

Original Article

EFFECT OF LOW DOSE PROPRANOLOL ON PERIOPERATIVE STRESS INDUCED HEMODYNAMIC CHANGES IN UPPER ABDOMINAL SURGERY

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SUMMARY:

Stress response is accompanied by an increased traffic in sympathetic efferent tracts resulting in potentially severe hypertension, tachycardia and is associated with post-operative morbidity. Study establishes the assumption that 'stress free' general anesthesia is necessarily advantageous. A recent study has suggested that different pre-medication may lead to an alteration in sympatho-adrenal stress response during surgery. Several agents and regimens have been devised to control this stress induced haemodynamic responses including alpha-blocker droperidol, lignocaine, low dose opioid and cervical extradural blockade.

It has been demonstrated that beta-adrenoceptor blocker, in therapeutic doses, caused only modest reduction in cardiac output while decreasing the incidence of arrhythmia and myocardial ischaemia after laryngoscopy and intubation. It is recommended that their administration to be continued until the day of surgery. Even a single dose of a beta-blocker given as a premedication decreases the incidence of episodes of myocardial ischaemia. Atenolol, a selective beta-blocker, per oral significantly reduces cardiovascular morbidity in non-cardiac surgery. Propranolol, a non-selective beta-blocker, has an added advantage of alleviating effect in anxiety. In addition, cost of propranolol is generally low and the systems required to use them according to the protocol used in this study are already in place.

This prospective study was performed to establish its effects on per-operative haemodynamic response in non-cardiac surgery.

The effect of propranolol on heart rate, systolic arterial pressure and derived value rate pressure

product (RPP) on peri-operative period was significantly different from that of placebo effect. The result showed that propranolol significantly reduces heart rate, SAP & thus RPP & reduces peri-operative morbidity and mortality.

INTRODUCTION:

Nociceptive surgical stimulation is accompanied by increased hypothalamo-pituitary activity, which is generally referred to as the stress response to injury. This is manifested by a release of trophic hormones with consequent increase in cortisol, thyroxine and suppression of insulin¹. Increased hypothalamic activity induced by nociceptive stimulation is accompanied by an increased traffic in sympathetic efferent tracts resulting in adrenergic response²⁻⁴. Thus it has been proposed that an abrupt increase in circulating catecholamines may be associated with potentially severe hypertension, tachycardia, which in turn may cause cardiac arrhythmias, myocardial ischemia, left ventricular dysfunction and rupture of cerebral aneurysm^{5,6} in susceptible individuals^{7,8}.

Until 1970's the stress response was thought to be an adaptive homeostatic response to a physiological insult, enhancing resistance to stress⁹. However, there is growing evidence that stress response is actually detrimental and is associated with post-operative morbidity. It has adverse effects on several key physiological systems like cardiovascular, respiratory and gastro-intestinal. In Cardiovascular system- stress response activates sympathetic nervous system, which increases myocardial oxygen demand by increasing heart rate and arterial pressure. Activation of sympathetic nervous system may also cause coronary artery vasoconstriction,

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reducing the supply of oxygen to the myocardium, which in turn would predispose to myocardial ischemia, aggravated by hypercoagulable state postoperatively— a stress response by ADH⁹.

Whilst there is general assumption that suppression of the autonomic response is advantageous. Edward et al in nineties demonstrated that in standardized clinical conditions, there was an increase in adrenaline production in patients receiving a balanced general anaesthesia as opposed to those receiving an epidural technique or a combination of both¹⁰. However, Wylie and Churchill-Davidson (1998) have suggested that “stress free” anaesthesia is necessarily advantageous¹¹.

Pre-medication is used to provide sedation and anxiolysis and to enhance the quality of induction, maintenance and recovery from anaesthesia. The ideal pre-medicant should be effective orally, with analgesic and non-emetic properties. A recent study has suggested that different pre-medication may lead to an alteration in sympatho-adrenal stress responses during surgery³. Several agents and regimens have been devised to control this stress induced haemodynamic responses including α -blocker droperidol¹² lignocaine¹³ low dose opioid¹⁴ and cervical extradural blockade^{10, 15}. But none of these have gained widespread acceptability.

