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Comparative Evaluation of the Effects of Addition of Intrathecal Fentanyl and Clonidine Added To 0.5% Hyperbaric Bupivacaine for Lower Segment Caesarean

Bhavya Gundepudi[1], Nikitha Reddy[2], Syed Moiz Mohiuddin Khan[1], Sireesha M[3], Rajeshwar P[4], Abhinav[1]

[1]3rdYear Post Graduate, Department of Anesthesia, Kamineni Academy of Medical Sciences and Research Centre, LB Nagar, Hyderabad, Telangana State, India.
[2]3rdYear Post Graduate, Department of Anesthesia, M N R Medical College, Hyderabad, Telangana, India.
[3]Assistant Professor, Department of Anesthesia, Kamineni Academy of Medical Sciences and Research Centre, LB Nagar, Hyderabad, Telangana State, India.
[4]Professor and HOD, Department of Anesthesia, Kamineni Academy of Medical Sciences and Research Centre, LB Nagar, Hyderabad, Telangana State, India.

Abstract

Background: To investigate the effects of fentanyl and clonidine when combined with bupivacaine during spinal anaesthesia for caesarean sections. To assess the length of analgesia by contrasting two groups. To correlate and contrast the two groups', newborn outcomes, hemodynamic effects and post-operative sedation.**Material and Methods:**A randomized prospective comparative study was performed at Kamineni Academy of Medical Sciences and Research Centre, LB Nagar, Hyderabad in 90 patients undergoing elective or emergency caesarean section. For medication injections, patients were randomly divided into 3 groups of 30. Physiological and demographic characteristics, the beginning of analgesia, the peak of cephalic spread, the upper level of sensory block, and the grade of motor block as determined by the Bromage motor scale were all observed throughout surgery. The mean and standard deviation of the additional results were calculated. Anova tables were used to assess statistical significance.**Results:**Groups' highest sensory levels were statistically extremely highly significant (P 0.001). In SBP, Three groups did not significantly differ from one another after five minutes (P>0.05). A significantly differed from groups B and C at 15 minutes (P 0.001). B&C, however, did not significantly differ from each other (P>0.05). A&B had a significant difference at 30 minutes (P 0.05). Groups A and B were connected with sedation level 1. Group C was connected to the sedation level 2. The correlations mentioned above were statistically extremely strong (P 0.001).**Conclusion:**The effectiveness of intraoperative analgesia was enhanced both by the intrathecal clonidine and the clonidine fentanyl combination. In contrast to clonidine alone, the combination of clonidine and fentanyl dramatically enhanced intraoperative analgesic effects and sustained postoperative analgesia. Hemodynamics within the operating room were stable. The analgesia lasted longer than expected. There were hardly any negative effects brought on by the medications' synergistic effects. The course of the foetus was not changed.

Keywords: Sensory block, Spinal anestheia, Hemodynamic effect, Bromage.

Corresponding Author: Dr. Bhavya Gundepudi, 3rd Year Post Graduate, Department of Anesthesia, Kamineni Academy of Medical Sciences and Research Centre, LB Nagar, Hyderabad, Telangana State, India.

Introduction

Relief of Pain is purchased always at a price – Ralph Waters.

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"For all the happiness mankind can gain is not in pleasure but in rest from pain". – John Dyrden.[1]

The aim of anesthesiology as a science is the removal of pain temporarily started initially with pain relief for surgeries, extending now to post operative pain relief, relief of chronic pain and cancer pain. Spinalanesthesia plays in important role of alleviating pain intraoperatively, extending sometime into postoperative period also. The entry of Corning's needle in 1885-into the subarachnoid space paved the way for the greatest leap into spinal anaesthesia. His words "Be the density of this observation, what it may have seemed to me on the whole, worth recording. This opened the prologue for the word "spinal anaesthesia". Cocaine was the drug first used experimentally in dogs. In men the first spinal anaesthesia was conducted by "August Bier" on 16.8.1898 with cocaine 3 ml as 0.5% solution followed by Matas in America and Tuffier in France.[2-5]

