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Sequential intrathecal injection of fentanyl and hyperbaric bupivacaine at different rates: does it make a difference? A randomized controlled trial

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Background: Previous studies have shown that sequential intrathecal injection of fentanyl and hyperbaric bupivacaine for cesarean section (CS) anesthesia provides a superior anesthetic effect than use of bupivacaine alone, and prolongs postoperative analgesia. Herein, we investigated whether rapid intrathecal injection of fentanyl followed by slow injection of hyperbaric bupivacaine affects the duration of postoperative analgesia, the effectiveness of anesthesia, and hemodynamic status.

Methods: Fifty-six parturients with American Society of Anesthesiologists physical status I or II, aged 18–40 years, and scheduled to undergo elective CS were randomly assigned to 2 groups of 28 patients each. The normal sequential group received sequential intrathecal injections of fentanyl and hyperbaric bupivacaine at the same rate, each with a 5 ml syringe. The rapid sequential group received a rapid intrathecal injection of fentanyl with an insulin syringe, followed by a slow injection of hyperbaric bupivacaine with a 5 ml syringe. The onset of sensory block, the timing of the first rescue analgesia, the doses of rescue analgesics, the degree of postoperative pain, the onset and duration of motor block, the incidence and duration of hypotension, and spinal anesthesia-related complications were recorded.

Results: While both approaches had comparable spinal anesthesia-related complications, incidence and duration of hypotension, and doses of ephedrine, the rapid sequential group exhibited a more rapid onset of sensory block, a higher sensory level, and more prolonged postoperative analgesia.

Conclusions: Rapid sequential injection of fentanyl and hyperbaric bupivacaine produced superior anesthesia and more prolonged postoperative analgesia than sequential injections of both at the same rate.

Keywords: Cesarean section; Fentanyl; Hyperbaric bupivacaine; Sequential intrathecal injection; Spinal anesthesia.

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Introduction

Spinal anesthesia is commonly practiced in cesarean delivery as it confers several benefits, including decreased blood loss, early maternal-baby contact, and good intra- and post-operative pain control. The most common local anesthetic (LA) injected intrathecally during cesarean delivery is hyperbaric bupivacaine. In addition to bupivacaine, several agents are injected intrathecally, either separately or as a mixture with bupivacaine, to ensure an excellent sensory and motor block and long post-op-

erative pain control. Addition of an opioid (e.g., fentanyl) to an intrathecally administered LA has been shown to produce a synergistic analgesic effect [1–3] by decreasing visceral pain, which improves the quality of the block [4], while also decreasing the required dose of LA, thereby providing hemodynamic stability [1]. It also prolongs the duration of post-operative analgesia [5,6].

Hypotension is a problem faced by most parturients while in the supine position due to compression of the inferior vena cava by the gravid uterus. It is usually aggravated during spinal anesthesia as a result of the sympatholytic effects of an LA, which causes a marked decrease in venous return, and this can have a poor effect on both the mother and her baby as a decreased placental blood flow that may result in fetal distress [7]. In this study, we aimed to describe a new technique of spinal anesthesia that can be used during a cesarean section (CS), which we presumed will provide prolonged post-operative analgesia and intra-operative hemodynamic stability by decreasing the incidence of hypotension. We also presumed that different rates of injection of LA and fentanyl would not affect hemodynamics or prolong post-operative analgesia.

Materials and Methods

This prospective double-blinded randomized study was conducted in the operating rooms of obstetric departments at university hospitals from January 2014 to July 2016. It was conducted after receiving the approval from the local ethics committee and written informed consent was obtained from 56 American Society of Anesthesiologists status I or II parturients full-term parturients with normal, uncomplicated pregnancies. These parturients aged 18–40 years old were scheduled for elective CS and joined this study. Parturients with complicated pregnancies, such as those with preeclampsia, pregnancy-induced hypertension, gestational diabetes, abnormal placenta (placenta previa), multiple gestation, a body mass index greater than 35 or less than 22, major systemic disease (cardiac, renal, or liver), a need for emergency CS, those allergic to the drugs used in this study, and those contraindicated for spinal anesthesia or who refused regional anesthesia were excluded from this study.

