ORIGINAL ARTICLE

Effects of clonidine on hemodynamic response and dural tightness in patients with supra-tentorial space occupying lesion undergoing craniotomy- a placebo controlled comparative study

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ABSTRACT

Background and Aims: hypotensive anesthesia is preferred in craniotomy. Current study was conducted to evaluate the effects of oral clonidine premedication upon hemodynamic status, dural tightness and quality of anesthesia using 3 point scoring system in patients scheduled for craniotomy under general anesthesia.

Methodology: Amongst twenty two selected cases they were grouped equally in this randomized single – blind comparative study. Group A and B patients received sugar tablet and oral clonidine 3 μg/kg as a premedication respectively. Monitoring of hemodynamic variables like heart rate, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, SpO_2, E_TCO_2 and dural tightness were performed.

Results: Diastolic arterial pressure was significantly low in Group B during positioning, performing burr hole and during dura incision. Mean arterial pressure was highly significant for Group B during positioning. Heart rate change was significantly high for Group B during burr hole. Regarding dural tightness, 10 patients in Group B and 6 in Group A had no dural swelling. 1 patient in Group B and 5 patients in Group A had minimal swelling and surgery continued. Once all results b being assessed using 'Three point scoring system', it became highly significant in Group B with respect to Group A.

Conclusion: Oral clonidine premedication provides optimal hemodynamic stability and good neuro-surgical comprising heart rate, mean arterial pressure and dural tightness. 'Three point scoring system' seems to be an effective tool for intra-operative monitoring of patients undergoing supra-tentorial craniotomy.

Keywords: Clonidine, Neuroanesthesia, Supra-tentorial space occupying lesion, Craniotomy, Hemodynamic, Dural tightness.

Citation: Chowdhury MMR, Islam MS, Bhowmick DK, Kamal MM, Akhtaruzzaman AKM. Effects of clonidine on hemodynamic response and dural tightness in patients with supra-tentorial space occupying lesion undergoing craniotomy- a placebo controlled comparative study. Anaesth Pain & Intensive Care 2015;19(3)233-239

INTRODUCTION

Craniotomy induced surgical stimuli predisposes sympathetic activation and marked changes in systemic arterial pressure, cerebral blood flow and intracranial pressure. Cerebrovascular changes can cause raised ICP, decrease in cerebral perfusion

pressure, more marked in patients having deranged auto-regulation and compromised cerebral compliance. Obtundation of the hemodynamic responses to painful stimuli is a prerequisite to ensure optimal cerebral homeostasis during neurosurgical procedure.

Alpha 2 adrenargic receptors are distributed widely within and outside the CNS, mostly in the region of pons and medulla which regulates transmission of sympathetic nervous system stimulation from higher centers to the periphery. Pre-synaptic α_2-receptors activation inhibits release of nor-epinephrine. Whereas, α_2-adrenoceptors situated post-synaptic in the dorsal horn and on vascular smooth muscle when stimulated prevents nociceptive signal transmission and causes vasoconstriction respectively.[1,2]

Clonidine is used primarily for its α_2 receptor mediated antihypertensive effects. Stimulation of α_2 receptors by Clonidine in the central nervous system has role on sedation for which clonidine is widely used as an adjunct to anesthesia and pain medicine[3].

Clonidine reduces sympathetic tone and the release of nor-epinephrine from nerve terminals[4]. During general anesthesia, clonidine reportedly enhances intra-operative circulatory stability by reducing catecholamine levels.[5] Therefore, the use of clonidine during surgery has been proposed as a way of improving perioperative hemodynamics, decreasing both the intracranial pressure and anesthetic requirements. Clonidine is well absorbed after oral administration. The peak concentration in plasma and the maximal hypotensive effect are observed 1 to 3 hours after an oral dose. The elimination half-life of the drug ranges from 6 to 24 hours, with a mean of about 12 hours.[6]

This central and peripheral effect of clonidine may explain the improvement in metabolic control. Clonidine given as a premedication improves cardiovascular stability and blunts the cardiovascular response to laryngoscopy, intubation and surgery.[7] Clonidine prevents fluctuation of hemodynamics throughout the entire perioperative period, which is very important in neurosurgical patients.[8]

This study was designed to determine whether premedication with oral clonidine provide optimal hemodynamic stability, as well as good neurosurgical compliances for craniotomy under general anesthesia and the three point scoring system can evaluate the patient's hemodynamic condition and the dural tightness, ultimately quality of surgical anesthesia.