There is one technique which is described as totally effective in abolishing haemodynamic responses i.e. large dose of either – Fentanyl >50 μ g/kg or morphine >2mg/kg have been shown to produce “stress free” condition in cardiac surgery^{4,16}, yet this is although inappropriate for routine surgical practice. Halter et al in mid seventies¹⁷ demonstrated a consistent increase in plasma catecholamines concentration after surgical incision in-patient anaesthetized with nitrous oxide and halothane in oxygen with neuromuscular blocker vecuronium. Sigurdson et al much earlier¹⁸ suggested that the pre-medication may alter the magnitude of the sympathoadrenal response to non-cardiac surgery.

It has been demonstrated that α -adrenoceptor blocker, in therapeutic doses, causes only modest reduction in cardiac output while decreasing the incidence of arrhythmia and myocardial ischaemia after laryngoscopy and intubation. It was recommended that its administration to be continued until the day of surgery^{14,15}. Even a single

dose of a α -blocker given as premedication decreases the incidence of episodes of myocardial ischaemia⁵.

Ramanathan et al previously¹⁹ used Labetolol, a non selective α and β -blocker, at a dose of 0.15mg/kg I.V followed by 0.25 to 0.3 mg/kg I.V. every 3 minute to block the haemodynamic responses to tracheal intubation. Another group Mangano et al²⁰ used Atenolol, a selective β -blocker, at a dose of 50 mg bid per oral significantly reduces cardiovascular morbidity in abdominal surgery.

Propranolol was the first effective beta-blocker with prolonged clinical use and experience with it extends more widely than any other member of this group. By opposing the haemodynamic response to stress, it has an ‘oxygen sparing’ effect and this is of benefit to patients suffering from angina of effort, its action is comparable to that of atenolol at cardiac receptor site, with an addition of extra-cardiac site.

Propranolol has been shown to exert an alleviating effect in anxiety. There are several pieces of evidence to suggest that β -blocker work through a peripheral mechanism rather than within the CNS, although propranolol is relatively lipophilic and does gain entry to the CNS and it is most effective in performance anxiety & thus stress, while other beta-blockers does not²¹. There is limited information on haemodynamic changes to propranolol produced by stress in abdominal surgery.

The cost of propranolol is generally low and it is used orally. Use of propranolol routinely in the preoperative preparation may replace the expensive preoperative cardiovascular testing. This may in turn substantially reduce the cost for cardiovascular testing.

As mentioned previously that information on haemodynamic changes to propranolol produced by stress during surgery is limited. Because of the easy availability and relative safety of propranolol, the study was undertaken to establish its effects on haemodynamic changes during surgery.

MATERIALS AND METHODS:

One hundred patients of ASA physical status admitted in hospitals for abdominal diseases had undergone operation of an average duration of 45 to 90 minutes under general anaesthesia were selected for the study. Both male and female patients within age group 20-40 years were included. The protocol was approved by the Departmental Ethical

Clearance Committee of BSMMU, Shahabag, Dhaka. Informed written consent was taken from each patient.

Each patient was allowed to draw one card randomly and grouped as Group I – control (who received placebo tablet sucrol) & Group II – case (who received tablet propranolol 10 mg) as oral pre- medications at night before operation and one hour before operation of surgery. The patient and the investigator were blinded regarding the groups.

The anaesthetic procedures were explained and reassured to each patient After arrival of patient in operation theatre intravenous access was secured. Monitoring of heart rate and blood pressure were started. Pre-oxygenation was done for 3 minutes. Oxygen saturation was monitored from the beginning.

