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The Efficacy of Labetalol versus Nitroglycerin for Induction of Controlled Hypotension during Craniotomy Surgery. A Prospective, Double-Blind and Randomized Study

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ABSTRACT: Craniotomy includes the temporary removal of bone flap from calvarium to access the intracranial contents, which is usually used to reduce intracranial pressure[1]. Induced or controlled hypotension is a method by which arterial blood pressure is predictably reduced, thus reducing bleeding. Therefore, the present study aimed to compare efficacy of labetalol versus nitroglycerin for induction of controlled hypotension during craniotomy of patients with brain injury.

Materials and Methods: In this randomized double-blind clinical trial, 60 patients of both sexes, American Society of Anesthesiologists (ASA) physical status I and II, age range from 20 to 60 years; scheduled for elective/emergency craniotomy surgery under general anesthesia (GA) entered into study based on inclusion criteria. All patients were monitored when entering operating room. Patients were divided into two groups (30 each). NTG group received nitroglycerin infusion at a dose of 2–5 µg/kg/min, LAB group received labetalol infusion at a dose of 0.5–2 mg/min. Measurements: Surgical condition was assessed by surgeon using average category scale (ACS) of 0–5, a value of 2–3 being ideal. In both groups mean arterial blood pressure (MAP) was gradually reduced till the ideal ACS for assessment of surgical condition, the target of ACS was 2–3 or lower. Results: Both studied drugs achieved desired hypotension and improved visualization of surgical field by decreasing bleeding in the surgical site, but ideal surgical conditions were created at mild hypotension (MAP 70–75) in LAB group while same conditionswere created at MAP of 65–69mmHg in NTG group.Mean heart rate (HR) was significantly higher in NTG group as compared to LAB group. Blood loss decreased significantly in LAB group.

Conclusion: Both labetalol and NTG are effective and safe drugs for induction of controlled hypotension during craniotomy. While, labetalol was better as it offered optimum operative condition with mild decrease in blood pressure, decreased surgical bleeding and less tachycardia during the surgery.

I. INTRODUCTION

A craniotomy is a surgical procedure in which a part of the skull is temporarily removed to expose the brain and perform an intracranial procedure. The most common conditions that can be treated via this approach include brain tumors, aneurysms, arterio-venous malformations, subdural empyemas, subdural hematomas, and intracerebral hematomas. The bone flap is temporarily removed, held at the surgical instrument table, and then placed back after the brain surgery has concluded. In some cases, depending on the etiology and indication for the procedure, the bone can be discarded, stored in the abdominal subcutaneous space, or cryopreserved under cold storage conditions. If the bone flap is discarded or not placed back into the skull during the same operation, the procedure is called a craniectomy.. The surgical procedure to reconstruct and place the bone flap back into the skull during a second intervention is known as cranioplasty.

Induced hypotension can be achieved by reducing arterial blood pressure 30–40% below its normal value or lowering mean arterial blood pressure (MAP) to 60 mm Hg reversibly and keeping it at that level during the procedure[2]. This can be created by hypotensive agents like beta-adrenergic blockers, calcium channel blockers, vasodilators, or by anesthetic medications such as propofol, opioids and inhalational drugs . Ideal hypotensive medications used to induce controlled hypotension should has specific features such as ease of administration and prescription, beingwith rapid onset and offsetwithout side effects on vital organs, having a predictable and dose-dependent actions .

Nitroglycerin (NTG) is a direct acting vasodilator drug that has been used to produce induced hypotension because of its rapid onset time, rapid offset time, and easy titration. But, it causes reflex

tachycardia and venous congestion in and around the site of surgery so leading to increase blood loss[3].

Labetalol is an adrenergic receptor blocking agent with alpha1- and predominant beta-adrenergic receptor blocking actions (alpha: beta blockade ratio of 1:7 for intravenously IV administration). It decreases blood pressure by lowering systemic vascular resistance (α1-blockade), whereas reflex tachycardia caused by vasodilatation is decreased by b-blockade with unchanging cardiac output[4].

