Original Article

Effect of intravenous lignocaine infusion on bispectral index during spinal anaesthesia for caesarean section: A prospective randomised double-blind study

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ABSTRACT

Background and Aims: Systemic lignocaine has been shown to have sedative effects. We designed this randomised-double-blind, placebo-controlled study to evaluate the effect of intravenous lignocaine on the bispectral index (BIS) during caesarean section under spinal anaesthesia. **Methods:** 80 patients scheduled for elective caesarean section under spinal anaesthesia were randomly allocated to 2 study groups. Group L received intravenous 1.5 mg/kg of lignocaine bolus, 15 minutes before spinal anaesthesia followed by an intravenous infusion 1.5 mg/kg/h for 60 minutes intravenously. The patients in the control group (C group) were given 0.9% sodium chloride in a double-blind fashion. Spinal anaesthesia was performed with 10 mg of 0.5% bupivacaine. The changes of Sao2, BIS and hemodynamic variables during caesarean section, Apgar score of neonate and the incidence of adverse effects were recorded. **Results:** BIS values were lower in the L group compared to C group ($P \leq 0.001$). Comparison of mean arterial pressure (MAP) changes during spinal anaesthesia and surgery reveal statistically significant difference between two groups through repeated measure analysis ($P \leq 0.001$), but comparision of heart rate (HR) changes during spinal anaesthesia and surgery failed to reveal any statistically significant difference between two groups. ($P = 0.261$). The Apgar scores did not reveal a significant difference between the two groups at first and five minutes after delivery ($P = 0.99$). **Conclusion:** Intravenous lignocaine infusion given with spinal anaesthesia in women undergoing elective caesarean delivery providing lower BIS values without respiratory depression, in the absence of foetal compromise.

Key words: Bispectral index monitor, caesarean section, intravenous lignocaine, spinal anaesthesia

INTRODUCTION

Supplementation of spinal anaesthesia with sedatives or anxiolytics has emerged as a routine practice to improve patient satisfaction without affecting fetal and neonatal outcomes. Systemic lignocaine has been shown to be have sedative effects and also, some investigators supposed that, the hypnotic-sparing effect of lignocaine occur only during surgical stimulation, suggesting an anti-nociceptive effects.[1]

Intravenous lignocaine infusion has shown many perioperative advantage such as reducing pain, nausea, opioid consumption, facilitating early recovery of bowel function after surgery, and reducing inflammation and hospital stay in patients

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undergoing surgery of the bowel or gall bladder.[2] It has been reported that neonatal acid-base balance and gas-exchange are not adversely affected by lignocaine and it seems to be devoid of depressive effects on the neonate.[3] Furthermore, it has been suggested that the I.V infusion of 1.5 mg/kg Lignocaine 1.5% infused for 10 min, at 30 min before induction of anaesthesia, followed by a constant infusion at 1.5 (mg kg/h/) of the same solution in patients undergoing caesarean section under general anaesthesia is safe and effective in attenuating the maternal stress response in the absence of fetal Apgar scores and neonatal acid-base status compromise.[4]

The depth of sedation could be monitored with clinical criteria. But observer-based (e.g., observer's assessment of awareness/sedation (OAA/S) score has the disadvantage of frequent patient stimulation, which may alter the actual level of sedation. Nevertheless, the bispectral index (BIS) provides a continuous objective assessment without patients involvement.[5]

A number of studies reported a significant changes in BIS values during spinal anaesthesia and the sensitivity of the BIS monitor to detect such a small change in sedation level.[6,7] One study pointed out the lack of sensitivity of the BIS monitor for spinal anaesthesia-induced sedation.[8] Even though several studies have demonstrated that local anaesthetics may have enhanced the sedative effects of inhalation or intravenous hypnotic agents used in general anaesthesia,[1,2] literature on the effects of intraoperative infusion of lignocaine during spinal anaesthesia on the BIS and hemodynamic changes was limited. Our hypothesis was that lignocaine may possess sedative effect without serious fetal and maternal side effects by decreasing BIS values in patients undergoing elective caesarean section under spinal anaesthesia. To test our hypothesis, we designed this study to evaluate the influence of the infusion of lignocaine on the bispectral index in patients undergoing caesarean section under spinal anaesthesia.

