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Original Article

The Effect of Subcutaneous Dexamethasone Added to Bupivacaine on Postcesarean Pain: A Randomized Controlled Trial

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Abstract

Background: Previous studies have shown a prolonged blockade of nerves using bupivacaine-dexamethasone microspheres. The goal of this study was to assess the effect of subcutaneous dexamethasone added to bupivacaine on post cesarean pain.

Methods: After randomization, 75 healthy parturients were allocated into three groups and received the following treatments: group A: bupivacaine 0.25% (20 ml, subcutaneously [s.c]) plus dexamethasone 16 mg (4 ml, s.c) plus normal saline (4 ml, intravenously [i.v]); group B: bupivacaine 0.25% (20 ml, s.c) plus dexamethasone 16 mg (4 ml, i.v) plus normal saline (4 ml, i.v); group C: bupivacaine 0.25% (20 ml, s.c) plus normal saline (4 ml, s.c) plus normal saline (4 ml, i.v). The visual analog scale (VAS), meperidine consumption, and time to first meperidine consumption were evaluated in the recovery room, 6, 12, 24, 48, and 72 hours postoperatively.

Results: The mean VAS in group A was less than groups B and C at 12, 24 , 48 and 72 hours after surgery (A< C< B respectively). The decrease in VAS was statistically significant between groups A, B and B, C (P=0.009 and P=0.015 respectively). The mean VAS in group A was significantly less than group C at 48 and 72 hours postoperatively (P=0.020 and P=0.024 respectively). Meperidine consumption was lower in group A compared with B and C groups, however it was not statistically significant (P=0.25 and P=0.11 respectively).

Conclusion: The addition of subcutaneous dexamethasone to bupivacaine prolonged the analgesia during 48-72 hours postoperatively. It may be an option for longer pain relief after cesarean section.
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Keywords ● Bupivacaine ● dexamethasone ● subcutaneous ● local anesthetics

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Introduction

Local anesthetics are widely used to provide post operative pain relief, but analgesia is rarely maintained for more than 4-8 hours with long-acting local anesthetics such as bupivacaine, ropivacaine, or levobupivacaine after incisional administration.[1] Various approaches have been tried to

prolong the local anesthetic action. Indwelling catheters are useful, particularly in the epidural space, but they are inconvenient to maintain in many other sites.[2] Alternative methods to prolong nerve block duration are under investigation.[3-5]

Different additives have been used to prolong regional blockade. Vasopressors can be used to constrict blood vessels and reduce vascular absorption of the local anesthetic. Clonidine has also been studied in combination with local anesthetics in axillary brachial plexus block.[6] Some studies have demonstrated the analgesic effect of systemic corticosteroids in combination with bupivacaine.[7,8] Dexamethasone is a high–potency, long-acting glucocorticoid with little mineral corticoid effect. It has been extensively used in the preoperative setting.[9,10]

Tissue injury-induced acute inflammation is known to play a significant role in the genesis of surgical pain. Dexamethasone should theoretically be beneficial in the management of acute surgical pain because of its potent anti-inflammatory effect.[11]

In the present study, we examined the effect of subcutaneous dexamethasone added to bupivacaine on the onset and duration of pain after cesarean section.

Patients and Methods

After obtaining the approval from the Ethics Committee of Isfahan University of Medical Sciences and obtaining informed consent, 75 women with ASA physical statuses I-II scheduled for elective cesarean section under general anesthesia were included in the study. The sample size was calculated at α error=0.05 with a power of 0.95 and d=0.8 (minimum difference of mean visual analogue score [VAS] between the groups) based on previous relevant clinical data.

We excluded patients with suspected or manifestations of bleeding disturbances, allergy to bupivacaine or dexamethasone, atopy, diabetes mellitus, liver or kidney diseases, abuse of drugs, and patients with pregnancy induced hypertension or pre-eclampsia.