METHODOLOGY

This randomized single-blind comparative study was conducted from January to September 2014 at Bangabandhu Sheikh Mujib Medical University, Bangladesh.

After institutional ethical committee approval and informed written consent, a total of 22 patients of ASA physical status 1 and 2, aged 30-50 years undergoing craniotomy under general anesthesia were recruited. They were grouped randomly by lottery method composed of 11 patients in each group where Group A received oral sugar tablet and Group B received oral clonidine 3 μg/kg.

Patient's refusal to participate in the study, emergency surgery, ASA–more than II, patient with morbid obesity, hypertension, on β blocker or α blocker, having coagulopathy or patient taking anti-platelet medications were excluded.

Patients received sugar tablet or clonidine tablet 90 minutes before induction of general anesthesia. A large bore intravenous catheter was placed. Electrocardiogram leads, blood pressure cuff and pulse-oximeter were also placed. Every patient's received inj. Midazolam 1mg intravenously before induction. Once pre-oxygenated with 100% oxygen for three minutes, inj. vecuronium 0.1mg/kg followed by propofol (2 mg/kg), fentanyl 2 μg/kg were given intravenously. Each patient was intubated with proper size endotracheal tube and Capnometer was placed with it. Anesthesia was maintained with N_2O in O_2 (60:40) and isoflurane at a MAC less than 0.5%. Inj. fentanyl in increments of 0.4 μg/kg[9] and inj. vecuronium was administered using syringe-pump at 1 μg /kg/min. Bladder catheterization was done. Proper positioning of patient with care of pressure areas and padding of eyes were done. Both groups received mannitol 20% 1 gm/kg (IV) when scalp incision was given. Controlled ventilation was adjusted to maintain E_TCO_2 at 28-32 mmHg in both groups. The time intervals between induction of anesthesia, intubation, and pin head-holder application were also kept as constant as possible, with time between induction of anesthesia and pin head-holder application never exceeding 30 min. Hemodynamic variables like systolic arterial pressure, diastolic arterial pressure, mean arterial pressure and heart rate of all patients were continuously recorded by using Philips monitor (IntelliVue MP30, Germany). All these were recorded before induction, just after intubation, during positioning, local

infiltration, skin incision, burr hole, dura incision, 30 min and 60 min after dura opening respectively.

Optimal anesthetic condition concerning dural tightness were assessed by scoring system in many occasions by different authors in their study.[10,11] In this study we used 'three point scoring system' based on mean arterial pressure, heart rate and dural tightness. Each was assessed with scores of 1-3, total point ranged from 3 to 9.

Mean arterial pressure rated 1 point if it was ≤ 60-70 mmHg, 2 point if it was 71- 90 mmHg and 3 point if it was ≥ 91 mmHg.

Heart rate rated 1 point if it was ≤70 b/min, 2 point if it was 71-90 b/min and 3 point if it was ≥ 91 b/min.

Dural tightness rated 1 point if there was no swelling, 2 points if there was minimal swelling but surgery continued and 3 points if there was severe swelling and surgery was postponed. Dural condition and tension were measured subjectively by surgeons. Tension of dura was used as a guide. Just before opening the dura, surgeons were asked to provide an assessment of the condition of the brain.

Isoflurane and N_2O were discontinued after skin closure. Patients were reversed with neostigmine 0.05 mg/kg and atropine 0.015 mg/kg and Extubation was done when adequate spontaneous ventilation resumed.

Adverse effects like hypotension (SAP<90 mmHg), bradycardia (HR <60bpm), respiratory depression, nausea, vomiting or allergic manifestations if occurred were recorded.

Statistical analysis was done using software SPSS (Statistical Package for Social science), version 17. Demographic data and hemodynamic data were analyzed using unpaired student's t-test. Dural tightness and three point scoring system were analyzed using chi-squire (X^2) test. Statistically significance was set at p-value <0.05.

RESULTS

Two groups matched statistically comprising age (p = 0.18), weight (p = 0.92) and sex (p=1.00) having no difference between them (Table 1).

