Original Article

Analysis of intrathecal clonidine as an adjuvant in the subarachnoid block on post-operative analgesia and safety profile in obstetric surgeries: A randomised controlled trial

Swati Sujeer,[1] Reena Ravindra Kadni,[1] Leeberk Raja,[2] Varghese K. Zachariah,[1] Priya Pushpavathi[1]

Departments of [1]Anaesthesia and [2]Community Medicine, Bangalore Baptist Hospital, Bengaluru, Karnataka, India

Abstract

Background: Clonidine has long been considered an 'off-label' medication for use in obstetrics. Different doses of clonidine are studied and it is found that higher doses are associated with sedation and haemodynamic instability. Hence, we analysed a mini dose of intrathecal clonidine of 30 μg for its impact primarily on post-operative analgesia and secondarily on the quality of spinal anaesthesia, haemodynamics, sedation and neonatal outcomes in caesarean sections.

Methods: One hundred participants were randomised them to receive the interventions. Group B received 11 mg of 0.5% hyperbaric bupivacaine (2.2 mL) and Group C received 10 mg of 0.5% hyperbaric bupivacaine with 30 μg of clonidine (2.2 mL). Motor, sensory and haemodynamic characteristics with time to rescue analgesics were observed in both the groups and analysed using univariate analysis.

Results: Time to rescue analgesics ($P < 0.001$), visual analogue scores in the post-operative period and time to grade 0 Bromage ($P = 0.002$) were statistically significant in Group C. Time to T6 dermatomal level and time to grade 4 Bromage were similar in both the groups. Apgar scores were comparable and no adverse events were noted in both the groups.

Conclusions: A low dose of intrathecal clonidine (30 μg) can prolong the duration of post-operative analgesia in caesarean section with comfortable maternal sedation and good neonatal outcome without significant complications.

(Clinical Trials Registry- India, number CTRI/2018/08/015250)

Keywords: Analgesia caesarean section, clonidine, spinal anaesthesia, alpha 2-adrenergic agonist

Address for correspondence: Dr Reena Ravindra Kadni, Senior Consultant, Department of Anaesthesia, Bangalore Baptist Hospital, Hebbal, Bellary Road, Bengaluru 560 024, Karnataka, India.
E-mail: docreena1@gmail.com

Submitted: 05-Feb-2022 **Revised:** 15-Jun-2022 **Accepted:** 22-Jun-2022 **Published:** 01-Dec-2022

INTRODUCTION

Lower segment caesarean section (LSCS) surgeries form a major category of obstetric surgeries. The preferred anaesthetic technique of choice for LSCS has been spinal anaesthesia (SA) traditionally.[1] The advantages of this technique range from being well awake during surgery, resulting in better mother–child bonding experiences to avoid polypharmacy and anaesthetic depressant drugs. Opioids as intrathecal adjuvants ensure superior quality pain relief but are associated with pruritus, nausea,

Access this article online	
Quick Response Code:	Website: www.jcsr.co.in
	DOI: 10.4103/jcsr.jcsr_25_22

How to cite this article: Sujeer S, Kadni RR, Raja L, Zachariah VK, Pushpavathi P. Analysis of intrathecal clonidine as an adjuvant in the subarachnoid block on post-operative analgesia and safety profile in obstetric surgeries: A randomised controlled trial. J Clin Sci Res 2023;12:28-34.

vomiting, urinary retention and late, unpredictable respiratory depression.[2] Clonidine has been used as an additive intrathecally in various lower-limb orthopaedic surgeries, urological surgeries and lower abdominal surgeries.[2,3] A need for opioid-free anaesthesia has been a driving force to look out for other safer alternative drugs.

The benefit of clonidine as an additive to hyperbaric bupivacaine has been known to result in prolonged, complete and effective analgesia. It also causes a reduction of up to 18% of the total intrathecal dose of hyperbaric bupivacaine.[4,5] Current evidence is not clear on the appropriate dose of clonidine to be administered and haemodynamic instability is common with higher doses.[1] We considered a single intrathecal dose of clonidine 30 μg in parturients undergoing LSCS under SA to analyse analgesia with a safer maternal and neonatal profile as a lower dose of clonidine is associated with decreased incidence of adverse effects.[6]

The primary objective of the research was to determine the effect of clonidine 30 μg on post-operative analgesia. The secondary objectives were to assess the sensory and motor block parameters, haemodynamic variations, sedation scoring and Apgar scores in newborns.

