Comparing the Analgesic Effects of Intrathecal Sufentanil plus Different Doses of Bupivacai in Painless Delivery

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ABSTRACT

Introduction: Painless delivery offers more calmness and collaboration during childbirth, and encourages pregnant women to have vaginal delivery We compared the combined effect of intrathecal sufentanil along with different doses of bupivacaine on the quality and duration of analgesia in painless delivery. Materials and Methods: This clinical trial targeted 40 women (36-40wk) during active labour phase. The subjects were assigned into two groups.and intrathecal injection consisted of sufentanil 5 µg + bupivacaine 1 mg; in the first group and , sufentanil 5µg + bupivacaine 2 mg.in the second group. Both groups were compared in terms of the quality and duration of analgesia, as well as the complications of intrathecal injection. Results: The demographic variables were the same in both groups. Analgesic duration was longer, though insignificant, in the second (bupivacaine 2mg) than first group. The mean pain score and the onset of analgesia were lower in the second group during all times of the study; the difference, however; was not significant There was not any statistically remarkable difference between the 1- and 5-minute Apgar scores, maternal sedation, nausea, vomiting, chills, maximum sensory level and pruritus of both groups. The mean fetal heart rate was lower, though clinically and statistically insignificant, in the high-dose bupivacaine group. Maternal sedation, maximum sensory level and Bromage score did not present any noticeable difference between the first and second groups. Conclusion: According to the results, the 2mg-bupivac group experienced a longer analgesic duration, lower mean pain score, shorter time to analgesia's onset of action and less complication compared with the 1mg-bupivac group; the difference, nevertheless, was statistically insignificant.

Key Words: *Bupivacaine; Painless Delivery; Spinal Anaesthesia.*

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INTRODUCTION

The process of childbirth is often associated with severe pain in pregnant women that may even mark the worst experience and fear of vaginal delivery [1]. The pain of childbirth is arguably the most severe pain most women will endure in their lifetime. Since pain relief in labor has always been surrounded with myths and controversies, providing effective and safe analgesia during labor have remained an ongoing challenge [2]. Painful delivery has important physiological effects on the mother, fetus and course of labour. Pain activates the sympathetic system and elevates plasma catecholamine levels. Subsequently, it results in tachycardia, hyperreflexia and maternal

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hypertension that in turn may reduce uterine blood flow [3].

Other postpartum pain-related complications include hyperventilation and psychological conditions like postpartum depression (PPD), posttraumatic stress disorder (PTSD), decreased placental perfusion, increased peripheral vascular resistance, elevated cardiac output, and high blood pressure (hypertension), which are efficiently tolerated by healthy pregnant women (ASA-I) while being problematic in those with underlying disorders [4].

Labour pain management can be carried out through various pharmacological and non-pharmacological techniques. None of the latter could meritoriously relieve the labour pain [5]. Non-pharmacological techniques of labour pain management are not serious in postpartum complications with their interventional effects being limitedly known [6]. Such neuraxial techniques as epidural, spinal, combined spinal-epidural (CSE) have been the most effective methods of labour pain relief. Neuraxial analgesia typically makes the use of local anaesthetics in solitary or in combination with opioids. Some auxiliary drugs, clonidine or neostigmine include the downturn of the required dosage of local anaesthetics or opioids for analgesia. Nevertheless, these auxiliaries are not any longer mainly used in labor analgesia in clinical practices. Neuraxial analgesia does not increase the risk of caesarean section, but may intensify the risk of assisted delivery [4].

As the most effective ways of labour pain relief, neuraxial techniques have aroused uppermost maternal satisfaction. Neuraxial techniques are advantageous in patients' consciousness -unaffected by drowsiness, decreased maternal catecholamine concentration, avoided excessive ventilation, high collaborative and active role during childbirth and, ultimately, enhanced and predictable pain relief that is highly preferred to the observed pain relief induced by all the other techniques [7].

Comparing the neuraxial analgesia techniques, in CSE, a spinal needle is advanced through the epidural needle to pass the dura and opioids with or without local anesthetics which are injected into the spinal fluid, and then the spinal needle is withdrawn, and epidural catheter will be inserted. The spinal opioids provide excellent analgesia in comparison with epidural method; the onset of analgesia is more rapid, and the spread of analgesic drugs to sacral nerve roots is more reliable [7]. Widely used for its analgesic property in childbirth, Bupivacaine is characterized by high quality sensory block versus motor block, and the use of low-dose bupivacaine in spinal anaesthesia does not lead to any cardiac toxicity.