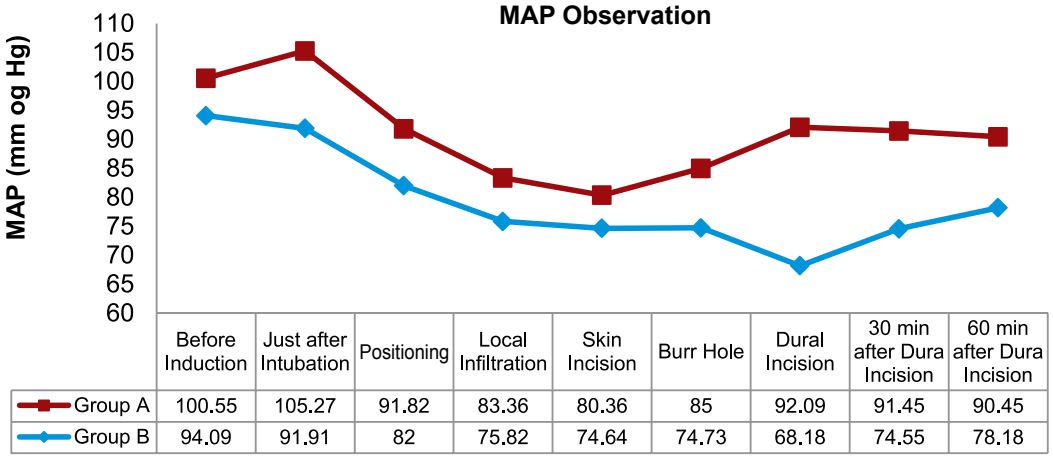
Table 1: Demographic variables

Variables		Group A n=11	Group B n=11	p-value
Age (years)		41.73 ± 8.95	39.0 ± 6.66	0.18 (NS)
Weight (kg)		60.09 ± 6.77	61.91 ± 6.73	0.92 (NS)
Sex	Male	6 (54.55)	7 (63.64)	1.00 (NS)
	Female	5 (45.45)	4 (36.36)	

All values were presented as mean ± SD or in frequencies. Data were analyzed using unpaired student's t-test and Chi-square test as appropriate. Statistically significance was set at p-value <0.05. (NS- Not significant)

Hemodynamic variables like heart rate (p = 0.44), systolic arterial pressure (p = 0.60) and diastolic arterial pressure (p = 0.27) were almost identical in both groups which were insignificant.

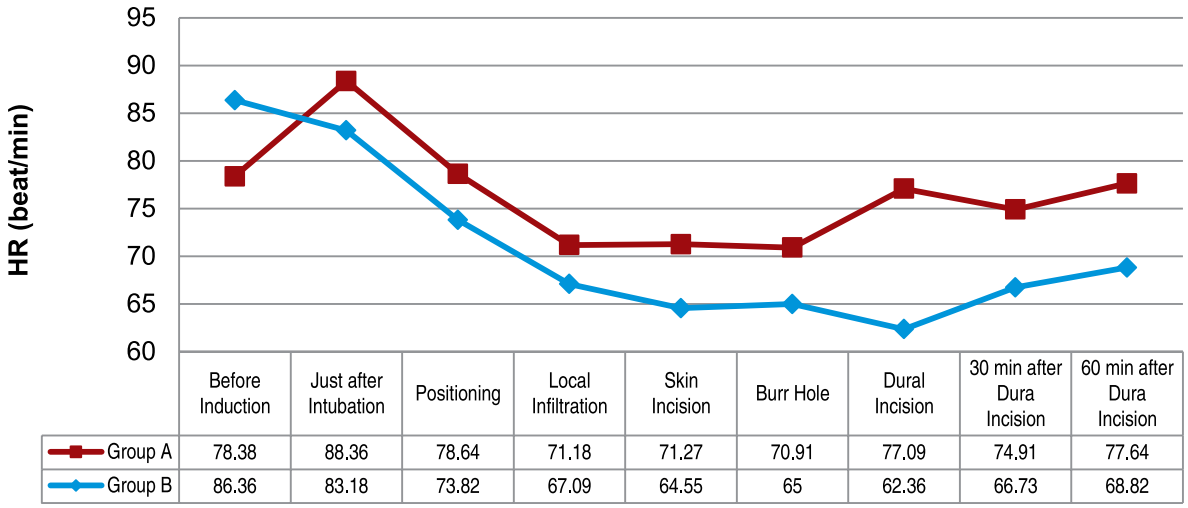
Systolic arterial pressure of Group B before induction was 127 ± 10 mmHg and during different evaluation period varied from 127.27 ± 10 mmHg to 94.82 ± 5 mmHg. On the other hand SAP of Group A before induction was 136.0 ± 12 mmHg and during



