Original Article

Comparison of Combined Fentanyl-Bupivacaine Versus Bupivacaine Monotherapy in Combined Spinal-Epidural Analgesia for Labor Pain Relief

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Abstract

Background: Combined spinal-epidural analgesia (CSE) is a generally acknowledged method for relieving labor pain with minimal adverse effects. **Objectives:** The objectives of the study were to assess the quality and safety of combined fentanyl and bupivacaine compared with bupivacaine alone in the management of labor pain. **Materials and Methods:** This was a single-blind randomized controlled trial conducted at the painless delivery unit in Al-Zahraa Teaching Hospital, Najaf, from June 1 to December 30, 2018, and included 60 parturient patients in labor. They were assigned into two groups with 30 participants in each; the first group received 10 mL of 0.125% bupivacaine combined with fentanyl 2 μg/ml epidurally as priming and intermittent top-up doses, with 2 mL of this solution given intrathecally. The other group received 10 mL of 0.25% bupivacaine epidurally as priming and subsequent doses, with 1 mL of this solution given intrathecally. Pain intensity was assessed using a visual analog scale (VAS). **Results:** The baseline VAS scores were high and not significantly different between both groups ($P > 0.05$). After conducting the procedure, there was a considerably lower mean VAS score (P value < 0.001) and maternal blood pressure (P value 0.014) in combined fentanyl and bupivacaine compared with bupivacaine alone, pulse rate, and fetal heart rate, and several administered doses were not significantly different ($P > 0.05$). No serious complications were reported; however, nausea, vomiting, and pruritus were reported in fentanyl-bupivacaine group while none in the bupivacaine alone group. **Conclusion:** Using a combined fentanyl-bupivacaine solution is more effective in relieving labor pain and in maintaining hemodynamic status than bupivacaine alone in the CSE technique, despite the occurrence of some adverse effects.

Keywords: CSE technique, epidural analgesia, neuraxial fentanyl, painless labor

Introduction

In the life of a family, the birth of a child is a very important event. However, during the birth process, every woman experiences significant pain in intensity. Pain during childbirth is a subjective feeling caused by stretching of the lower uterine segment, the opening of the cervix, the pressure of the fetus on the pelvic floor and muscles, and the stretching of the vulvar ring and the skin of the perineum.[1] The topic of childbirth analgesia has concerned mankind since time immemorial. All current methods of analgesia for childbirth are not ideal, and they must be selected individually. The choice of the optimal method of labor analgesia for each specific woman is carried out together with an obstetrician-gynecologist and an anesthesiologist since the effectiveness of different methods of labor analgesia is not the same.[2]

The combination of these drugs allows the dose of local anesthetic to be reduced. As a result, pain perception

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channels are blocked, but motor nerve sensitivity is preserved. Allows women in labor to feel the urge to push and maintain the ability to push without experiencing severe pain. The rational approach and the choice of a method of analgesia significantly help to avoid the excessive influence of these factors on a woman, to get rid of pain, and to properly adjust to the childbirth process. Regional anesthesia is the recommended option for different types of surgery. However, relying solely on local spinal anesthesia is not reliable in maintaining postoperative sensory analgesia. Using local anesthetics in combination with adjuvant drugs aims to increase the anesthesia's effectiveness during surgery, providing effective pain relief after surgery, facilitating early mobility, accelerating motor function recovery, and reducing the side effects. This approach is known as multimodal analgesia.[3]

Various factors, beyond pain treatment, influence a mother's overall contentment with labor discomfort. When administered independently, epidural opioids did not sufficiently alleviate pain during childbirth. However, the inclusion of the short-acting fat-soluble opioid fentanyl with bupivacaine yielded more favorable results. Nevertheless, it remains uncertain whether the concurrent administration of opioids and bupivacaine effectively decreases the occurrence of operational delivery. In addition, it is unclear whether the enhanced pain relief justifies the disadvantages associated with using a controlled substance.[1,3,4] We aimed in this study to assess the effectiveness and safety of fentanyl-bupivacaine in combined spinal-epidural analgesia in comparison to bupivacaine alone.

