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ORIGINAL ARTICLE

INTRATHECAL CLONIDINE AS AN ADJUVANT WITH HYPERBARIC BUPIVACAINE FOR CAESAREAN SECTION

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ABSTRACT: BACKGROUND: Intrathecal adjuvants has gained popularity with the aim of prolonging the duration of block, quality of block and decreased resource utilization compared with general anaesthesia. However they are not free from side effects. We evaluated the effect of addition of intrathecal clonidine (45 micgm) to hyperbaric bupivacaine on perioperative and neonatal outcome following lower segment caesarean section. Study period: January –July 2012. **METHODS**: 60 female Patients undergoing elective cesarean section (LSCS) were randomly allocated to two groups of 30 each to receive intrathecally either 10 mg hyperbaric bupivacaine alone(group B) or 45 µg of clonidine (group C), added to 10 mg hyperbaric bupivacaine. The onset time to reach T 6 sensory and Bromage 3 motor level, the regression time for L1 sensory and Bromage 0 motor block, Sedation scores, hemodynamic changes, APGAR score and side effects were recorded. **RESULTS**: Onset of bromage 3 motor block and time to reach T 6 sensory dermatome level was statistically similar between group B and group C. The time for regression of sensory block to L1 dermatome was increased by addition of clonidine ($p < 0.001$ B vs. C). The duration of postoperative analgesia was 164.42±24.64 min in group B and 260.71±38.46 min in group C which was statistically significant. ($P<0.001$). New born apgar score shows that addition of clonidine is safe for new borns. **CONCLUSION**: Addition of 45 µg clonidine to hyperbaric bupivacaine in spinal anesthesia for LSCS significantly prolongs the duration of postoperative analgesia without any increase in maternal and neonatal side effects.

KEYWORDS: APGAR score, bupivacaine, clonidine, intrathecal, neonate.

INTRODUCTION: Spinal anesthesia has become the preferred anesthesia for cesarean section. Spinal anesthesia is simple to perform, economical, produces rapid onset of anesthesia and complete muscle relaxation. It has the advantage of being free from the risks of intubation but its duration of action is limited. Internationally, obstetric anaesthesia guidelines recommend spinal and epidural over general anaesthesia (GA) for most caesarean sections (CSs).[1, 2]

The primary reason for recommending regional blocks is the risk of failed endotracheal intubation and aspiration of gastric contents in pregnant women who undergo GA.[3] While there is evidence that GA is associated with an increased need for neonatal resuscitation, [4] but evidence about specific delivery indications and about neonatal outcomes subsequent to resuscitation is limited.

Clonidine prolongs the duration of action of intrathecally administered local anesthetics and has potent antinociceptive properties.[5] A recent report established 1 µg/kg intrathecal clonidine as an adequate dose for prolonging bupivacaine spinal anesthesia in pregnant females.[6] It was observed that intrathecal clonidine upto 150 µgs prolongs spinal anesthesia and analgesia but hemodynamic instability was seen with higher doses.[7] Various intrathecal adjuvants to local anaesthetics have found to improve the quality and extend duration of spinal block. As with lipophilic opioids, it is

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possible to achieve analgesia from systemic, epidural, or intrathecal administration of clonidine. Adding clonidine to intrathecal (IT) bupivacaine provides effective, prolonged, and dose dependent analgesia with a consequently decreased requirement for supplemental analgesics.[8] It has been used successfully as a sole analgesic for pain relief in labor[8] and also as a sole analgesic for pain relief after caesarean section.[9]

In 1953, Virginia Apgar, M.D. published her proposal for a new method of evaluation of the newborn infant. APGAR score is a clinical test performed on a newborn one and five minutes after birth. It is a composite measure of breathing effort, heart rate, muscle tone, reflexes, and skin colour and is an indicator of the newborn's need for medical attention shortly after birth. APGAR score (AS) is routinely used for assessment of newborns immediately after birth and consists of five variables viz. Respiratory efforts, heart rate, color, muscle tone, and reflex irritability. It is being used as a standardized tool for expressing the physiologic condition of newborn at birth and also to record fetal to neonatal transition.