All the patients were induced with thiopentone sodium (4-5 mg/kg) and fentanyl 1 µgm/kg. During the procedure ventilation of lung was assisted or controlled with 100% oxygen. No inhalation gases like N₂O or halothane were used before intubation. Intubation was facilitated with Inj. Suxamethonium 1-1.5 mg/kg bolus. In those patients intubation took more than 40 sec were excluded from the study. Anaesthesia was maintained with 70% N₂O in O₂ and 0.5 v/v percent halothane. Muscle relaxant used was vecuronium with initial bolous dose of 0.08-0.1 mg/kg & increment with one third of bolous doses. Analgesia was maintained with incremental doses of fentanyl. At the end of the operation extubation was done with Inj Neostigmine (0.05 mg/kg) and Inj Atropine (0.02 mg/kg).

Heart rate and automated non-invasive arterial blood pressure were recorded before intubation, just after intubation, at 10 minutes interval during the operative procedure and after extubation, using a Datex Ohmeda (Helsinki, Finland) monitor. Rate pressure product (RPP) values were taken as derived values from multiplication of heart and systolic arterial blood pressure.

Data collected in a pre-designed data collection sheet were compiled on a master chart. All data are plotted on sigma plot and all results are expressed as mean±SD. Data were analyzed by students unpaired ‘t’ test and considered significant if p<0.05.

OBSERVATION AND RESULTS:

All the observations were presented in a tabulated form. Observed parameters were expressed as mean±SD.

The groups were homogenous as regard to age, weight, height and ASA physical status. The duration of surgery was also statistically matched with each other. The effect of placebo and propranolol on heart rate, systolic arterial pressure and rate pressure product at immediately after intubations and during pre-operative period showed significant difference than that of base line values (Table –I).

Baseline values of heart rate of the two groups were similar. Base line systolic arterial pressures (SAP) were also similar. But it was significantly different within groups. Heart rate was significantly higher in placebo group (group I) immediately after intubation and at 10, 20, 30, 40 minutes of per-operative period compared to the propranolol group (group II) (Table II).

Table-I

Age, weight and height of the study subjects

Variables	Group I	Group II	t value	p value
Age (yrs)	31.2± 9.4	33.3± 9.1	-1.104	0.272
Weight (kg)	50.2 ± 5.9	49.6 ± 6.2	0.462	0.645
Height (cm)	154.4± 3.4	155.2± 4.7	-0.729	0.468

Table-II

Changes in preoperative Heart Rate (bpm) during upper abdominal surgery

Groups	Baseline	Heart rate at time after intubations							Post operative
		0 min	10 min	20 min	30 min	40 min	50 min	60 min	
Group I	76±6	109±8	102±9	95±9	88±7	83±6	82±6	80±11	111±7
Group II	74±4	77±6	73±7	69±6	67±6	66±4	66±5	66± 6	75±6
t value	2.256	22.048	17.777	16.658	16.995	14.549	8.648	3.430	31.57
p value	0.026	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.003	<0.0001

Values are expressed as mean ± SD. P value expressed as significant if p< 0.05 (CI-95%).

Table -III*Changes in preoperative systolic arterial pressure (mmHg) during upper abdominal surgery*

Groups	Baseline	Systolic blood pressure at different time after intubations							Post-operative
		0 min	10 min	20 min	30 min	40 min	50 min	60 min	
Group I	115±7	128±6	123±6	119±7	117±7	117±6	117±6	119±5	125±5
Group II	114±7	116±7	111±10	112±9	112±8	113±5	111±5	110±2	116±8
t value	0.838	9.377	7.492	4.477	3.543	3.351	3.346	2.934	6.130
p value	0.404	<0.0001	<0.0001	0.00002	0.0006	0.0012	0.0016	0.0092	<0.0001

Values are expressed as mean ± SD. P value expressed as significant if $p < 0.05$ (CI-95%).

Baseline values of systolic arterial pressure (SAP) of the two groups were similar. But it was significantly different between groups. Systolic arterial pressure (SAP) values were found to be significantly higher in placebo group immediately after intubations and at 10, 20, 30, 40 minutes of per-operative period compared to the propranolol group (Table III).

