Analgesic Efficacy of Intravenous Lidocaine Infusion in Cesarean Section under Spinal Anesthesia: A Prospective Randomized Double-Blind Study

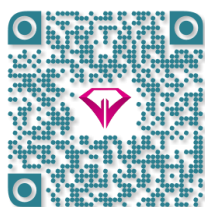**Marzieh Beigom Khezri[1]** , **Maryam Rajabi[1]**, Siamak Yaghoobi [1], Hamideh Pakniat[2]

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ABSTRACT

Background & Objective: Nowadays, conventional analgesic agents that are usually used for pain killing after cesarean sections do not provide enough analgesia with infrequent serious side effects. Lidocaine has been suggested as an adjuvant analgesic agent for postoperative pain relief. We designed this randomized double-blind, placebo-controlled study to evaluate the analgesic efficacy of intravenous lidocaine in patients undergoing a cesarean section under spinal anesthesia.

Materials & Methods: Eighty patients undergoing elective cesarean section under spinal anesthesia were randomly divided into two groups to receive intravenous 1.5 mg/kg of lidocaine 2% bolus 15 minutes prior to spinal anesthesia followed by an intravenous infusion of 1.5 mg/kg/h for 60 minutes (L group) or 0.9% sodium chloride (C group) in a double-blind fashion. The time until the first request for an analgesic, the duration of sensory and motor blockade, hemodynamic variables and adverse events were recorded.

Results: The difference in sensory (95% CI 10.18 to 18.01; $P{\leq}0.001$) and motor (95% CI 35.50 to 50.19; $P{\leq}0.001$) blockade durations between groups L and C were significant. Similarly, the mean time until the first analgesic request was longer in group L (175.37±21.43) than in group C (157.12±15.25); the difference between the two groups was significant (95% CI9.95 to 26.54; $P{<}0.001$).

Conclusion: Intravenous lidocaine given as a supplementary agent in patients undergoing cesarean section under spinal anesthesia prolonged the duration of the sensory and motor blockade of spinal anesthesia and delayed the first analgesic request by patients without hemodynamic disturbance, respiratory depression and compromising the fetus.

Keywords: Anesthesia, Cesarean section, Pain, Lidocaine, Spinal

Introduction

Despite multimodal analgesia, severe postoperative pain is still an important problem. Insufficient analgesia leads to increase plasma catecholamine concentrations, leading to adverse effect on all organ systems **(1)**. In neuraxial anesthesia by only local anesthesia, a higher dose of local anesthesia isused and is associated with higher side effects **(2,3)**. The correlation between the local anesthetic (LA) dose used in spinal anesthesia and the occurrence of maternal side effects is well recognized **(1)**. However, the reduction of LA dosage leads to increased incidence of intraoperative pain (1-3). Several drugs have been adjusted to local anesthetics to induce sufficient analgesia with lesser side effects, such as opioids, midazolam, epinephrine, ketamine, clonidine, magnesium and gabapentin **(4,5)**. Opioids are usually used to provide better analgesia and reduce side effects. However, it has been shown that a single administration of an opioid may induce delayed or persistent hyperalgesia **(6)**. Intravenous Non-Steroidal

Anti-Inflammatory Drugs (NSAIDs) are also used for post-operative pain relief. The adverse drug reactions associated with the administration of NSAIDs are related to the direct and indirect irritation of the gastrointestinal tract and platelet Aggregation **(7)**. Nevertheless, in parturients, the beneficial effects have to be balanced against maternal and neonatal side effects.

Lidocaine is an available and cheap local anesthetic that possesses analgesic, sedative, anti-inflammatory, and anti-hyperalgesic properties **(8-15)**. Nowadays, Na+ channel blockers are commonly used in neuropathic pain treatment **(11)**. It is suggested that intravenous lidocaine produces analgesia via direct or indirect interaction with Na+ channels, different receptors and nociceptive transmission pathways **(11)**. Koppert *et al.* declared that lidocaine provides analgesia during surgery and decreases central

hyperalgesia by its effect on mechanosensitive receptors (8).

