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A comparison of different doses of spinal levobupivacaine combined with S-ketamine and clonidine for elective cesarean section: a prospective, randomized, and double-blind study

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Objectives

This study aimed to investigate the block characteristics and adverse effects of using different doses of spinal plain levobupivacaine combined with S-ketamine and clonidine during cesarean section.

Patients and methods

This prospective, randomized, controlled, double-blind clinical trial was conducted on 120 female patients scheduled for elective cesarean section. Patients were randomly assigned into three equal groups: group I received 10 mg of levobupivacaine 0.5% along with 12.5 mg of S-ketamine and 25 µg of clonidine intrathecally; group II received 7.5 mg of levobupivacaine 0.5% along with 12.5 mg of S-ketamine and 25 µg of clonidine intrathecally; and group III received 5 mg of levobupivacaine 0.5% intrathecally along with 12.5 mg S-ketamine and 25 µg clonidine. Hemodynamic parameters, the onset of the sensory block, the level of the sensory blockade, duration of the sensory block, the motor blockade and duration of the motor blockade, the quality of intraoperative analgesia, and the occurrence of side effects were recorded.

Results

Comparison of onset and duration of sensory block did not reveal any significant differences among the groups. Duration of motor blockade and the time to first analgesic request was significantly longer in group I than in groups II and III, and it was significantly longer in group II than in group III. The incidence of intraoperative nausea, vomiting, pruritus, and shivering was comparable in all groups. As regards hypotension, there was a significant reduction in its incidence in group III compared with groups I and II. As regards bradycardia, there was a significant reduction in its incidence with decreasing dose of levobupivacaine (group III showed the least incidence).

Conclusion

Spinal anesthesia using small doses of levobupivacaine with a combination of S-ketamine and clonidine was effective in cesarean section both intraoperatively and postoperatively with less adverse effects.

Keywords:

clonidine, elective cesarean section, S-ketamine, spinal levobupivacaine

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Introduction

Neuroaxial anesthesia is now the preferred technique for lower segment cesarean sections. Although epidural, spinal, continuous spinal, and combined spinal-epidural techniques have all been advocated, most cesarean sections are performed under single-shot spinal anesthesia [1]. Opioids have been administered intrathecally as adjuncts to increase the duration of postoperative analgesia. Although they ensure superior quality of analgesia, they are associated with many side effects such as pruritis, nausea, vomiting, urinary retention, and especially late and unpredictable respiratory depression [2]. This has directed the research toward the use of newer and better local anesthetic additives for several adjuncts, such as neostigmine, ketamine, midazolam, and

clonidine [3]. Intrathecal clonidine prolongs sensory as well as motor block of spinal anesthesia. It decreases local anesthetic requirements and provides prolonged postoperative analgesia [4–6]. It is said that ketamine HCl administered intrathecally not only antagonizes the N-methyl-d-aspartate receptors but also creates a sensory and motor blockage by blocking the calcium channels [7–11]. Lee *et al.* [12] have also noted that the effect of ketamine HCl is created by interacting with the opioid receptors in the spinal cord. Miyamoto *et al.* [13] investigated the effects of ketamine on the development of tolerance to morphine and morphine antinociception during intrathecal infusion and they suggested that a combination of morphine with ketamine may have an advantage in long-term use of opioids for controlling visceral as well as somatic pain.

This study aimed to investigate the block characteristics and adverse effects of using different doses of intrathecal plain levobupivacaine combined with S-ketamine and clonidine during cesarean section.

Patients and methods

After approval from the local ethical committee of Benha University Hospital and after obtaining patient's informed written consent, this prospective, randomized, controlled, double-blind clinical trial was conducted on 120 female patients of ASA I or II, between 19 and 43 years of age, scheduled for elective cesarean section. The study took place from July 2014 until January 2015. Patients with morbid obesity, cardiac diseases, diabetes mellitus, hepatic or renal insufficiency, pre-eclampsia, coagulation disorders, those receiving any anticoagulants, and those receiving any drugs that may interfere with the action of the study drugs were excluded. Patients were randomly allocated using a computer generated random number table into three equal groups.

Group I received 10 mg of levobupivacaine 0.5% intrathecally along with 12.5 mg S-ketamine and 25 µg clonidine.