However, AS has major limitations like having a limited time frame and including subjective components. Each of these is given a score of 0, 1 and 2. The score is traditionally reported at 1 and 5 min after birth.[10] A score of 0-3 at 5 min is a suggestive criterion for asphyxial insult and is a predictor of neonatal mortality. Infants with a score of ≥7 are considered normal.[10] No anesthetic agent or technique is ideal for parturients. The normal spontaneous vaginal delivery (NSVD) should always be the primary choice since it is more physiological.

However, in special cases where NSVD may not be applicable, the choice of anesthesia depends on the cause of the intervention, its degree of emergency, the patient's demand, obstetric requirements, and the expertise of the anesthetist.

The anesthetist must select a method that is the safest and most comfortable for the mother and that ensures the least depressing working conditions for the newborn and the optimal working conditions for the surgery. General and regional anesthesia techniques are used in anesthesia for Cesarean delivery; Regional anesthesia is more frequently preferred in recent years due to its advantages including the patient's demand, conscious patient, no risks of aspiration, no respiratory depression in newborns, and no uterine atony.

Its side effects in the mother include neurotoxicity, hypotension, nausea, vomiting, respiratory depression, urinary retention, delayed gastric emptying, postdural headache, total spinal block, anterior spinal artery syndrome, back and belly aches, cry and hypothermia.

And fetal side effects develop depending on the systemic absorption of neuraxial adjuvants or their side effects on the mother.[11] Cause of fetal distress in both anesthetic methods is the reduction in the amount of O2 available to the fetus as a result of the reduction of uteroplacental blood flow. Maternal, placental, and fetal factors play roles in such reduction. The effect of anesthetic drugs is direct or through the changes in the mother.[12]

Clonidine, alpha 2 adrenergic receptor agonist with a 200:1 ratio of alpha 2: alpha1 receptor binding has been widely used as analgesic adjuvant for pain therapy. Clonidine is extensively used intrathecally at a dose range of 15 -150 µg as an adjuvant to local anaesthetic agents.[13, 14] We decided to use 45 mics of clonidine to avoid its adverse effects.

METHODS: This study was a randomized, prospective, comparative study. After obtaining the Ethical Committee approval and written informed consent, 60 patients ASA (American Society of

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Anesthesiologists) grade I-II scheduled for caesarean section, between January – July 2012 were enrolled for the study. Exclusion criteria includes Patients with pregnancy induced Hypertension on treatment, fetal distress, placenta previa, previous LSCS, noted to have dysrhythmias on the electrocardiogram (ECG), hypothyroidism, body weight of more than 100 kg, or height less than 150 cm, spinal deformity and h/o allergy.

Standard monitoring was used, including non-invasive arterial blood pressure (BP), ECG, heart rate (HR) and pulse oximetry (SpO2). Preloading was done with 10 ml/kg of crystalloid solution. With the patient in the sitting position, spinal anesthesia was performed at the level of L2-L3 through a midline approach using a 25-gauge Quincke spinal needle which was inserted with the bevel pointing upwards. Patients were randomized into two groups using sealed envelope technique. The dose of hyperbaric 0.5% bupivacaine, 10 mg (2.0 ml) and total spinal volume (2.3 ml) was identical in study groups.

Patients allocated to group B received 2 ml hyperbaric 0.5% bupivacaine 10 mg +0.3 ml of preservative free normal saline. Patients allocated to group C received 2 ml hyperbaric 0.5% bupivacaine 10mg +0.3 ml of preservative free normal saline containing 45 µg clonidine. Immediately after the block, each parturient was placed with a wedge under right hip.