In addition to the nervous system, local anesthetics have a positive effect on the hemostatic system and the inflammatory pathway (7). The safety of IV lidocaine has been evaluated in pregnant women and obstetrical anesthesia (16-18). It is reported that lidocaine administrated intravenously, can be easily detected in umbilical cord blood with no obvious effect on neonatal outcomes (16-18).

Although the analgesic and anti-hyperalgesic effect of perioperative lidocaine was shown in several studies (8-15), some other studies indicated IV lidocaine's lack of analgesic effect (19-22). Furthermore, literature is limited on the effects of the intraoperative infusion of lidocaine during spinal anesthesia in cesarean sections. The administration of all local anesthetic through the neuraxial route has been associated with neurotoxic effects in a dose-dependent manner (23). It has been suggested that clinically applicable concentrations of lidocaine can induce apoptosis, whereas higher concentrations make unspecific cell death and necrosis after used locally (23-26).

In order to reduce the incidence of complications associated with local anesthetics, we can use simultaneous different routes of local anesthetic. No investigation to date has reported neurotoxic effects at the concentrations achieved systemically (24). We hypothesized that intravenous lidocaine given with spinal anesthesia may provide better pain relief after a cesarean section compared to conventional analgesic agents, without delay in the recovery of the sensory or motor blockade of spinal anesthesia and serious side effects such as hyperalgesia, pruritus, as well as hemodynamic and respiratory depression. To test our hypothesis, we conducted this randomized double-blind, placebo-controlled study to evaluate the postoperative analgesic effect of IV lidocaine given with spinal anesthesia in patients undergoing a cesarean section.

Materials and Methods

Our clinical trial (IRCT201610023051N11) was confirmed in the ethics committee of Qazvin University of Medical Sciences (ID number: IR.QUMS.REC.1394.216). After receiving the committee's approval and obtaining 96 patients' consent who were between 18-45 years of age with ASA physical status of I or II who were planned for cesarean section under spinal anesthesia were entered in a prospective, double-blind randomized controlled trial at Kosar Hospital, which is an obstetric educational and training center in Qazvin, from December 2015 to December 2016. Exclusion criteria included severe bleeding and coagulation disorder, septicemia, a history of CNS disease, hyperthyroidism, diabetes, history of hepatorenal disease, cardiovascular diseases and complete heart block, usage of beta blockers and glycosides, hypertension, eclampsia and

pre-eclampsia, allergy to lidocaine, addiction to opioids or other psychotropic drugs, contraindication of regional analgesia, placenta previa, placental abruption, cesarean section for fetal heart rate deceleration and meconium. The recommendations by the Consolidated Standards of Reporting Trials (CONSORT) to record a randomized, controlled clinical trial (17), were followed (Figure 1).

Patients were randomly divided into two groups each comprising 40 to receive IV Lidocaine 1.5mg/kg of 2% bolus, 15 minutes prior to spinal anesthesia followed by an intravenous infusion of 1.5 mg/kg/h for 60 minutes (lidocaine group) after starting the surgery. In the same way, the patients in the control group (group C) received 0.9% sodium chloride in a double-blind procedure. Randomization achieved using computer generated random numbers in closed opaque packets. The allocation was done by a resident and the drugs were made ready by a nurse; both of them were not involved in the study. The anesthetist was not aware to the patient's group assignment, and a blinded observer documented the data of the study. No premedication was administered excepting for the drugs planned by the study protocol. All patients received an intravenous preload of 5-7 mL/kg lactated Ringer's solution before a spinal block. Then, using an aseptic technique, for all participating patients a 25-G Quincke needle was used in the sitting position via a midline approach between the L4 and L5 interspaces by the same resident who was unaware of the patients' assignment. Spinal anesthesia was achieved with 10 mg of 0.5% bupivacaine.