On arrival at the operating room, the parturients were connected to a Hewlett-Packard monitor to record an electrocardiogram (ECG), non-invasive blood pressure (NIBP), and peripheral capillary oxygen saturation (SpO_2). A wide bore IV cannula (G18) was inserted into all parturients, and 1 liter of crystalloid (lactated ringer) was infused over 15 min. The parturients were assisted into the sitting position, and sterilized surgical drapes were placed to their back. Spinal anesthesia was administered at L4–L5 using a complete aseptic technique. The parturients were then divided into 2 groups of 28 patients each using a computer-generated sequence of random numbers and a sealed envelope technique as this is a randomization protocol. The control group received normal sequential spinal anesthesia (NS group) via a G27 pencil point spinal needle. Once cerebrospinal fluid appeared, 25 μg of fentanyl (0.5 ml) was injected over 3–4 seconds using a 5 ml syringe and mixed with cerebrospinal fluid (via barbotage). This was followed by injection of 10 mg of hyperbaric bupivacaine (0.5%) using a 5 ml syringe for 12–15 seconds. The contents of both syringes were injected slowly and sequentially. The parturients in the rapid sequential test group (RS group) received spinal anesthesia via 2 different syringes, the first being an insulin syringe containing 0.5 ml (25 μg) of fentanyl that was injected rapidly (within 1 second), causing it to mix with cerebrospinal fluid (via barbotage). This was immediately followed by a slow injection (over 12–15 seconds) of 10 mg of hyperbaric bupivacaine (0.5%) using a 5 ml syringe such that there was no time lag between these injections. After spinal anesthesia was administered, the parturients were asked to lie down at 30 degrees with their head slightly elevated and laterally tilted to the left. The technique was performed by an experienced anesthesiologist, both the parturient and the anesthesiologist who monitored the patient and collected the data were blinded to the technique. The sensory level was assessed by the cold ice technique. After the T6 level was reached, the surgeon was asked to operate. Demographic data were recorded. ECG and oxygen saturation were monitored continuously, and once spinal anesthesia was administered, NIBP was measured every 3 min for 30 min and then every 5 min and recorded every 30 min. The occurrence of hypotension (NIBP ≤ 100/60) was recorded, and an anesthesiologist was allowed to manage it by giving ephedrine (5–10 mg, intravenous [IV]) and IV fluids. The total dose of ephedrine used was recorded, and the duration until hypotension was treated was also recorded. The duration to the onset of sensory block (defined as the time needed to lose cold sensation when using the ice-cold test at the T6 dermatomal level) was also recorded, and the sensory level was assessed every minute. The highest level of sensory block after 10 min was recorded. Motor blockade was assessed every 5 min by the Bromage scale [8] as follows 0: no motor block (able to raise an extended leg), 1: unable to raise an extended leg (able to flex the knee), 2: unable to flex the knee (only able to move the foot), and 3: unable to flex the ankle (unable to move the foot or knee). The onset of motor block (defined as the time from giving spinal anesthesia until a modified Bromage score of 3 was reached) and the duration of motor block (defined as the time from the onset of motor blockade until complete recovery, indicated by a Bromage score of 0) was recorded. The occurrence of spinal anesthesia-related complications including hypotension, nausea, vomiting, shivering, itching, total spinal and respiratory depression, and a failed spinal anesthesia and need for general anesthesia was recorded. The duration of post-operative analgesia and

the time of first rescue analgesia were recorded. The degree of post-operative pain was assessed by a visual analogue scale (VAS) score [9] at 6 hours post-surgery. Using a ruler, the score was determined by measuring the distance (mm) on a 100-mm line between the "no pain" anchor and the patient's mark; the scale provided a range of scores from 0–100. A higher score indicated a greater intensity of pain. Based on the distribution of pain VAS scores in patients who described their post-operative pain intensity as none, mild, moderate, or severe, the following cut-off points for VAS-rated pain have been recommended: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm) [10]. Rescue analgesia administered in the form of 100 mg of pethidine (intramuscular, IM) and 1 g of paracetamol (IV) was given on the first call for analgesia and then repeated on demand. The total doses of pethidine and paracetamol given during the first 24 hours were recorded.