Spinal anesthesia for caesarean section has always enjoyed popularity as it eliminates the complication of pulmonary aspiration and avoids the problem of difficult tracheal intubation observed with general anaesthesia. Other advantages of this technique are its simplicity, rapid onset and dependability.[6]

The demonstration of opiate receptors in substantia gelatinosa of spinal cord (Yaksh and Rudy 1976) has created interest in the intrathecal administration of opiates. The use of intrathecal morphine for providing postoperative pain relief in caesarean section was started in the year 1988 by EzzazAboulesish et.al. The advantages of neuraxial opioids over neuraxial local anesthetics are that it produces prolonged, intense, selective, segmental analgesia without motor blockade and sympathetic dysfunction.[7,8]

Opiods and local anesthetics administered together have a potent synergistic analgesic effect. Intrathecal opiods enhance analgesia from subtherapeutic dose of local anesthetic and make it possible to achieve successful spinal anesthesia using otherwise inadequate doses of local anesthetic. The α2 adrenergic mechanism have been exploited for more than 100 yrs. Vetenarians have used α2 agonist for many years for regional analgesia, but the experience with these agents in humans, dates back only slightly more than 10 years.[9-11]

In 1984 Tamsen, Gordh after testing neurotoxicity in animals and then injected a parenteral preparation of α2 agonist clonidine, epidurally intwo patients with chronic pain. Since then the complete toxicologic assessment in animal studies has suggested that clonidine is safe for Intrathecal use.[12]

Aim of the Study

1. To evaluate the effects of fentanyl and clonidineadded to Bupivacaine, for caesarean section in spinal Anaesthesia
2. To evaluate the duration of analgesia by comparing two groups.
3. To evaluate the hemodynamic effects, post-operative sedation and neonatal outcome between the two groups.

Material and Methods

Following approval by the institutions ethical committee, this prospective study was done at Kamineni Academy of Medical Sciences and Research Centre, LB Nagar, Hyderabad in 90 patients undergoing elective or emergency caesarean section after getting informed consent from each patient and explaining the procedure. This is a randomized prospective comparative study.

Inclusion Exclusion Criteria:

Term, parturient, ASA I an ASA IE who were fit to undergo spinal anaesthesia for caesarean section, age between 18-35 yrs., are selected. Patients with medical and obstetrical

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complications and impaired placental function were excluded; patients who were converted to general Anaesthesia were also excluded from the study.

Preoperative Preparation:

Preoperatively all patients were seen by the anesthetist. The procedure was explained in detail and informed consent was obtained. No premedication was given. Patients were randomly allocated into 3 groups of 30 each.

A. Control Group - Injection (0.5%) Bupivacaine 1.8 ml + 0.4 ml NS
B. Study group 1 inj. (0.5%) Bupivacaine 1.8 ml + Clonidine 30 μg) + 0.2 ml NS.
C. Study group 2 Inj (0.5%) Bupivacaine 1.8 ml + Clonidine (30 μg) +fentanyl (10μg)

Procedure:

- On arrival to operation theatre, basic monitoring was applied to all patients and basic pulse rate, blood pressure, oxygen saturation and respiratory rate were recorded.
- Intravenous line with 18 g canula was established and preload of 250-300 ml of crystalloid was given to all patients.
- Following resuscitative measures were kept ready before the start of the procedure: Boyles machine with oxygen source, laryngoscope and appropriate size blades, suction apparatus, vasopressors (Ephedrine), naloxone and other emergency drugs.
- The subarachnoid block was performed in right lateral position with 23 G spinal needle through L3, 4 space. Free flow of CSF was ensured before introducing the drug. The drug injected was according to the group assigned.

A. Injection (0.5%) Bupivacaine 1.8 ml + 0.4 ml NS
B. inj. (0.5%) Bupivacaine 1.8 ml + Clonidine 30 μg) + 0.2 ml NS.
C. Inj (0.5%) Bupivacaine 1.8 ml + Clonidine (30 μg) + fentanyl (10μg)

Drugs were measured in a sterile tuberculin syringe. Thorough aseptic precautions were taken during the addition of injection and making the final injection.