II. MATERIALS & METHODS

This is a prospective randomized observer blinded study conducted at a Tertiary Care Hospital in Southern Bihar and carried out on 60 adult patients of both sexes during the period from May 2021 to March 2022 after approval by the hospital Ethical Committee. The CONSORT 2010 statement was followed in reporting this study.

Inclusion criteria included American Society of Anesthesiologists(ASA) physical status I–II and age between 20 and 60 years patients scheduled for craniotomy under general anesthesia.

Exclusion criteria included age ≤ 20 years, known allergy to the anesthetic agents, history of major psychiatric disorders, patients with asthma

or a history of obstructive airways disease, history of substance abuse and current opioid use, patientswith compromised renal, hepatic,

and cardiac function, hypertension, and coagulation disorders or patients on medications affecting coagulation system.

All included patients were asked to take part in the study by the study participants soon after admission to the ward and a written informed consentwas signed by each patient. The "blind" study group included; the study participants, operation nurse, and the Neurosurgeon.

The anesthetist performing the GA was not blinded to the drugs being given and he is not one of the study participants. But, the anesthetist collecting data and keeping records of different parameters was unaware of groups or drugs received and he is one of the study participants.

Thus, blinding was properly achieved.

Patients were randomly allocated into two groups of 30 patients each according to drug used. In NTG group, patients received an intravenous infusion of at a rate of 2–5 μg/kg/min. In LAB group, patients

received labetalol infusion at a rate of 0.5–2mg/min. In both groups MAP was decreased in steps of 5 mm Hg till the surgeon told average category scale

(ACS) of 2–3, or till lowest target MAP value of 60mmHg was attained. On achievement of target MAP or ACS of 2–3, this was kept in the range by fine adjustment of the studied drugs in each group. In all patients when MAP and heart rate (HR) remained unchanged during induced

hypotension and maintained at its value for 5–10 min, the surgeon evaluated the ACS and the anesthetist confirmed the observations

at random intervals. Systolic, diastolic, MAP and HR were recorded before induction of anesthesia and every 3 min for 15 min and then every 5 min till the end of anesthesia. SpO2, EtCO2, temperature were monitored continuously.

The amount of blood loss was estimated by collecting the blood and fluid from the surgical site by suctioning into the suction bottle.

The anesthetist estimating the amount of blood loss was unaware of groups or drugs received and he is one of the study participants. HR below 50 beats/min was considered as bradycardia, and was managed with 0.5 mg atropine intravenously. MAP below 60mm Hg was initially managed with a 50% reduction in the infusion dose of the study drugs and further stoppage of the infusion if no response was obtained in 5 min. Ephedrine 5mg intravenously was administered for the resistant hypotension.

The operative field visibility was evaluated by the same surgeon according to the ACS. Five minutes before the end of surgery, the studied drugs were

discontinued. The neuromuscular blockade was reversed by mixture of IV neostigmine 0.05 mg/kg and atropine 0.02 mg/kg and extubation was done when the patient was fully awake, respiration is regular with adequate tidal volume and transferred to post anaethesia recovery unit (PACU) for observation.

To detect the optimum operative field in relation to MAP, the MAP measurements were analyzed in subgroups of 5 mm Hg, therefore three subgroups were made in each group; MAP ranged between 75

and 70, 69–65 and 64–60mmHg. Duration of surgery, duration of anesthesia, duration of controlled hypotension, and theamount of intraoperative blood loss were recorded. Any postoperative side-effects were observed and recorded. Surgeon's satisfaction was scored by the same surgeon with a 4-point scale (1 = bad, 2 = moderate, 3 = good, 4 = excellent).

III. STATISTICAL ANALYSIS

Sample size was performed before patients' recruitment. Based on a previous report; to create a desired power of 80% and an alpha error of 0.05

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power to detect a significant difference of 10 mm Hg in the MAP and to detect a between-group difference of 20% in the scale used to evaluate the amount of blood in the surgical field. It was necessary to recruit 30 patients per group keeping in our consideration the possible dropouts. The sample size calculation was made using a priority sample size calculator for a Student's t-test. Data were summarized in the form of mean and standard deviations and were analysed using Student's-t-test and Chi-square test. The Windows version of SPSS 11.0.1 was used for statistical analysis. Power of significance (P value b 0.05) was considered statistically significant.