Our primary outcome was to determine the duration of post-operative analgesia and the secondary outcomes were to detect the hemodynamic status during the operation, time to sensory block, time to motor block, highest sensory level, duration of motor block, requirement of rescue analgesia and spinal anesthesia-related complications.

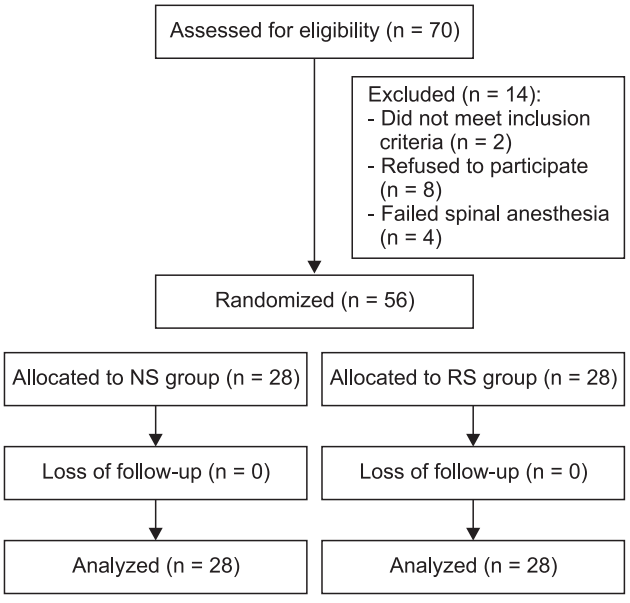

Fig. 1. CONSORT, Patient flow chart. Seventy patients were screened for eligibility, 2 patients were excluded because they did not meet the protocol's inclusion criteria, 8 patients refused to participate in the study and 4 others were excluded due to failed spinal anesthesia. So, a total of 56 patients were randomized into the study groups after receiving consent from them (28 patients for each group), and they completed the study (Fig. 1).

Sample size

We used the PASS program (version 2011. NCSS, LLC., USA) with the alpha error set at 5% and power set at 80%. The results of a pilot study showed that the mean time to rescue analgesia was 3.27 ± 1.01 hours in the NS group and 4.21 ± 1.26 hours in the RS group. Based on these data, the sample size needed was 28 cases per group (56 in total).

Initially, 70 patients were screened for eligibility, of which 2 patients were excluded because they did not meet the protocol's inclusion criteria, 8 patients refused to participate, and 4 others were excluded due to failure of spinal anesthesia. So, a total of 56 patients were selected to undergo elective CS and randomized into the study groups after their consent (28 patients in each group), and they completed the study.

Statistical analysis

All statistical analyses were performed using a standard SPSS software package (SPSS statistics for windows version 17, SPSS Inc., USA). Student's t-test was used to analyze parametric data, which are expressed as mean ± SD. Non-parametric data were presented as medians (interquartile ranges) and were analyzed using the Mann-Whitney test. Categorical variables were analyzed using the χ^2 test and are expressed as number of patients. $P < 0.05$ were considered statistically significant.

Results

Baseline patient characteristics and the duration of the operation were presented between the study groups (Table 1).

The onset of sensory block was more rapid in the RS group than in the NS group: 1.3 ± 1.9 min versus 1.7 ± 1.1 min, respectively; P = 0.032. Additionally, the T6 level was reached in a significantly shorter time in the RS group than in the NS group. Moreover, parturients in the RS group achieved a significantly higher level of sensory block (T2–T6 compared to T4–T10 in

Table 1. Demographic Data

Variable	NS group (n = 28)	RS group (n = 28)
Age (yr)	30.2 ± 5.4	29.3 ± 4.8
ASA (I/II)	25/3	24/4
BMI	32.8 ± 6.7	34.7± 6.1
Parity	2 (1–3)	2 (1–3)
Gestational age (weeks)	38.2 ± 0.9	38.6 ± 0.6
Duration of operation (min)	30.2 ± 5.3	31.7 ± 6.1

Values are presented as mean ± SD, number of patients or median (interquartile range). NS group: normal sequential, RS group: rapid sequential. ASA: American Society of Anesthesiologists, BMI: body mass index.