Group II received 7.5 mg of levobupivacaine 0.5% intrathecally along with 12.5 mg S-ketamine and 25 µg clonidine.

Group III received 5 mg of levobupivacaine 0.5% intrathecally (12.5 mg S-ketamine +25 µg clonidine).

The total volume of the intrathecal mixture was constant (2.4 ml) in all groups.

All patients were subjected initially to medical history, a complete physical examination, and laboratory investigations. They were premedicated with ondansetron 0.1 mg/kg intravenously and ranitidine 50 mg intravenously 1 h before surgery. In the operating room, a peripheral wide bore intravenous line was inserted, and the baseline parameters (heart rate, noninvasive blood pressure, peripheral oxygen saturation, and ECG) were recorded and intravenous infusion was started with Ringer's lactate solution administered at the rate of 10–15 ml/kg before the subarachnoid block.

Under complete aseptic conditions, a subarachnoid block was performed in the L3–L4 or L4–L5 interspace using a 25 G Quincke spinal needle in the lateral position. After administration of drugs into intrathecal space, patients were made to lie in the supine position with left uterine displacement.

All patients were administered oxygen through a nasal cannula at a rate of 3 l/min.

The measured parameters included the following: hemodynamic parameters (heart rate and mean arterial pressure), which were recorded every 2 min for the initial 10 min, and then every 5 min until the end of surgery; the onset of the sensory block (the time of the intrathecal injection until the time the highest level of the block was achieved); the level of the sensory blockade, which was assessed with the pin-prick test; duration of the sensory block (the time of maximum sensory block until regression of the block to L1); the motor blockade, which was assessed according to the modified Bromage scale (Table 1); and the duration of the motor blockade (the time of intrathecal injection until no motor weakness could be detected).

The quality of intraoperative analgesia was evaluated by the patient at 10-min intervals using the following four-point scale: 1, excellent analgesia, no sensation at all from the surgical site; 2, adequate analgesia, sensation of motion only; 3, inadequate analgesia, discomfort, but the patient declines additional analgesia; 4, major discomfort, additional analgesics are necessary. When the intraoperative pain score was 4, repeated boluses of 25 µg of intravenous fentanyl were administered. General anesthesia was considered when the patient remained uncomfortable despite being given 100 µg of fentanyl. The time to first analgesic request (primary outcome) was taken from the time of maximum sensory block until the patient's first analgesic request.

The presence of side effects such as hypotension (mean arterial pressure <30% of the baseline treated with rapid infusion of Ringer's lactate solution and intravenous ephedrine at 5–10 mg incremental doses in case there was no response to intravenous fluid administration), bradycardia (heart rate <50/min treated with intravenous atropine 0.01–0.02 mg/kg), nausea, vomiting, pruritus, and shivering were also recorded.

Statistical analysis

- (1) Data were analyzed by using SPSS (IBM, New York, USA), version 16.
- (2) Quantitative data were presented as mean and SD and were analyzed using the analysis of variance test.

Table 1 Modified bromage score [14]

Grade	Criteria	Degree of block (%)
0	Free movement of legs and feet	Nil (0)
1	Just able to flex knees with free movement of feet	Partial (33)
2	Unable to flex knees, but with free movement of feet	Almost complete (66)
3	Unable to move legs or feet	Complete (100)

- (3) Significant analysis of variance test was further analyzed using the post-hoc test to determine the significant group.
- (4) Qualitative data were presented as number and percentages and were analyzed using the χ^2 -test.
- (5) A *P*-value less than 0.05 was considered statistically significant, whereas a *P*-value less than 0.01 was considered statistically highly significant.
- (6) Sample size was estimated according to a pilot study for the first 10 patients in each group by assuming α error = 0.05 and a power of 80% to detect an assumed clinically significant difference between the measurements of the primary outcome between groups.

Results

The demographic characteristics and duration of surgery were similar among the groups (Table 2).

Comparison of onset and duration of sensory block did not reveal any significant differences among the groups. Duration of motor blockade and the time to first analgesic request were significantly longer in group I compared with groups II and III, and it was longer in group II compared with group III (Table 3).

The incidence of intraoperative nausea, vomiting, pruritus, and shivering were comparable in all groups (Table 4).