Patients were monitored by electrocardiogram, non-invasive measurement of blood pressure, and pulse oximetry (SpO_2). The mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO2) were recorded by an anesthetist unaware of patient assignment 5 min before the intrathecal injection and also 5, 10, 15, 30, 45, and 60 min after injection. If systolic blood pressure (SBP) was 20% below the baseline (5 min before the intrathecal injection) or less than 90 mmHg, Ephedrine 5 mg was administered intravenously. Also, if HR was less than 50 beats/min, Atropine Sulfate 0.5 mg was administered intravenously.

Before surgery, patients were educated to use the verbal rating scale (VRS) from 0 to 10 (0: no pain, and 10: maximum imaginable pain) for pain assessment. If the VRS exceeded four and the patient needed a supplement analgesic, Diclofenac Na sup was given. No additional analgesic was administered unless needing by the patient. The primary outcomes of this randomized, double-blind and placebo-controlled clinical trial was to evaluate the duration of spinal analgesia and time to first requirement of analgesic supplement. Second outcome included evaluating the onset time of sensory block, the onset of motor block, the duration of sensory and motor blockade, hemodynamic variables, the incidence of hypotension,

Table 1. Comparison of rat weights in the studied groups after 7 and 14 days. Data is expressed as mean±SEM. (n=6)

variable	C N=40	L N=40	P-value
Age (years)	29.45±6.79	30.7±6.97	0.419
Weight (kg)	79.84±6.00	77.8±9.00	0.241
Duration of surgery (min)	81.4 ±17.6	81.7 ±18.8	0.842

Data are presented as mean ± SD.C=control, L=lidocaine

Table 2. Antimicrobial susceptibilities of the K. pneumoniae isolates (n=100).

Groups	C (n=40)	L (n=40)	P-value
Onset time of sensory block (second)	77.27±2.50	76.47±2.73	0.176
Onset time of motor block (second)	91.42±5.92	88.75±5.03	0.033
Duration of sensory block (min)	128.77±8.26	142.87±9.27	<0.001
Duration of motor block (min)	190.55±19.11	233.40±13.38	<0.001
Time to first request of analgesic (min)	157.12±25.15	175.37±43.21	<0.001

Data are presented as mean ± SD.C=control, L=lidocaine

Ephedrine requirements, bradycardia, hypoxemia (saturation of peripheral oxygen (SpO_2)<90), and the adverse events of drugs such as, pruritus, and postoperative nausea and vomiting or births with a low Apgar score.

In this study, postoperative analgesia was defined as the time that the first analgesic was needed (VRS ≥4) from the time of injecting the intrathecal anesthetic. Sensory block was evaluated by pinprick test. The onset of sensory block was defined as the time between the end of injecting intrathecal anesthetic and the absence of pain at the T10 dermatome; the duration of sensory block was defined as the time for recovery of the sensory blockade to the T10 dermatome which was assessed by pinprick. Motor block was evaluated by the modified Bromage score (0. no motor loss, 1. inability to flex the hip, 2. inability to flex the knee, and 3. inability to flex the ankle), the onset of motor block was assumed as the time from the intrathecal injection to Bromage block 1, whereas the duration of motor block was defined since the time modified Bromage score was zero.

In order to estimate the sample size, data from previous similar studies was concerned. A sample size of 25 patients per group was enough to distinguish a 20 min difference in the mean duration of analgesia between groups using the Mann-Whitney U test, with a power of 0.9 and an α equal to 0.05. We recruited 40 patients in each group to allow for dropouts and protocol violations. Data was analyzed by SPSS 15 (SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed for normal distribution by the Kolmogorov-Smirnov test. Parametric data represented as mean and standard deviation (SD) and was analyzed by independent t-test. The χ2 test was used to determine the frequency of the side effects. A P-value<0.05 was considered significant, statistically.

