Clonidine Premedication Decreases Hemodynamic Responses to Pin Head-Holder Application during Craniotomy

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ABSTRACT

Aim: The purpose of this study was to evaluate the effect of intravenous Clonidine hydrochloride on hemodynamic changes associated with laryngoscopy and pin head-holder application in patients undergoing craniotomies. **Method**: Fifty, adult patients of ASA grade I & II were included in this study and divided in two groups of 25 each. Group-I patients received 5 ml of normal saline 10-15 minutes before induction while in group-II injection Clonidine hydrochloride 2 mcg/kg was given. We observed mean blood pressure and heart rate at 1, 3 and 5 minutes after laryngoscopy and application of pin head- holder. We also studied intraoperative events and postoperative side effects. **Results**: Increase in heart rate and blood pressure during laryngoscopy and pin insertion was attenuated by Clonidine hydrochloride ($P < 0.001$). The number of patients developed hypertension were more in control group than Clonidine group and required another drug to stabilize the hypertensive response. Two patients in Clonidine group developed bradycardia but treated with drug. **Conclusion**: We concluded that intravenous Clonidine hydrochloride given in the dose of 2 mcg/kg was safe and appropriate as a premedication drug for adequate control of heart rate and blood pressure thus, maintaining intracranial pressure for neurosurgical anesthesia.

Keywords: Clonidine Hydrochloride, Premedication, Craniotomy, Hemodynamic response.

Introduction

Anesthesia for craniotomy presents special considerations .The brain is enclose in a rigid skull and the majority of craniotomies are perform for the treatment of space occupying lesions. At the same time, the brain is a vascular organ presenting potential for massive perioperative hemorrhage. Tolerance of the brain to interruption of substrate delivery is minimal. Maintenance of adequate blood flow to the brain is of fundamental importance in neuroanesthesia. In the Presence of a space-occupying lesion, the brain has limited compensatory ability before intracranial pressure (ICP) increases. During this time even minute increase in ICP may lead to displacement of brain tissue and cerebellar tonsillar herniation. As the ICP depends on MAP, we anesthesiologists' play a very important role in maintaining the ICP throughout the surgery by controlling the MAP. The skull pin head holder used to secure the head produces an intense nociceptive stimulus when applied and results in abrupt increases in blood pressure and intracranial pressure [1]. Anesthetic and physiologic factors controlled by the anesthesiologist have profound effects on the brain. Interactions between anesthesia and surgical outcome can be expected. Maintenance of stable hemodynamic during anesthesia for intracranial surgery is essential to optimize cerebral perfusion and to prevent acute increases in ICP. Many different approaches have been used with varying success to prevent the acute increases in blood pressure often seen in association with the stimulation of intubation and pin head-holder application [2].

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The centrally acting α2-agonist Clonidine decreases hemodynamic responses to painful stimuli during anesthesia, anesthetic requirements and the stress response to surgery. Injection Clonidine is well suited as a premedication for neurosurgery. The present study was designed to assess the effects of intravenous Clonidine hydrochloride on hemodynamic changes during laryngoscopy and pin head-holder application that affect intracranial pressure during craniotomy. We also studied safety and efficacy of the drug.

Method

This study was conducted after the permission of ethical committee and after taking informed consent of 50 patients of age group of 18-70 year, weighing 40-108 kg and ASA grade I and II who were posted for craniotomy. Patients allergic to protocol drugs, on regular antihypertensive drugs, with infratentorial tumor, tumor near brainstem, intracranial pathology causing alteration in conscious state and patients taking nimodipine therapy were excluded from the study. All the patients were subjected for physical and systemic examination preoperatively. Routine investigation like complete blood count, renal function test, liver function test, blood glucose, serum electrolytes, and electrocardiogram, chest X-ray, HIV and HBsAg were done. Patients were randomly allocated in two groups, of 25 each. Group A patients received injection normal saline 5 ml while in group B injection Clonidine hydrochloride 2mcg/kg was given 10-15 minutes before induction (A dilution of 15 mcg/ml). All patients were given their regular medications. No sedative premedication was used. After taking into the operation theatre, vital sign monitor was attached to the patient and baseline heart rate, blood pressure, Spo2, $EtCO_2$ and respiratory rate were measured. Pre oxygenation was done. All patients were induced with injection glycopyrrolate 0.2 mg, injection fentanyl citrate 4mcg/kg, injection thiopentone sodium 5mg/kg intravenously. Oral intubation was done with appropriate size flexometallic cuff tube after injection vecuronium bromide 0.1mg/kg. Patients were maintained with 50% oxygen, 50% nitrous oxide, sevoflurane and injection vecuronium bromide 1mcg/kg/minute as an infusion. Muscle relaxation was reversed with injection glycopyrrolate 0.4mg and injection neostigmine bromide 0.05mg/kg. To assure comparability between the groups, the intubation was graded by the authors as