	Before Induction	Just after Intubation	Positioning	Local Infiltration	Skin Incision	Burr Hole	Dural Incision	30 min after Dura Incision	60 min after Dura Incision
Group A	100.55	105.27	91.82	83.36	80.36	85	92.09	91.45	90.45
Group B	94.09	91.91	82	75.82	74.64	74.73	68.18	74.55	78.18

Figure 1: Comparison of mean arterial pressure

effects of clonidine on hemodynamic response and dural tightness



	Before Induction	Just after Intubation	Positioning	Local Infiltration	Skin Incision	Burr Hole	Dural Incision	30 min after Dura Incision	60 min after Dura Incision
Group A	78.38	88.36	78.64	71.18	71.27	70.91	77.09	74.91	77.64
Group B	86.36	83.18	73.82	67.09	64.55	65	62.36	66.73	68.82

Figure 2: Comparison of mean heart rate at different time interval

different evaluation period ranged from 141.46 ± 28 mmHg to 110.90 ± 16 mmHg. The changes were not statistically significant in both groups.

Although diastolic arterial pressures of both the groups were within acceptable range during different observation period, Group B exhibited relatively low during positioning, burr hole and dura incision which were significant statistically ($p = <0.05$).

Mean arterial pressure of both groups followed the same trend regarding fluctuation of pressure as that of systolic arterial pressure, having no statistically significant changes. Only MAP during positioning in clonidine group revealed change which was significant statistically ($p \leq 0.05$) (Figure 1).

In Group B, heart rate (Figure 2) found gradually decline and then rise again after dura was opened. On the other hand in Group A, though heart rate was rising initially but started to fall after intubation. No statistically significant changes were found during different evaluation periods except during burr hole which was statistically significant ($p \leq 0.05$).

In Group B 10 (90.9%) patients had had no dural swelling while 1 patient (9.09%) had minimal swelling and the surgery continued. On the other hand in Group A 6 (54.5%) patients had no dural swelling but the remaining 5 (4 5.5%) patients developed minimal swelling and surgery continued (Figure 3).

The 'three point scores' were obtained from mean arterial pressure, heart rate and dural tightness during dural opening (Table 2). Among Group B, we found 9 patients (81.82%) had scored 3-4, which

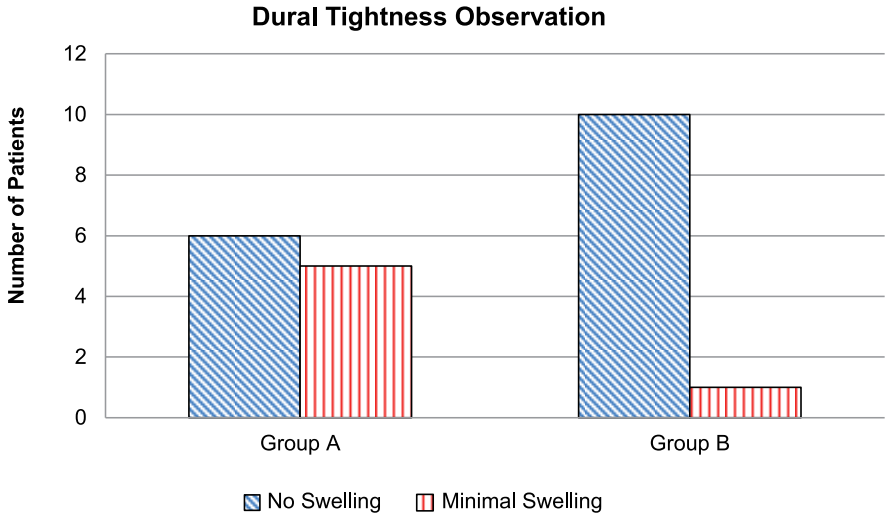


Figure 3: Comparison of dural tightness during dural incision in two groups

was considered as good and the rest 2 patients (18.18%) scored 5-7, considered as acceptable with respect to three points score. On the contrary only 1 patient (90.91%) scored 3-4 in Group A, considered as good but the remaining 10 patients (90.91%) had acceptable scores between 5-7. No group had scored "8-9". Group B became significant statistically (P< 0.01) in comparison to Group A.