Immediately after the intrathecal injection the patients were gently turned to supine position with leftward tilt by a wedge under right buttock 100% oxygen was given through Magills breathing system till the delivery of baby.

Assessment of Patient and Recording of Data:

Time of subarachnoid block was noted.

Following observations were made:

1. Time of onset of analgesia
2. Time of maximum cephalic spread
3. Upper level of sensory block.
4. Grade of motor block obtained according to bromage motor scale.

Bromage motor scale:

0. No paralysis
1. Inability to raise extended legs.
2. Inability to flex the knee joint
3. inability to flex the ankle joint

After the establishment of an adequate level of analgesia, the surgeons were allowed to operate and the time of beginning of surgery was noted.

Blood pressure, pulse rate, respiratory rate and Spo2 were monitored intraoperatively every 2 minutes for the first 10 minutes and every 5 minutes till the end of surgery. Patients were watched for side effects like hypotension, bradycardia, and vomiting, itching and respiratory depression.

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Any hypotension (30 % fall from base line) was treated with oxygen, intravenous fluid and inj. ephedrine. Any bradycardia (pulse rate <60 mt) was treated with inj. atropine
Nausea and vomiting were treated with inj. metaclopromide
Pruritis if complained was treated with inj. chlorpheniramine maleate.

Two segment regression time:
Time to decrease from maximum sensory level to 2 segments below that level was noted.
Sedation state was assessed by
Brain and Ready sedation score
1. Awake and alert
2. Drowsy
3. Sleepy but easily arousable on call.
4. Sleepy but difficult to arouse.

In the postoperative period, any complications to the mother and baby, especially that is attributed to opioids like respiratory depression, nausea, vomiting, pruritus were noted (one of the expected complication i.e., urinary retention could not be studied as all the patients were invariably catheterized).
Total duration of analgesia was taken as the period from the time of giving subarachnoid block till the patient's first requirement of analgesic medication. Pain was evaluated using 10 cm linear visual analogue scale (VAS) with 0 for no pain and 10 for worst pain. If VAS was more than 6, supplementary analgesia was given and the study was assumed to be concluded at that point.

Foetal Outcome:
Immediately after delivery, foetalwell being was assessed by 1 mt. and 5 mt. Apgar score. During the postoperative period, the well being of the baby whether exclusively sedated or not and the nature of cry were noted.
Reflexes like sucking reflex, rooting reflex and moro reflex were tested. Presence of seizures, if any, was also noted. All mothers and their babies were followed up till their discharge.

Statistical Method:
Results were expressed as mean ± standard deviation. Statistical significance was determined by Anova table.

Results
Statistical Analysis
The Randomization of three groups was done by matching their age, height, and weight of their demographic factors and base Physiological factors such as pulse rate, SBP, respiration rate and SPO2 by ANOVA (Analysis of Variance). The differences between them were interpreted by the Post hoc test of Bonferroni. Similarly, the time for maximum loss of sensation, the 2 segment regression time, pain free time and Apgar score at 1 minute and 5 minutes were compared between groups by ANOVA.
The intra and post-operative pulse rate and SBP at different intervals were compared between groups by ANOVA and interpreted the difference by Post hoc test of Bonferroni.The sensation level and sedation score were analyzed and interpreted by $\chi 2$ test (Chi- square). The above statistical procedures were performed by the statistical package IBM SPSS statistics 20. The P - values less than 0.05 ($P<0.05$) were treated as significant in two tail condition.

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Randomization by group matching

The three groups were namely A (Bupivacaine only), B (Bupivacaine + intrathecal clonidine) and C (Bupivacaine + intrathecal fentanyl + Clonidine). Each group 30 Caesarean Sections were selected and data were collected before during and after surgery. For Randomization the three groups were matched according to their selected and related demographic characteristics and base level Physiological characteristics.