The anesthesiologist performing the block recorded the baseline value of vital signs (BP, HR, SpO2,) before performing the spinal anesthesia, and once in every 5 minutes inside the OT, then after every 15 minutes in the Post Anesthesia Care Unit (PACU) till the recovery of sensory and motor function. For the purpose of the study, hypotension was defined as a systolic blood pressure of <90 mm Hg and Bradycardia was defined as HR <50 beats/minute.

The sensory dermatome level was assessed by pin prick sensation using 23 gauge hypodermic needle along the mid clavicular line bilaterally every minute after spinal block till the T 6 level is reached. The motor dermatome level was assessed according to the modified Bromage scale: Bromage 0, the patient is able to move the hip, knee and ankle; Bromage 1, the patient is unable to move the hip, but is able to move the knee and ankle; Bromage 2, the patient is unable to move the hip and knee, but is able to move the ankle; Bromage 3, the patient is unable to move the hip, knee and ankle.

The Bromage scale was recorded pre-spinal injection and every minutes after the spinal injection until the highest dermatome was reached. In the PACU, the sensory level and Bromage scale were recorded every 15 minutes until the patient was discharged from the PACU. All durations were calculated considering the time of spinal injection as time zero. When sensory levels of anesthesia were not equal bilaterally, the higher level was used for the statistical analysis. Patients were discharged from the PACU after sensory regression to the L1 segment, and Bromage scale of 0. APGAR score of all the babies at 1 and 5 minutes were recorded following the delivery of new born.

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Table I The APGAR score

SIGN	SCORE 0	SCORE 1	SCORE 2
Heart Rate	Absent	< 100/min	> 100/min
Respiration	Absent	Weak	Good Cry
Muscle Tone	Flaccid	Some Flexion	Well Flexed
Reflexes	No Response	Grimace	Cough/ Sneeze
Colour	Pale/Blue	Blue Extremities	Com-pletely Pink

STATISTICAL ANALYSIS: Statistical analysis was done using the Statistical Package for Social Science (SPSS15.0 Evaluation version). To calculate the sample size, a power analysis of α=0.05 and α=0.90, showed that 30 patients per study group were needed. Data are expressed as either mean and standard deviation or numbers and percentages. Continuous covariates were compared using analysis of variance (ANOVA). The comparison was studied using the Chi-square test or Fisher's exact test as appropriate, with the P value reported at the 95% confidence interval. P<0.05 was considered statistically significant.

Inj ranitidine 50 mg and metoclopramide 10 mg premedication was given to the study patients on the previous night and 1 hour before surgery. The level of sedation was evaluated just before surgery, intra operatively and post-operatively every 15 minutes using the Ramsay sedation scales: scale 1-patient anxious, agitated, or restless; scale 2-patient cooperative, oriented, and tranquil alert; scale 3, Patient responds to commands; scale 4, Asleep, but with brisk response to light glabellar tap or loud auditory stimulus; scale 5 - Asleep, sluggish response to light glabellar tap or loud auditory stimulus and scale 6- asleep, no response. Patient's neurological assessment was done every day and recorded during hospital stay.

Analgesia was supplemented based on visual analogue score in the post-operative period. The duration of postoperative analgesia, defined as the time from IT injection of the drug to the time when patient first requests analgesia in postoperative period was noted.

RESULTS: The duration of postoperative analgesia was 164.42±24.64 min in group B, 260.71±38.46 minutes in group C. This difference was clinically and statistically extremely significant between the groups B and C (P<0.001). The duration of postoperative analgesia, defined as the time from IT injection of the drug to the time when patient first requests analgesia in postoperative period.

60 patients were enrolled in the study. all the patients completed the study protocol were included in the data analysis. Thus group B and group C consisted of 30 patients each. There was no significant difference in the demographic data between the three study groups [p >0.05] (Table 2).

