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THE COMPARATIVE STUDY BETWEEN FENTANYL AND LIGNOCAINE-TRAMADOL-MAGNESIUM SULFATE COMBINATION ON INTRAOPERATIVE HEMODYNAMICS AND INTUBATION SURGE IN PATIENTS UNDERGOING SURGERY UNDER BALANCED GENERAL ANESTHESIA

Anaesthesiology

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ABSTRACT

INTRODUCTION- Laryngoscopy and endotracheal intubation invariably cause hemodynamic changes associated with increased heart rate, increased blood pressure and occasional disturbance in cardiac rhythm. These hemodynamic changes arise as a form of autonomic reflex and due to release of norepinephrine and to a lesser extent epinephrine. Effective attenuation of sympathoadrenal response is an important goal in anaesthesiology. Not only the intubation surge but the intraoperative hemodynamic maintenance is also a very challenging step for a successful balanced general anaesthesia.

METHODOLOGY- 60 normotensive patients belonging to ASA 1 and ASA 2 (age between 18 to 60 yrs)scheduled for elective surgical procedure were divided randomly into two groups of 30 each. All patients received premedication with Midazolam. Group F will received Fentanyl 2ug/kg 3 minutes before intubation and group M received Tramadol 1mg/kg , Lignocaine 2% 1.5mg/kg and Mgso4 2gm over 10 minutes 15 minutes prior to intubation. Pre-oxygenation was done for 5 minutes before laryngoscopy. Induction of anaesthesia was done with Propofol. Intubation was done by using Succinylcholine. Intraoperative hemodynamics was maintained by O2, N20, Sevoflurane and Atracurium. Heart rate, SBP, DBP and MAP were documented non-invasively at baseline ,before induction,1 minute ,3,5,15 and 30 minutes after intubation.

RESULT- There was no statistically significant difference in the demographic characteristics between the two groups. Immediately after intubation heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure were better controlled in Fentanyl receiving patients. But thereafter intraoperative hemodynamics (HR,SBP,DBP,MAP) are better maintained in patients receiving the Three Drug Combination of Lignocaine-Tramadol-Magnesium Sulfate(statistically significant).

Moreover intraoperative requirement of Non-depolarising muscle relaxant is significantly less frequent in the Three Drug Combination receiving patients as compared to Fentanyl receiving patients. Post-operative timing of receiving first dose of rescue analgesic is also delayed in Lignocaine-Tramadol-Magnesium Sulfate receivers.

KEYWORDS

Fentanyl, Lignocaine-Tramadol-Magnesium Sulfate, Hemodynamics, Intubation Surge and General Anesthesia

INTRODUCTION

Hemodynamic response to laryngoscopy and intubation was first described by Reid and Brace[1]. The hypertensive response to anaesthetic induction with endotracheal intubation may be harmful in patients with cardiovascular disease, increased intracranial pressure, or anomalies of the cerebral vessels. Recommendations for attenuating the reflex hypertension and tachycardia elicited by upper airway irritation are therefore manifold. Besides minimizing the cardiovascular response, anaesthesia induction for patients at risk must also satisfy the following requirements: it must be applicable regardless of patient collaboration, prevent impairment of cerebral blood flow, and avoid arousal of the patient; it should neither be time-consuming nor affect the duration or modality of the ensuring anaesthesia[2].

The mechanisms of the responses to laryngoscopy and endotracheal intubation are proposed to be by somatovisceral reflexes[3]. Laryngoscopy and endotracheal intubation cause stimulation of proprioreceptors at the base of the tongue , that cause reflex sympathetic activation of vagal and glossopharyngeal afferent. This activation cause hypertension, tachycardia and increased intracranial tension. (due to increased cerebral blood flow and increased cerebral metabolic rate).These responses vary with depth of anaesthesia, duration and difficulties of laryngoscopy and endotracheal intubation, These effects can be well tolerated by ASA physical status 1 and 2 patients but can be detrimental for elderly patients, patients with cardiovascular and neurological diseases.

This hemodynamic surge is a problematic issue for gastro intestinal surgeries especially prolonged and major surgeries.