1 = easy and quick 2 = requiring manipulation or additional instrumentation 3 = difficult, requiring repeated or prolonged attempts

Hemodynamic interventions were done according to the following protocol

Hypotension, defined as SBP >20% below the preoperative reading, was treated by using bolus of lactated Ringer's solution intravenously or 3mg injection mephentermine if more profound or prolonged hypotension. Hypertension, defined as SBP >30% above baseline, was treated by using injection propofol 0.5mg/kg. Bradycardia, defined as HR < 60 bpm was treated with injection glycopyrrolate or injection atropine. Hemodynamic variables were allowed to stabilize after any interventions before intubation or pin head-holder application. Systolic blood pressure (SBP), mean blood pressure (MAP), heart rate (HR), SpO2 and EtCO2 were measured before induction followed by 1 minute, 3 minutes and 5 minutes each after laryngoscopy and pin head-holder application. Intraoperative adverse events like hypotension, hypertension, bradycardia, arrhythmias were recorded along with interventions undertaken to correct them. In the postoperative period for 24 hours the patients were monitored carefully for signs of hypoxia, cyanosis, raised ICP, vomiting, pain, shivering and sedation (sedation was graded as 1= awake and communicative, 2= awake but drowsy, 3= asleep but easily roused and 4= unarousable).

Calculation: - Results for parametric data were reported as Mean ± SD. The resultant data between groups was analyzed by using unpaired student's t-tests whereas Z test was used to analyze data within groups. Intubation and pin head-holder application was analyzed as independent events. A p value of <0.05 was significant.

Result

The characteristics of patients in two groups were comparable in terms of age, gender, weight, heart rate, blood pressure and intubation score (Table-1).

Table 1: Patients characteristics

	Group-A	Group-B	P value
Age(years)	44.4 +/- 14.06	46.48 +/- 16.36	0.58
Weight(kg)	62.6 +/- 11.4	60.6 +/- 11.4	0.45

Sex(M/F)	18/7	20/5	1
Heart rate(bpm)	78.84 +/- 6.7	78.12 +/- 6.31	0.58
SBP(mm of Hg)	125.44 +/- 8.6	126.88 +/- 8.5	0.55
Intubation score(1-3)	1	1	1

Table 2: Heart rate changes

	Heart rate per min.	Group- A	Group- B	P value
	Baseline	78.84 +/- 6.71	78 +/- 6.31	0.65
Laryngoscopy	1 minute	82.78 +/- 7.05	82.81 +/- 6.69	0.98
	3 minute	96 +/- 8.19	85.93 +/- 6.95	<0.001
	5 minute	109 +/- 9.20	87 +/- 7.07	<0.001
Pin head holder	1 minute	89.88 +/- 7.65	84 +/- 6.76	<0.001
	3 minute	98 +/- 8.32	87 +/- 7.01	<0.001
	5 minute	102 +/- 8.73	88 +/- 7.13	<0.001

This table shows heart rate changes. In *control group heart rate increased both during laryngoscopy and pin head-holder application while in clonidine group it remains unchanged and statistically significant.*

Table 3: Mean arterial pressure changes

	Mean arterial pressure changes mm of Hg	Group- A	Group- B	P value
	Baseline	95 +/- 6	93.55 +/- 5.69	0.38
Laryngoscopy	1 minute	102 +/- 6.42	98.15 +/- 5.98	<0.001
	3 minute	112 +/- 7.08	101.03 +/- 6.26	<0.001
	5 minute	125 +/- 7.56	110 +/- 6.71	<0.001
Pin head holder	1 minute	103 +/- 6.48	98.22 +/- 5.97	0.052
	3 minute	109 +/- 6.9	104.45 +/- 6.55	<0.001
	5 minute	120 +/- 7.56	109 +/- 6.66	<0.001