METHODS

Following institutional ethical committee approval (dated 9th December 2015; approval number IR.QUMS.REC.1394.216) and informed patients consent, 96 patients aged between 18-45 years of age with ASA physical status of I or II scheduled for elective caesarean section under spinal anaesthesia were recruited prospectively in a double-blinded randomised manner during December 2015 to December 2016. Exclusion criteria included complete heart block, severe bleeding and coagulation disorder, septicemia, history of Central Nervous System (CNS) disease, hyperthyroidism, hypertension, history of hepatorenal disease, cardiovascular disease, diabetes, allergy to lignocaine, placenta previa, placental abruption, caesarean induced deceleration fetal heart rate (FHR), meconium, addiction to opioids or other psychotropic drugs, contraindication of regional analgesia, eclampsia and preeclampsia, user of beta blocker and glycoside.

Patients were randomly allocated to one of two groups of 40 each to receive intravenous 1.5 mg/kg of lignocaine bolus, 15 minutes prior to spinal anaesthesia followed by an intravenous (IV) infusion 1.5 (mg/kg/h) for 60 minutes (L group) after the onset of surgery. The patients in the control group (group C) were given likewise using 0.9% sodium chloride in a double-blind fashion. Randomisation was performed using computer-generated random numbers in the sealed opaque envelopes. The allocation was managed by a resident external to the project and the drugs prepared by a nurse not involved in the study. The anaesthetist was blinded to the patient's group assignment, and the observer was a clinical nurse blinded to the randomised intervention who performed all patient assessments and recorded the study data. No premedication was given except for the drugs predetermined by the study protocol. All patients received an intravenous preload of (55-7 ml/kg) lactated Ringer's solution before subarachnoid block. After using an aseptic technique, a 25-gauge Quincke needle was inserted intrathecally via midline approach between L4-5 interspaces with the patient in the sitting position by the same anaesthetist who was unaware of the patients' assignment. Spinal anaesthesia was performed with intrathecal injection of 10 mg of 0.5% hyperbaric bupivacaine. The BIS values, mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were recorded by an anaesthetist blinded to the patient group 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, 0.5 mg of atropine sulfate was administered intravenously.

The surgery was allowed to commence when the sensory block level reached T6. To relieve the postoperative pain, supplement analgesic, diclofenac Na suppository 100 mg every 8 hours was given pain as needed (q 8 h PRN). We observed all patients undergoing cesarean section under spinal anesthesia until the return of motor block and ability of patients to move ankle, which is usually prolonged to 1 hour after the patients' arrival to PACU.

The primary outcome of this randomised, double-blind and placebo-controlled clinical trial was to evaluate the changes of (BIS) values during caesarean section (60 minutes after the start of surgery) and. The secondary outcomes were to assess the hemodynamic variables and adverse events such as hypoxemia (saturation of peripheral oxygen (SpO_2) <90), headache, shivering, pruritus, neonatal Apgar scores, postoperative nausea and vomiting.

Based upon the previous studies,[3,9] and a pilot study using a lignocaine infusion on 20 patients, a sample size of 25 patients per group was required to detect a 20 %difference in the mean of BIS values between the groups using the independent *t*-test, with a power of 0.9 and an α equal to 0.05. We included 40 patients in each group to allow for dropouts and protocol violations. Data were analysed using SPSS (SPSS 15, SPSS Inc, Chicago, IL, USA). Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Parametric data were expressed as mean and standard deviation (SD) and analyzed by independent *t*-test. The effect of time on hemodynamic and BIS parameters was analyzed using repeated measurement analysis of variance. The χ^2 test was used to analyze the Apgar scores. A $P < 0.05$ was considered as statistically significant.

RESULTS

96 patients were recruited in the study, but 16 of them were excluded due to logistical reasons or other factors violating the study protocol [Figure 1]. There were no significant differences between the two groups regarding the demographic characteristics (age, body weight) and duration of surgery [Table 1].

Comparison of bispectral index changes during spinal anaesthesia and surgery were statistically significant difference between two groups through repeated measure analysis as shown in Figure 2. The BIS values

