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Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing surgeries under spinal anaesthesia: A randomized double blinded study.

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Abstract:
Background and aims*: Clonidine is added to intrathecal local anaesthetics to improve intraoperative analgesia and to increase the duration of sensory and motor block. Aim of this study was to evaluate and compare the effect of addition of two different doses of clonidine {25microgram and 50 microgram} to 15mg hyperbaric bupivacaine in patients undergoing surgeries under spinal anaesthesia.*
Material and Methods: *Ninty patients enrolled in the study were randomly divided into three group of 30 each. Group A received 15 mg hyperbaric bupivacaine, where as group B and C received 25 mcg and 50 mcg clonidine respectively as an adjuvant to 15 mg hyperbaric bupivacaine. The volume of solution was kept constant to 3.5ml by adding saline wherever needed.*
Result: *The onset of motor and sensory block, duration of spinal anaesthesia and duration of analgesia was recorded and compared in all 3 group. It was greatest in group C followed by group B and group A. Episode of hypotension and bradycardia were more in group C than in group B and A and it was easily treatable.*
Conclusion: *50 mcg clonidine added to 15mg hyperbaric bupivacaine provides better sensory and motor blockade and prolonged post operative analgesia.*
Keywords: *Alpha2 adrenoreceptors,intrathecal clonidine,bupivacaine,spinal anaesthesia.*

I. Introduction

Subarachnoid blockade is the most commonly used regional anaesthetic technique for lower abdominal and limb surgeries. Various adjuvant are being used with local anaesthetic for prolongation of intraoperative and postoperative analgesia. However, there use is thwarted either due to adverse effects of adjuvant or unreliable postoperative analgesia.

Clonidine, a selective partial alpha2 adrenergic agonist is being extensively evaluated as an adjuvant to intrathecal local anaesthetics and has proven to be a potent analgesic.[1, 2, 3] It is known to increase both sensory and motor blockade of local anaesthetics. Optimal dose in adult in terms of effects v/s side effects of intrathecal clonidine is controversial.[4]

In our present study, we analysed the analgesic efficacy of intrathecal clonidine in two different doses of 25 microgram and 50 microgram in combination with bupivacaine and intrathecal bupivacaine alone for lower abdominal and limb surgeries under spinal anaesthesis.

II. Methods And Material

After obtaining approval from the research ethical committee and informed consent, 90 adult patient in ASA physical status 1 and 2, age between 18-60 years of either sex presenting for lower abdominal and lower limb surgeries under spinal anaesthesia were enrolled in this prospective, randomized double blinded study. Exclusive criteria included emergency surgery, deformities of the spine ,hypersensitivity to any of the drug in the study and contraindication to spinal anaesthesia, patient refusal ,bleeding diathesis.

Before surgery ,patient were given instruction to use a 10 point verbal rating scale {VRS} with 0 indicating no pain and 10 indicating the worst imaginable pain. Baseline VRS were recorded in the operating room. ECG, Pulse oximetry, and non invasive blood pressure were recorded. Following infusion of 1000 ml lacted ringer's solution and with the patient in the sitting position under strict asepsis, a lumbar puncture was performed at L3-L4 intrvertebral space through a midline approach using a 25 G quincke needle.

Using a computer generated random list, patient were randomized to three groups: group A, B and C {n=30 for each group}. All patient received drug volume of 3.5 ml containing hyperbaric bupivacaine hydrochloride {15mg}. The study group received clonidine 25mcg {group B} or 50 mcg {group C} diluted to 0.5ml with 0.9% saline added to bupivacaine in the same syringe, the control group {A} received an identical solution of 0.9% saline added to bupivacaine. Patient attending anaesthetist and operating room personnel were not aware of patient allocation. Thereafter, patients were placed in the supine position for surgery. All patients

received antibiotics prophylaxis according to the hospital protocol. Patients were premedicated with Tab rantitidne 150 mg and Tab alprzolam 0.5mg H.S.

Heart rate (HR), blood pressure (BP) and oxygen saturation {spo2} were monitored and recorded after the block every 5 minutes for half an hour then 15 minutes until the end of surgery. The sensory block level was assessed with pin prick method and the motor block was assessed with modified bromage scale. Modified ramsay sedation scale was used for intraoperative sedation.