MATERIAL AND METHODS

We conducted a randomised control led trial on parturients requiring LSCS under SA in a tertiary care teaching hospital between August and December 2018 after obtaining approval from the institutional review board on Jan 30, 2018 and registered with Clinical Trials Registry- India (CTRI/2018/08/015250). According to the current evidence, the total duration of analgesia between the bupivacaine group and the bupivacaine with clonidine group was 154.2 ± 35.1 and 230.4 ± 54.6.[2] We calculated a sample size of 37 in each group with a mean difference of 30 min and 95% confidence interval and a power of 80%. However, we recruited 50 in each group with a total sample size of 100. The study was in adherence with the consort guidelines (Figure 1).

Women with 37 weeks of gestation posted for elective LSCS were recruited. Indications for LSCS such as previous LSCS, cephalo-pelvic disproportion, failure of progression of labour and abnormal foetal presentation with a singleton pregnancy were included in the study. The exclusion criteria were pregnancy-induced hypertension, placenta previa, acute foetal distress, abnormal coagulation profile, twin pregnancy, pregnancy with cardiac and respiratory problems and body mass index (BMI, Kg/m^2) >30. Those fulfilling the inclusion criteria were enrolled in the study after a pre-anaesthetic check-up and written informed consent. Participants in both the study groups were blinded regarding the intervention. They were randomised into two groups (Group B and Group C) using computer-generated random number tables, which were enclosed in sealed envelopes.

Pre-medication with intravenous (IV) ranitidine 50 mg and metoclopramide 10 mg was given. Co-loading was done with 10 mL/Kg of Ringer's lactate solution. Standard monitoring was done using non-invasive arterial blood pressure, pulse oximetry and electrocardiography in both the groups.

With full aseptic precautions, SA was administered with patients in the left lateral position at L3-L4/L2-L3 level through a midline approach using a 26G Quincke. In Group B, patients received 11 mg of 0.5% hyperbaric bupivacaine (2.2 mL) and patients in Group C received 10 mg of 0.5% hyperbaric bupivacaine with 30 μg of clonidine (2.2 mL). The total volume of drugs in each group was 2.2 mL. Hyperbaric bupivacaine was directly loaded into the 5-mL syringe up to 2.2-mL marking and clonidine 30 μg (0.2 mL) was drawn in a sterile tuberculin 1-mL syringe and then mixed with 2 mL of hyperbaric bupivacaine in a 5-mL syringe.

We monitored baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure and oxygen saturation (SpO_2) and recorded at 1, 3 and 5 min. These parameters were then recorded at the intervals of 5 min to 30 min and at every 15 min till the end of the surgery. Patients in both the groups were given diclofenac suppository 75 mg per rectally at the end of the surgery. The primary outcome of post-operative analgesic effect was measured with the time to request for first rescue analgesia and visual analogue score (VAS).[2,7]

Patients were given iv paracetamol 15 mg/Kg stat as a rescue analgesic and continued every 8 h once the patient complained of pain in both the groups. Time to request the first rescue analgesia was the endpoint of our study which reflected the total duration of analgesia. The secondary objectives portrayed the safety profile of the drug. The outcome variables were assessed in the following ways. The sensory block level assessment was done with the loss of temperature discrimination to the cold swab along the midclavicular line. The motor block assessment was done using a modified Bromage scale. SA parameters were observed in terms of the time taken to achieve T6 sensory level, grade 4 motor block, the time to two dermatomal