Materials and Methods

Study design, setting, and patients

This single-blind randomized controlled trial was conducted at a painless delivery center in Al-Zahraa Teaching Hospital in Al Najaf Al Ashraf City from June 1 to December 30, 2018. A total of 60 parturient patients in labor with cervical dilatation of (3 cm) were enrolled in the study. There were two equal groups of patients; the first group consisted of 30 patients to whom the CSE technique was performed with fentanyl added to the local anesthetic solution (fentanyl group or F group). The second group consisted of 30 patients to whom the CSE technique was performed with pure local anesthetic solution (Bupivacaine group or B group). As a result of insufficient analgesia within 20 min after the first top-up injection in F group and B group, they were removed from the trial (global failure pattern of epidural analgesia). Because the impact of the primary epidural dosage may be confounded with the effect of the intrathecal dose. As a result, in F group 28 patients completed the trial, while in B group, 27 patients completed it.

Procedure

A signed informed consent was obtained from each participant before recruitment in the study. An intravenous (I.V). cannulation was inserted and a bolus of 500 mL 0.9% saline solution was commenced before the block.

Baseline values of noninvasive arterial blood pressure (BP), pulse rate, and fetal heart rate (FHR) were monitored and recorded. In the sitting position, the back of each patient was sterilized with 10% chlorhexidine solution. After dryness, it was covered with sterile drapes. Boney landmarks were identified then local infiltration by 3 mL of lidocaine 2% solution at the intended point was done.

With a midline approach, the Tuohy needle (18Gx3 1/2) was advanced firmly through the skin and subcutaneous tissues, with the bevel cephalad. Then a 10 mL plastic syringe filled with saline was attached to the Tuohy. Continuous gentle pressure was applied to the plunger by the right hand while the left hand held the Touhy with the dorsum against the patient's back. The loss of resistance technique was used to identify the epidural space.

A small-sized spinal needle (27G) was inserted through a Tuohy needle for intrathecal administration of the analgesic solution. After the removal of the spinal needle, a plastic catheter introducer was fixed to the Tuohy, and the epidural catheter (20 G), a multiholed type with threading assist guide was advanced thoroughly for up to 15–20 cm. Tuohy needle was removed carefully with the catheter held in site then the catheter was withdrawn to leave 5 cm in the epidural space. A bacterial filter was attached to the free end of the catheter, and the catheter was checked for any blood or CSF. A test dose was used, and then after fixation of the catheter to a pin pad, the first dose of the epidural portion was given 10 mL of the analgesic solution. Then the patient was laid in the supine with left uterine displacement. This dose should be repeated when pain recurs. Oxygen supply through a face mask is used when desaturation or hypotension occurs. Frequent measurements of BP every 5 min for 30 min or until the patient became stable. Ephedrine was used for the treatment of hypotension if needed.

Bupivacaine with fentanyl and pure bupivacaine solutions

In the first group (F group) 10 mL of 0.125% bupivacaine with fentanyl (2 μg/mL) was the priming dose and the intermittent top-ups were given epidurally, 2 mL of this solution was injected intrathecally.

In the second group, B group, 10 mL of 0.25% bupivacaine was the priming, and subsequent doses were given epidurally, 1 mL of this solution was aspirated and diluted with normal saline into 2 mL and then injected intrathecally.

Data collection sheets:

gathered the clinical data of the patients.

Assessment of patients

At baseline all patients were interviewed and their clinical data were reported, their pain was rated according to the visual analog scale (VAS). And then subsequently each 15 min, as well as BP and pulse rate for the mother and FHR.

Statistical analysis

This was performed with the aid of the Statistical Package for the Social Sciences version 25 for Windows. Appropriate statistical tests were applied accordingly at a level of significance of ≤0.05.

Results

The mean age of the patients in F group was 27.9 (range 15–41) years and 29.4 (range: 18–40) in the B group with no significant difference (P value = 0.744). The majority of women were multiparous with a mean parity of 2.6 ± 1.7 in the F group and 3 ± 2 in the B group with no significant difference ($P > 0.05$) [Table 1].

