

Effect of Labetalol-Fentanyl and Fentanyl alone for attenuating pressure responses to intubation and skull pin insertion in neurosurgery: A Comparative study

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Abstract:

Background: Laryngoscopy and endotracheal intubation are noxious stimuli capable of producing a huge spectrum of stress responses such as tachycardia, hypertension, laryngospasm, bronchospasm, raised intracranial pressure and intraocular pressure. Simultaneously skull pin insertion during neurosurgical technique aggravates the noxious stimulus causing acute hypertension even in an adequately anaesthetized patient. These haemodynamic changes are generally temporary without any sequelae in normotensive patients, but can accelerate the development of complications, e.g., myocardial ischemia, arrhythmia, infarction and cerebral haemorrhage in patients with coronary artery disease, hypertension or cerebrovascular disease. Different pharmacological agents are used in order to prevent haemodynamic responses. Intravenous Fentanyl has showed a promising result, preventing the increase in plasma concentrations of catecholamines and decreasing the central sympathetic outflow. Another agent labetalol, is a unique oral and parenteral antihypertensive drug that is a α_1 and nonselective β_1 and β_2 adrenergic antagonist.

Objectives: To evaluate the effectiveness of Labetalol-fentanyl for attenuating pressure responses to intubation as well as skull pin insertion in patients undergoing neurosurgery under general anaesthesia.

Materials & method: This prospective, randomized controlled trial was conducted in the Department of Anaesthesia Analgesia and Intensive Care Medicine, Dhaka Medical College Hospital from 18th March 2019 to 17th September 2019. Total 60 patients undergoing elective neurosurgery and requiring pin insertion were enrolled for the study and allocated into two groups. Group A: patients given intravenous 0.25 mg/kg Labetalol and fentanyl 2 μ g/kg combination. Group B patients were given intravenous Fentanyl alone. Following that haemodynamic condition and outcome was assessed at different points of time.

Result: Mean age was found to be 45.8 \pm 11.5 years. It was observed that almost two-thirds (63.3% & 60.0%) of patients had ASA grade I in group A and group B respectively. After induction, mean heart rate increased in both groups but more in group B. It was 92.4.7 \pm 7.8 beat/min and 97.3 \pm 7.4 beat/min in group A and group B respectively. After pin insertion, mean heart rate was 84.1 \pm 5.4 beat/min in group A and 98.5 \pm 85.4 beat/min in group B. After intubation MAP in group B was statistically significantly high (111.4 \pm 15.6 mmHg) as compared to group A (99.8 \pm 9.5 mmHg) and was unstable up to 5 minutes. The statistically significant difference between groups was also observed at the time of pin insertion (97.5 \pm 9.7 mmHg in group A vs. 110.6 \pm 12.9 mmHg in group B), after pin insertion (94.9 \pm 10.3 mmHg in group A vs. 111.5 \pm 10.4 mmHg in group B). Intraoperative HR & MAP were almost normal and remained stabilized in group A patients.

Conclusion: Labetalol-Fentanyl combination was more effective compared to Fentanyl alone in attenuating the pressure responses to intubation and skull pin insertion in neurosurgery.

Key words: Endotracheal intubation, Skull pin insertion, Labetalol-Fentanyl, Fentanyl, Haemodynamic response.

Introduction:

Proper & steady immobilization of the head-neck prior to operative procedure in the brain is an important element of neurosurgical practice. It is commonly achieved using a skull pin-holder. These pins are forced through the layers of the scalp and periosteum into the external lamina of the skull, by manually squeezing the two arms of the C-clamp towards each other, allowing the ratchet gears to glide, until the pins are initially seated in the skull. But this skull-pin head holder causes stress in the haemodynamic response (increase in heart rate and mean arterial pressure)¹. These alteration of hemodynamic response can be harmful for patients with cardiac diseases, like IHD, heart failure, stroke, intracranial hypertension, intracranial aneurysms, and patients with compromised intracranial compliance. Different anaesthetic techniques and pharmacological agents, e.g., dexmedetomidine^{1, 2}, clonidine or oral temazepam³, local lignocaine infiltration⁴, intravenous fentanyl⁵, Gabapentin⁶, etc, have been used to blunt this deleterious effect with variable success.

