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Effects of Oral Clonidine Premedication on the Onset and Duration of Spinal Anesthesia with Hyperbaric Bupivacaine A Prospective, Double-Blind, Randomized, Controlled Study

Dr.Suganthi.K.S, M.D, Dr.Kalyanasundaram.K, M.D

I. Introduction

Of all the regional an aesthesia techniques sub-arachnoid block, because of its clearly defined end-point is the easiest to perform and most widely used for surgeries below the umbilicus and lower extremities.The advantages of sub arachnoid block are, there is reduced blood loss, attenuation of neuro endocrine response, increased blood flow to lower limbs, decreased platelet aggregation. Well maintained airway in a conscious patient, reduced mortality and marked decrease in hospital cost.

In order to prolong the duration of sub-arachnoid block, vasoconstrictors were added to local anaesthetics but one rare outcome is ischemia of spinal cord.Hence the need to find a drug which do not damage the spinal cord but which effectively prolongs the duration of spinal anaesthesia could be an alpha 2 agonist clonidine which inhibit nerve conduction in Aalpha and C fibres without ischemic damage of spinal cord.

II. Methods

A randomized, double-blind, prospective study was conducted on 60 patients belonging to American Society of Anesthesiologists' Grade I and II, between the age group 20 to 60 years scheduled for below umbilicus and lower limb surgeries under sub arachnoid block were selected.

These patients were randomly allocated tone of two groups of thirty patients each.

Group I- placebo Received placebo per oral+ 12.5mg of hyperbaric bupivacaine .5% - 2.5ml

Group II-Clonidine Received clonidine 150ug per oral +12.5mg of hyperbaric Bupivacaine .5% - 2.5ml

An informed written consent was obtained from each patient prior to the procedure. Patients with infection at puncture site, coagulopathy, true hypersensitivity to drugs used, diabetes andhypertention, psychiatric and neurological disease were excluded from the study.All patients were kept nil per mouth overnight and Clonidine or placebo was administered 60minutes prior to entering the operation room per orally.No patient received any other premedication.

III. Procedure

In the operation theatre, all patients were connected to electrocardiograhy, peripheral oxygen saturation and non invasive blood pressure monitor and all basal parameters were recorded. The patients were explained about the procedure of spinal anastheia. An IV line was inserted with 18 gauge cannula and all patients preloaded with Ringer lactate solution 1oml/kg body weight.Patients were placed in left lateral decubitus position and operating table was kept horizontal. Under strict aseptic precautions lumbar puncture was performedusing 25 or 26 gauge spinal needle at L2-3 or L3-4 intervertebral space. Once a free flow of cerebrospinal fluid was obtained, the local anaesthetic was injected at the rate of 1ml/3sec.Patient was then turned to supine position and retained in that position for 20minutes before being positioned for surgery. The table was kept in horizontal position throughout the procedure. Dermatomal levels of sensory anaesthesia were evaluated by pin prick and studied every minute for the first twenty minutes and then at ten minute interval until analgesia to pinprick recovered to L1 segment.

The highest level of sensory analgesia was noted and the followimg parameters were evaluated and noted.

A) Time from injection to attainment of highest level of sensory blockade.
B) Time for two segment regression of sensory blockade
C) Time for two segment regression of sensory blockade.
D) Time for regression of sensory block to L1 segment
E) Time for onset of complete motor blockade. This was assessed and gradedat the same time interval as sensory blockade using modified Bromage scale.

1- Unable to move feet or knees
2- Able to move only feet.
3- Starts to move the knees

4- Detectable hip weakness in supine position along with complete knee flexion.
5- no detectable hip weakness in supine position
6- Able to bend knees partially while standing.
F) Time for recovery of motor blockade to L2 level (hip flexion)
G) Central effects:Sedation score done using Filos et al
1.Awake
2.Drowsy but responsive to verbal stimuli
3.Drowsy but arousable to physical stimuli
4. Unarousable.

IV. Results

Intra operatively, the blood pressure and heart rate were monitored at 1min interval for the first 10minutes and later every 10min for one hour

All parameters were statistically analysed using the students t test for unpaired observations between the groups. The sedation score was analysed using the Chi- square test with Yates correction.
A P value of>.05 was taken to be statistically not significant (NS), a P value of < .05 as statistically significant (S) and a P value of < .01 as statistically highly significant (HS) and a P value of < .001 as statistically very highly significant (VHS).