IV. RESULTS

Table 1 shows demographic characteristics of the patients. No significant differences were noted between the studied groups for age, gender,

weight, and ASA status (P N 0.05). Table 2 shows the results of the studied variables during surgery of the studied patients. The time to reach target ACS of 2–3 was significantly shorter in LAB group compared to NTG group (4. 7±1. 1min VS. 6. 5±1. 3 min, P=0.02). Duration of anesthesia (min), duration of surgery (min) and duration of controlled hypotension (min) were similar in both groups (P N 0.05). The average blood loss in LAB group was significantly lower as compared to NTG group (172.5 ± 28.5 ml vs. 142.6 ± 24.5 ml in NTG group vs. LAB group respectively, P = 0.01). Surgeons in LAB group were more satisfied during surgery. The mean of surgeon satisfaction score in LAB

group was 3.3, and in NTG group was 2.7 (P = 0.01). Table 3 shows that the intraoperative systolic, diastolic and MAP did not differ significantly in the two groupswhen compared in three different

subgroups depending on MAP (P = 0.45). The intraoperative HR remained significantly lower in LAB group compared to NTG group (P=0.01). Ideal operative condition (ACS of 2–3) in LAB group reached optimumlevels (ACS 2.5±0.5) early at MAP of 75–70mmHg. However, at the same level of MAP (75–70) the ACS was 3.5±0.5 showing that

more hypotension was required to achieve optimal surgical condition in NTG group. ACS of 2–3 (mean 2.5 ± 0.3 was reached when MAP reduced to 65–60 mm of Hg in NTG group. In the current study ACS for LAB group was better than that of NTG group at all levels of MAP (P = 0.02) showing that labetalol provided better surgical conditions than NTG group. No significant side effects of hypotensive anesthesia were observed in all patients.

Table – 1
Demographic characteristics between the studied groups

Variables	NTG group (n = 30)	LAB group (n = 30)	P value
Age (years) mean ± SD	47.6 ± 8.3	49.3 ± 6.5	0.5
Gender (M:F)	14:16	11:19	0.7
Weight (kg) mean ± SD	76.7 ± 7.8	83.5 ± 9.2	0.1
ASA (I:II)	18:12	16:14	0. 8

Table – 2
Comparison of studied variables during surgery between the studied groups

Variables	NTG group (n = 30)	LAB group (n = 30)	P value
The time to reach target ACS (min) mean ± SD	6.5 ± 1.3	4.7 ± 1.1	0.02
Duration of surgery (min) mean ± SD	95.8 ± 18.5	87.5 ± 15.9	0.09
Duration of anesthesia (min) mean ± SD	106 ± 16.4	98.5 ± 16.8	0.12
Duration of controlled hypotension (min)	99.8 ± 14.5	92.5 ± 16.5	0.49
Intraoperative blood loss	172.5 ±	142.6±	0.01

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(ml) mean ± SD	28.5	24.5	
Surgeon's satisfaction (1–4) mean ± SD	2.7 ± 0.6	3.3 ± 0.5	0.01

Table – 3
Haemodynamic responses and (ACS) between the studied groups

NTG group

MAP subgroup (mm Hg)	SBP (mm Hg)	DBP (mm Hg)	MAP (mmHg)	HR/min mean ± SD	ACS
Base line	115 ± 16	63.2 ± 7.9	80.6 ± 12.1	98.1 ± 9.6	
75–70	97 ± 5	57.8 ± 4.6	68.9 ± 2.1	90.9 ± 8.5	3.5 ± 0.5
69–65	88 ± 5	49.2 ± 5.3	66.4 ± 1.9	86.7 ± 5.8	2.9 ± 0.5
64–60	80 ± 5	46.3 ± 3.5	62.9 ± 2.1	81.2 ± 5.6	2.5 ± 0.3