The hemodynamic alteration mainly occurred due to stress responses. Concomitant laryngoscope and endotracheal intubation accelerate the condition. The application of pins, direct laryngoscopy and endotracheal intubation, are noxious stimulus, which can provoke untoward response in the cardiovascular, respiratory and other physiological systems. Significant tachycardia and hypertension can occur with tracheal intubation^{7, 8}. Clinically, this manifests as precipitous increases in heart rate (HR) and blood pressure (BP) that can be detrimental to patients¹⁻⁹. Schutta et al have shown experimentally that arterial hypertension can lead to acute cerebral edema and herniation of the brain within two minutes¹⁰. Neurological disorder like vascular lesions (cerebral aneurysms or arterio-venous malformations), an acute elevated blood pressure may cause injury of vascular wall and present with subarachnoid or intracerebral hemorrhage.

Opioids have been the mainstay in providing systemic analgesia and local anaesthetics have been effectively used for providing regional anesthesia⁹. But it associated with different adverse effects. Previous study reported that intravenous labetalol and fentanyl are promising pharmacological agents can be used to attenuate the pressure response to intubation and skull pin insertion in neurosurgery¹¹. Fentanyl is a synthetic opioid which attenuates the cardiovascular response by its action on opioid receptors, preventing the increase in plasma concentrations of catecholamines and decreasing the central sympathetic outflow. Yildiz et al demonstrated that the hemodynamic response to skull pin insertion was effectively suppressed with fentanyl administration¹². Similarly, Ozkose et al have shown that a combination of both the fentanyl and local infiltration was more effective than either one of them alone in reducing the hemodynamic response to Mayfield head holder placement¹³.

Another agent labetalol, is a unique oral and parenteral antihypertensive drug that is α 1 and nonselective β 1 and β 2 adrenergic antagonist. Previous study noted that Labetalol is an effective and safe drug for attenuation of sympathomimetic responses to endotracheal intubation¹⁴. Labetalol lowers the blood pressure by decreasing systemic vascular resistance (α -1 blockade) whereas reflex tachycardia triggered by vasodilation is attenuated by simultaneous beta blockade and cardiac output remains unchanged. Therefore aim of the present study was to evaluate the effectiveness of Labetalol-fentanyl for attenuating pressure responses to intubation as well as skull pin insertion in patients undergoing neurosurgery under general anesthesia.

Methodology:

This prospective, randomized controlled trial was conducted in Department of Anaesthesia, Analgesia and ICU, Dhaka Medical College Hospital, Dhaka, from 18th March 2019 to 17th September 2019. The protocol was approved by

the Ethical Review Board, DMCH. Total 60 patients of ASA physical status I and II, underwent neurosurgery requiring skull pin insertion under general anaesthesia were included in the study. Patients having history of drug allergy, hypertension, IHD, COPD, hepatic or renal diseases, emergency surgery, on β blockers were excluded. Study subjects were divided into two groups, group A and group B thirty patients in each. Pre-anaesthetic check up with all routine blood investigations with Chest x-ray and ECG were done. Baseline heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), mean arterial pressure (MAP) were recorded. Blood pressure was monitored by non invasive procedure. Two IV lines secured. Heart rate was recorded by ECG.

Patients of Group A was given intravenous 0.25 mg/kg labetalol diluted in normal saline upto 10 ml by 10cc syringe 5 minutes prior and 3cc syringe contained fentanyl $2\mu\text{g}/\text{kg}$ 3 minute prior to intubation. Group B patients given intravenous 10ml normal saline by 10cc syringe 5 minutes prior to intubation and 3cc syringe contained $2\mu\text{g}/\text{kg}$ fentanyl 3 minutes prior to intubation. After preoxygenation patients were induced with thiopentone sodium (5mg/kg) and vecuronium bromide (0.1mg/kg). Intubation was done with 8.0 mm and 7.0mm sized armoured endotracheal tube for male and female patients respectively by the anesthetist. Anesthesia was maintained with O₂:N₂O (50:50), 1% Isoflurane and inj. vecuronium. HR, SBP, DBP and MAP were recorded immediately after loading doses of labetalol and fentanyl, before induction, at the time of intubation, after intubation, at the time of skull pin insertion, immediately after pin insertion and 5, 10, 15 mins after pin insertion. At the end of surgery neuromuscular block was reversed. Incidence of hypotension or bradycardia was recorded. All the information was recorded in data collection sheet. Statistical analysis of the data was done using the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) software version 22. Qualitative data such as sex, ASA physical

status, adverse effects was compared using Chi-square test. Quantitative data such as age, numeric rating scales, time to first analgesic request and total analgesic requirement in 24 h will be compared using independent t-test. $P < 0.05$ will be taken as statistically significant.