A random-number table was used to generate a randomized schedule specifying the group to which each patient would be assigned upon entry into the trial. In the case of exclusion, the next patient was randomized per schedule.

Preoperative fluid therapy was based on 4.2.1 rule using ⅓-⅔ solution in all patients.[1]

In the operating room standard monitoring was applied (the lead II electrocardiography, pulse oximetry, non-invasive blood pressure monitor, expiratory gas analyzer). Anesthesia was induced with sodium thiopental (5 mg/kg) and succinylcholine (1.5 mg/kg) in all patients. Trachea was intubated with a cuffed tracheal tube. Anesthesia was maintained with halothane (0.5 MAC) and a mixture of oxygen (50%) in nitrous oxide (50%).

After the first twitch response in Train of Four monitoring of ulnar nerve, atracurium (0.2 mg/kg) injected for neuromuscular blocking. The patients' lungs ventilated with a tidal volume 10 ml/kg and respiratory rate was adjusted to give 38-45 mmHg end-tidal carbon dioxide.

After clamping the cord, fentanyl (1.5 µg/kg) was injected and followed by 3µg/kg/h infusion.[12]

At the time of skin closure, while still on the operating table, the patients were randomly allocated into one of the three groups. Each group consisted of 25 parturient. The patients received the following treatments: group A: bupivacaine 0.25% (20 ml, subcutaneously [s.c]) plus dexamethasone 16 mg (4 ml, s.c) plus normal saline (4 ml, intravenously [i.v]). The parturients in group B received bupivacaine 0.25% (20 ml, s.c) plus dexamethasone 16 mg (4 ml, i.v) plus normal saline (4 ml, i.v). And the parturients in group C received bupivacaine 0.25% (20 ml, s.c) plus normal saline (4 ml, s.c) plus normal saline (4 ml, i.v).

All the drugs were labeled with the randomization number of the parturients. Drug administration began at the time of skin closure. Subcutaneous drugs were infiltrated in the site of incision. After completion of surgery, neuromuscular blockade was reversed with atropine (0.02 mg/kg) and neostigmine (0.04 mg/kg) then the participants were extubated in awake state.

The patients and the staff involved in data collections were unaware of the group assignment. In case of emergency, the anesthesiologist who was responsible for the patient had access to the nature of the drugs administered to the patient. On arrival in the recovery room, when the patient was amenable to evaluation, pain intensity was assessed by VAS ranging from 0 (no pain) to 10 (worst pain imaginable) and then re-assessed at 6, 12, 24, 48, and 72 hours after recovery. If analgesia was considered inadequate at any stage, the anesthesiologist could give additional boluses of 50 mg meperidine until VAS was < 4.

Systolic and diastolic blood pressure, opioid consumption, and time to first opioid administration were measured at the same time. Statistical analysis was performed using SPSS software version 11 using ANOVA. Values for quantitative variables were reported as mean±SD (standard deviation), and for qualitative variables as count and percent. A value of $P<0.05$ was considered statistically significant.

Results

Seventy five patients completed the study. No patient was excluded from the study. Data did not differ significantly between the three groups concerning demographic and baseline hemodynamic status (table 1).

There was no significant difference in mean VAS at 6 h after surgery between the three groups (table 2). The mean VAS in group A was less than groups B and C at 12, 24, 48, and 72 hours after surgery but this decrease in VAS was statistically different between groups A and B and between groups B and C in above mentioned hours (P=0.009 and respectively P=0.015). Also, the mean VAS in group A was significantly less than group C at 48 and 72 hours after surgery (P=0.020 and P=0.024 respectively). The mean pain scores in group A was less than group C at 12 and 24 hours after surgery but it was not statistically significant (P=0.1).

There were significant differences for mean pain score at 48 and 72 hours between the three groups after surgery (P=0.02).

However, the mean meperidine consumption did not differ significantly between the three groups (table 2).