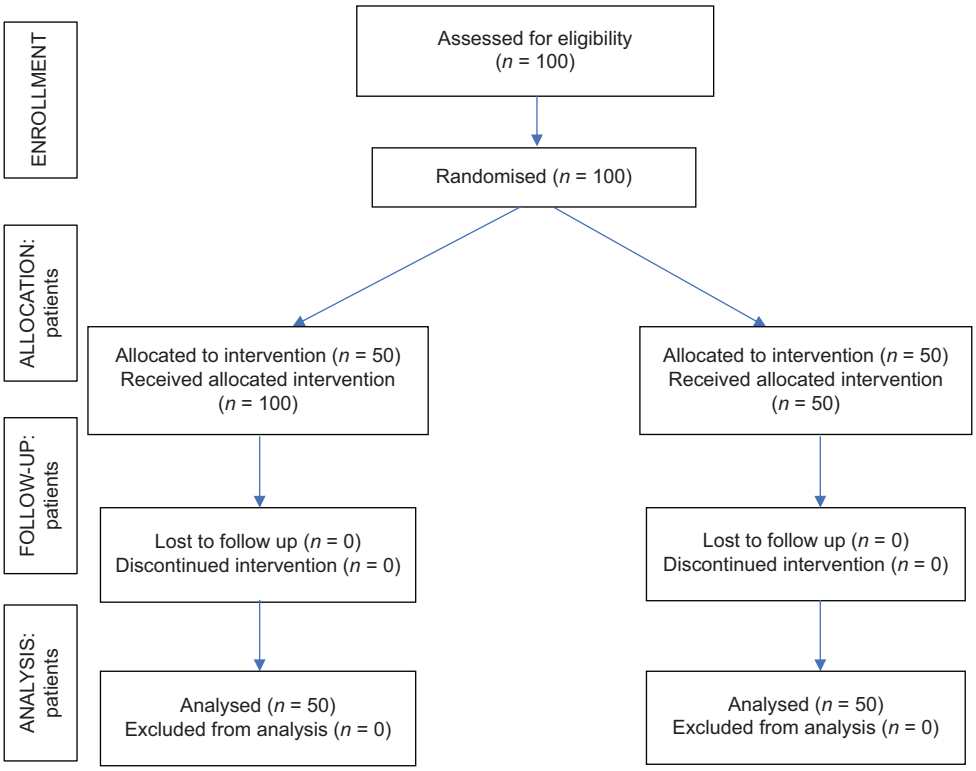

Figure 1: Consort flow diagram

sensory regression, sensory regression to L1 dermatome, motor block regression to modified Bromage 0 and changes in haemodynamic parameters.

The Apgar scores of the delivered babies were recorded at 1, 5 and 10 min.[5] The patient's sedation was assessed using the Ramsay sedation scale (RSS) before the block and thereafter every 15 min.[7] Hypotension (decrease in SBP >20% from the baseline value) was treated with IV ephedrine 6 mg. Bradycardia (pulse rate <50/min) was treated with iv atropine 0.6 mg. Oxygen saturation measured by pulse oximeter (SpO_2) <95% was treated with oxygen supplementation with a face mask at 5 L/min.

Statistical analysis

The data were entered into Microsoft Excel (2013). Descriptive and inferential statistical analysis was done. Continuous variables were presented as mean and standard deviation. Categorical variables were presented as frequency and percentages. Student *t*-test (two-tailed, independent) was used to test the association outcomes with continuous variables between the two groups. Chi-square/Fisher's exact test was used for categorical variables. $P < 0.05$ was considered statistically significant. Statistical analysis was done using the Statistical analyses were performed using the SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

The demographic characteristics in both the groups were similar (Table 1). In Group B, patients complained of pain after 201 min from the time the intrathecal drug was administered and Group C required rescue analgesics after 387 min which was delayed significantly ($P < 0.0001$). There was no difference in the mean duration of time to achieve (T6), time to grade 4 motor block and two-segment regressions between the two groups. However, the time to sensory level regression to L1 dermatome ($P = 0.004$) and time to grade 0 Bromage ($P = 0.002$) were significantly longer in Group C (Table 2).

Table 1: Age and body mass index distribution in both the groups

Variable	Group B	Group C	*P* value
Age (years)	29.9±4.6	29.0±4.1	0.337
BMI (kg/m^2)	25.37±1.21	25.73±1.35	

Data are presented as mean±standard deviation
BMI=Body mass index

Table 2: Intraoperative variables of spinal anaesthesia in both the groups*

Time (min)	Group B	Group C	*P*-value
Time to reach T6	3.5±1.3	3.8±2.3	0.476
Time for grade 4 motor block	4.5±2.00	4.3±2.2	0.636
Two-segment regression	70.3±22.2	79.9±28.7	0.065
Sensory L1 dermatome	98.8±27.8	118.0±37.0	0.004
Bromage 0	125.7±27.6	149.3±44.7	0.002

*Data are presented as mean ± standard deviation

There was a decreasing trend for blood pressures in both the groups. The SBP (mm Hg) was not significant between both the groups in the intraoperative period. The fall in SBP in the immediate post-operative period was found to be statistically significant between the two groups. In the post-operative period, Group C had a significant drop in DBP during the post-operative period compared to Group B. There number of cases in both the groups who required ephedrine to treat the hypotension were similar. However, there was no incidence of persistent hypotension or hypotension not responding to vasopressor. A trend of lower HR (70–76/min) was seen in Group C than Group B. No episode of bradycardia was noted in both the groups (Table 3).