Table 2: Three points scoring in both groups [n (%)]

Scoring	Group		p-Value	Significance level
	A	B		
Good (Score 3-4)	1(9.09)	9(81.82)	<0.01***	HS
Acceptable (Score 5-7)	10(90.91)	2(18.18)		
Not acceptable (Score 8-9)	0(0.0)	0(0.0)		

Values were expressed as number and within parentheses are percentages over column total. Data were analyzed using Chi-squire test. Statistically significance was set at p-value <0.05. (HS- **Highly Significant**)

DISCUSSION

Craniotomy is the most common surgical management for supra-tentorial space occupying lesion, where hypotensive anesthesia is preferred. Well Controlled hemodynamic variables is considered gold standard, where maintenance of optimal cerebral perfusion pressure is desired.

Clonidine possesses some unique properties that make it a suitable adjunct for managing neurosurgical patients intra-operatively. Clonidine decreases total peripheral resistance, renal vascular resistance, heart rate and blood pressure[12] through α_2-receptor mediated action. It depresses electrical function and decreases cortical response, thereby leads to reduced anesthetic requirements associated with clonidine administration.[13]

Positioning (head-holder insertion) is an intense painful stimulus which simultaneously with endotracheal intubation and surgical incision remarkably increases mean arterial pressure and heart rate[14]. Most institutions follow the technique of tightening head holder in anesthetized patients using pressure equals to 80 pounds. To avoid undesired elevation in blood pressure, heart rate and ICP, obtunding these stimuli should be preferred during neurosurgery.

The effect of clonidine on intra-operative hemodynamic status as well as dural tightness during dural incision was evaluated. In this study, we collected data of mean arterial pressure and heart rate at same time. In addition, data for dural tightness during dural incision to establish three point scoring system were also collected. In a previous study by Selina et. Al,[15] monitoring of only mean arterial pressure and pulse were done not including dural tightness into consideration.

Both the groups did not differ with respect to age, weight and sex. All preoperative baseline hemodynamic variables were almost identical in both groups ($p > 0.05$). Effect of clonidine on hemodynamic responses was monitored. Just after intubation there was increase in SAP from (136 ± 12) mmHg to (141 ± 28) mmHg in Group A where as in Group B there was a slight decrease from (127 ± 10) mmHg to (124 ± 18) mmHg ($p = 0.17$). This correlates with another study,[16] where the effect of clonidine pre-medication on hemodynamic responses was measured during micro-laryngoscopy and fiberoptic bronchoscopy.

Baseline HR in Group B was higher but per-operative HR was lower than the Group A. In addition, in Group B, HR change to laryngoscopy was not observed. This correlates with other studies[17] that had demonstrated a bradycardia or unchanged HR as the response to intubation after clonidine pretreatment.

Clonidine reduced baseline MAP in comparison to placebo group. Nevertheless, insignificant difference regarding blood pressure response to laryngoscopy between groups was revealed. Possibly this result predicts the desired optimal level of anesthesia conducted to patients according to titration.

Our study shows the changes in mean pressure at different time intervals following intubation. The mean pressure of both groups at different time intervals from intubation followed the similar pattern as systolic and diastolic blood pressure did. The mean pressure of the Group B decreased steadily throughout the intra-operative period, while that of the Group A showed fluctuation in successive period of evaluation. In a previous study,[18] oral clonidine (5 μg/kg) was used as pre-anesthetic medication and observed the fluctuation of mean arterial pressure during head pin insertion in case of skull base procedure. According to their study fluctuation of mean arterial pressure was minimum.