Table 1: Matching of three groups according to their demographic characteristics:

Variables	Group	N	Mean	S D	ANOVA 'F'	Df	Significance
Age	A	30	24.6	4.4		2,117	
	B	30	24.1	3.6	1.092		P>0.05
	C	30	25.4	3.8			
Weight	A	30	58.5	5.0		2,117	P>0.05
	B	30	59.4	8.3	0.319		
	C	30	59.6	7.2			
Height	A	30	155.8	6.1			
	B	30	154.2	4.2	2.021	2,117	P>0.05
	C	30	156.8	6.4			

The three groups were matched in respect of their age, weight and height and shown in the [Table 1]. They were not significantly differed between them (P>0.05).

Table 2:matching of three groups according to their Physiological characteristics

Variable	Group	n	Mean	SD	ANOVA'F'	Df	Significance
Base PR	A	30	85.2	5.8	1.466	2,117	P>0.05
	B	30	87.3	7.2			
	C	30	85.2	5.9			
Base SBP	A	30	121.5	9.6	0.015	2,117	P>0.05
	B	30	121.6	10.2			
	C	30	121.2	7.9			
Base RR	A	30	18.4	1.0	2.831	2,117	P>0.05
	B	30	19.0	1.0			
	C	30	18.6	0.9			
Base SPO2	A	30	97.2	0.9	3.748	2,117	P>0.05
	B	30	96.9	1.0			
	C	30	96.6	0.8			

The Physiological characteristics of three groups were matched and stated in the above table - 2. There were no significant differences were observed between groups in respect of their base Physiological characteristics (P>0.05).

Maximum Sensory level, Time and 2 Segment regression time:

The maximum sensory level and maximum time taken to reach the level were compared between three groups. The 2 segment regression time was also compared between the three groups.

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Table 3:Comparison of sensory level between three groups

Max Sensory level	GROUPS				$\chi 2$	df	Significance
	A	B	C	Total			
T4	1	1	7	9	76.795	8	P<0.001
T 5.	2	11	17	30			
T 6.	12	18	6	36			
T 7.	15	0	0	15			
T 8.	1	0	0	1			

The above table -3 associates the maximum sensory level of three groups. The group A was associated with T7, B was associated with T6 and C was associated with T5. The above associations were statistically very highly significant (P<0.001).

Table 4:Duration of time (minutes) to attain Sensory blockade or level between groups

Groups	n	Mean	SD	ANOVA 'F'	d.f	Significance	Significantly differed groups
A	30	3.8	0.8	8.003	2,117	P<0.01	C differed with B and not differed with A. A&B not differed.
B	30	3.6	0.7				
C	30	4.3	0.8				

The sensory time between the groups were compared in the table-4. The mean time of A was 3.8±0.8 minutes with mean time of B (3.6±0.7) and C (4.3±0.8) not differed significantly (P>0.05). But the means of B (3.6±0.7) and C (4.3±0.8) were differed significantly (P<0.01).

Table 5:two segment regression time (minutes) to attain Sensory level between groups

Groups	n	Mean	SD	ANOVA 'F'	d.f	Significance	Significantly differed groups
A	30	69.4	8.6	177.952	3,117	P<0.001	A,B&C were differed significantly between Them.
B	30	89.5	5.7				
C	30	101.1	8.1				

The two segment regression time between the groups were compared in the above table 5. The means of three groups were differed significantly between them (P<0.001).

Table 6:Comparison of pulse rates between groups at different intervals

Interval	Group	n	Mean	SD	ANOVA 'F'	df	Significance	Significantly differed groups
5 Min	A	30	88.2	7.6	4.370	3,117	P<0.01	A vs. B Significant AvsC, and BvsC not significant
	B	30	93.5	9.1				
	C	30	90.6	7.5				
15 Min	A	30	92.5	9.1	2.107	3,117	P>0.05	A,B & C were not significant
	B	30	95.5	8.5				
	C	30	91.8	8.3				

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30 Min	A	30	91.2	6.7	5.012	3,117	P<0.01	A vs. B Not Signify B vs. C significant A vs. C Not Signify
	B	30	94.2	7.6				
	C	30	89.4	6.1				

The above table -6 shows the pulse rate at different intervals like at 5 minutes 15 minutes and 30 minutes. The group A was significantly differed with group B (P<0.05) and C was not significantly differed with groups A and C (P>0.05) at 5 minutes. At 15 minutes no significant difference was observed between the three groups (P>0.05). At 30 minutes B significantly differed with C (P<0.01) and at the same time A&B and A&C were not significantly differed (P>0.05).