As regards hypotension, significant reduction in the incidence of hypotension was observed in group III compared with groups I and II (Table 4).

As regards bradycardia, there was a significant reduction in the incidence of bradycardia with decreasing dose of

levobupivacaine (group III showed the least incidence) (Table 4).

Discussion

Spinal anesthesia with bupivacaine is administered for lower abdominal and lower limb surgeries with sufficient motor blockade to facilitate the surgeon's work. Bupivacaine also provides effective pain relief during the initial postoperative period. Adjuvants such as opioids and ketamines are sometimes combined with local anesthetics for spinal anesthesia [18]. The rationale for combining adjuvants to local anesthetic drugs is to lower the dose of each agent, thereby their toxicity, and maintain analgesic efficacy while reducing the incidence and severity of side effects [19].

Parpaglioni *et al.* [15] reported a minimum intrathecal levobupivacaine dose of 10.58 mg in cesarean section. Alley *et al.* [16] evaluated three intrathecal doses of levobupivacaine and bupivacaine (4, 6 and 8 mg) in healthy volunteers and found no differences in the clinical profile of sensory and motor blocks and recovery from spinal anesthesia.

In the present study, group III showed the least reduction of mean arterial blood pressure and incidence of bradycardia compared with groups I and II. The onset and duration of sensory block showed no significant difference between the groups. Duration of motor block was the least in group III. The time to first analgesic request was significantly decreased in group III.

The findings of Onur *et al.* [14] was in accordance with ours as regards the motor and sensory block characteristics with different doses of levobupivacaine during spinal block for patients undergoing day-case knee arthroscopy. Gunusen and colleagues found

Table 2 Demographic characteristics of patients and duration of surgery

Title	Group I	Group II	Group III	<i>P</i> -value
Age (years)	27.92 ± 5.97	28.4 ± 5.62	28.75 ± 5.82	0.81
Weight (kg)	84 ± 10.58	85.25 ± 10.16	84.7 ± 9.65	0.85
Height (cm)	160.52 ± 9.45	162.32 ± 8.56	161.76 ± 8.43	0.43
ASA (I: II)	30: 10	28: 12	32 : 8	0.58
Duration of surgery (min)	37.1 ± 3.87	36.625 ± 4.48	38.1 ± 5.17	0.3

Data are presented as mean and SD except ASA presented as numbers.

Table 3 Onset and duration of sensory block, duration of motor block, and time to first analgesic request

Title	Group I	Group II	Group III	<i>P</i> -value
Onset of sensory block (min)	4.95 ± 1.46	5.2 ± 1.74	5.45 ± 1.9	0.42
Duration of sensory block (min)	201.2 ± 31.9	199.07 ± 28.9	192.5 ± 29.4	0.4
Duration of motor blockade (min)	176.02 ± 31.1	171 ± 34.2	156.9 ± 27.4	0.02*
Time to first analgesic request (min)	254.25 ± 33.9	245.1 ± 36.8	232.75 ± 29.9	0.02*

Data are presented as mean and SD; *Significant.

Table 4 Adverse effects

Title	Group I	Group II	Group III	P-value
Hypotension	22 (55)	19 (47.5)	11 (27.5)	0.037*
Bradycardia	16 (32.5)	11 (30)	6 (17.5)	0.04*
Nausea and vomiting	18 (45)	14 (35)	9 (22.5)	0.1
Pruritus	4 (10)	3 (7.5)	2 (5)	0.7
Shivering	5 (12.5)	5 (12.5)	3 (7.5)	0.7

Data are presented as *n* (%); *Significant.

that the incidence of hypotension was higher in the levobupivacaine 10 mg group, even though this group presented more effective anesthesia and greater patient and surgeon satisfaction compared with the levobupivacaine 5 and 7.5 mg groups. As a result, we believe that levobupivacaine 7.5 mg combined with fentanyl 15 µg is suitable for combined spinal-epidural anesthesia in elective cesarean section, and this is in agreement with our study [17].

Conclusion

Spinal anesthesia using small doses of levobupivacaine with combination of S-ketamine and clonidine was effective in cesarean section both intraoperatively and postoperatively with less adverse effects.

Acknowledgements

Conflicts of interest

None declared.

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