At 1 h from the administration of the study drug, the mean RSS was significantly higher in Group C compared to Group B ($P < 0.001$) $P < 0.001$. Up to 5 h post-SA, it continued to the RSS remained significantly higher in Group C. However, the sedation score did not exceed grade 3 (Table 4).

VAS scores in the post-operative period, were significantly lower in Group C compared to Group B ($P < 0.001$), and this persisted for up to 3 hours (Table 5).

The Apgar score in the newborns were similar in both the groups. At 1, 3 and 5 min, the scores in Group B were 8.10 ± 0.30, 8.96 ± 0.20 and 9.12 ± 0.33, and in Group C, the scores were 8.06 ± 0.24, 8.96 ± 0.20 and 9.20 ± 0.40, respectively. No adverse events were noted in both the groups.

DISCUSSION

The post-operative analgesic duration was prolonged by 186 min in Group C with a lower VAS score in the same group. Other parameters such as the time to achieve (T6) and grade 4 motor block were similar between the two groups. However, the time to sensory level regression to L1 dermatome and time for motor block regression to Bromage grade 0 were significantly longer. No adverse fall in blood pressure or HR was observed in both the groups. RSS scores were higher throughout the intraoperative and post-operative period in Group C up to 5 hours, but none exceeded a score of 3, though it was clinically significant but was not the same statistically. Apgar score in the newborns was similar in both the groups.

Obstetric patients limit the usage of many additives owing to foetal safety profile. Clonidine, an α_2-adrenergic agonist, has an analgesic effect mediated by postsynaptically situated α_2-adrenoreceptors in the dorsal horn of the spinal cord, and evidence suggests that it may be enhanced in pregnancy.[1,8] Its role as an adjuvant to bupivacaine in intrathecal space leads to a decreased need for intraoperative and post-operative analgesia.[1,2,3,8,9] We considered a single dose of clonidine 30 μg intrathecally as an additive to bupivacaine to analyse its efficacy in obstetric patients. We hypothesised that the low-dose intrathecal clonidine as an adjuvant is sufficient for better post-operative analgesia with minimal adverse effects on maternal and neonatal outcomes.

The total duration of analgesia in patients undergoing LSCS with intrathecal clonidine 75 μg premixed with bupivacaine was found to be 337 ± 18.2 min,[7] whereas we observed a longer duration of 387.94 ± 152.47 min with a lower dose. Post-operative analgesia of 360.71 ± 86.51 min was observed with intrathecal clonidine 50 μg in obstetric patients which was comparable with our study.[4] A meta-analysis[8] presented that the time to first rescue analgesia increased by 135 min overall with the administration of clonidine. However, all the studies included had used clonidine in a dose of 75 μg or more. Overall, it was observed in our

Table 3: Intraoperative and post-operative systolic and diastolic blood pressure variations in both the groups*

Time (min)	SBP			DBP			HR		
	Group B	Group C	*P*-value	Group B	Group C	*P* -value	Group B	Group C	*P* -value
Pre-operative	119.0±13.6	120.2±12.3	0.633	72.4±13.1	74.1±13.1	0.513	95.1±12.3	90.9±10.0	0.1
15	103.9±18.8	103.1±18.1	0.825	55.6±12.4	57.8±15.6	0.433	93.3±14.8	88.9±15.4	0.148
30	99.3±14.7	101.5±13.4	0.445	53.8±10.8	55.5±12.4	0.471	93.0±14.1	89.5±15.1	0.227
45	104.8±14.8	100.7±13.9	0.17	59.2±12.9	53.7±10.4	0.024	92.4±12.9	84.9±15.3	0.011
60	109.1±15.2	103.5±11.1	0.069	63.9±13.8	57.7±11.4	0.032	89.9±12.9	83.4±13.9	0.032
90	116.6±11.8	113.3±11.9	0.536	69.2±10.8	69.3±9.6	0.995	179.7±288.4	81.1±12.2	0.248
Post-operative	112.6±13.8	104.4±12.4	0.002	68.9±13.1	63.4±11.5	0.028	85.0±13.3	76.5±11.8	0.001
15	111.8±12.7	103.0±12.7	0.001	69.6±10.9	63.4±12.2	0.009	83.4±13.5	73.3±12.5	<0.001
30	113.2±11.1	101.9±17.6	<0.001	71.0±10.7	63.6±12.3	0.002	81.0±12.6	71.8±12.0	<0.001
45	113.6±13.2	106.5±12.9	0.014	70.7±10.3	66.8±12.4	0.121	81.1±14.5	71.3±11.5	0.001
60	115.7±12.7	108.7±12.8	0.028	73.0±8.5	68.8±13.1	0.136	80.0±14.9	71.7±11.8	0.012