At baseline, the mean VAS for F group was 7.14 ± 1.00 compared to 7.25 ± 0.98 in B group with no statistically significant difference ($P > 0.05$), After intervention, the VAS scores were lowered remarkably in both groups ($P < 0.001$), but the mean VAS was lowered more in F group compared to the B group where the mean VAS score reduced by 53.5% in the F group and 40.7% in the B group compared to their corresponding baseline values ($P < 0.001$) [Table 2].

Changes in maternal BP, pulse rate, and FHR are demonstrated in Table 3, A statistically significant difference was found between both groups in the mean SBP after intervention where it was 126.3 ± 15.2 mm Hg in the F group and 115.5 ± 16.7 mm Hg in the B group (P value = 0.014). No significant differences had been found between groups regarding maternal pulse rate (MPR) and FHR ($P > 0.05$).

Table 1: Descriptive statistics of age and parity in both studied groups

Variable	Statistics	F group (n = 28)	B group (n = 27)	P value
Age (year)	Mean ± SD	27.9 ± 11.2	29.4 ± 10.7	0.744 ns
	Range	15–41	18–40	–
Parity	Nulliparous n (%)	3 (11.0)	4 (15.0)	0.705 ns
	Multiparous n (%)	25 (89.0)	23 (85.0)	
	Mean ± SD	2.6 ± 1.7	3.0 ± 2.0	0.318 ns

SD: standard deviation, ns: not significant

Table 2: Comparison of mean visual analog scale (VAS) score before and after intervention in both studied groups

Assessment time	F group (n = 28)		B group (n = 27)		P value between groups
	Mean VAS	SD	Mean VAS	SD	
Baseline (before intervention)	7.14	1.0	7.25	0.98	0.682 ns
After intervention	3.32	0.67	4.30	0.61	<0.001 sig
Mean difference	3.82	0.68	2.95	0.64	<0.001 sig
Change rate	53.5%	7.4%	40.7%	6.8%	<0.001 sig
P value within groups	<0.001 sig		<0.001 sig		

SD: standard deviation, ns: not significant

Table 3: Comparison of hemodynamic parameters of the studied groups before and after intervention

Parameters		F group (n = 28)	B group (n = 27)	P value
		Mean ± SD	Mean ± SD	
Maternal SBP mmHg	Baseline	130.3 ± 13.9	129.4 ± 15.1	0.829 ns
	After intervention	126.342 ± 15.2	115.5 ± 16.7	0.014 sig
Maternal PR pulse/min	Baseline	98.5 ± 9.5	102.2 ± 10.2	0.174 ns
	After intervention	98.1 ± 11.19	101.9 ± 11.6	0.225 ns
FHR beat/min	Baseline	139.7 ± 6.9	141.3 ± 7.7	0.428 ns
	After intervention	136.7 ± 7.4	135.6 ± 9.9	0.648 ns

SBP: systolic blood pressure, PR: pulse rate, FHR: fetal heart rate

Table 4: Number of required doses of agents in both groups

No. of doses	F group ($n = 28$)		B group ($n = 27$)	
	No.	%	No.	%
One-dose	5	0.18	4	0.15
Two doses	9	0.32	10	0.37
Tree doses	14	0.50	13	0.48
Total	28	1.00	27	1.00

P value = 0.613 not significant

Table 5: Incident complications after conducting case analgesia in both studied groups

Complications	F group ($n = 28$)		B group ($n = 27$)	
	No.	%	No.	%
Pruritus	6	21.5	0	0.0
Nausea	6	21.5	0	0.0
None	16	57.0	27	100.0

P value < 0.001 significant

Regarding the number of required agents' doses (priming and subsequent doses), in the F group five patients (18%) received only a single dose, nine patients (32%) received two doses, and 14 patients (50%) received three doses; while in B group 4 (15%), 10 (37%), and 13 (48%), respectively, however, no much difference between the two groups regarding the number of doses used (*P* value of 0.613) [Table 4].

Regarding complications; namely, pruritus, nausea, and vomiting, in F group, six patients (21.5%) suffered from pruritus and six patients (21.5%) suffered from nausea. No patient suffered from such complications in the B group [Table 5].