Lipid-soluble opioids such as fentanyl and sufentanil are the most commonly used for increasing neuraxial analgesia property of local anaesthetics. Simultaneous administration of opioids and local anaesthetics can prolong analgesic duration and quality, and decline the local anaesthetic dosages. The addition of neuraxial opioids is associated with such dose-related side effects as pruritus, sedation and nausea. Besides, intrathecal prescription of opioids may lead to hypotensively-independent fetal bradycardia. Despite being uncertain, its mechanism of action may be allied to increased uterine activity subsequent to rapid onset of action for analgesia [7].

With respect to the importance of painless delivery that brings pregnant women to more calmness and collaborative role during childbirth, and encourages them to have vaginal delivery, and that far less has been found on the efficiency and complications of different doses of bupivacaine along with intrathecal opioids esp. sufentanil, the conduction of this study was sought.

MATERIALS AND METHODS

Once approved by the university committee of ethics, and written consent reached from participants, this study targeted 40 normal healthy women (ASA-I) in their weeks of 36-40 of pregnancy during active labour phase (cervix dilation at 4-6 cm).

Inclusion Criteria

The inclusion criteria involved the lack of any subsequent cases including: patient refusal, infectious injection site, severe coagulation disorders, hypovolemic shock, increased intracranial pressure caused by mass lesion, and sufficient expertise of the anaesthetist. Other factors like systematic infection, neurologic disease, mild coagulation disorders, and contraindication were relative and case-dependent. The human immunodeficiency virus (HIV) and liver infection were not contraindicated for neuraxial anaesthesia in pregnant women [3].

Exclusion Criteria

The exclusion criteria consisted of the history of opioids and analgesics use within the past 24 hours, patients' reluctance to continue with analgesia, severe preeclampsia, heart diseases, hypertension, and advanced Gestational diabetes mellitus (GDM), coagulation disorders or anticoagulant use, fetal, distress etc.

The subjects were selected based on block random sampling, and assigned into two groups. The first group received sufentanil 5 µg (manufactured by Aburaihan company, Iran) + bupivacaine 1 mg (manufactured by AstraZenca company, France) while the second group received sufentanil 5µg + bupivacaine 2 mg of intrathecal injection.

Patients' pain score was measured and recorded using a 10-cm pain scale (rated from 0 as ''No Pain'' to10 as ''Severe Pain'' during contradictions) as a visual method before block sampling. Additionally, gestational systolic/diastolic

blood pressure and heart rate were recorded on patients' report sheet. The combined epidural-spinal (CSE) anaesthetic technique was performed at either L3-L4 or L4-L5 interspaces in the sitting position using the 18-g Touhy's epidural needle and loss of resistance (LOR) technique. Either 25-g or 26-g spinal needle was inserted in the subarachnoid space to inject 2cc of the drug, once the cerebral spinal fluid (CSF) was observed.

It is worth noting that all drugs were procured with the same volume from similar pharmaceutical company, and the type of injectable drug was not disclosed to the interviewer. All drugs were prepared in identical syringes of 2cc volume by a nurse anaesthetist with injection information remaining unveiled to both the auditor and the patient. Only someone who prepared the drugs, was aware of the injectable drugs, and marked the syringes with 1 or 2 to signify the case group.

Epidural catheter was then inserted in epidural interspace at 3-5cm in depth without dose-testing administration. Immediately after epidural catheter insertion, the patients rested in supine position so as to record their hemodynamic variables and pain intensity using the VAS scale every 5 or to 15 minutes, and then every 15 minutes until delivery or patient's request for the first application of an auxiliary reliever. The severity of pruritus (via VAS scale), gestational heart rate and blood pressure as well as fetal heart rate were all recorded at the same time. In case of insufficient analgesia and >30-mm VAS-rated pain within the first 30 minutes of spinal administration, the patient was excluded from the study. The duration of analgesia was estimated since drug administration in spinal interspaces to the patient's request for the first application of an analgesic. Drug's onset of action was measured since drug injection to <30-mm score pain.