V. Age, Weight And Gender:

The mean age of patients in the placebo group was 34.93± 9.92 years while that in the clonidine was 37.8±10.65 years. The mean weight of the patients in placebo group was 62.67±11.39kg as compare to that in the clonidine group which was 57.67±7.92. The mean height of the patients in placebo group was 162±10.3 cms as compared to that in the clonidine group which was 166.6±10.9.

Group	Age (years) Mean ± SD	Weight (Kg) Mean ± SD	Height (cm) Mean ± SD
Placebo	34.93± 9.92	62.67±11.39	162±10.3
Clonidine	37.8±10.65	57.67±7.92	166.6±10.9

There was statistically no significant difference in the two groups with respect to age, weight and gender.
No significant difference in the height of sensory level between the placebo group and clonidine group.

Time for injection to attainment of highest sensory blockade

The mean time from injection to attainment of sensory blockade in the placebo group was 13 ± 4.61minutes while that in the clonidine group was 9.13 ±3.29 minutes.

Time taken for attainment of highest sensory blockade.

Group	Mean	SD	SEM
Placebo	13	4,61	1.19
Clonidine	9.13	3.29	0.85

Intergroup comparison showed a statistically significant difference in the time for injection to attainment of highest sensory blockade between the two groups ($0.01 < P < 0.02$)

Intergroup comparision of time taken to attainment of highest sensory blockade

	t	P	Significance
Placebo/Clonidine	2.61	0.01<P<0.02	SS

SS = Statically Significant

Time for two segment regression of sensory blockade

The mean time for two segment regression of sensory blockade in the placebo group was 71.67 ± 10.22 minutes while that in the clonidine group was 126.67 ± 19.93 minutes

Time for two segment regression of sensory blockade

Group	Mean (min)	SD	SEM
Placebo	71.87	10.22	2.64
Clonidine	126.67	19.93	4.93

Intergroup comparision of two segment regression of sensory blockade showed a statistically very highly significant difference between the placebo and clonidine groups($P < 0.001$)

Intergroup comparison of two segment regression of sensory blockade

	t	P	Significance
Placebo/clonidine	9.27	<0.001	VHS

VHS = Very Highly Significant

Time for four segment regression of sensory blockade

The mean time for four segment regression of sensory blockade in the placebo group was 112.83 ± 19.25 minutes, while that in the clonidine group was 186.33 ± 23.66 minutes.

Time for four segment regression of sensory blockade

Group	Mean (min)	SD	SEM
Placebo	112.33	19.25	4.97
Clonidine	186.33	23.69	6.12

Intergroup comparison of four segment regression of sensory blockade showed a statistically very highly significant difference between the placebo and conidine groups ($P < 0.001$)

Intergroup comparison of four segment regression of sensory blockade

	t	P	Significance
Placebo/clonidine	9.27	<0.001	VHS

VHS = Very Highly Significant

Time for regression of sensory blockade to L1 segment

The mean time for regression of sensory blockade to L1 segment in the placebo group was 169.87 ± 20.91 minutes, while in the clonidine group was 264.87 ± 27.04 minutes

Time for regression of sensory blockade to L1 segment

Group	Mean (min)	SD	SEM
Placebo	169.87	2091	5.4
Clonidine	264.67	27.04	6.98

Intergroup comparison of the regression of sensory blockade to L1 segment showed a statistically very highly significant difference between the placebo and clonidine groups ($P< 0.001$)

Intergroup comparison of four segment regression of sensory blockade

	t	P	Significance
Placebo/clonidine	10.6	<0.001	VHS

VHS = Very Highly Significant

Time for onset of complete motor blockade

The mean time for onset of complete motor blockade in the placebo group was 6.2 ± 2.51minutes, while that in the clonidine group was 6.07 ± 1.91minutes.