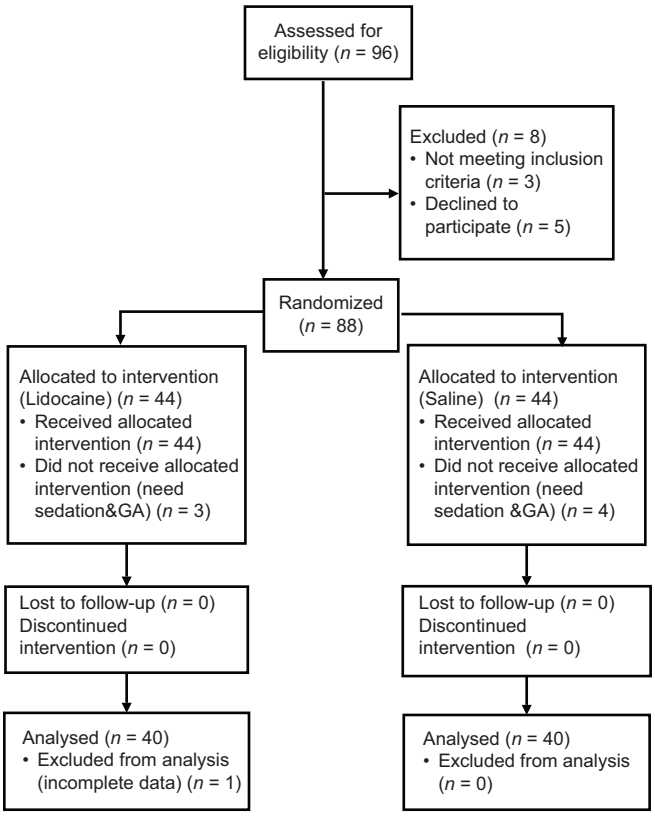

Figure 1: Consort flow diagram

were lower in the L group compared to C group at all the times (C95%CI 6.89 to 7.92; $P < 0.001$).

Despite pre-block volume loading, transient hypotension occurred at various time points in two groups. These patients were treated with 5 mg of (IV) ephedrine boluses to maintain SBP within 20% of baseline values or 90 mmHg. Comparison of mean arterial pressure (MAP) changes between two groups through repeated measure analysis was statistically significant ($P < 0.001$), but the comparison of heart rate (HR) changes during spinal anaesthesia and surgery failed to reveal any statistically significant difference between two groups through repeated measure analysis ($P = 0.261$) as shown in Figure 3. In addition, the overall difference in ephedrine requirement between the two groups was not significant ($P = 0.71$). There were no significant difference among the Apgar scores of neonates at one ($P = 0.99$) and five ($P = 0.99$) minutes between the two groups. The comparison of the SpO_2 changes during spinal anaesthesia and surgery was insignificant between two groups through repeated measure analysis ($P = 0.545$). Table 2 shows the other adverse effects such as pruritus, shivering, headache, nausea in two groups were comparable.

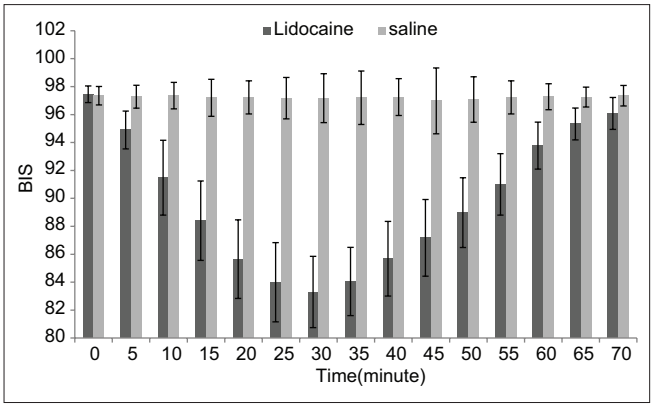

Figure 2: Bispectral Index (BIS) in the two groups. BIS values were expressed as mean and error bars representing standard deviation (SD) value

DISCUSSION

This study demonstrated that intravenous lignocaine infusion given with spinal anaesthesia in women undergoing elective caesarean section, provide sedative effects with lower BIS values in the absence of fetal compromise and respiratory depression. The overall results of current study are consistent with some studies which reported that systemic lignocaine has been shown to have sedative effects.[3,5,10,11]

It was shown that lignocaine or bupivacaine increased the hypnotic effect of IV thiopentone and propofol in a dose dependent manner.[5,10] The results of this study are indirectly supported by studies which have shown the sedative effects of general anaesthesia and decrease the dose of propofol or inhalational anaesthetics required for induction of anaesthesia when administered by a variety of routes.[5,10,12] These studies suggest that lignocaine may have attenuated the intensity of nociceptive signals being transmitted to the central nervous system.[12,13]

On the opposite side, Luo *et al.* in their studies reported that systemic lignocaine did not diminish or abolish the brain response to acute noxious electric stimulation based on functional magnetic resonance imaging on rats.[14] However, most of the other studies have shown that lignocaine has sedative effects in the central nervous system, so it can be used as an anaesthetic adjunct during general anaesthesia.[5,12,13,15] Nevertheless, literature on the effects of intraoperative infusion of lignocaine during spinal anaesthesia on the BIS and hemodynamic changes was limited. The results of this study showed that BIS monitor could detect small change in sedation level and is sensitive and valuable device for patients undergoing surgery