Table 2. Effectiveness of Analgesia

Variable	NS group (n = 28)	RS group (n = 28)	P value
Onset of sensory block (T6 level) (min)	1.7 ± 1.1	1.3 ± 1.9	0.032
Highest level of sensory block	T_4–T_{10}	T_2–T_6	< 0.001
Time of first rescue analgesia (h)	3.3 ± 1.1	4.3 ± 1.3	0.002
Number of patients who needed a rescue analgesic	15	7	0.030
Doses of postoperative pethidine and paracetamol	100 mg pethidine 1–2 gm paracetamol	100 mg pethidine 2–3 gm paracetamol	
Degree of pain 6 h post operatively (VAS [mm])	35 (20–60)	25 (10–40)	0.019

Values are presented as mean ± SD, number of patients or median (interquartile range). NS group: normal sequential, RS group: rapid sequential.

Table 3. Motor Block

Variable	NS group (n = 28)	RS group (n = 28)	P value
Onset of motor block (min) (Bromage scale > 3)	2.3 ± 0.9	2.2 ± 0.9	0.350
Duration of motor block (min) (return to Bromage 0)	2.1 ± 0.4	2.3 ± 0.4	0.116

Values are presented as mean ± SD. NS group: normal sequential, RS group: rapid sequential.

Table 4. Spinal Anesthesia-related Complications

Variable	NS group (n = 28)	RS group (n = 28)	P value
Lowest systolic blood pressure during cesarean section (mmHg)	62.1 ± 4.3	60.1 ± 6.1	0.059
Hypotension duration (min)	3.0 ± 1.8	3.4 ± 1.1	0.122
Ephedrine dose (mg)	16.6 ± 10.9	16.6 ± 10.9	0.738
Nausea	4	3	1
Vomiting	1	1	1
Pruritus	5	6	1
Shivering	8	6	0.761
Failed block	3	4	1

Values are presented as mean ± SD or as a number of patients. NS group: normal sequential, RS group: rapid sequential.

the NS group (P < 0.001) and had longer pain-free periods, as indicated by the longer time period before the patient asked for rescue analgesia: 4.3 ± 1.3 hours in the RS group versus 3.3 ± 1.1 hours in the NS group (P = 0.002). Fewer parturients required rescue analgesia in the RS group (7 patients) than in the NS group (15 patients) (P = 0.030), and VAS scores were significantly lower in the RS group (25 mm, range of 10–40 mm) than in the NS group (35 mm, range of 20–60 mm) (P = 0.019; Table 2).

There was no significant difference between the 2 groups in either the onset or the duration of motor block (Table 3).

There was no significant difference between the 2 groups in the occurrence of spinal anesthesia related complications, and there were no significant differences in blood pressure values nor the duration or dose of ephedrine used. Additionally, there were no significant differences in the perioperative incidences of nausea, vomiting, pruritus, shivering or the incidence of failed block between the 2 groups (Table 4).

Discussion

In previous studies, different doses of either LA or opioids have been used in attempts to determine the lowest dose that will provide effective analgesia without hypotension [5,11]; however, the method of administration of both LA and fentanyl has rarely been addressed. In our study, both drugs were administered separately using different syringes, and injection was performed at different rates. The rationale was to achieve a high level of fentanyl distribution by using an intrathecal route, in order to induce a high level of solid sensory block to ensure effective intra- and post-operative analgesia in addition to a longer duration of postoperative analgesia. The slow separate injection of bupivacaine provided effective surgical anesthesia and avoided LA-related side effects, such as hypotension. In the current study, the separate administration of intrathecal bupivacaine and intrathecal rapid fentanyl injections provided adequate and prolonged postoperative analgesia. The results of the sequential separate injection of intrathecal LA and opioid have been discussed in a previous study [7], with the authors concluding that sequential intrathecal injection of fentanyl and hyperbaric bupivacaine offered a more effective sensory block and decreased the incidence of hypotension. However, to our knowledge, the effect of using different rates of injection of hyperbaric bupivacaine and fentanyl has not been studied before.

In our study, a new method of injecting fentanyl and hyperbaric bupivacaine separately and intrathecally was applied in which we used 2 different syringes (an insulin syringe to inject fentanyl and a 5 ml syringe to inject hyperbaric bupivacaine) and a G27 pencil-point spinal needle. Injecting fentanyl via the insulin needle meant that the fentanyl was injected more rapidly (within 1 second) than the hyperbaric bupivacaine, which was

injected with a 5 ml syringe (over 12–15 seconds).