In this table mean arterial pressure increased in control group than clonidine group ($p < 0.005$). MAP increased maximum at 5 minutes from 95 +/- 6 to 125 +/- 7.56 after laryngoscopy and 120 +/- 7.56 after pin head holder application in control group, while in clonidine group it increased from 93.55 +/- 5.69 to 110 +/- 6.71 and 109 +/- 6.66 each.

Table 4:No. of patients requiring intervention and amount of drugs use

Drugs	Group- A	No. of pts.	Group- B	No.of pts.	P value
Fluid bolus(ml)	100 +/- 39.51	2(8%)	121 +/- 57.64	8(32%)	0.580
Propofol(mg)	90 +/- 23.12	25(100%)	49 +/- 24.38	6(24%)	<0.001
Glycopyrrolate(mg)	0	0	0 +/- 0.04	2(8%)	1

The number of patients developing hypertension during laryngoscopy and pin head-holder application in group A was significant.Propofol was given to all patients in group A whereas in group B, only 6 patients were given which was statistically significant. The amount of propofol given also differed in both groups that show that the patients pre-treated with Clonidine did not develop as much hypertension as the patients in control group. In comparing for hypotension, a larger proportion of patients developed hypotension in group

B. Fluid bolus was given to 8% patients in group A as compared to 32% in group B. No patients required injection mephentermine for hypotension. When bradycardia was compared, it was seen in only 2 patients in the Clonidine group and the maximum decrease in HR was up to 55bpm and treated with inj. glycopyrrolate. In group A, no patient developed bradycardia. As we also recorded ECG changes and observed that only 1 patient in group A, developed arrhythmia in the form of occasional atrial premature complexes that subsided spontaneously in a 2-3 minutes. In postoperative care unit we saw that none of the patient developed hypoxia or cyanosis due to respiratory depression. Nausea and vomiting due to raised ICP or side effect of various anesthetic drugs were not seen. We observed that only 1 patient in group A and 2 patients in group B had developed bradycardia which was treated with injection glycopyrrolate. In group A 15patients and 12patients in group B (p=0.39) had a sedation score of 1, 10 patients in group A and 12 patients in group B had a sedation score of 2 while only 1 patient had a score of 3 in group B. As all the p values were more than 0.05 is statically insignificant.

Discussion

Control of hemodynamic parameters during neurosurgical procedures is of great concern to the neuroanesthesiologist whose goals include ensuring optimal cerebral perfusion pressure. Clonidine appears to possess many properties that make it an appealing adjunct to the Intraoperative management of neurosurgical patients [1]. The present study was randomized controlled demonstrated that hemodynamic changes associated with laryngoscopy and pin insertion in patients undergoing craniotomy can be ameliorated more efficiently when Clonidine was used as intravenous premedication. Mean age of both groups were close to each group. Baseline weight, pulse and mean pressure were also showed a significant similarity between each group.