Results

Among 96 patients subjected for this study, 16 patients were excluded for the violations of the study protocol, and 80 patients were recruited and randomly allocated to their treatment groups (Figure 1). There were no significant differences between the two groups for the demographic properties (age, body weight, and duration of surgery) (Table 1).

Table 2 shows the mean onset times of sensory block which were 76.47±2.73 and 77.27±2.50 seconds in group L and group C, respectively. The difference between the groups L and C (95% CI -1.96 to 0.36; P=0.176) was insignificant. The mean duration of sensory block time showed 142.87±9.27 minutes in group L and 128.77±8.26 minutes in group C. The difference between the two groups (95% CI 10.18 to 18.01; P≤0.001) was shown to be significant. As illustrated in Table 2, the mean onset times of motor block were 88.75±5.03 seconds in group L and 91.42±5.92 seconds in group C, with statistically significant difference between the two groups (95% CI -5.12 to -0.22; P=0.033). The mean duration of the motor blockade in group L (233.40±13.38 minutes) was longer than group C (190.55±14.11 minutes), showing a statistically significant difference between

the two groups (95% CI 35.50 to 50.19; $P \leq 0.001$). Similarly, Table 2 demonstrates that the mean time from the first analgesic demand was also significantly longer in group L (175.37±21.43 minutes) than group C (157.12±15.25 minutes), and the difference was significant (95% CI 9.95 to 26.54; $P<0.001$).

However, similar volume loading before anesthetic block transient hypotension happened at different times between the two groups. These patients were treated by 5 mg boluses of intravenous Ephedrine to keep the fall of SBP within 20% of the baseline value or at 90 mmHg. The overall difference in Ephedrine necessity between the two groups was statistically insignificant ($P=0.71$). The mean variations of MAP an HR were considered as the difference between the highest and

the lowest mean arterial pressure and heart rate between patients and compared in the groups. Table 3 shows that difference of MAP variation between two groups were insignificant ($P=0.843$), as was the overall difference in Ephedrine necessity ($P=0.71$). Also, as expressed in Table 3, the difference in the mean HR variation between the two groups was insignificant ($P=0.335$). Table 4 shows the two groups with no difference significantly in intraoperative and postoperative side effects including pruritus, shivering, nausea, vomiting, and respiratory depression. There were no adverse effects for the all newborns in our study. There were no significant differences in the Apgar scores of neonates at one ($P=0.99$) and five ($P=0.99$) minutes between the two groups.

Table 3. Changes in hemodynamic variables

Groups	C N=40	L N=40	P-value
Variation of MAP	15.97±5.72	15.67±7.66	0.843
Variation of HR	23.07±7.17	24.57±6.64	0.335