A large array of pharmacotherapy has been tried to prevent laryngoscopic surge with varying degree of success such as Lignocaine, Induction agent (usually Propofol), Opioid (Fentanyl, Sufentanyl), Vasodilators (Nitroprusside , Nitroglycerine) Calcium channel blocker (Verapamil.,Diltiazem), Beta blocker (Esmolol, Labetalol) Magnesium Sulfate, Gabapentin, Pregabalin but none of the above mentioned drugs has so far been proved fully efficacious to blunt the hemodynamic stress response during laryngoscopy and endotracheal intubation and all these agents have some limitations such as respiratory depression, hypotension, tachycardia, bradycardia, rebound hypertension or allergic reactions.

The mechanism of action of MgSO4 in prevention of intubation surge and intraoperative hemodynamic maintenance appears to result from the inhibition of catecholamine release from adrenal medulla which maintains plasma concentration of epinephrine practically unchanged, also reduces the increased circulating nor epinephrine when compared to that of control group [4]and it also blocks catecholamine receptors. Therefore MgSO4 causes sympathetic block and indirectly causes vasodilatation and reduces blood pressure level and improves intraoperative hemodynamic stability. It also has a systemic and coronary vasodilatation effect by antagonising calcium ion channel on vascular smooth muscle and synaptic nerve endings[5]. Due to this competitive calcium channel blocking property at nerve endings, MgSO4 decreases neuromuscular transmission. As a result it decreases intraoperative requirements of muscle relaxants (NDMR).

AIMS AND OBJECTIVES OF THIS STUDY-
GENERAL OBJECTIVE:

Our aim is to study – The efficacy of this Three Drug Combination in attenuating hemodynamic surge following intubation and maintenance of hemodynamic stability in intraoperative period as compared to Fentanyl.

Specific Objective:

1. The efficacy of this three drug combination to blunt the intubation surge with respect to Fentanyl.
2. The ability of this three drug combination to maintain hemodynamic stability in intraoperative period.
3. The quantitative requirement of other drugs in intraoperative period.
4. The analgesic requirement in immediate post operative period.

MATERIALSANDMETHOD

Study Design- Prospective Randomized Double Blinded Comparative Study.

Study Period- 12 MONTHS (9 months for data collection and 3 months for data analysis).

Place Of Study- Operation theatre of general surgery, plastic surgery, ENT, oncosurgery and urosurgery department of Medical College Hospital, Kolkata.

Study Population- Patients in the age group of 18-60 years with ASA 1 and 2 who will undergo surgery of less than 4 hours duration under G.A.

Sample Size /design- Considering primary outcome of SBP immediately after intubation a 24% variance with 20% effect difference, two tailed alpha error of 5% and power of 80%, the calculated sample size was 25 patients in each group. We hereby included 30 patients in each group to counteract dropouts if any.

Inclusion Criteria

1. Patients with ASA 1 or 2.
2. MALLAMPATI grade 1 or 2.
3. Patients scheduled for elective operation.
4. Age group 18 to 60 years.
5. Patients of either sex.

Exclusion Criteria

1. Unwilling patient.
2. Emergency surgery.
3. Anticipated difficult intubation.
4. Patients with cardiovascular disease.
5. COPD and Asthma patients.
6. Patients with renal disease.
7. Obese patients (BMI >24.9).
8. Underweight patient (BMI<18.5).
9. Patients on beta blocker or calcium channel blocker.
10. Patients with CNS disease.
11. ASA grade 3 and above.

Study Protocol-

Prospective patients were screened during pre-anaesthesiacheck up for eligibility of enrolment in the study. Eligible patients were offered the study related information verbally and in writing. Willing patients were requested to give written informed consent for participation in the study. 60 numbers of patients were prospectively enrolled for the study after obtaining their written informed consent.

RESULT AND ANALYSIS

Our study showed that out of 60 patients in Group-M 30(50.0%) patients were treated with combination of lignocaine- tramadol-magnesium sulphate and in Group-F 30(50.0%) patients were treated with fentanyl respectively for patients undergoing surgery under balanced general anaesthesia.There were no significant differences in demographic parameters of the patients of the two groups ($p>0.05$). Thus the patients of the two groups were matched for all the base parameters.