Intravenous route was chosen to provide exact drug dosing and the gap between administration of drug and induction of patients. A gap of 10-15 minutes was chosen because onset of action of intravenous Clonidine is 2-28 minutes. An average of 15 minutes was taken. Costello *et al* [2] used oral Clonidine while Farve *et al*[3] administered Clonidine 3 mcg/kg 10 minutes before surgery. The dose, route of administration and time interval was similar to our study. In our study the MAP showed an increase during both laryngoscopy and pin head-holder application in both the groups. However, in the placebo group the average MAP rise was higher during both laryngoscopy and pin head-holder application than clonidine group. Selina F *et al*[4] noted the MAP of the experimental group decreased steadily throughout the perioperative period, while in control group plateau reached up to 107 mm of Hg. at the time of burr hole and then gradually declined. It was proved that study group was better. According to W. Scott Jellish *et al* fluctuation of MAP was minimal [1]. Dorothee *et al* noted that patients treated with Clonidine had lower values of MAP than patients with placebo[5].Oral Clonidine premedication in craniotomy a study conducted by Traill *et al* noted that in Clonidine group lower SBP on arrival in the operative room, preinduction and post intubation than control group[6].On comparison between the two groups at the various intervals we found that except from one reading (1min after laryngoscopy) all the time there was a significant difference in HR between the two groups. Maximum increase in average HR was seen 5min after laryngoscopy, when the mean HR increased by 46.84% ± 8.8% in group A and 26.16% ± 6.67% in group B. The difference in HR between the two groups was 22 ± 2.19 that was highly significant ($p<0.001$). Selina F *et al*[4] in their study observed that just after intubation the rise in HR between the two groups was not statistically significant but once incision was made increased in HR was very significant until 60min after dura opening. The pulse rate of Clonidine group was maintained within normal range throughout the intraoperative period. Bradycardia was noticed in 50% patients in the high-dose group, 10% in the low-dose group, and in 5% in the placebo group [8]. In our study only 8% patient's developed bradycardia. Scott Jellish in their study shows that baseline heart rate was lower in patients who received Clonidine. Combination of oral Clonidine and lidocaine scalp injection at pin H-H sites blunted the blood pressure and heart rate response [1]. Dorothee [5] noted that patients treated with clonidine had lower values of heart rate from the preinduction to the early postanesthesia recovery periods than patients who had received placebo. They studied endocrine effect and noted that plasma cortisol and aldosterone concentration was also decreased. Devendra Gupta[7] studied oral atenolol and Clonidine premedication on cardiovascular response to nasal speculam insertion and stated that heart rate increased on speculam insertion in control group, while no changes in atenolol and clonidine group. They also noted that 10 out of 22 patients in control group developed hypertension as compared to only 2 in each clonidine and atenolol groups.Fentanyl requirement in control group was 136.9±77.6mcg/kg/hr as compared

to clonidine group 73.8±36.6mcg/kg/hr and atenolol group 70.8±28.7mcg/kg/hr. that is statistically significant. Propofol requirement was also greater in the control group 143.08±53.29mcg/kg/hr whereas in clonidine group it was 119.23±20.80mcg/kg/hr and 118.42±22.67mcg/kg/hr in atenolol group. Bradycardia was seen in 2 patients in atenolol group without hypotension that responded to atropine. This establishes that the adverse events in our study were like theirs. KritonFilos *et al*[8] studied 2 doses of clonidine 2-2.5mcg/kg and 4-4.5mcg/kg with a placebo. In the low-dose group the maximum decrease of MAP ranged between 18-19%, whereas in the high dose ranged between 25-34%. In the high dose group 30% of patients, but none in the low-dose group or in the placebo group were treated for hypotension. 65% patients experienced an increase in MAP >115 mm Hg throughout the study period, whereas no patient in the clonidine treated groups exhibited a MAP increase.

Hence, our study showed that those patients not pre-medicated with Clonidine required another drug to stabilize the hypertensive response during laryngoscopy and pin head-holder application. Saline requirement was greater in the Clonidine group but it was not very significant though it was seen that the extent of hypotension was not very substantial as the SBP never decreased below 85mm Hg.

Samantaray A *et al*[9] observed the average pain score was less in the clonidine. As our study gave an insignificant p value ($p>0.05$), it was postulated that it could be because their dose was higher (3mcg/kg) as compared to ours (2mcg/kg). Their results on bradycardia were similar to our study. The average sedation score revealed $p= 0.74$ and respiratory depression gave $p=0.73$. This result is also parallels to our study as p values for the sedation score was always more than 0.05.

As a result of this study we believed that intravenous Clonidine given in the dose of 2mcg/kg 10min before induction is appropriate and safe as a premedication drug.

Conclusion

We concluded that preoperative intravenous clonidine hydrochloride in a dose of 2mcg/kg 10-15 minutes before induction was very effective in controlling fluctuations in heart rate and blood pressure during laryngoscopy and pin head-holder application in craniotomy patients. It also produces stable hemodynamic throughout the surgery. Clonidine hydrochloride was safe in terms of hemodynamic parameters like overt bradycardia and hypotension in the given dose.

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Conflict of Interest: None

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