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Demographic data	Group B	Group C	P value	significance
AGE	25.2 ± 4.80	26.5±3.24	>0.05	NO
ASA Grade I	28	27	>0.05	NO
ASA Grade II	2	3	>0.05	NO
Height	156.7±5.21	154.3±4.87	>0.05	NO
Weight	56.54±8.34	55.47±7.84	>0.05	NO

Table 2: Demographic data (mean±SD) in the study groups

The time to reach T6 sensory dermatome, Bromage 3 scale were similar between group B and group C. The regression of the sensory block to L1 dermatome was affected by the addition of clonidine to the spinal bupivacaine. ($p<0.001$)(Table 3).

Group	B	C	P value	Significant
Time to reach T 6	3.2±1.1	3.1±0.8	>0.05	No
Time to Bromage 3	4.4±1.4	4.3±1.2	>0.05	No
Time to reach L1	113.2±22.9	184.6+26.8	<0.001	Yes
Time to Bromage 0	159.4±17.5	175.0+23.3	>0.05	No

Table 3: sensory, motor block onset and regression time in minutes (mean ± SD)

The median and range of Highest sensory level recorded were T5 (T4 –T6) in group B, T4 (T3-T6) in group C, were statistically comparable ($p>0.05$) among study groups.

The total amount of fluids administered following spinal anesthesia, amount of ephedrine or atropine, bradycardia, hypotension, need of additive analgesia, blood transfusion, shivering and nausea or vomiting in the intraoperative or in PACU were comparable in the two groups; $p>0.05$ (Table 4). Sedation level was significantly higher in clonidine added group ($p<0.001$). Values are in mean ± SD.

Perioperative characteristics	Group B	Group C	P value	significance
Intravenous fluid(ml)	1050.7±151.5	1010.0+136.7	>0.05	NO
Sedation	2.0±0.6	3.5±0.4	<0.001	YES
Blood Transfusion	0	0	>0.05	NO
Additive analgesia	0	0	>0.05	NO
PONV	1	0	>0.05	NO
Bradycardia	2	3	>0.05	NO
Hypotension	3	4	>0.05	NO
Atropine	2	3	>0.05	NO
Ephedrine	4	5	>0.05	NO
Respiratory depression	0	0	>0.05	NO
Shivering	2	0	>0.05	NO

Table 4: perioperative characteristics (mean±SD) in two study groups

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The mean ±SD values of heart rate (H R) and mean arterial pressure (MAP) measured in O T and PACU were comparable between the groups.

The change in mean heart rate at all-time points was insignificant between the groups. Five patients, two in group B and three in group C had bradycardia that was easily treated with the use of 0.6 mg of intravenous atropine. The incidence of hypotension in group B (3 patients) and in group C (4 patients) was also not significant.

We found no sedation in group B but significant Sedation was observed in bupivacaine-clonidine combination groups. Statistically significant difference exists in sedation caused by addition of intrathecal clonidine to bupivacaine (P<0.001). The SpO2 was higher than 95% in all patients in the three groups both in the intraoperative and in the PACU. Study patients did not show any neurological impairment related to spinal anesthesia such as back, buttock or leg pain or weakness, headache or any new neurological deficit. No patients suffered from respiratory depression during the study. (Table 5)

APGAR	Group B	Group C
Apgar 1 min	8.65±o.23	8.45±0.38
Apgar 5 min	9±0	9±0

Table 5: Apgar 1 and 5 minutes. (mean±SD)

APGAR were comparable between the two groups with no statistical significance. (p>0.05)

APGAR Score of babies (at 1, and 5 min) was unaffected when 45 µg intrathecal Clonidine used in cesarean section.

DISCUSSION: Prolongation of duration of spinal block is desirable both for long procedures and for postoperative pain relief. Different agents, such as epinephrine, phenylephrine, adenosine, magnesium sulfate, and clonidine have been used as adjuvant for prolonging the duration of spinal anesthesia.