We found unpaired Student t-test showed that the mean heart rate of the patients of Group-M was higher than that of Group –F immediately after intubation, but there is no significant difference in heart rate between two groups thereafter until upto 60 minute. Then at 60,90,120,150and 180 minutes Group- M showed a lower heart rate as compared to Group –F indicating a better long term maintenance of heart rate in Group-M.

In our study showed that unpaired student t-test showed that the mean SBP of the patients of Group-M was higher than Group-F after intubation though both the groups are able to prevent intubation surge. Then there is no significant difference of mean SBP of the two groups during the intraoperative period upto 1 hour but the mean SBP of Group-M is lower than Group-F during the whole period. There is again rise of SBP in Group-F at 60 minutes and also at 150 and 180 minute of the operation when there is a lower SBP in Group-M as compared to Group- F-indicating better intraoperative and long term maintenance of SBP in Group-M.

We showed unpaired student t-test showed that the mean DBP of the patients of Group-M was higher than that of Group-F immediately after intubation and at 3 minute after intubation but no surge is noted in either group. Then there is no significant difference in the mean DBP of both the groups during the intraoperative period until the end period the operation at 180 minute when again Group-M showed a lower DBP as compared to Group-F-indicating better intraoperative and long-term maintenance of DBP in Group-M.

In our study showed that unpaired student t-test showed that the MAP of the patients of Group-M was higher than that of Group-F after receiving drug , immediately after intubation and at 3 minute after intubation but no surge is noted in either group. Then there is no significant difference in the MAP of both the groups during the intraoperative period and until upto 180 minute when again Group-M showed a lower MAP as compared to Group-F.During the period of 6 minute to 180 minute Group-M showed a comparative lower MAP most of the times indicating better intraoperative and long-term maintenance of MAP in Group-M.In both the groups 2(6.7%) patients required Diclofenac-75 mg as additional analgesic during intraoperative period($Z=0.01$;$p=0.99$). The mean amount of hourly need of Muscle relaxant was significantly lower for the patients treated with combination of Lignocaine-Tramadol-Magnesium sulfate than that of the patients treated with Fentanyl ($p=0.014$).

DISCUSSION

The randomised double blind study was undertaken to compare the efficacy of this Three Drug Combination(Lignocaine-Tramadol-Magnesium Sulfate) in attenuating hemodynamic surge following intubation and maintenance of hemodynamic stability in intraoperative period as compared to Fentanyl. Consenting patients of either sex, aged between 18 to 60 years, ASA physical status 1 & 2, MALLAMPATI grade 1 or 2 ,posted for elective surgery under balanced general anaesthesia were selected for this study. Difficult intubation takes longer time and invariably associated with marked hemodynamic changes even in well premedicated patients. So, patients with anticipated difficult intubation were excluded from this study.

Laryngoscopy and endotracheal intubation are associated with rise in heart rate, blood pressure and occasional disturbances in cardiac rhythm.[3] Although in normotensive subjects these responses of blood pressure and heart rate are transient and short lived, they may prove to be detrimental in high risk patients especially in those with cardiovascular disease, increased intracranial pressure and anomalies of cerebral blood vessels [6].So , effective attenuation of hemodynamic response to laryngoscopy and tracheal intubation and maintaining intraoperative hemodynamics within physiological level is of great importance in prevention of perioperative morbidity and mortality.

Lidocaine and Magnesium sulfate are widely used in order to decrease the hemodynamic response to airway management, with proven effectiveness that Magnesium sulfate blocks the release of catecholamines from adrenergic nerve terminals and adrenal medulla which maintains plasma concentration of epinephrine practically unchanged, also reduces the increased circulating norepinephrine when compared to that of control group and it also blocks catecholamine receptors.[5,7] has cardio protective and antiarrhythmic action, and induces coronary and systemic vasodilatation by antagonizing calcium ion in vascular smooth muscle.[5]Lidocaine has an antagonistic action on sodium channels, NMDA receptors, reduces the release of substance P, and has glycinergic action,[8] resulting in decreased airway reactivity.It also reduces post operative ileus and incidence of post operative nausea and vomiting (PONV)as evidenced by some experimental studies.