DISCUSSION:

Surgical anaesthesia is a harmless and reversible insensibility, which allows operation of considerable magnitude to be carried out hindrance to the surgeon or to detriment to the patient. Anaesthetic stages consist of sleep, analgesia and muscle relaxation, which could now be produced by separate and several medications. But yet nociceptive surgical stimulation is accompanied by increased hypothalamo-pituitary activity, which is manifested by a release of trophic hormones with consequent increase in cortisol, thyroxine & suppression of insulin¹. Increased hypothalamic activity is accompanied by an increased traffic in sympathetic efferent tracts resulting in adrenergic responses in 1970^{2,3}. In cardio-vascular system stress response activates sympathetic nervous system, which increases myocardial oxygen demand by increasing heart rate and arterial blood pressure⁹.

The goal of adequate anaesthesia is to keep the patient throughout the operative procedure "stress free". Edwards et al earlier demonstrated that in standardized clinical conditions, there was an increase in adrenaline production in patients receiving a general anaesthesia as opposed to those receiving an epidural technique or a combination of both¹⁰. A recent study has suggested that different pre-medication may lead to an alteration in sympathoadrenal stress response during surgery³.

Several agents and regimens have been devised to control this stress induced haemodynamic response including alpha-blocker, droperidol¹², lignocaine¹³, low dose opioid¹⁴, and cervical extradural blockade¹⁵.

So search for an appropriate and easily available pre-medication to make general surgical anaesthesia more stress-free is going on for the last few years. It has been demonstrated that beta-adrenoceptor blocker, in low therapeutic doses, causes only modest reduction in cardiac output while decreasing the incidence of arrhythmia and myocardial ischaemia after laryngoscope and intubations^{14,15}. Even a single dose of beta-blocker given as premedications decreases the incidence of myocardial ischaemia⁵. Propranolol has been shown to exert an alleviating effect in anxiety in addition to beta-blockade. Furthermore it is generally of low cost and there is convenience about its dosing and routes of administration.

The result of this trial demonstrate that in patients who are not at risk for coronary artery disease and who are undergoing non cardiac surgery, stress induced haemodynamic response can be substantially reduced by premeditation with low dose oral propranolol. In pre-operative period heart rate of group I is (76.32± 5.82) and remains slightly higher than the group II (74.02±4.24) but after surgical incision, heart rate rises sharply (109.10±8.25) in group-I where in group-II heart rate (76.6±6.37) remains close to pre-operative value. Throughout the operative period result shows a significant value irrespective of heart rate, systolic arterial pressure and simultaneously rate pressure product. Pine et al found that a concentration of propranolol of 100 ng/ml produce complete receptor blockade, where as 8 ng/ml produce a 50% blockade²². In our study, we are not able to measure

serum concentration of propranolol but it can be shown from the performed study that 10 mg bid oral dose can maintain much more than 8 ng/ml plasma level which is sufficient to produce therapeutic blockade. At the same time Johnson et al showed that maximum improvement in angina pectoris occurs at 64 % to 98 % beta blockade²³.

There is the rationale for using low dose propranolol pre-medication for the prevention of peri-operative risk of myocardial ischaemia. Studies conducted over the past decade have established the association between chances of preoperative myocardial ischaemia is more in untreated patients than those who gets some of any sympatholytic agents. The study, we performed here, have demonstrated an association between peri-operative ischaemia and an elevated heart rate and have suggested that mitigation of this heart rate response may reduce the incidence or severity of ischaemia. Thus, we concluded that oral pre medication with low dose propranolol, as could attenuate the heart rate response and limit the development of ischaemia, might substantially reduce longer-term cardiac complications.

CONCLUSION:

From this study it may be concluded that oral pre-medication with low dose propranolol significantly attenuates stress induced haemodynamic changes in upper abdominal surgery.

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