Result & Observation:

Total of 60 patients fulfilling inclusion/exclusion criteria were studied. Results and observations are given below:

Table I shows the demographic profile of the patients. Mean age was found to 44.5 ± 11.5 years in group-A and 45.8 ± 11.5 years in group-B. The difference was not statistically significant ($p > 0.05$) between two groups. Out of 60 patients, 47(78.3%) cases were male (22 in group-A and 25 in group-B), whereas 13(21.7%) cases were female (8 in group-A and 5 in group-B). Male – female ratio was 3.6:1. It was observed that almost two third (63.3% & 60.0%) patients had ASA grade I in group A and group B respectively. The difference was not statistically significant ($p > 0.05$) between two groups.

Table II shows the heart rate (HR) changed in between group. Tachycardia was pronounced in group-B, but in group-A heart rate was almost stable. At baseline, mean heart rate was found 90.3 ± 7.3 beat/min in group A and 90.1 ± 8.2 beat/min in group B. After intubation, mean heart rate was increases in both group but more in group B. It was 92.4 ± 7.8 beat/min in group-A and 97.3 ± 7.4 beat/min in group B. After pin insertion, mean heart rate was 84.1 ± 8.4 beat/min in group A and 98.5 ± 12.7 beat/min in group B. The difference was statistically significant. 5 minute after and 10 minute after the difference was statistically significant between two groups ($p < 0.05$)

Table III shows the systolic blood pressure (SBP) between groups with respect to time. After intubation and pin insertion blood pressure was gradually increases in both groups, but SBP was predominant in group-B. It was observed that mean systolic BP was found 126.3 ± 12.5 mmHg in

group A and 125.4 ± 11.5 mmHg in group B at preanaesthesia or baseline. After intubation mean systolic blood pressure was increased in both groups, but more in group B (126.7 ± 12.8 mmHg in group A and 141.3 ± 17.5 mmHg in group B). After pin insertion blood pressure again elevated as 125.2 ± 12.4 mmHg in group A and 145.8 ± 12.7 mmHg in group B. Following that SBP return to normal. At 15 min, mean systolic blood pressure was 103.6 ± 8.7 mmHg in group A and 105.8 ± 10.0 mmHg in group B. So it was observed that SBP was precisely attenuated in group A patients.

Table IV shows diastolic blood pressure during follow up it was observed that at preanesthesia, mean diastolic BP was found 78.5 ± 6.3 mmHg in group A and 79.1 ± 6.5 mmHg in group B. After intubation and pin insertion mean diastolic blood pressure were increases in both groups, but more in group B. It was found 85.1 ± 6.3 mmHg in group A and 90.1 ± 7.1 mmHg in group B. During 5 min after pin insertions mean DBP was 78.3 ± 8.1 mmHg in group A and 75.8 ± 8.3 mmHg in group B. At 15 min, mean diastolic blood pressure was 76.5 ± 7.8 mmHg in group A and 72.9 ± 7.5 mmHg in group B.

No significant difference was observed in the MAP (Table V) before anaesthesia (baseline), at

time of intubation, 10 min after pin insertion and 15 min after insertion. But significant difference was observed after intubation, at time of pin insertion, after pin insertion and 5 min after pin insertion. After intubation, the mean arterial blood pressure in group-B was statistically high (111.4 ± 15.6 mmHg) as compared to group A (99.8 ± 9.5 mmHg) and was unstable upto 5 minute time. The statistically significant difference between groups was also observed at time of pin insertion (97.5 ± 9.7 mmHg in group A vs. 110.6 ± 12.9 mmHg in group B), after pin insertion (94.9 ± 10.3 mmHg in group A vs. 111.5 ± 10.4 mmHg in group B) and 5 min after pin insertion (88.2 ± 9.5 mmHg in group A vs. 93.6 ± 9.8 mmHg in group B). It was statistically significant. Intraoperative heart rate and mean arterial blood pressure values were almost normal and close to base levels without requirement of any other medication and remained stabilized throughout the intraoperative period in group-A patients.

Table VI shows incidence of adverse events. Nausea and vomiting was developed in total 7 patients, 5 (16.7%) patients in group-A and 2 (6.7%) in Group-B. Hypotension was developed in 5 (16.7%) patients in group-A and 9 (30.0%) patients in Group-B. The difference was statistically non significant.