The mechanism by which intrathecal alpha 2-adrenergic agonists prolong the motor and sensory block of local anesthetics is not clear. It may be an additive or synergistic effect secondary to the different mechanisms of action of local anesthetic and alpha 2 adrenergic agonist. The local anesthetics act by blocking sodium channels, whereas the alpha 2 adrenergic agonist acts by binding to pre synaptic C fibre and post synaptic dorsal horn neurons. Intrathecal alpha 2 adrenergic agonist produces analgesia by depressing the release of C fibre transmission by hyperpolarization of post synaptic dorsal horn neurons.[15]

Li et al. observed that Glutamate is involved in excitatory neurotransmission nociception and plays an essential role in relaying noxious stimuli in the spinal cord.[16] Intrathecal injection of alpha 2 adrenergic agonists produces potent antinociceptive effects by altering spinal neurotransmitter release and effectively treats acute pain.[15, 16] Adding clonidine to IT bupivacaine provides effective and prolonged analgesia with a consequently decreased requirement for supplemental analgesics.

The duration of postoperative analgesia in our study was 164.42±24.64 min in group B min and in group C it was 260.71±38.46 min. These observations suggest that Intrathecal clonidine significantly prolongs the duration of pain free period after caesarean delivery.

Our findings are consistent with the findings of Kothari et al[17] who observed that by adding

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clonidine, duration of sensory block and postoperative analgesia was prolonged. The onset time of motor block was comparable in two groups indicating that Intrathecal clonidine does not influence the onset of motor block after bupivacaine Spinal anaesthesia.

Also motor recovery is not affected by addition of clonidine to IT bupivacaine. Kothari et al, [17] also showed that motor recovery is more dependent on dose of bupivacaine rather than on the dose of clonidine. Singh et al also observed prolong sensory block following intrathecal clonidine with preserved apgar and blood gas levels.[18]

In a study conducted by De kock et al Motor recovery was not affected by addition of 50 μg intrathecal clonidine.[19] motor recovery is longer by increasing dose of bupivacaine not by adding clonidine to intrathecal bupivacaine.[20]

By addition of 45 μg intrathecal clonidine we found that patients were drowsy (assessed by Ramsay sedation scale) as compared to those without clonidine. addition Intrathecal clonidine increases sedation but patients were responsive to simple verbal commands. APGAR scores of neonate (at 1 and 5) were not impaired by addition of 45 μg intrathecal clonidine to 0.5% hyperbaric bupivacaine.

The IT clonidine dosage of 45 mics used in our study had no clinically relevant maternal or neonatal side-effects. Bradycardia in SA, particularly with clonidine as an additive is a worrisome side effect. However, we did not observe any significant fall in heart rate with the addition of IT clonidine. the hemodynamic effects of clonidine after neuraxial or systemic administration begin within 30 min and reach a maximum within 1-2 hours.[21]

The fall in SBP following spinal anaesthesia and delivery coincided with the sympatholysis effect of bupivacaine and blood loss caused by placental separation and the use of intravenous oxytocin after delivery of the baby. Our study also showed prolong sensory block ($p<0.001$), and higher sedation. Fetal apgar showed no difference between the two groups. Our findings support the observations done by Kothari et al and Singh et al who used higher dose of clonidine (50-75 mics).[17,18]

CONCLUSION: In conclusion, addition of clonidine prolonged the sensory block significantly when used with hyperbaric bupivacaine intrathecally without increasing the incidence of significant adverse effects. Addition of clonidine does not cause any adverse-effect on the new borns apgar score. We support the addition of clonidine 45 μg with bupivacaine in spinal anesthesia when prolong post-operative analgesia is desired.