*Data are presented as mean±standard deviation

SBP=Systolic blood pressure; DBP=Diastolic blood pressure; HR=Heart rate

Table 4: Ramsay sedation score comparison in both the groups*

Time (min)	Ramsay Sedation Score				
	Group B	Group C	Group B (min-max)	Group C (min-max)	*P*-value
Before surgery	1.4±0.5	1.3±0.5	1–2	1–2	0.415
1	1.5±0.5	1.4±0.5	1–2	1–2	0.314
3	1.8±0.4	1.8±0.5	1–2	1–2	0.832
10	1.9±0.3	2.0±0.4	2–2	2–2	0.369
15	2.1±0.5	2.3±0.6	2–3	2–3	0.216
30	2.3±0.5	2.5±0.6	2–3	2–3	0.115
60	2.2±0.6	2.7±0.5	2–3	2–3	<0.001
120	2.2±0.7	2.9±0.4	1–3	3–3	<0.001
180	2.0±0.7	2.8±0.4	1–3	2–3	<0.001
240	2.1±0.7	2.7±0.5	1–3	2–3	<0.001
300	1.9±0.7	2.4±0.6	1–3	2–3	0.001

*Data are presented as mean±standard deviation

Table 5: Visual Analogue Score comparison in both the groups*

Time (min)	Visual analogue score		
	Group B	Group C	*P*-value
15	0.4±0.8	0.1±0.7	0.073
30	1.2±1.3	0.1±0.3	<0.001
45	2.1±1.5	0.2±0.5	<0.001
60	3.2±1.6	1.0±1.2	<0.001
120	3.9±1.4	1.3±1.2	<0.001
180	3.9±1.5	2.0±1.3	<0.001
240	3.2±1.5	2.5±1.2	0.213
300	3.6±1.1	3.2±1.4	0.5
360	3.8±1.3	3.3±1.3	0.559
420	4.3±1.2	3.7±1.2	0.401
480	4.0±0.0	4.0±0.9	1
720	4.0±0.0	5.0±0.0	0.073

*Data are presented as mean±standard deviation

study that low-dose clonidine provided equivalent analgesia as higher doses.

In contrast, another study[10] observed 422.06 ± 112.47 min of analgesia in a similar group of patients with intrathecal clonidine 30 μg which was profoundly higher than our study. A low dose of intrathecal clonidine 30 μg can provide a significant duration of analgesia in obstetric patients, which raises the question of the requirement to use higher doses. A study[7] compared two groups of premixed and sequential drug administration of intrathecal clonidine 75 μg with bupivacaine and found that the time to the sensory block of T4 was 4.4 ± 0.3 and 3.2 ± 0.13 min, respectively. In our study, it was observed that Groups B and C took 3.51 ± 1.34 and 3.78 ± 2.28 min, respectively, to achieve T6 sensory level. We observed that with a low dose of intrathecal clonidine, the onset time to surgically required sensory block was achieved in an acceptable time. In Group B, 24/50 and, in Group C, 28/50 had achieved T4 sensory block by 5 min. Yet another study in the parturient observed that the onset of sensory block to T6 was 2.1 ± 1.6 min and 2.4 ± 2.1 min with intrathecal clonidine doses of 50 and 75 μg, respectively, which were quite faster onset.