Time for onset of complete motor blockade

Group	Mean (min)	SD	SEM
Placebo	6.2	2.51	0.65
Clonidine	6.07	1.91	0.49

Intergroup comparison showed no statistically significant difference in the time of onset of complete motor blockade between the placebo and clonidine groups (P> 0.1)

Intergroup comparison of the onset of complete motor blockade

	t	P	Significance
Placebo/clonidine	0.16	>0.1	NS

NS = Not Stisfactory

Time for recovery of motor block to L_2 (hip flexion)

The mean time for recovery of motor blockade to L_2 in the placebo group was 112.07 ± 28.28 minutes, while that in the clonidine group was 156.63 ± 56.59 minutes

Time for recovery of motor block to L_2 (hip flexion)

Group	Mean (min)	SD	SEM
Placebo	112.07	28.28	7.3
Clonidine	156.63	56.59	14.61

Intergroup comparision showed a statistically significant difference in the recovery of motor blockade to L_2 segment between the placebo and clonidine groups (0.02< P < 0.02)

Intergroup comparison of the time to recovery of motor blockade to L_2 (hip flexion)

Most of the patients in the clonidine group were sedated intraoperatively while only one patient was sedated in the placebo group. The sedation score achieved in these patients was 2 i.e., these patients were drowsy but responsive to verbal stimulus. None of these patients had a sedation score of three or four. This data was analyzed using the Chi- square test with Yates correction, which indicated a statistically very highly significant difference between the two groups. (P<0.001).

Group	Number of patients		Total
	Sedated	Not Sedated	
Placebo	2	28	30
Clonidine	26	4	30
Total	28	32	60

$\chi^2 = 32.205$ P < 0.001
VHS = Very High Significant

Maximal change in heart rate (Δ HR_{max})

The baseline heart rate and lowest heart rate achieved during the study period were tabulated. The maximal change in heart rate (Δ $\mathbf{HR_{max}}$) from the base line was then derived and the mean and standard deviation of Δ $\mathbf{HR_{max}}$ calculated in the placebo and clonidine groups. The Δ $\mathbf{HR_{max}}$ in the placebo group was 16.47 ± 9.54 beats / minute while that in the clonidine group was -20.27 ± 13.53. intergroup calculated in the placebo and clonodine group. The Δ $\mathbf{SBP_{max}}$ in the placebo group was -32.89 ± 6.48 mmHg while that in the clonidine group was -28.8 ± 22.2 mmHg. Intergroup comparision of Δ $\mathbf{SBP_{max}}$ revealed no statistical difference (P >0.1) between the two groups.

Maximal change in systolic blood pressure (Δ SBP_{max}) from the baseline (+ indicates increase, - indicates decrease)

Group	Mean (min)	SD	SEM
Placebo	-32.8	16.48	4.26
Clonidine	-28.8	22.2	5.73

mmHg = millimeters of mercury

Intergroup comparison of the maximal change in systolic blood pressure (Δ SBP_{max})

	t	P	Significance
Placebo/clonidine	0.55	>0.1	NS

NS = Not Significant

Maximal change in diastolic blood pressure (Δ DBP_{max})

The baseline diastolic blood pressure and the lowest diastolic blood pressure achieved during this period were tabulated. Maximal change in diastolic blood pressure **(Δ DBP_{max})** from the base line was the derived and the mean and standard deviation of Δ DBP_{max} calculated in the placebo and clinidine groups. The Δ DBP_{max} revealed no stistical difference (P>0.1) between two groups.

Maximal change in diastolic blood pressure **(Δ DBP_{max})** in the pacebo group was -27.13 + 13.62 mmHg while that in the clonidine group was -19.13 + 16.37 mmHg.

Maximal change in Diastolic blood pressure (Δ DBP_{max}) from the baseline (+ indicates increase, - indicates decrease)

Group	Mean (min)	SD	SEM
Placebo	-27.13	13.62	3.52
Clonidine	-19.13	16.7	4.31

Intergroup comparison of the maximal change in Diastolic blood pressure (Δ DBP_{max})

	t	P	Significance
Placebo/clonidine	1.418	>0.1	NS

NS = Not Significant

Maximal change in mean arterial pressure (Δ MAP_{max})

The baseline mean arterial blood pressure and the lowest mean arterial blood pressure achieved during this period were tabulated. Maximal change in mean arterial blood pressure **(Δ MAP_{max})** from the base line was the derived and the mean and standard deviation of Δ MAP_{max} calculated in the placebo and clonidine groups. The Δ MAP_{max} revealed no statically difference (P>0.1) between two groups.