After operation, H.R., B.P., Oxygen saturation, sedation score and VRS score at rest and with movement {active knee flexion} were recorded

during the first hour at 15,30,45,and 60 minutes and thereafter every hour upto 8 hour after spinal injection ,then at 12 and 24 hour. The time from intrathecal injection to two dermatome sensory regression, to L3 dermatome and motor block regression to modified bromage 0 were recorded. All duration were calculated in relation to the time of spinal injection. Duration of pain relief was defined as the time from spinal injection to the first request for rescue analgesia which consisted of intravenous infusion of diclofenac 75mg.

Occurrence of nausea, vomiting, purities and respiratory depression were recorded throughout the study duration. Hypotension {defined as decrease in systolic blood pressure >30% of the baseline value or systolic blood pressure <90 mm hg} was treated with intravenous boluses of 6 mg ephedrine. Bradycardia defined as a pulse rate of <50 beats/min was treated with boluses of 0.3-0.5mg atropine. Respiratory depression {R.R <8 OR SPO2<95%} was treated with oxygen supplementation and respiratory support if required. All data collection was performed by a blinded observer.

Statistical analysis was performed with the SPSS. The categorical data were presented as number (percent) and were compared among groups using chi square test. The quantitative data were presented as mean and standard deviation and were compared by ANOVA {analysis of variance test}.The post HOC test tu key test was used for further analysis in the significant groups. Probability was considered to be significant if less than 0.05.

III. Result

Spinal anaesthesia was successful in all 90 patients involved in the study. The demographic profiles of the patients among the groups were comparable with regards to age, weight, and height and shown in table 1.

Tabel 1: patients chareacteristics

Mean+_SD	Group A	Group B	Group C	ANOVA F value	P Value
Age (years)	39.06+_12.937	42.00+_11.389	40.60+_9.792	0.496	0.611 NS
Weight (Kg)	58.83+_7.316	57.13+_7.440	60.60+_7.789	1.595	0.209 NS
Height (cm)	157.57+_6.745	158.73+_6.389	159.53+_8.174	0.575	0.565 NS

As our study was randomized, difference in age, weight and height was not statistically significant among the 3 groups.

The onset of motor block and sensory block [in minutes] is shown in table 2 and 3.

Table 2: The Onset Of Sensory Block {In Minutes}

Group	**N**	**Onset of sensory action**		**Anova F-value**	**P** Value
		Mean in Minutes	**SD**		
Group B	30	95.33	21.613	1.88	0.158 NS
Group C	30	97.00	28.303		
Group A	30	107.67	29.558		

Table 3: The Onset Of Motor Block {In Minutes}

Group	**N**	**Onset of Motor action**		**Anova F-value**	**P** Value
		Mean in Minutes	**SD**		
Group C	30	138.67	29.330	0.90	0.41 NS
Group B	30	132.33	29.906		
Group A	30	142.67	30.954		

Time of onset of motor and sensory block was also compared and the difference in 3 group was not statistically significant. The duration of action was compared between 3 groups by using ANOVA. The difference between the 3 groups was found to be statistically significant as shown in table 4.

Table 4: Comparison Of Duration Of Action

Group	**N**	**Duration of action**		**ANOVA F –value**	**P** Value
		Mean in Minutes	**SD**		
Group B	30	192.50	31.397	24.4	<0.001 HS
Group C	30	211.00	30.011		
Group A	30	168.50	25.736		

The duration of analgesia was compared between 3 groups by using ANOVA. The difference between 3 groups was found to be statistically significant as shown in table 5.

Table 5: Comparison Of Duration Of Analgesia

Group	**N**	**Duration of analgesia**		**ANOVA F-value**	**P** Value
		Mean in Minutes	**SD**		
Group B	30	354.50	69.69	69.7	<0.001 HS
Group C	30	397.83	85.77		
Group A	30	198.17	45.03		

Sedation score was compared between 3 groups.The difference among 3 groups was found to be statiscally significant .The sedation in the patient with clonidine was found to be dose dependent as shown in table 6.