LAB group

MAP subgroup (mm Hg)	SBP (mm Hg)	DBP (mm Hg)	MAP (mmHg)	HR/min mean ± SD	ACS
Base line	118 ± 15	65 ± 7	82 ± 17	97 ± 10	
75–70	94 ± 6	62 ± 6	70 ± 2	84 ± 8	2.5 ± 0.5
69–65	86 ± 5	49 ± 6	68 ± 2	80 ± 1	2.4 ± 0.4
64–60	77 ± 5	47 ± 4	63.8 ± 2	70 ± 5	2.1 ± 0.3

V. DISCUSSION

The major finding of the present study is that both NTG and labetalol achieved hypotension as needed for craniotomy surgery and MAPremained in similar range in both groups during the time of controlled

hypotension. While optimum surgical field as indicated by ACS of 2–3 was achieved with only minimum lowering in MAP with labetalol

whereas similar conditions were achieved with moderate reduction of MAP in patients where NTG was used. Our results are in agreement with Sajedi P et al.[5], who found that labetalol and remifentanil infusion can induce effective controlled hypotension under GA, while remifentanil is a short-acting narcotic drug, patient satisfaction was better

and recovery time was shorter. From economic point of view, labetalol was recommended than remifentanil. In our study, optimum surgical conditions was achieved in LAB group although the heart rate was 60 beats per minute. In accordance with our results, Nair et al. [6], demonstrated that β blockers premedication provide better operative

conditions during craniotomy due to decrease in heart rate below 60 beats per minute. Also Scott et al. [7], assessed the use of labetalol together with

inhalation anesthesia and found that satisfactory conditions are achieved for safe controlled hypotension as labetalol and halothane have additive hypotensive action. The duration of hypotension can be controlled in the presence of halothane by gradual withdrawal which leads to rapid recovery of pre-surgery blood pressure.

Induction of hypotension stimulates the release of endogenous catecholamines. Labetalol is a nonselective beta's receptor antagonist that

abolishes vasoconstriction caused by alpha's receptor. Its effect is due to decrease systemic vascular resistance and blood pressure without reflex tachycardia that lead to increase cardiac output. In contrast the endogenous catecholamines have little effect on vascular smooth muscles

when NTG is used to produce hypotension, because of direct action of NTG on them. This will induce vasodilatation with more oozing at site

of surgery and reflex tachycardia is a contributory factor . The mean duration of surgery was slightly shorter in LAB group as well as there was significant decrease in mean blood loss in LAB group in comparison to NTG group. The surgical duration has been shown to be shorterwhen controlled hypotension is used because of better surgical field visualization and less time lost in repeated suctioning . Surgical bleeding is affected by arterial pressure, venous pressure and regional capillary circulation. In craniotomy the visibility of operative field is affected mainly by capillary bleeding that can be decreased by achieving induced hypotension and by using local vasoconstrictors.

NTG produces hypotension by dilating venous vessels, lowering both venous return and cardiac output, peripheral vasodilatation associated with NTG might increase amount of bleeding.

Labetalol lowers the blood pressure primarily by blocking peripheral arteriolar alpha-adrenoceptors thus reducing peripheral vascular resistance

and combined beta-blockade effect protects the heart from reflex sympathetic stimulation with unchanging cardiac output which has been shown previously to reduce the amount of blood loss.

Wu et al. [8] compared the clinical efficacy of compound-induced hypotension during endoscopic sinus surgery. In their study, sodium nitroprusside

alone and in combination with labetalol were used to produce hypotension during surgery. They found that induced hypotension with sodium nitroprusside and labetalol were an ideal compound in the clinical use and induce satisfied synergistic effect.

In the current study, no significant side effects of controlled hypotension were observed in all patients. In contrast to our results, Sajedi P et al. [5] found that the frequency and severity of nausea and hypotension in labetalol group was significantly more. This could be explained by the use of additional doses of narcotic, moreover hypotension in labetalol group was significantly more which may be explained by giving labetalol infusion after bolus dose for induction of controlled hypotension.

VI. CONCLUSION

Both labetalol and NTG are effective and safe drugs for induction of controlled hypotension during craniotomy. While, labetalol was better as it offered optimum operative condition with mild decrease in blood pressure, decreased surgical bleeding and less tachycardia during the surgery.

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