologic reaction often reported as the worst postoperative complication by most patients.[14] Therefore, postoperative pain relief strategies are of great importance. Using corticosteroids has been reported in some studies. Dexamethasone is a potent anti-inflammatory corticosteroid that secretes endorphins and can be effective in healing postoperative pain.[4,31] Similarly, initial postoperative pain was higher in the present patients receiving intrathecal dexamethasone than those receiving intravenous dexamethasone. However, this trend was significantly reversed over time and within 24 h.

Coloma *et al*. in 2001 examined the effect of dexamethasone on pain of patients with anorectal surgery and concluded that the incidence rate of pain was not statistically significant between the case and control groups,[31] which could be due to the drugs used for induction and maintenance of anesthesia. Pervaiz Kazemi *et al*.,[47] Baxendale *et al*.,[22] and Rabery and Smith[7] reported the same result and showed that dexamethasone has analgesic and anti-inflammatory effects in patients undergoing anorectal surgeries.

Different studies have shown the effect of dexamethasone on pain relief, for example, dexamethasone also helps in relieving pain after oral surgery.[22,48]

According to numerous studies on the effectiveness of dexamethasone and the results of this study in patients undergoing cesarean section, it can be concluded that dexamethasone helps restore well-being through reducing postoperative itching, nausea, vomiting, and pain and inflammation.[9]

Limitation and recommendation

The study limitation was the effect of dexamethasone on morphine-induced urinary retention due to categorization of patients could not be performed from the beginning of surgery (due to the nature of surgery).

Conducting other studies to assess other affected variables, doing some studies in other surgeries (non cesarean section) and performing study with larger study population are suggestions for future studies.

Conclusion

To promote the quality of healthcare before, during, and after the operation, especially cesarean section,

it is necessary to provide favorable conditions. In the meantime, the importance of postoperative care and desirable hospitalization due to its close relationship with maternal satisfaction, reduction of temporary and permanent maternal disability, promotion of effective mother–child communication, continuation of breastfeeding, return to effective health, encouragement to continue the process of childbirth, reinforce of psychological dimension, effective communication between parents and children, promotion of effective communication between the health-care provider and the mother, hope for the proper care of the child by the mother, etc., is very important. Therefore, the use of effective drug management is more necessary because one of the priorities of treatment is to provide patient satisfaction in addition to maintain physical and mental health. We had some limitations, such as inaccessibility to soothing agents used in private hospitals, lack of comparisons of complications in primiparous and multiparous women, lack of data to compare dexamethasone with other single or combined injections, inadequate time to increase the sample size, and failure to study the effect of dexamethasone on urinary retention due to having a Foley catheter. The results of our studies and others suggest that taking corticosteroid anti-inflammatory drugs, like dexamethasone, might be advised to reduce postoperative nausea, vomiting, itching, and pain and complications associated with opiates. Given that dexamethasone has been used more than any other drug, its route of administration and effectiveness have been carefully analyzed, highlighting the need for examining the effect of dexamethasone on other patients in different surgical procedures and it is desirable to analyze the efficacy in different ages and in male and female gender to obtain more precise results.

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Conflicts of interest

There are no conflicts of interest.

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