The motor block degree was assessed based on Bromage score as follows:

0. Free movement of pelvis, legs and feet
1. Able to flex knees, move feet with pelvis remained unmoved
2. Unable to flex pelvis and knees with ankles moved
3. Complete block of movement in lower extremities

Moreover, maternal sedation scores (ranging from 0: Awake, 1: Drowsy, 2: Easy to rouse and 3: Deep asleep and difficult to rouse or unable to react to commands) were recorded.

Chills and vomiting were recorded every 5, 10, 15 minutes after blocking, and then every 15 minutes until the patient's request for the first application of an auxiliary analgesic.

The 1-/5-minute neonatal Apgar scores were measured and recorded in the report sheet.

Meanwhile, any tendency for itching and its site were recorded by the observer, and the pain score of the request for the first application of an auxiliary analgesic was noted. In case of a VAS-rated pruritus at >40 mm, about 50-µg intravenous naloxone was administered to treat the itching as per the patient's request.

Once extra analgesia was demanded, am amount of 10-cc Marcaine %125 was injected to the epidural interspace by the catheter with the demand time which was noted.

ANOVA and Compared T-test were used to compare the quantitative data, while Chi-square was used for qualitative data. The probability level was considered to be <0.05 as statistically significant.

RESULTS

For the sake of this study, 40 primi parous women candidate for combined spinal epidural analgesia in two groups were evaluated. Twenty patients received sufentanil 5 µg + bupivacaine 1 mg as Group A, while 20 received sufentanil 5 µg + bupivacaine 2 mg of intrathecal injection as Group B. Both groups were compared in terms of the quality, onset and duration of analgesia as well as the complications of intrathecal injection. The prenatal demographic variables were the same in both groups, as displayed in table (1).

Table 1: Pre-interventional comparison of maternal age, gestational age, weight, dilatation in both groups

	Group A		Group B		
Variable	**Mean**	**SD**	**Mean**	**SD**	**P-value (t-test)**
Age (Year)	24.5	4.7	21.5	3.2	0.06
Gestational Age (Week)	38.6	1.15	39.2	0.7	0.12
Weight (Kg)	70.1	6.9	68.9	10.3	0.66
Dilation (cm)	4.7	0.59	4.8	0.66	0.78

None of the groups required any naloxone.

In group A, almost 4 subjects (%20) underwent caesarean section, while all the patients of group B (%100) had a vaginal childbirth.

There was not any significant difference between the neonatal Apgar scores of both groups.

1-minute Apgar score: (A=8.7±0.44; B=8.9±0.3; P-value=0.22)

5-minute Apgar score: (A=9.7±0.44; B=9.9±0.3; P-value=0.22)

The mean score of systolic blood pressure remained low within different time intervals in both groups, indicating no statistically significant difference.

The groups did not exhibit any significant different in their diastolic blood pressure.

The mean pain score was lower, though insignificant, in group B than A within almost all time intervals in both groups, indicating a descending trend in the pain intensity of both over the time (Table 2).

Table 2: Comparison of VNS-rated pain scores in both groups

	Group A		Group B		
Time	**Mean**	**SD**	**Mean**	**SD**	**P-value (t-test)**
Pre-injection	9.8	0.36	9.9	0.22	0.30
Minute 5	4.7	3.06	4.3	2.9	0.63
Minute 10	3.6	2.9	3.1	2.8	0.55
Minute 15	2.07	2.4	1.8	1.8	0.74
Minute 30	1.5	1.9	1.3	1.5	0.79
Minute 45	1.4	1.7	1.05	1.5	0.45
Minute 60	1.4	1.4	1.1	1.7	0.66
Minute 75	1.4	1.5	1.6	1.8	0.72
Minute 90	2.1	2.4	2.1	2.4	0.98

Although the duration of analgesia was longer in the second group, it was statistically insignificant. Moreover, the time to analgesia's onset of action was shorter in the 2mg-bupivac group than 1-mg-bupivac group; the difference, however, was not statistically significant, as shown in Table (3).