Table I: Demographic profile of the patients (n=60)

Demographic profile	Group A n(%)	Group B n(%)	P value
Age distribution			
Mean \pm SD	44.5 ± 11.5	45.8 ± 11.5	0.905
Gender distribution			
Male	22 (73.3)	25 (83.3)	0.168
Female	8 (26.7)	5 (16.7)	
ASA status			
I	19 (63.3)	18 (60.0)	0.985
II	11 (36.7)	12 (40.0)	

Table II: Trends of heart rate (HR) in the studied group (n=60)

HR (Time point)	Group A (Mean ± SD)	Group B (Mean ± SD)	P value
Baseline	90.3±7.3	90.1±8.2	1.025
at time of intubation	86.5±7.4	93.7±8.1	0.092
after intubation	92.4±7.8	97.3±7.4	0.001
at time of pin insertion	86.5±9.7	95.2±12.9	0.001
after pin insertion	84.1±8.4	98.5±12.7	0.001
5 min after	78.5±7.4	88.6±7.8	0.033
10 min after	75.2±8.3	85.2±8.6	0.019
15 min after	79.1±7.4	82.2±7.8	0.197

Table III: Evaluation of systolic blood pressure (SBP) between groups with respect to time (n=60)

SBP (Time point)	Group A (Mean ± SD)	Group B (Mean ± SD)	P value
Baseline	126.3±12.5	125.4±11.5	1.008
at time of intubation	128.1±13.2	134.6±15.2	0.068
after intubation	126.7±12.8	141.3±17.5	0.003
at time of pin insertion	123.5±11.7	144.1±14.9	0.001
after pin insertion	125.2±12.4	145.8±12.7	0.001
5 min after	114.8±9.4	123.5±13.8	0.025
10 min after	108.5±9.3	118.4±11.8	0.019
15 min after	103.4±8.7	105.8±10.1	0.742

Table IV: Evaluation of diastolic blood pressure (DBP) between groups with respect to time (n=60)

DBP (Time point)	Group A (Mean ± SD)	Group B (Mean ± SD)	P value
Baseline	78.5±6.3	79.1±6.5	1.023
at time of intubation	80.7±5.2	86.5±5.4	0.361
after intubation	85.1±6.3	90.1±7.1	0.047
at time of pin insertion	82.4±6.7	85.2±5.9	0.096
after pin insertion	84.2±6.4	86.8±6.7	0.958
5 min after	78.3±8.1	75.8±8.3	0.108
10 min after	77.5±9.3	74.4±11.8	0.019
15 min after	76.5±7.8	72.9±7.5	0.059

Table IV: Evaluation of Mean arterial blood pressure between groups with respect to time (n=60)

MAP (Time point)	Group A (Mean ± SD)	Group B (Mean ± SD)	P value
Baseline	95.2±9.4	94.6±12.3	0.832
at time of intubation	97.4±11.2	103.7±15.1	0.073
after intubation	99.8±9.5	111.4±15.6	0.001
at time of pin insertion	97.5±9.7	110.6±12.9	< 0.00
after pin insertion	94.9±10.3	111.5±10.4	< 0.00
5 min after	88.2±9.4	93.6±9.8	0.033
10 min after	85.5±9.5	89.2±8.6	0.119
15 min after	82.7±7.4	86.5±7.8	0.057

Table VI: Evaluation of any adverse events (n=60)

Adverse events	Group A n(%)	Group B n(%)	P-value
Hypersensitivity or rash	0	0	P-value
Hypotension	5(16.7%)	9(30.0%)	0.227
Nausea, vomiting	5(16.7%)	2(6.7%)	0.232
Cardiovascular collapse	0	0	
Myoclonus	0	0	

Discussion:

In our study the two groups were comparable in terms of age, ASA and haemodynamic stability during surgery. The pre-operative heart rate and blood pressure of the two groups were having no significant difference. After giving of study drug, heart rate and blood pressure was stabilize in the both group, but comparatively better in group-A. Overall demographic features of 60 patients revealed that majority of the patients i.e. 66.6% (n=40) were between 35-50 years (19 patients in group –A and 21 patient in Group-B) mean age was found to 45.8±11.5 years. Male – female ratio was 3.6:1.