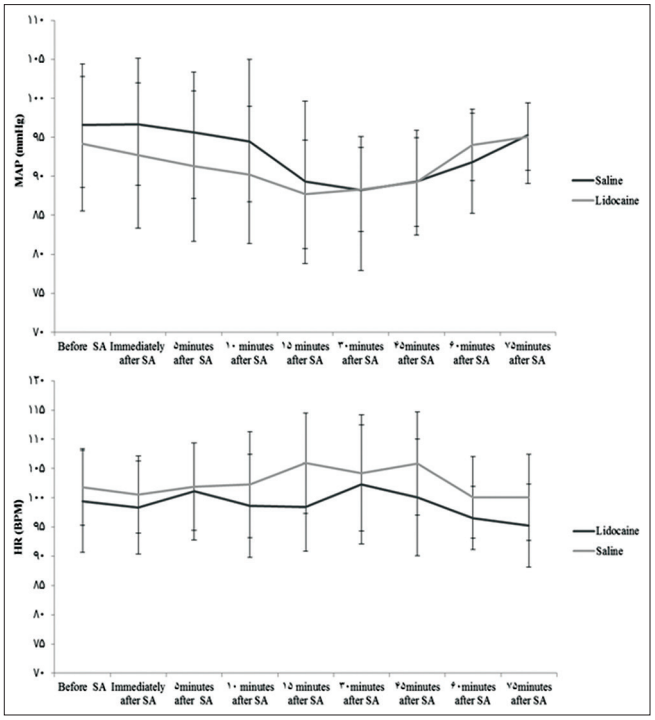

Figure 3: Hemodynamic variables in the two groups. Data are presented as mean ± SD, MAP: Mean arterial blood pressure (mmHg), HR: Heart rate (bpm), SA: Spinal anaesthesia. *P* values are from Repeated measures analysis

Table 1: Demographic data for two study groups

Variable	Saline	Lignocaine	*P*
Age (years)	79.6±45.29	97.6±7.30	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

Table 2: Side effects

Variable	Category	Groups		*P*
		Lignocaine *n* (%)	Saline *n* (%)	
Ephedrine requirement	Yes	(5.12) 5	(5.17) 7	0.765
	No	(5.87) 35	(5.82) 33	
Shivering	Yes	(5) 2	(10) 4	0.675
	No	(95) 38	(90) 36	
Nausea	Yes	(5.7) 3	(15) 6	0.481
	No	(5.92) 37	(85) 34	

Values are (percent) number of patients

under spinal anaesthesia, and this finding is consistent with results of Ozkan-Seyhan *et al.* and Kim *et al*.[3,9] studies.

The another finding which should be taken into account is that transient hypotension episodes and decreasing of mean arterial pressure (MAP) in lignocaine group was greater than control group, but the heart rate (HR) changes during spinal anaesthesia and surgery and vasopressor requirement in the two groups were similar. This finding is consistent with the results of Taniguchi

et al. who reported that at 4 hours after injection of lignocaine, all of the hemodynamic parameters except the central venous pressure and heart rate were lesser in the endotoxemic controls than in the other groups.[16] Lignocaine has been considered as a vasodilator due to its action of inhibiting the sodium channels of efferent vasoconstrictor sympathetic nerves and preventing the conduction of action potentials.[17] Furthermore, it may be also facilitated by the effect of lignocaine on the β-adrenoceptors of vascular smooth muscle, lessening the release of adrenaline from vasodilator nerves, and/or by stimulation of the vascular endothelium to release vasodilators such as prostaglandins or nitric oxide.[18,19]

Nevertheless, this finding implies that these changes may not be clinically meaningful because of the vasopressor requirement in the two groups were similar, and in other words, the infusion of lignocaine had the minimal clinical effect hemodynamic parameters.

All newborns in our study were free of any adverse effects, a finding to be similar to previous studies.[7,8,20]

Since literature on the effects of intraoperative infusion of lignocaine during spinal anaesthesia on the BIS was limited, we chose a dose of lignocaine with the acceptable efficacy and the least toxicity for mother and the fetus.[7,12,20,21]

However, our study had some limitation in that we did not evaluate the placental transfer of lignocaine, maternal satisfaction, the dose response effects of lignocaine on BIS changes. Future clinical trials will help provide more definitive results.

CONCLUSION

Based on the present data, intravenous lignocaine infusion in women undergoing elective caesarean section under spinal anaesthesia could provide sedative effects with maternal lower BIS values without maternal and fetal compromise.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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