Table – 6 Comparison of mean Sedation Score.

Group	**N**	**Sedation score**		**Kruskal- Wallis Test χ^2 (df=2)**	**P** Value
		Mean	**SD**		
Group B	30	2.03	.414	33.9	<0.001 HS
Group C	30	2.63	.556		
Group A	30	1.93	.254		

Mean B.P. and pulse rate recorded at different time interval after anaesthesia is shown in table- 7 and 8.

Table – 7 Comparsion of mean MAP in 3 groups at different time interval.

MAP (mm hg) Drug	**Pre op**	**5 min**	**15 min**	**30 min**	**45 min**	**60 min**	**2nd hr**	**3rd hr**	**4th hr**	**5th hr**	**6th hr**	**10 hr**	**14 hr**	**18 hr**	**24 hr**
Group B	94.12	84.73	82.33	81.67	82.43	84.13	85.07	85.20	85.87	86.10	90.87	92.13	91.97	92.30	93.47
Group C	93.89	83.07	80.43	79.77	80.07	82.17	83.43	83.00	83.93	85.27	88.43	91.73	93.20	83.87	94.97
Group A	94.01	83.90	81.38	80.72	81.25	83.15	84.25	84.10	84.90	85.68	89.65	91.93	92.58	93.08	94.22

Table – 8 Comparsion of Mean Pulse Rate at different time interval.

Drug Pulse	**Pre op**	**5 min**	**15 min**	**30 min**	**45 min**	**60 min**	**2nd hr**	**3rd hr**	**4th hr**	**5th hr**	**6th hr**	**10 hr**	**14 hr**	**18 hr**	**24 hr**
Group B	82.33	75.10	73.37	74.00	74.57	73.17	78.03	79.90	77.80	77.50	78.63	80.57	78.83	81.23	81.77
Group C	84.43	76.43	70.97	70.97	73.70	74.63	72.73	75.70	77.20	76.00	80.17	81.93	79.77	80.03	83.30
Group A	83.90	76.00	75.30	74.43	73.30	75.27	78.93	77.23	78.80	79.57	80.53	81.13	82.13	83.23	82.63

Hypotension and bradycardia was seen more in group C followed by group B and group A as shown in table 9 and 10.

Table – 9 Comparison of incidence of Hypotension

Group	**N**	**Hypotension**		χ^2	**P** Value
		No	**Yes**		
Group B	30	28	2	-	-
Group C	30	26	4		
Group A	30	29	1		

Table – 10 Comparison of incidence of Bradycardia

Group	**N**	**Bradycardia**		χ^2	**P** Value
		No	**Yes**		
Group B	30	27	3	-	-
Group C	30	26	4		
Group A	30	29	1		

The incidence of nausea and vomiting was more in group C as compare to group B and group A. Since the incidence was very low in 3 groups, the P value could not be calculated.

IV. Discussion

Local anaesthetics are the commonest agent used for the spinal anaesthesia, but their relatively short duration of action may lead to early analgesic intervention in the postoperative period.[5, 6]

A number of adjuvant to local anaesthetics have been used intrathecally to prolong the intraoperative as well as post operative analgesia.

Clonidine is a selective partial agonist for alpha 2 adrenoreceptors.Its analgesic effect is mediated spinally through activation of post synaptic alpha2 receptors in substantia gelatinosa of the spinal cord .It is known to increase both sensory and motor blocks of local anaesthetics by 30-50%.

In our study, the cases were randomly allotted in respective groups, physical parameters like age, height and weight in all 3 groups was comparable and statistically not significant. Differences in onset of sensory and motor blockade were not significant.

In our study, the mean duration of action with 3cc bupivacaine {group A} was 168.50+_ 25 minutes while it was 192.50+_ 31.39 minutes with 3 cc bupivacaine + 25mcg clonidine {group B}. Mean duration of action was significantly higher i.e 221+_ 30.01 minute with 3cc bupivacaine + 50mcg clonidine {group C} (CF value 24.4)and it was statistically significant.