The haemodynamic changes caused by airway manipulation are due to sympathoadrenal discharge from epipharyngeal and parapharyngeal stimulations which in turn causes a significant rise in the catecholamine level which increases blood pressure and pulse which may lead to cardiovascular complication and increased intracranial pressure. Insertion of skull pins into the periosteum give rise to haemodynamic response and also causes increase in stress hormones which can affect outcome of the patient¹⁵. Neurosurgical patients are with reduced intracranial compliance so even mild increase in cerebral blood flow can cause severe cerebral damage. In these situations the hemodynamic and metabolic effects on the human brain is important.

Labetalol did not influence global or regional cerebral blood flow or cerebral oxygen metabolism and cerebral blood flow and auto regulation is preserved even with dose as high as 1 mg/kg¹⁶. 0.25mg/kg labetalol was used before 5 minutes of intubation and found heart

rate, blood pressure below baseline at all time including immediately after intubation and pin insertion. In group B, HR and MAP was significantly raised but was within higher normal range suggesting that fentanyl also had attenuated pressure response but in labetalol group (Group-A) it was better controlled. In this study after induction, mean heart rate was increases in both group but more in group B. It was 92.4.7±7.8 beat/min and 97.3 ± 7.4 beat/min in group A and group B respectively. After pin insertion, mean heart rate was 84.1± 5.4 beat/min in group A and 98.5±85.4 beat/min in group B. Similarly after intubation and pin insertion systolic blood pressure was gradually increases in both groups, but increasing blood pressure was predominant in group-B. After intubation mean systolic blood pressure was increased in both groups, but more in group B (126.7±12.8 mmHg in group A and 141.3±17.5 mmHg in group B). After pin insertion systolic blood pressure again elevated as 125.2±12.4 mmHg in group A and 145.8±12.7 mmHg in group B. following that SBP return to normal. At 15 min, mean systolic blood pressure was 103.6±8.7 mmHg in group A and 105.8±10.0 mmHg in group B. So it was observed that SBP was precisely attenuated in group A patients. In consistent with our study Patel et al studied labetalol and fentanyl and found significantly less increase in heart rate, systolic, diastolic and mean arterial pressures after intubation in group LF as compared to group F. They found minimum increase in group LF and concluded that addition of single dose intravenous labetalol to fentanyl gives better haemodynamic stability to laryngoscopy and intubation as well as skull pin insertion than fentanyl alone¹⁷.

The results of our study showed that intravenous labetalol with fentanyl notably improved hemodynamic stability in comparison to fentanyl alone. In previous studies, various methods have been recognized for preventing hemodynamic response to the placement of skull pin^{5, 6}. In accordance to our study Babita and et al¹⁸ studied the effect of injection fentanyl (2µg/kg) and injection labetalol (0.25mg/kg) on sympathomimetic response to laryngoscopy and intubation in vascular surgeries and found in decrease HR, SBP and DBP in both group before intubation due to effect of the drugs. The increase in HR and MAP after intubation was minimal in fentanyl and labetalol. They found HR and SBP significantly decreased below the baseline at 7 minutes. This might be because of the taking over effect of drug. Presynaptic alpha-2 receptors are spared by labetalol so that the released norepinephrine can continue to inhibit further release of catecholamines via the negative feedback mechanism resulting from the stimulation of alpha-1 receptors. Moreover this drug targets 5-10 times more specific beta blockade and prevent rebound hypertension and tachycardia.

Chung et al¹⁹ had reported decrease in pressure response with a single dose of fentanyl 2µg/kg given preoperatively. Fentanyl suppresses the haemodynamic response by increasing the depth of anaesthesia and decreasing the sympathetic discharge. In this study significant difference of MAP was observed after intubation, at time of pin insertion, after pin insertion and 5 min after pin insertion. Intraoperative heart rate and mean arterial blood pressure values were almost normal and close to base levels without requirement of any other medication and remained stabilized throughout the intraoperative period in group-A patients.

Conclusions:

Use of rigid skull pin holder during neurosurgical procedures is invasive and painful, accompanied by an abrupt alteration of haemodynamic response. These may lead to

further brain oedema, increased intracranial pressure or intracranial haemorrhage. Present study concluded that addition of a single dose of Labetalol 5 minutes prior to intubation to fentanyl gives better control of heart rate and all arterial pressure during laryngoscopy and intubation and skull pin insertion. There was no significant increased risk of bradycardia or hypertension. Labetalol has been used effectively to blunt haemodynamic response to laryngoscopy and intubation and skull pin insertion. It combination with Fentanyl synergizes the pharmacological effect. Solabetalol-fentanyl combination can be used for attenuating pressure responses to intubation and skull pin insertion in neurosurgery.

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