Table 7:Comparison of SBP between groups at different intervals:

Interval	**Group**	**n**	**Mean**	**SD**	**ANOVA 'F'**	**df**	**Significance**	**Significantly differed groups**
5 Min	A	30	120.6	11.4	2.136	3,117	P>0.05	Three groups were not differed significantly
	B	30	116.2	13.5				
	C	30	120.9	8.8				
15 Min	A	30	102.4	12.4	14.357	3,117	P<0.001	Significant. differed with B & C. but B & C not differed.
	B	30	115.8	9.9				
	C	30	112.2	12.0				
30 Min	A	30	105.9	12.5	7.838	3,117	P<0.01	A&B differed Sig. A&C and B&C not differed.
	B	30	115.1	9.7				
	C	30	110.8	8.4				

The SBP at different interval between the groups were shown in the above table-7. At 5 minutes, three groups were not significantly differed between them (P>0.05). At 15 minutes A significantly differed with the groups B and C (P<0.001). But B&C was not significantly differed between them (P>0.05). At 30 minutes A&B differed significantly (P<0.05). But A vs C and Bvs. C were not significantly differed (P>0.05).

Pain free time (minutes):

The pain free, the duration of time without pain was analyzed between the three groups to identify in which group the pain was lasting.

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Table8: Comparison of pain free time (minutes) between the groups:

Groups	n	Mean	SD	ANOVA 'F'	d.f	Significance	Significantly differed groups
A	30	125.8	23.1	177.955	3,117	P<0.001	All were differed significantly between them
B	30	178.2	14.4				
C	30	221.6	28.4				

The pain free time between the groups were compared in the above table 8. The means of three groups were 125.8±23.1, 178.2±14.4 and 221.6±28.4 respectively. They were significantly differed between them (P<0.001).

Table 9: Comparison of sedation between three groups

Sedation level	GROUPS				$\chi 2$	Df	Significance
	A	B	C	Total			
0	17	2	0	19	96.092	6	P<0.001
1	13	23	3	39			
2.	0	5	21	26			
3	0	0	6	6			
Total	30	30	30	90			

The sedation levels of three groups were associated in the above table-9. The sedation level 1 was associated with groups A and B. The sedation level 2 was associated with group C. The above associations were statistically very highly significant (P<0.001).

Table 10: Comparison of Apgar scores at 1 minute and 5minutes

Time	Groups	n	Mean	SD	ANOVA'F'	Df	Significance	Significantly differed groups
1 Min	A	30	7.6	0.5	0.122	3,117	P>0.05	All were not significant
	B	30	7.5	0.6				
	C	30	7.5	0.7				
5 Min	A	30	9.1	0.5	4.790	3,117	P<0.05	A & B only significant. Others NS
	B	30	8.8	0.5				
	C	30	9.0	0.3				

The Apgar score at 1 minute and 5 minutes were compared between the three groups in table 10. At 1 minute the Apgar were not significant between groups (P>0.05). At the Apgar scores of groups A&B was significantly differed (P<0.05). The others A&C and B&C were not statistically significant (P>0.05).

Inter-operative Complications

Nausea and vomiting occurred in 7.5% of all three groups. All were treated with inj. Metaclopromide.

Pruitus developed in only one patient i.e. 2.5% of group A patient.

In group B, 7.5% of patients developed pruitus.

In group C, 12.5% of patients developed pruritus

All were treated with inj. Chlorpheniramine maleate.

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Post-Operative Complications

Nausea and vomiting occurred in 5% of patients in group A and group B and 2.5% in group C and they were treated with inj. Metaclopromide. Pruritus occurred in 2.5% of patients in group B and 7.5% of patients in group C and they were treated with inj.chlorpheniramine maleate.