Dobrydnjovet et al in their study in orthopedic patients on postoperative pain relief following intrathecal bupivacaine combined with intrathecal clonidine found prolonged analgesia and decreased morphine consumption post operatively.

In our study the mean duration of analgesia was 198.17+_ 45.038 minutes with group A, while it was 354.50 +_ 69.69 minutes with group B and it was still higher i.e 397.83+_85.79 minutes with group C. This data was statistically analysed with ANOVA. Each of these groups were compared with each other and data was statistically significant and are dose dependent.

Chiari et al[11] in a dose response study using intrathecal clonidine as sole analgesic was more pronounced with 100 mcg (60-180 minutes) and 200 mcg (75-210 minutes) then with 50 mcg (25-150 minutes).

Stephan strebel et al[7] has done study on dose response relationship of intrathecal clonidine in small dose and concluded that the clonidine group has longer duration of pain relief along with delayed 1st request for supplemental analgesia.

L Niemi et al[12] studied the effect of 3 mcg/kg of clonidine. The duration of analgesia was similar to our study but hypotension and bradycardias more in their study. Our study thus implies that it is possible to achieve equally good analgesia without side effects when clonidine is used in doses as low as 25-50 mcg.

B.S.Sethi et al[13] noted duration of analgesia more as compared to our group because they have used 1 mcg/kg whereas we have used only 25 mcg an 50 mcg.

Sedation which was assessed by Ramsay's sedation score from I to VI depending upon whether patient is awake or in deep sleep. In our study mean sedation score was 1.93+_0.254 with 3cc bupivacaine, 2.03+_0.414 with bupivacaine + 25 mcg clonidine and 2.63+_0.254 with 3cc bupivacaine + 50 mcg clonidine. The data was analysed by Kruskal Wallis Test and found to be statistically significant. None of the patients in whom clonidine was used had a sedation score of >3. The 3 groups were further compared with each other using student's test. The difference was statistically significant between the 3 groups. The result of our study is comparable with that done by B.S.Sethi et al[13], in which the efficacy of low dose intrarhecal clonidine was studied. In our study,

incidence of sedation as assessed by sedation score which was higher in the clonidine group than in the control group 3 to 6 hours after injection which was stastically significant ($p<0.001$).

The incidence of hypotension was more in group C (4 patients out of 30) followed by group B (2 patients out of 30), it was least with group A (1 patient out of 30). The study done by B.S.Sethi et al[13], showed a decrease in mean heart rate from 45 minutes until the end of 6 hours, was greater in clonidine group than in the comtrol group ($p<0.001$). The mean arterial pressure (MAP) also showed a similar trend and thus was statistically significant, lower MAP in the clonidine group from 45 minutes after drug administration until the end of 6 hours($p<0.001$).

Similarly incidence of bradycardia was more in group C (4 patients out of 30) followed by group B (3 patients out of 30).

It was least with group A (1 patient out of 30) which was managed by Inj. atropine. Several other investigations have studied the dose dependant effect of intrathecal clonidine.

Negri et al[14] found the addition of 105 mcg clonidine to hyperbaric bupivacaine was exerting minimal influence on hemodynamic parameters.

Racket et al[15] found that intrathecal clonidine (105 mcg) in patients resulted in a decrease in systolic blood pressure of only 15% from resting values.

Nausea and vomiting was also more in group C followed by group B. It was least with group A. However statistical test could not be applied because the occurrence of side effects was very less. No significant respiratory depression was seen in this study.

Clonidine is a good adjunct to an anesthetist's armory of drugs and its use intathecally as an additive to bupivacaine does extend the duration of spinal anesthesia significantly. Further it also provides excellent post operative analgesia and can be combined with other modalities for providing better pain relief in immediate post operative period. In addition to above, clonidine also provide sedation thus helping to relieve anxiety related with surgery.

To conclude use of clonidine with bupivacaine does increase the efficacy of anesthesia, post operative analgesia and provides sedation. Clonidine in dose of 50 mcg added to 3cc bupivacaine had a better efficacy when compared with 25 mcg clonidine with 3 cc bupivacine with comparable side effects. However the side effects were not very significant among the groups and were easy to treat.

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