Mean arterial pressure was lower in most of the period for Group B. It was highly significant during positioning ($p = 0.01$) in clonidine group. There

was highly significant change in diastolic arterial pressure during positioning ($p = 0.04$), burr hole ($p = 0.03$) and dural incision ($p = 0.001$) in case of diastolic arterial pressure, in Group B.

Only 6 (54.54%) patients of Group A and 10 (90.91%) patients of Group B had no dural swelling but it was statistically insignificant. Considering three point scoring system with MAP, HR and Dural tightness during dura opening, Group B became highly significant ($p \leq 0.01$) in comparison to Group A.

Hypotension is a potential complication when clonidine co-administered with anesthetic induction agents. In our study, no patient in both groups required rescue treatment for hypotension. In another study[19] vasopressors were required for 8 patients in clonidine group and 2 patients in placebo group where CPP came down below 60 mmHg. Perhaps it was due to different method of clonidine administration. Intravenous clonidine has the propensity to develop accentuated hypotension compared to orally administered form. No other complications were observed.

CONCLUSION

The present study shows that oral clonidine premedication in Neuroanesthesia for patients with supra-tentorial space occupying lesion provides stable hemodynamics and optimal intra-cranial pressure intra-operatively. Moreover, in our opinion '3 point scoring system' represents an effective tool to assess per-operative condition in supra-tentorial craniotomy.

Conflict of interests: The authors have no conflicts of interest to disclose.

Funding: None

Authors Contribution:

MMRC: Data collection
MSI: Manuscript writing
DKB: Protocol designing, reference collection
MMK: Data collection

AKMA: Statistical analysis, manuscript correction, over-all supervision

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My most unforgettable experience

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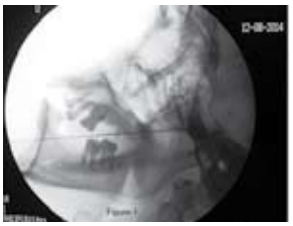
This story is about a 41 year old male patient who was suffering from trigeminal neuralgia of right side of face for 4 years and was on maximum dosage of carbamazepine (1600 mg/day) without effective control of symptoms. During his attacks of pain he visited many doctors including some dentists. Unfortunately, as happens with many patients of trigeminal neuralgia, he was advised multiple tooth extractions. When he finally visited us for his pain, he still thought that the root cause of his pain was the bad teeth of his upper jaw. He did not have any other comorbidity except facial pain in specific to V2 area (maxillary division of trigeminal ganglion) area. We evaluated and scanned him with MRI to rule out any vascular loop on trigeminal ganglion. We offered him radiofrequency ablation of V2 under fluoroscopic guidance after proper sensory localization (Figure 1). Procedure was successful in numbing the affected area without any complication. During procedure of ganglion localization, blood was aspirated once so the needle was manipulated and relocated till no further blood flow was seen (Figure 2). He was discharged after 4 hours of observation with advice of oral paracetamol to control pain because of procedure itself.



Next morning he was admitted in a poor general condition; repeated, forceful vomiting, drowsy, dehydrated, feeble pulse, heat rate 112/min, blood pressure 100/60 mmHg. Attendants were visibly aggrieved and repeated saying that the patient was absolutely fine the day before and that bad condition was just because of the RF procedure done. They suspected that RF must have caused brain injury (it was stated to the patient and his attendants as one of the possible complications of the planned procedure during informed consent). I was personally petrified, thinking that the patient must have some intracranial pathology like raised intracranial pressure (ICP) due to intra cranial bleed etc. However, his clinical picture did not fit well with features of raised ICP except projectile and repeated vomiting. Neck was supple and meningitis was most unlikely. Attendants were reassured and the patient resuscitated. Neurologist's opinion was sought and an urgent brain CT was done, which was within normal limits. The condition of the patient improved within 4-6 hrs, so he was discharged the next morning.

Before departing, he came to us and thanked for immediate care. He regretted attendants' doubts about treatment and rude behavior. And then he disclosed that after leaving the hospital he took a large meal of spicy snacks as he was very hungry. He had been fasting for two days due to extreme anxiety. Then he developed severe gastroenteritis. He neither mentioned it to any family member nor informed us. We were also taken aback by his serious condition and failed to rule out the most common causes first. He left us wiser with some sweet-sour memories.