Value are presented as mean ± SD, MAP = mean arterial blood pressure (mmHg); HR = heart rate (bpm). C=control, L=lidocaine. The mean variation of MAP and HR was defined as the difference between the highest and the lowest mean arterial pressure and heart rate in each patient.
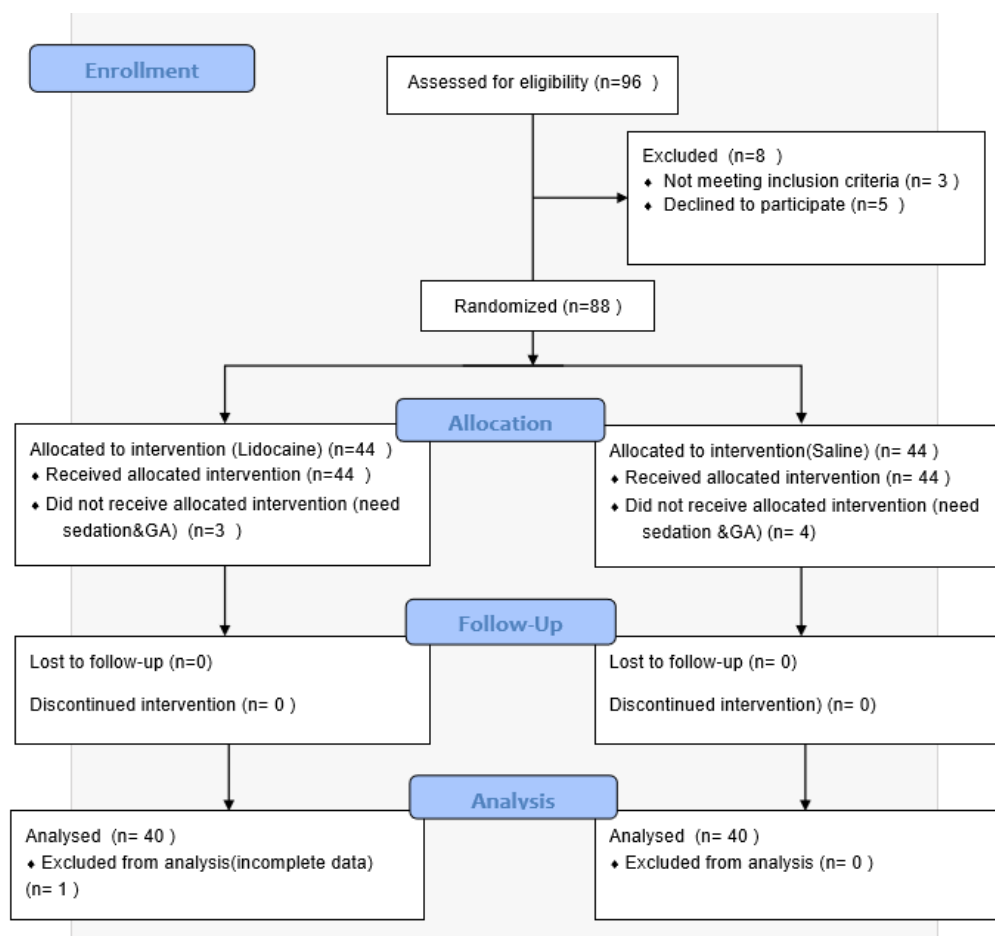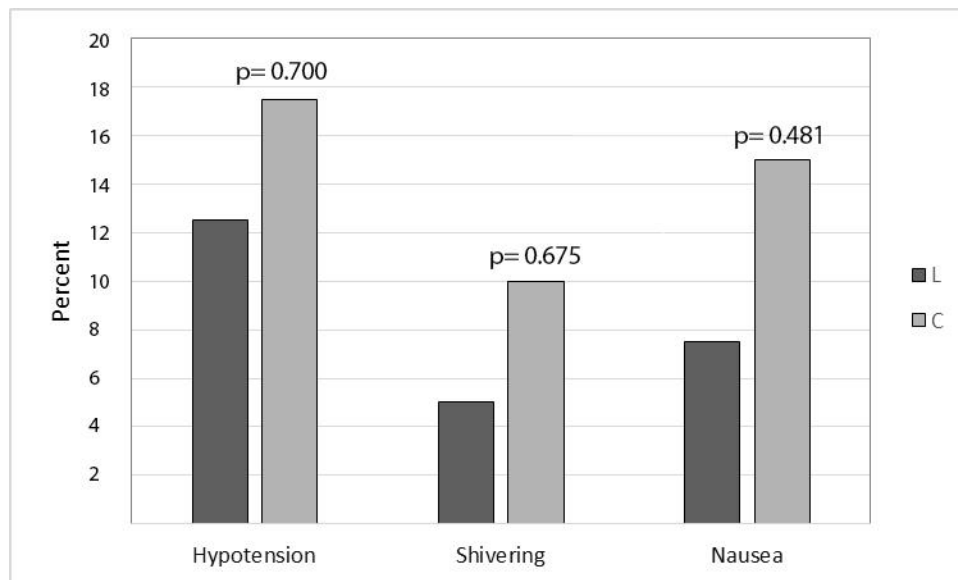