Discussion

Many factors can affect the progress of normal labor under the CSE technique such as maternal age, and parity,[5,6] and many previous studies focused on that. Here in this study, we tried to find out by statistical analysis if any of those factors had any effect on the final results. Before the commencement of the procedure, we recorded the mean VAS score to compare the baseline results between the two groups and with the subsequent results. Comparison between the mean VAS scores of the two groups after conducting the analgesia showed that F group had significantly lower VAS scores than the B group as illustrated in Table 5. This can reveal that a mixed solution (fentanyl and bupivacaine) is more effective than a sole bupivacaine solution despite of low concentrations used in the mixed one. This high efficacy can be attributed to drug synergy which is defined as cooperative agents interacting in such a way that their combined effect exceeds their individual effects. Hence, in the mixed solution, agents were increasing each other's effectiveness; although they had different sites of action (fentanyl acts on the μ2 receptors in the spinal cord, while the bupivacaine blocks the voltage-gated sodium channels and so blocks membrane depolarization of the neuronal axons).[7]

Maternal BP also regularly monitored and recorded because it is by far the most important determinant of uterine blood flow and is affected by position (aortocaval compression), sympathectomy (regional analgesia), and hypovolemia. As uterine blood flow is not autoregulated so prolonged or severe hypotension (systolic pressure less than 100 mm Hg) will cause fetal compromise. The impact of regional analgesia on uteroplacental flow (UBF) is controversial, a decrease in catecholamines has the potential to increase UBF, however, hypotension when present, may counteract these effects.[2] Comparison between the mean MSBP of the two groups after conducting the analgesia showed that the B group had significantly more drop than F group, with a *P* value of 0.014; however, both were still within the safe limit, as illustrated in Table 5. This can reveal that the mixed solution in F group is more stable than the sole solution used in the B group in concern of hypotension which is a common side effect of regional analgesia.

Because neuraxial blocks generate fluctuating drops in BP that might be followed by a drop-in heart rate, the MPR was also frequently measured and recorded. These effects are proportionate to the dermatomal level and sympathectomy extent. At T1–T4, sympathetic cardiac accelerator fibers may be affected by a high sympathetic block and profound hypotension with bradycardia may result.[2] Comparison between the mean MPR illustrates that there were no significant differences between the two groups. This can reveal that both solutions are equally stable in terms of maternal bradycardia.

Fetal well-being during labor is of most importance. One of the ways to assess fetal well-being is to monitor FHR using a sonographic device. A normal range of FHR is 110–160 beats/min in the uterine period. A baseline FHR is the average FHR during a 10-min period if <110 b/min is termed fetal bradycardia which is common during prolonged compression of the umbilical cord (myocardial depression caused by fetal hypoxemia), placental transfer of the drugs and maternal hypotension. The reaction of the FHR to uterine contraction is used to determine fetal well-being during childbirth. Deceleration is a phrase used to describe the slowing of FHR caused by a parasympathetic response and is defined in connection to uterine contractions. Early deceleration is caused by altered fetal cerebral blood flow (fetal head compression). It happens just before the peak of uterine contractions and then returns to normal once the contraction is through. Late deceleration happens after the peak of the contract and recovers to normal once the contraction is over; it is caused by uteroplacental insufficiency, such as in

parental hypotension, spinal and epidural anesthesia, and placental impact greatly.[7-15] Regular measurements and comparisons of the means of FHR after conducting the procedure showed that there was no significant difference between the two groups, so, both solutions are equally safe for the fetus.

It is thought that when the local anesthetic is used alone a higher concentration should be used to provide adequate analgesia but this could affect labor progress by reducing the parturient's ability to push effectively.[16-18] In our study, we tried to exclude this effect with (0.25% bupivacaine) solution by recording the number of doses needed from the start until the delivery. There was no significant difference between the two groups regarding the number of doses used in the procedure.