Table 3: Comparison of the mean onset of action and duration of analgesia in both groups

Variable	1mg-bupivac (Group A)	2mg-buvipac (Group B)	P-value
Duration of Analgesia (min)	123.4±29.3	132.3±44.3	0.523
Analgesia's Onset of Action (min)	12.25±7.6	10.0±6.2	0.317

Nearly %45 of high-dose recipients reached the maximum analgesia i.e. <30-mm pain score at the minute 5, while %35 of the low-dose recipients experienced complete analgesia at the same time as the majority of group B patients (%70) having a completely painless delivery at the minute 10. The difference, though, was not statistically significant. Table (5) demonstrates the frequency distribution, and percentage of both groups in terms of the analgesia's onset of action (table 4).

Table 4: Frequency distribution and percentage of both groups in terms of the analgesia's onset of action

	Onset of Action (min)				
	1-5	**6-10**	**11-15**	**>15**	**Total**
Group A	7(%35)	4(%4)	6(%30)	3(%15)	20(%100)
Group B	9(%45)	5(%25)	5(%25)	1(%5)	20(%100)
Total	16(%40)	9($22.5)	11(%27.5)	4(%4)	40(%100)

P-value= 0.69

The mean fetal heart rate was lower in the second than the first group at all times of injection, keeping the minutes 30, 45 and 75 statistically significant, though clinically insignificant and normal, between the both.

The mean maternal heart rate was lower in Group A than B at all times of injection; the difference, however, was insignificant.

Peri-interventional vomiting[1] was seen in only two patients, and nausea was observed in just one patient in the low-dose group. No complaint was made for nausea or vomiting at other times.

None of the patients had chills in pre-interventional stage. Nonetheless, 4 patients in the 2nd group and 1 in the 1st group experienced chills in post-interventional stage (P>0.05).

Upon minute 5, none were reported with pruritus; other times, the difference was not significant (Table 5).

Table 5: Comparison of mean VAS-rated pruritus within the 1st 90 minutes in both groups

Time	Group A		Group B		
	Mean	**SD**	**Mean**	**SD**	**P-value (t-test)**
Minute 10	0.6	1.3	0.4	1.2	0.66
Minute 15	0.87	1.6	0.84	1.7	0.95
Minute 30	1.4	1.7	1.4	2.2	0.95
Minute 45	1.2	1.5	1.7	2.9	0.51
Minute 60	1.2	1.6	1.4	2.1	0.79
Minute 75	1	1.36	0.92	1.73	0.88
Minute 90	0.77	1.36	0	0	0.13

Bromage score was identical to 0 in 36 patients (one in group A scored 1 within the minutes 60 to 90, and three in group B scored 1 within the minutes 5 to 15). All 40 patients had a sedation score of zero.

There was no significant difference between study groups according to sensory levels, and almost all patients experienced T4 and T5 sensory level after the establishment of complete analgesia.

[1] Vomiting before Intrathecal injection

DISCUSSION

Along with epidural catheter administration, intrathecal anesthesia and opioids have been widely used as the most effective ways for painless delivery due to their shorter time to onset of action [7, 8]. Rapid analgesia operates by injecting drugs into intrathecal interspaces, the duration of which can be extended by catheter-mediated re-administration of drugs in case of need.

Solitary use of local anaesthetics like bupivacaine in intrathecal spaces are not extensively applicable to have a painless delivery. That is to say, combined use of local anaesthetics and opioids in intrathecal spaces can together enhance the quality of analgesia for a painless delivery.

In general, the group B recipients of 5µg sufentanil+2mg-bupivacaine experienced a longer analgesic duration, lower mean pain score, shorter time to analgesia's onset of action, and less complication compared with the group A 5µg sufentanil+1mg-bupivacaine group; Both groups insignificantly differed in terms of motor block, chills, nausea and vomiting. The observed differences between the high-dose and low-dose groups were not statistically significant in most cases. If the sample size was larger, the differences, currently indicative of the effectiveness of sufentanil+2mg-bupivac, would reach a significant level.

Lee et al. compared two distinct doses of bupivacaine (2.5 & 1.25 mg) combined with 25-µg intrathecal fentanyl. They found no significant difference between the onset of action, and the quality of analgesia in both groups. The mean duration of analgesia was longer in the high-dose group, and there was not any significant difference between the postpartum complications of injected analgesia in both groups, which was consistent with this study [9].