No significant difference in the time to first meperidine administration was found between the three groups (P=0.25). There was no difference in hemodynamic parameters at all the times after surgery between the three groups. (tables 3 and 4)

Table1: Patients' demographic data and baseline hemodynamic status before intervention

Variables	Group A (mean±SD, n=25)	Group B (mean±SD, n=25)	Group C (mean±SD, n=25)
Age (years)	26.2±4.55	28.26±5.66	28.12±5.5
Weight (kg)	68.82±10.18	65.96±7.95	65.04±7.17
Gestation (weeks)	37.2±2.5	37.6±2.1	37.3±2.2
Parity (number of nulliparous women)	9	10	9
SBP (mm Hg)	110.6±13.2	108.8±8.5	110.1±16.2
DBP (mm Hg)	68±7.07	64.2±5.03	65±6
HR(beat/min)	89±3.02	89.42±3.68	90.7±3.69
ASA I/II	15/10	14/11	15/10

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, ASA: American Society of Anesthesiologists physical status. Comparisons were made with ANOVA.

Table 2: Mean VAS in various periods after surgery, opioid consumption and time to first opioid administration

VAS	Group A (n=25)	Group B (n=25)	Group C (n=25)
at recovery time	5.21±3.47	5.35±2.8	5.15±3.02
6 hours	7.9±1.5	7.1±1.2	7.8±1.8
12 hours	5.2±1.8*	6.7±1.8 *#	5.6±2.1 #
24 hours	3.5±1.1 *	4.8±1.6 *#	3.7±1.1 #
48 hours	1.32±0.55 ···*	3±1.05 *#	2.08±0.86 ···#
72 hours	0.25±0.43 ···*	1.5±0.75*#	1±0.57 ···#
Meperidine consumption (mg)	37.2±17.2	47.7±24	51±27
Time to first opioid administration (h)	6.45±2.2	6.52±2.9	5.05±1.7

* P=0.009 in group A versus group B, ··· P=0.02 in group A versus group C, # P=0.015 in group B versus group C. Comparisons were made with ANOVA and data are presented as mean±SD.

Table 3: Mean systolic blood pressure (mm Hg)

Time	Group A (n=25)	Group B (n=25)	Group C (n=25)	P value
at recovery	108.6±9.5	105.8±9.8	103.0±16	0.32
6 h	112±8.16	112.3±7.1	109±14.2	0.59
12 h	112±7.0	113.4±7	109.2±5.7	0.56
24 h	112.6±7	113.07±7.79	110.6±8.69	0.46

Data are presented as mean±SD.

Table 4: Mean heart rate (beat/min)

Time	Group A (n=25)	Group B (n=25)	Group C (n=25)	P Value
at recovery	89±3.02	89.42±3.68	90.7±3.69	0.15
6 h	81.20±2.87	80.80±2.04	81.20±2.43	0.80
12 h	79.12±2.75	87.96±1.39	79.2±1.29	0.90
24 h	78.56±2.36	78.79±1.39	78.80±1.15	0.70

Data are presented as mean±SD.

Discussion

We performed a prospective, randomized study to compare the effect of subcutaneous dexamethasone added to bupivacaine on postoperative pain after elective cesarean section. Our data showed that mean pain score in group A was significantly less than in groups C and B at 12, 24, 48, and 72 hours after surgery.

Previous studies showed that the addition of corticosteroid microspheres to local anesthetics prolonged the duration of blockade of peripheral nerves.[2,13,14] In one study, addition of small amounts of dexamethasone to bupivacaine incorporated in microcapsules prolonged local analgesia compared with microcapsules with plane bupivacaine after subcutaneous administration in humans.[15] In another study, incorporation of dexamethasone into bupivacaine microspheres significantly prolonged intercostals nerve block in sheep.[2] Also, a prolonged percutaneous blockade of sciatic nerve in rat using bupivacaine dexamethasone microspheres was demonstrated.[13] It has been reported that the intercostals injection of dexamethasone- containing bupivacaine microcapsules produced a prolonged duration of anesthesia and analgesia.[14] Investigators believe that there is a causative relationship between the suppression of inflammation and the remarkable longer duration of analgesia.[2]