DISCUSSION

For Randomization, the three groups were matched with their age, height, weight, pulse, SBP, respiration and SPO2 and found that there was no significant difference between them (P>0.05). Hence, there groups were comparable groups. The sensory level T4 was obtained by A group 1(2.5%), B group 2(5%) and C group 10 (25%). The above attainment by C group was significantly greater than the other A& B groups (P<0.001). The mean time of C was significantly greater than B (4.3±0.8 > 3.6±0.7) and A and C were equal (4.3±0.8 = 3.8±0.8). The two segment regression time for C group was significantly more than B and the same for B was significantly more than A.(101.1±8.1 > 89.5 ± 5.7 > 69.4 ±8.6 and P<0.001).[13,16]

The Pulse rate at 5 minutes of B group was significantly greater than A and C groups. (93.5 ±7.6 > 88.2±7.6 &90.6 ±7.5) and A group C group was equal (88.2±7.6 = 90.6 ±7.5). At 15 minutes, the pulse rates of three groups were more or less equal. (92.5±9.1 = 95.5±8.5 = 91.8=8.3 and P>0.05). At 30 minutes the pulse rate of C group was lesser than B group (89.4 ±6.1<94.2 ±7.6 and P<.0.01).[17-19]

The same of A vs. B and A vs. C were more or less equal (91.2±6.7 = 94.2 ±7.6 and 91.2 ±6.7 = 89.4±6.1 and P>0.05).[20]

The SBP at 5 minutes of three groups were 120.6 ±11.4, 116.2 ±13.5 and 120.9 ± 8.8 minutes respectively. The means were not significantly differed (P>0.05). At 15 minutes, the mean SBP of A group was 102.4 ± 12.4 and the same was significantly lower than B and C groups (102.4 ± 12.4 < 115.8 ± 9.9 & 112.2 ±12.0 and P<0.01). At 30 minutes, the mean SBP of B group was significantly higher than B group (115.1± 9.7 > 105.9 ±12.5 and P<0.01). The mean SBP of A vs. C and B vs. C were not significant (P>0.05).[21,22]

The pain free time of C group was significantly greater than B group and B group was significantly greater than A group (221.6 ±25.4 >178.2±14.4 >125.8±23.1and P<0.001).[23]

The sedation level of A (57.5%) and B (70%) groups was associated with level 1 and C (72.5%) was associated with level 2. The improvement was very highly significant (P<0.001).[24]

The Apgar score between the three groups was not significant at 1 Minute, But at 5 minutes, A group was significantly improved than B (9.1±0.5 > 8.8 ±0.5 and P<0.05). The A vs. C (9.1±0.5 = 9.0±0.3) and B vs.C (8.8 ±0.5= 9.0±0.3) were not significant (P>0.05).[25]

From the above results and discussions the C group administration is better than the above two groups namely A and B groups.

- Evidences to conclude, improved quality of analgesia is the post-operative period (Paech M. J. et al).
- There is not of much difference in the onset of analgesia, similar to studies by Singh Harbhej et al.
- Two segment regression took longer time (C>B>A), similar to study conducted by Belzarena Sergio et al.
- Duration of analgesia increased (C>B>A), consistent with cong FC et al.

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Hemodynamics

- There is less incidence of hypotension and Bradycardia, consistent with studies by Cang Fc, Chang PG et al.

Complications

- No respiratory depression occurred in any of these patients, consistent with study conducted by Lan et al.
- Pruritus developed in 12.5% in Group C, consistent with the study conducted by Cang Fc, Tsai YC et al.

Fetal Outcome

Low dose opiods do not have adverse effects on fetus and neonates (Ohen S, Arn et al) (Fernado F, Bonello E et al).

CONCLUSION

The above study bears out the following facts.

1. Intrathecal clonidine and the clonidine fentanyl combination, both improved quality of Intra Operative analgesia.
2. Combination of clonidine with fentanyl increased the intra operative analgesic efficacy and significantly prolonged postoperative analgesia compared with clonidine alone.
3. Stable Intra Operative hemodynamics was obtained.
4. Duration of analgesia was prolonged.
5. The incidence of side effects due to additive effects of the drugs was minimal.
6. Fetal outcome was not altered.

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