As observed in this study, the increased dosage of bupivacaine did not result in such complications as nausea, vomiting, pruritus, chills, maternal sedation score and muscle weakness. Remarkable was the lower mean fetal heart rate of the high-dose than low-dose group at all times of injection, keeping the minutes 30, 45 and 75 statistically significant, though clinically insignificant and normal, between the both.

Wong et al. studied the dose-dependence of sufentanil (2.5, 5 & 7.5 µg) + bupivacaine 2.5 mg in painless delivery. Accordingly, solitary use of bupivacaine did not lead to a satisfactory analgesia, while the combined use of bupivacaine+2.5µg-sufentanil was comparable to the higher doses in terms of observed analgesia. In other words, bupivacaine might decrease the need for higher doses of sufentanil - associated with complications [10]. Sufentanil has been more limited to be used due to its high costs compared with other similar drugs [11]. However, Likler et al. showed that sufentanil was highly preferred to fentanyl since its use resulted in lower motor block and pain score [12]. Investigating the effect of the minimum local analgesic dose (MLAD) of intrathecal bupivacaine and fentanyl on the painless delivery of 120 patients (assigned to 4 groups) with 2-6cm cervical dilation, Stoks et al. (2001) considered either the solitary impact of bupivacaine or its combined impact with fentanyl 5, 15 and 25µg. The intended MLAD for bupivacaine was 1.99 mg in the 1st-stage delivery. MLAD exhibited a significantly decreased dose in all recipients of combined bupivacaine+fentanyl than the recipients of solitary bupivacaine. The dose-dependent effect of fentanyl on MLAD remained uncertain. Analgesia's onset of action was not affected by fentanyl addition. The dose-dependent effect of fentanyl on pruritus and the duration of analgesia was also observed. Furthermore, there was not any significant difference between patients' nausea and vomiting and the degree of sensory block and motor block [13].

In a study, [14] provided an overview of the basic principles and techniques of performing epidural analgesia, its specificities for women in labor, its effects on the mother and fetus, as well as the dilemmas that accompany this method. [15] evaluated the analgesic effects of continuous epidural anesthesia for painless labor, and the results of their study indicated that continuous epidural anesthesia had good analgesic effects regarding labor, it shortened the active period of first and second stages of labor, reduced rate of Cesarean sections, and did not increase incidence of postpartum hemorrhage, fetal distress, neonatal asphyxia, or other complications.

[16] evaluated and compared the efficacy of bupivacaine fentanyl (BF) and bupivacaine-sufentanil (BS) administered in combined spinal-epidural for labor analgesia. The results of their study showed that the both combinations provided equally efficacious analgesia.

[17] in a study, examined the effect of addition of sufentanil to bupivacaine 0.5% heavy, on various characteristics of subarachnoid block, when given to parturients. The findings indicated that the addition of 1ml (10 µg) sufentanil to 2 ml of bupivacaine heavy (0.5%) intrathecally hastened the onset, and prolonged the duration of sensory and motor blockade, and hemodynamic parameters were not affected with the inclusion of sufentanil.

Camman et al. (1998) aimed at investigating the duration, quality and complications of analgesia on all research groups. To this end, they provided a group with intrathecal sufentanil 5.2/10mg combined with epidural saline 10cc, a group with epidural bupivacaine 12.5/25mg combined with intrathecal normal saline 2cc and a group with intrathecal sufentanil ½.5/5mg combined with epidural bupivacaine 2.5/25/6/12.5mg. Ultimately, they found that the combined dose effect of drugs significantly increased compared with their solitary effect, and eventually resulted

in a satisfactory analgesia during delivery. Furthermore, the recipients of the combined sufentanil+bupivacaine presented a significant dose-dependent increase in the duration of analgesia, which was in line with the results of the present study [18].

The findings of this study indicated that both doses of bupivacaine were risk-free for the fetus, and high-dose bupivacaine did not change the neonatal Apgar scores.

CONCLUSION

According to the results, the 2mg-bupivacaine group experienced a longer analgesic duration, lower mean pain score, shorter time to analgesia's onset of action, and less complication compared with the 1mg-bupivac group. The findings, nonetheless, require further investigations with a larger sample size to be verified.

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