Figure 1. Consort flow diagram

Figure 2. Side effects

Values are the number of patients (%). C=control, L=lidocaine

Discussion

Based on the data found in the present study, it is concluded that intravenous lidocaine given as a supplementary agent in patients undergoing cesarean section under spinal anesthesia could cause elongated intraoperative anesthesia and prolonged the time to the first analgesic demand after cesarean delivery, as compared with the control group. These results are consistent with findings of some prior studies (14,15). However, some other studies have indicated intravenous lidocaine's lack of analgesic effect (19-22). The difference between these results can be explained by differences in population (age, gender), types of surgery and anesthesia or methodologies. Nevertheless, the analgesic properties of lidocaine have been shown to depend on either sodium channel blocking by lidocaine, or its suppression of the inflammatory process (11,22,27).

The other finding that should be emphasized on, is that IV lidocaine given as a supplementary agent in patients undergoing cesarean section under spinal anesthesia clearly increases the duration of both sensory and motor blockades; a finding contrary to our impression. In a literature search, we could not find anything that truly discusses the effect of intravenous lidocaine given as supplementary agent on the duration of sensory and sensory blocks of spinal anesthesia with bupivacaine. However, this finding is partially consistent with the idea that IV lidocaine duplicates a substantial share of the effects of regional anesthesia after visceral surgery (9,24).

We selected a dose of lidocaine within the common dose range used by other studies for post- operative pain relief (18,19). This dose of lidocaine is a judicious compromise between efficacy and toxicity for both mother and fetus (16-18).

Nevertheless, all local anesthetics are neurotoxic in a dose-dependent way. It has been revealed that clinically concentrations of local lidocaine promote apoptosis, whereas higher concentrations induced unspecific cell death and necrosis (24,26). In order to decrease the incidence of side effects associated with local anesthetics, we used different routes of local anesthetic. No study to date has reported on neurotoxic effects at the concentrations reached systemically (24).

The other finding that should be taken into account is that although transient hypotension episodes, as well as the decrease of mean arterial pressure (MAP) and vasopressor requirement in the two groups were similar, this outcome is inconsistent with the results of a study carried out by Taniguchi et al., which reported that at 4 hours after an injection of lidocaine, all of the hemodynamic variables, except for the heart rate and central venous pressure, were lower in the endotoxemic controls than in the other groups (28). The difference between these results could be explained by differences in populations (age, gender), the types of surgery and anesthesia or methodologies. However, lidocaine is considered a vasodilator due to its blocking of the sodium channels of efferent vasoconstrictor sympathetic nerves and inhibiting the production and conduction of action potentials (28). In addition, this effect may be also facilitated by the effect of lidocaine on the β-adrenoceptors of vascular smooth muscles, regulating the release of adrenaline from vasodilator nerves, and/or by stimulation of the vascular endothelium to release vasodilators such as prostaglandins or nitric oxide (28,29). Nevertheless, in

this present study, changes in hemodynamic variables were not clinically meaningful because of the small amount of variation.

All newborns in our study were free of any adverse effects, a finding in agreement with previous studies, (13-15) which reported a similar neonatal Apgar in patients who received IV lidocaine during the cesarean section compared to control group.

However, our study had some limitations; we did not evaluate the dose-response or the effect of the continuation of therapy. Further studies are recommended to evaluate the effect of different doses of lidocaine combined with lower dose of bupivacaine in spinal anesthesia to shorten the recovery of sensory and motor pathways blocked for ambulatory surgeries (9,23).

Conclusion

Based on the data found in the present study, it is concluded that intravenous lidocaine as a safe and cheap supplementary agent in patients undergoing cesarean section under spinal anesthesia, can provide a higher quality of analgesia and better patient satisfaction during surgery.

Acknowledgments

Conflict of Interest

Authors declared no conflict of interests.

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