After conducting the procedure, it was noticed that; in the F group several patients experienced nausea and pruritus as some side effects. This could be attributed to the presence of opioids (fentanyl). The presence of drugs in both CSF and blood caused the intrathecal and epidural opioids' side effects. Therefore, following the intrathecal and epidural opioid administration, the pharmacokinetic behavior will profoundly affect its side effects.[19]

The opioids intrathecal administration (esp. water-soluble) produces high concentrations of drugs immediately in CSF that depends on dose. There will be a cephalad migration of the drug due to the bulk flow of CSF, which ascends in a cephalad direction from the lumber region, reaching the cisterna magna by 1–2 h and the fourth and lateral ventricles by 3–6 h. The body movement does not affect CSF movement, although coughing, sneezing, or straining does. Vascular reabsorption of intrathecal opioids although it is irrelevant clinically to some degree does occur.[20]

Fentanyl is highly lipid-soluble when it's administered intrathecally and it will exhibit rapid onset and short duration of action. It penetrates the spinal cord quickly, leaving little drug to ascend cephalad in CSF. Its removal from the CSF occurs due to spinal cord penetration and vascular reabsorption as secondary from both.[21]

Opioid delivery through epidural results in high drug concentrations in the CSF. Lipophilicity has a significant impact on dura penetration, although molecular weight may also play a function. A large venous plexus runs through the epidural space. As a result, vascular reabsorption after opioid epidural delivery is substantial. Following fentanyl injections into the epidural space, CSF concentrations peak in 10–20 min, while the peak of blood concentrations at about 5–10 min. The blood concentrations of opioids that are similar to an equivalent dose of intramuscular injection are the results of the administration of fentanyl in epidural space.[22] Pruritus is the most popular side effect of neuraxial opiates. Occasionally,i can be more annoying than the pain itself or same the pain. Pruritus seems to be more susceptible in enceinte pregnant women after neuraxial administration of opioids more than other populations; it might be because of an estrogen interaction with opiate receptors or opioid receptors.[23,24] In this study, pruritus was minor, of short duration, started at the trunk shortly after the analgesia and the incidence was lower after the subsequent doses. The neuraxial opioid-induced pruritus exact mechanism is unclear. While opioids can cause histamine to be released from mast cells, this will not seem to be the pruritus cause. Pruritus could be caused by opioids without changing plasma histamine levels.[25] Moreover, rash as a result of neuraxial opioid administration is quite uncommon. Antihistamines, ironically, might be an effective therapy for pruritus because of their calming properties. Pruritus also does not appear to be related to the systemic absorption of opioids.[26] No single mechanism can explain all instances; although, many mechanisms have been postulated. Postulated mechanisms include:

- Presence of "itch center" in the central nervous system (trigeminal nucleus in the medulla).
- Medullary dorsal horn activation and antagonism of inhibitory transmitters.
- Theory linking pain and pruritus (c-fibers transmit pain and pruritus).
- Modulation of serotonergic pathway.[27]

Even after much study, the neuraxial opiates-induced pruritus management remains complicated. Several therapies were explored, but the evidence is mixed, and only a few studies have proved their effectiveness. To reduce opioid-induced pruritus, mixed opioid receptor antagonists, MOR antagonists, D2 receptor antagonists, and serotonin 5-HT3 receptor antagonists, have been displayed to be generality effective.[27]

Hypotension may be accompanied by and nausea may accompany the hypotension which may occur after conducting the procedure or may be related to the presence of fentanyl, and since it occurred mostly in the F group which had a lower incidence of hypotension, it is attributed to the fentanyl.

The induced vomiting and nausea from epidural and intrathecal opioids are likely the result of the drug's cephalad migration in CSF and subsequent interaction with opioid receptors in the area postrema (chemoreceptor trigger zone). Decreased emptying of the stomach with the vestibular system's sensitization to motion produced by opioids may also play a role in vomiting and nausea induced by neuraxial opioids. Antiemetic drugs may need to be used. In this study, mild nausea only occurred in several patients and required no intervention.[27-29]

Conclusion

From this study, we conclude that the use of mixed solution (0.125% bupivacaine with fentanyl 2 μg/mL) was more

effective in relieving labor pain and was hemodynamically more stable than the sole solution (0.25% bupivacaine), despite the occurrence of some adverse effects such as nausea and pruritus in several patients in the F group, they were minor and required no intervention.

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Conflicts of interest
There are no conflicts of interest.

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