Similarly, the time to Bromage grade 4 in a study[7] was 5.8 ± 0.4 and 4.8 ± 0.4, and in our study, it was 4.5 ± 2.0 and 4.3 ± 2.2 min in Groups B and C, respectively. Complete motor block was achieved faster in our study with low-dose clonidine. We assume that less dilutional effect and decreased impact on baricity of intrathecal bupivacaine by the low dose of clonidine used made the difference in our results. In contrast, a quicker onset was observed in a study, with 3.29 ± 2.65 and 3.2 ± 2.7 min with clonidine groups in comparison to our values.[4] The total volume of drug they used was 2.5 mL compared to 2.2-mL volume in our study which could have facilitated the faster onset of both sensory and motor blocks.[4]

A study[11] observed that the onset of sensory and motor blocks depended on the dose of bupivacaine rather than clonidine. The authors[11] concluded that clonidine in a dose of 1 μg/Kg effectively reduced the dose of bupivacaine. The incidence of hypotension in Group BC_{50} was 22.9% and in Group BC_{75} was 23.5% in a study.[4] We observed nearly 60% hypotension in both the groups which were not clinically significant and responded to vasopressor. They preloaded their patients with 12–15 mL/Kg of colloids, whereas we co-loaded with 10 mL/Kg of crystalloids, which could have resulted in a higher incidence of defined hypotension. The role of prophylactic vasopressors could have played a role in its prevention.

In a study[4] the duration of motor block was 224.7 ± 35.2 min with 50 μg clonidine versus 230.5 ± 33.2 min with 75 μg clonidine. In our study, the two groups had a moderately significant difference in the time taken to reach Bromage 0 postoperatively with Group B 125.7 ± 27.6 min and Group C 149.3 ± 44.7 min, which was less compared to the above study. The prolonged duration of the motor blockade can benefit in difficult surgical circumstances but not may be required in all. It was observed that the time duration taken for motor block regression was significantly higher when higher doses of clonidine were used.[8]

The time to two-segment regression time was nearly 78 min a study[12] where intrathecal clonidine 75 μg was used which was comparable to our study. Time duration to two-segment regression and Bromage grade 0 was not statistically significant, which can be attributed to the

low dose of clonidine. Prolongation of nerve blockade by clonidine is explained to be dose dependent.[13] The difference in RSS in our study at 1 hour after SA was strongly significant between the groups with Group C subjects having a slightly higher sedation score at 2.7 ± 0.5 as against Group B with 2.2 ± 0.6. However, sedation never exceeded grade 3. Additional oxygen was not required by any patient. A study[7] observed that majority of patients had sedation scores of 2 or 3 with clonidine 75 μg. The incidence of sedation was higher with higher doses of intrathecal clonidine.[8] The low dose of clonidine was not associated with sedation compared to higher doses as reported in other studies.[10,14] When sedation is desirable, higher doses can be used. A study[15] used 75 μg of clonidine with 100 μg of morphine and a predominance of drowsy patients were observed in both the groups. The addition of opioids along with clonidine can all the more increase the sedation scores.

Breastfeeding was instituted in both the groups within half-an-hour of shifting the patient to the postoperative care unit and the sedation did not affect the bonding between mother and baby. Sedation with clonidine 30 μg was comparable with the sedation associated with SA in our study. In terms of neonatal outcomes, no significant differences were seen with Apgar scoring at 1 and 5 min in the patients receiving clonidine ≥75 μg and placebo[8] and we observed the same in our findings.

We assessed the clinically important parameters to achieve safe anaesthesia and analgesia in our participants. A meta-analysis[16] concluded that intrathecal clonidine is a safe and effective adjuvant in obstetric neuraxial anaesthesia practice. A low dose of intrathecal clonidine as an alternative option can be considered to practice safely for obstetric patients. Clinical researches as larger randomised trials and systematic reviews for only low doses of intrathecal clonidine can be considered in the future for confirmation of its effective role in obstetrics. From our findings in this study, we suggest that a dose of clonidine 30 μg can be safely considered in parturients.

Our study had few limitations. Twenty-four-hour analgesic consumption was not included in the study. Double blinding was not done due to technical issues of workforce resources. The total consumption of vasopressor was not recorded.

We conclude that a low dose of intrathecal clonidine (30 μg) can be safely considered an additive in the subarachnoid block to prolong the duration of post-operative analgesia for caesarean sections. Comfortable sedation to mothers with the absence of adverse effects on both maternal and neonate profiles makes it a safe alternative intrathecal adjuvant in obstetrics.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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