The mechanism of the analgesia induced by corticosteroids is not fully understood. This effect is suspected to be mediated by their anti-inflammatory or immune-suppressive effects.[16,17] The use of corticosteroids as an adjuvant to local anesthetic for peripheral nerve blocks has rarely been described, and its mechanism of action is not clearly understood. Corticosteroids cause skin vasoconstriction on topical application. The vasopressor effects of topical steroids are mediated by occupancy of classical glucocorticoid receptors rather than by non-specific pharmacological mechanism.[18,19]

According to the traditional theory of steroid action, steroids bind to intracellular receptors and modulate nuclear transcription.[20] Also, corticosteroids may have a local effect on the nerve and the dexamethasone effect may be related to this action.[21]

In the present study, mean pain score in group C was significantly less than group B at 12, 24, 48, and 72 hours after surgery (table 2). In one study, dexamethasone (8 mg, i.v) did not have any effect on postoperative analgesia in major orthopedic surgery.[22] Methyl prednisolone (125 mg) was shown to improve analgesia after lower limb orthopedic surgery.[23] Based on the theory of 5:1 glucocorticoid potency ratio,[9,10] this would be equivalent to 25mg dexamethasone. However, in our study, dexamethasone (16 mg i.v) in group B had no effect on relief of pain after surgery compared with group C.

In our study, the mean pain scores in group A was less than group C at 12 and 24 hours after surgery but it was not statistically significant at recovery time and at 6 h postoperatively. It may be resulted from the diminished effects of drugs on injured tissues.[11] Also, in several studies, it has been shown a prolonged relief of pain with delayed onset using dexamethasone.[9,10]

Our result showed a decreased postoperative meperidine consumption over 72 hours and prolonged time to first opioid administration in patients receiving subcutaneous dexamethasone (group A) compared with intravenous dexamethasone (group B) and group C. However, this effect was not statistically significant. The mechanisms behind the blockade-prolonging effect of glucocorticoids are mostly unknown, but possibly the inhibition of synthesis and/or release of various inflammatory mediators are involved.[15]

In one study on 50 patients undergoing elective hip arthroplasty under spinal anesthesia, dexamethasone (40 mg i.v) immediately before the surgery, did not have any significant effect on cumulative morphine consumption at any time.[24] Dexamethasone may increase sedation requirements through its central nervous system–stimulating side effects.[24] Insomnia and agitation are described as characteristic side effects of dexamethasone when used in the treatment of chemotherapy-induced emesis.[25] However, no sings of agitation were observed in our patients and there was no difference in adverse events such as nausea, vomiting, pruritus and hemodynamic parameters between the groups.

In a meta-analysis of 51 studies including more than 1900 patients receiving doses of 15-30 mg/kg methyl-prednisolone, no significant increases in the risk of side effects were found.[26]

In reviewing the literature, we could not find any clinical study demonstrating a significant increase in the incidence of serious adverse effects after single-dose glucocorticoid administration. The absence of evidence does not prove the absence of risk, though.

A limitation of our and other studies of single-dose steroid use is the lack of both strict follow-up methodology and statistical power to meaningfully assess the incidence of uncommon

adverse effects. We suggest another study with different or may be higher dose of intravenous dexamethasone to evaluate its efficacy on postoperative pain. Also, we diluted our drugs with normal saline that might reduce the efficacy of drugs compounds.

Conclusion

Although, the addition of subcutaneous dexamethasone to bupivacaine could not reduce pain intensity during 6 hours after cesarean section, it prolonged analgesia during 48-72 hours after operations.

Postoperative meperidine consumption in patients receiving subcutaneous dexamethasone was non-significantly less than the patients received intravenous dexamethasone and placebo group.

Conflict of Interest: None declared

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