REFERENCES:

1. American Society of Anesthesiologists Task Force on Obstetric Anesthesia Practice guidelines for obstetric anesthesia: an updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. Anesthesiology 2007;106:843–63
2. Cyna AM, Dodd J. Clinical update: obstetric anaesthesia. Lancet. 2007; 370: 640–42.
3. Bloom SL, Spong CY, Weiner SJ, Landon MB, Rouse DJ, Varner MW et al. Complications of anesthesia for cesarean delivery. Obstet Gynecol. 2005; 106: 281–87.
4. Gordon A, McKechnie EJ, Jeffery H. Pediatric presence at cesarean section: justified or not? Am J Obst Gynecol. 2005; 193: 599–605.
5. Van Tuijl I, Giezeman MJ, Braithwaite SA, Hennis PJ, Kalkman CJ, van Klei WA. Intrathecal low-

dose hyperbaric bupivacaine-clonidine combination in outpatient knee arthroscopy: a randomized controlled trial. Acta Anaesthesiol Scand. 2008; 52: 343–49.

6. Sethi BS, Samuel M, Srivastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Ind Jrnl of Anaesth. 2007; 51: 415–19.
7. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small-dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: a dose-response study. Anesth Analg. 2004; 99: 1231–8.
8. Chiari A, Lober C, Eisenach JC, Wildling E, Krenn C, Zavrsky A, et al. Analgesic and hemodynamic effects of intrathecal clonidine as a sole analgesic agent during first stage of labor: A dose response study. Anesthesiology. 1999; 91: 388–96.
9. Filos KS, Goudas LC, Patroni O, Polyzou V. Intrathecal clonidine as a sole analgesic for pain relief after caesarean section. Anesthesiology. 1992; 77: 267–74.
10. American Academy of Pediatrics, Committee on Fetus and Newborn, American College of Obstetricians and Gynecologists and Committee on Obstetric Practice. The Apgar score. Pediatrics. 2006;117: 1444–7.
11. Gale R, Slater PE, Zalkinder-Luboshitz I. Neonatal advantage of epidural anesthesia in elective and emergency cesarean sections: a report of 531 cases. European Journal of Obstetrics Gynecology and Reproductive Biology. 1986; 23: 369–77.
12. Petropoulos G, Siristatidis C, Salamalekis E, Creatsas G. Spinal and epidural versus general anesthesia for elective Cesarean section at term: effect on the acid-base status of the mother and newborn. Journal of Maternal-Fetal and Neonatal Medicine. 2003; 13: 260–66.
13. Elia N, Culebras X, Mazza C, Schiffer E, Tramer MR. Clonidine as an adjuvant to intrathecal local anaesthetics for surgery: systematic review of randomised trails. Req Anesth Pain Med. 2008; 33: 159-67.
14. Bischoff P, Kochs E. Alpha 2 agonists in anesthesia and intensive medicine. Anasthesiol Intensivmed Notfallmed Schmerzther.1993; 28: 2-12.
15. Fairbanks CA, Wilcox GL. Spinal antinociceptive synergism between morphine and clonidine persist in mice made acutely or chronically tolerant to morphine. J Pharmacol Exp Ther. 1999; 288: 1107-16.
16. Li X, Eisenach JC. Alpha 2A adrenoceptor stimulation reduces capsaicin induced glutamate release from spinal card synaptosomes. J Pharmacol Exp Ther.2001; 299: 939-44.
17. Kothari N, Bogra J, Chaudhary AK. Evaluation of analgesic effects of intrathecal clonidine along with bupivacaine in cesarean section. Saudi J Anaesth. 2011; 5: 31–5.
18. Singh R, Gupta D, Jain A. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on post-operative pain after caesarean section: a randomised control trail. Saudi j anaesth.2013;7:283-90.
19. De Kock M, Gautier P, Fanard L, Hody JL, Lavand'homme P. Intrathecal ropivacaine and clonidine for ambulatory knee arthroscopy: a dose-response study. Anesthesiology. 2001; 94: 574–8.
20. Gaumann DM, Brunet PC, Jirounek P. Clonidine enhances the effects of lidocaine on C-fiber action potential. Anesth Analg. 1992; 74: 719–25.
21. Eisenach JC, De Kock M, Klimscha W. Alpha (2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology. 1996; 85: 655–74.

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