Maximal change in mean arterial blood pressure **(Δ MAP_{max})** in the placebo group was -27.33 + 12.64 mmHg while that in the clonidine group was -27.13 + 18.15 mmHg.

Maximal change in mean arterial blood pressure (Δ MAP_{max}) from the baseline (+ indicates increase, - indicates decrease)

Group	Mean (min)	SD	SEM
Placebo	-27.33	12.64	3.26
Clonidine	27.13	18.15	4.69

Intergroup comparison of the maximal change in mean arterial blood pressure (Δ MAP_{max})

	t	P	Significance
Placebo/clonidine	0.0345	>0.1	NS

NS = Not Significant

VI. Discussion

Vasoconstrictors have been used as adjuncts to prolong the duration of local anesthetic-induced subarachnoid blockade. Prolongation of local anesthetic blockade has been attributed to localized vasoconstriction thereby decreasing the uptake of local anesthetic from the subarachnoid space. Collins et. al suggested that intrathecal adrenaline directly stimulated α_2 adrenergic receptors in the spinal cord dorsal horn and exerted an anti nociceptive effect through descending inhibitory path ways in the spinal cord. In this

descending inhibitory path ways, noradreline is the neuro transmitter responsible for suppressing the activation of spinal cord dorsalhorn neuron by noxious stimuli.

In addition to vasoconstrictor, intrathecal chlodine is also effective in prolonging the local anesthetic induced sensory and motor blockade. Racle et. al demonstrated that intrathecal clonidine 150 μ g prolonged motor 38% and sensory 46% blockade when used as an adjunct to spinal anesthesia with bupivacaine in human. However the effect of oral clonidine on subarachnoid local anesthetic blockade in humans is controversial. While ota et. al reported that oral clonidine prolong the duration of tetracaine sensory analgesia by 93%, bonnet et. al fail to demonstrate significant prologation of bupivacaine induced sensory and motor blockade following clonidine 150 μ g or 0.3 mg orally. In this study it was found that oral clonidine 150 μ g prolonged the duration of bupivacine induced sensory blockade (regression to L_1) by 56% and motor block by 39%. It decreased the time taken for attainment of highest level of sensory blockade-9.13 minutes when compare to placebo group which was 13 minutes. However, oral clonidine did not affect the onset of complete motor blockade. These findings are in concurrence with those observed in earlier studies.

Butterworth and stricharh have demonstrated in animal experiments that analegica after neuraxial administration of α2 adrenergic agonist may in fact result from direct inhibition of impulse conduction in A α and C fibres. Clonidine has been demonstrated to potentiate inhibitory effects of local anesthetic on C fibre activities. Previous studies suggest that clonidine also affect peripheral sensory nerves as a sole agent or in combination with local anesthetics. Therefore, oral clonidine may exert its effect within the central nervous system, at peripheral nerve roots or by potentiation of effects of local anesthetics. Hemodynamic consequences such as bradycardia and hypotension were seen more frequently when the dose of oral clonidine exceeded 150 microgram. In this study the dose of oral clonidine was restricted to 150 microgram. This could have resulted in lower incidents of bradycardia and hypotension (1 patient). Both these patients responded effectively to intravenous atropine 0.6 mg and ephedrine 6 mg respectively.

In this study it was noted that the patients pre-medicated with clonidine had very high incidence of mild sedation when compared to placebo group. This finding is in agreement with the results of previous studies where oral clonidine was used as a pre-medicant.

VII. Conclusion

Pretreatment with 150 microgram of clonidine hydrochloride administered orally 60 minutes prior to spinal anesthesia with 0.5% hyperbaric bupivacaine.

1. Hastens the onset of sensory blockade but does not affect the onset of motor blockade.
2. Prolongs the duration of both sensory and motor blockade.
3. It is not associated with any greater change in heart rate and blood pressure than that seen following spinal anesthesia without clonidine pre-medication.
4. Produces significantly higher incidence of mild sedation intra-operatively.

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