In 2017 Mendonca F.T.et al. [9] in their study of comparison between Magnesium Sulfate and Lignocaine found that there is increase in heart rate in both the group after laryngoscopy and intubation, followed by

gradual decline. There was a trend to higher HR values in Group M , also with no statistical difference. The tendency of increased heart rate in Group M can be physiologically explained by the direct vasodilator effect of this drug. In 2013 Nooraeiet al.[5] compared the effect of Lidocaine and Magnesium Sulfate on hemodynamic variables of laryngoscopy and found that there was no significant difference in the heart rates after intubation between the two groups. Puri et al.[10] showed in their study minimum increase in HR in both the groups receiving Magnesium Sulfate and Lignocaine .As illustrated in table 3 in our study the mean heart rate of Group M and F was not statistically significant before giving the drugs. Hence both the groups are comparable. The mean heart rate of the patients of Group-M was higher (96.00±15.88)than that of Group –F (86.67±15.38) immediately after intubation(showing Fentanyl as a betterdrug in preventing intubation surge than that of the Three Drug Combination) , but there is no significant difference in heart rate between two groups(p value between 0.07 to 0.62) thereafter until upto 45 minute. Then at 60 ,90, 120, 150 and 180 minutes Group-M showed a lower heart rate(74.25±5.50) as compared to Group –F(93.25±17.56). This indicates a better long term maintenance of heart rate in Group-M (because of short duration of action of Fentanyl in comparison to MgsSO4-Tramadol-Lignocaine Combination) during intraoperative period and at the time of extubation .

Puri et al.[10] compared the effects of magnesium sulphate and lidocaine on cardiovascular response to intubation in coronary artery disease patients undergoing CABG and found that MAP decreased ($P < 0.001$) after magnesium administration alone compared with the control group ($P < 0.05$) at preinduction stage. It decreased after the induction of anaesthesia, but the decrease was significant ($P< 0.01$) only in the control group and there was no significant difference between the two groups immediately before intubation. MAP increased after intubation and was significantly higher in control group compared with the magnesium group immediately after and 3 min after intubation ($P < 0.01$). Compared with baseline, the post intubation MAP values were significantly higher only in the control group ($P < 0.01$). In 2013 Nooraei et al. compared the effect of Lidocaine and Magnesium Sulfate on hemodynamic variables of laryngoscopy and found better control of blood pressure values with magnesium sulfate[5]. They found that there was a significant difference in the mean arterial pressure increase between the two groups since in the magnesium sulfate group this increase occurred in the first minute whereas in the lidocaine group it occurred during the first two minutes. MAP is better controlled by Fentanyl group immediately after intubation but during rest of the intraoperative period and also during extubation MgSO4-Lignocaine-Tramadol group showed better maintenance of MAP .This is probably due to longer duration of action of MgSO4.

CONCLUSION

This prospective, randomised,double blinded study showed that both the drugs are effective in preventing intubation surge and maintenance of intraoperative hemodynamics. Though patients receiving Fentanyl(Group-F) have a better control of intubation surge following endotracheal intubation , but in terms of long term maintenance of intraoperative hemodynamics, requirement of Non-depolarising muscle relaxant during the perioperative period and the timing of postoperative first dose of rescue analgesic, the Three Drug Combination of Mgso4-Tramadol- Lignocaine (Group-M) is a better agent than the Fentanyl group.

Table-: Distribution of under all parameters

	Group-M (n=30)	Group-F (n=30)	TOTAL	p-value
Diclofenac-75 mg	2(6.7%)	2(6.7%)	4 (6.7%)	<0.0001
Hourly need of MR [maintenance] (mg)	26.56±7.00	32.75± 7.34	$^{t}33^{=2.57}$	0.014
Rescue analgesic timing (hour)	5.06±1.82	4.01±1.90	$^{t}58^{=1.83}$	0.04

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