The most important finding of this study was that an effective sensory block and a prolonged duration of postoperative analgesia was achieved using this method and that patients in the rapid sequential group had a rapid onset of sensory block and a higher sensory block level. These effects could be attributed to the rapid rate of injection of fentanyl, which caused it to mix and circulate freely, depending on the force of injection, with the cerebrospinal fluid, allowing it to reach more distant segments of the spinal cord, thereby preventing visceral pain. Keera and Elnabtity [7] studied the effect of separately injecting intrathecally administered fentanyl and hyperbaric and found that separately injecting intrathecal fentanyl allowed it to work at a higher level in the spinal cord so that it prevented visceral pain, provided superior analgesia and prolonged sensory block. They suggested that these findings were due to the method by which the intrathecal drugs spread: when the patient is lying in a supine position, hyperbaric bupivacaine spread as a result of gravity down the slope of the lumber curvature, while the hypobaric fentanyl moves freely with the cerebrospinal fluid and thus achieved a wider range of spread, allowing it to induce sensory block at higher levels of the spinal cord. This explanation can be applied to both groups in our study. Moreover, we suggest that rapidly injecting fentanyl (within 1 second via an insulin syringe) allows it to block even higher levels and that may explain why higher levels of sensory block were attained in the current study.

The results of the current study also show that this technique achieved a prolonged duration of postoperative analgesia, as clearly indicated by the longer duration before the patients asked for rescue analgesia (4.3 ± 1.3 hours), reduced the dose of rescue analgesic, and decreased post-operative pain perception, as indicated by lower VAS scores. This may have been due to the longer time required to regain sensation after the higher level of sensory block. However, Goma et al. [10] stated that in CS, the addition of intrathecal fentanyl to LAs improved postoperative analgesia for only a brief period of 2–4 hours. This may have been due to the different techniques of administration used between the studies because Goma mentioned that they mixed fentanyl with LA, whereas we used sequential intrathecal injections.

In this study, we show that there was no significant difference between the 2 methods in the onset or duration of motor block, possibly because the rapid sequential injection of fentanyl enhanced somatic analgesia without affecting the degree or level of LA-induced motor blockade [12].

We also found that there was no significant difference between the 2 groups in the incidence of hypotension, its duration, or the total dose of ephedrine used, potentially because the difference in the rate of injection of fentanyl did not affect the LA-induced sympathetic blockade [12].

Nausea and vomiting commonly occur during peritoneal traction and exteriorization of the uterus during a cesarean delivery and are frequently related to hypotension, which is a common side effect of spinal anesthesia [4]. The decrease in the incidence of hypotension and blood pressure values observed during this study may explain the observed decrease in the incidences of nausea and vomiting. Moreover, in another study, the incidence of intra-operative vomiting was lower in patients who received lower doses of parenteral narcotics [13]. In our study, a lower dose of parental narcotics was required because post-operative analgesia was prolonged. However, we did not find any significant difference between the groups regarding the rates of nausea and vomiting, indicating that rapid intrathecal injection of fentanyl does not affect the incidence of these side effects.

The rates of other spinal anesthesia-related complications, such as pruritus, shivering, and failed block, were not significantly different between the 2 groups, perhaps because equal doses of intrathecal fentanyl and hyperbaric bupivacaine were used in both techniques.

Unfortunately, we did not measure the temperature of the drugs used, and this can be considered a limitation to the study, as differences in temperature may have affected the basicity and spread of the drugs; hence, further studies may be needed to help shed light on these points.

In conclusion, rapid intrathecal injection of 25 μg of fentanyl followed by slow intrathecal injection of 10 mg of hyperbaric bupivacaine provided adequate and prolonged postoperative analgesia while ensuring optimal spinal anesthesia during cesarean delivery, and, with it being a sequential technique, it was also associated with low incidences of intraoperative hypotension and vasopressor requirements.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Rania M. Hussien (Conceptualization; Data curation; Methodology; Project administration; Resources; Software; Validation; Visualization; Writing – original draft; Writing – review & editing)
Amal H. Rabie (Data curation; Supervision; Writing – review & editing)

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