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Comparison between Lidocaine, Magnesium Sulphate and Verapamil for Attenuating Stress Response of Intubation during Induction of General Anesthesia

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Abstract: Background: Endotracheal intubation is one of most common procedure occurring every day in operating room. One of major concern is the stress response that occur during endotracheal intubation. Stress response appears in form of hypertension and tachycardia. Many trials had been established to control that stress response. Pharmacological additives to anesthetic drugs had been used like lidocaine, magnesium, calcium channel blockers and others. **Objectives:** To evaluate the effects of introducing intravenous lidocaine (1.5mg/kg) versus magnesium sulphate (30mg/kg) versus verapamil (0.1mg/kg) 3 minutes before intubation on patient hemodynamics for attenuating the stress response. **Patients and Methods:** In our study, we compared the effect of lidocaine, magnesium sulphate and verapamil to control the stress response. Patients were randomly allocated in three equal groups (25 each). Group I received 1.5 mg/kg lidocaine. Group II received 30mg/kg magnesium sulphate. Group III received 0.1mg/kg verapamil. All groups received medication 3 minutes before intubation. Blood pressure and heart rate has been recorded in pre-induction, pre-intubation, immediate post intubation and 5 minute post intubation. **Results:** The three drugs could be used as stress inhibitors as the change in blood pressure and heart rate between the basal reading and other readings is less that 20%. There is no significance difference between the groups regarding blood pressure. Magnesium sulphate couldn't control heart rate like other groups significally. **Conclusion:** We conclude that any of three drugs could be used to control the stress response of intubation. Adding small dose of opioids to magnesium will help to abolish the reflex tachycardia that occur during intubation.
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1. Introduction

The hemodynamic response to stimuli caused by laryngoscopy & intubation is a common phenomenon, resulting from the release of endogenous catecholamines reflexively to the upper airway afferents when stimulated. The management of this defensive reflex is necessary because it prevents adverse events, such as tachycardia, systemic hypertension, pulmonary hypertension & arrhythmias, which may result in stroke or myocardial infarction **(Mendonca et al., 2017).**

Many drugs have been tried in different studies for blunting hemodynamic responses to laryngoscopy and intubation but all such maneuvers had their own limitations **(Prasad et al., 2015).**

Lidocaine has blocking action on sodium channels & N methyl D aspartate (NMDA) receptors, reduces the release of substance P & has glycinergic action which decreases the airway reactivity **(Finnerup et al., 2005).**

Magnesium sulphate act as an attenuator for stress response by inhibition of catecholamine release from the adrenal medulla & maintains the plasma concentration of epinephrine practically unchanged. It is a systemic & coronary vasodilator by antagonizing calcium ion in vascular smooth muscles **(Panda et al., 2013).**

Calcium ions has an important role in the release of catecholamines from the adrenal gland & adrenergic nerve endings, which affects plasma concentrations of catecholamines in response to sympathetic stimulation. The calcium blockers such as verapamil inhibit the increase in plasma adrenaline induced by laryngoscope during intubation **(Mikawa et al., 1996).**

Aim of the Study

To evaluate the effects of introducing intravenous lidocaine (1.5mg/kg) versus magnesium sulphate (30mg/kg) versus verapamil (0.1mg/kg) 3 minutes before intubation on patient hemodynamics for attenuating the stress response.

Primary objective:

Evaluation of introducing lidocaine (1.5mg/kg) versus magnesium sulphate (30mg/kg) versus verapamil (0.1mg/kg) 3 minutes before intubation on patient hemodynamics for attenuating the stress response.

Secondary objective:

Evaluation of any specific complications related to lidocaine, magnesium sulphate or verapamil as an attenuator of stress response.

2. Patients and Methods

Type of Study: prospective, randomized, single blind study.

Study Setting: Ain Shams University Hospitals.

Study Period: from April to July 2019.

Study Population:

Inclusion Criteria:

(ASA Grade I & II) aged from (18 to 40) years old of both sexes scheduled for elective surgery.

Exclusion Criteria:

1- Patients with hypertension, bradycardia, cardiac, coronary, renal, hepatic, cerebral diseases and peripheral vascular diseases.

2- Obese patients (BMI ≥ 35), pregnant and nursing women.

3- Patients with history suggestive of sensitivity to drugs used during the study.

4- Anticipated difficult airway and in whom intubation attempts lasted longer than 15 s will be excluded from the study.

Sampling method:

Patients were randomly allocated into one of three equal groups, (25 patients in each group) to receive:

1. Group I (lidocaine group): 1.5mg/kg lidocaine, or
2. Group II (Magnesium group): 30mg/kg magnesium sulphate or
3. Group III (verapamil group): 0.1mg/kg verapamil.

Sample Size: 75 patients.

Ethical Considerations:

The study had performed after ethical committee approval and informed consent from the patients. The study protocol had been explained to the patient after taking their consent to the type of anesthesia and surgical procedure.

Patients Monitoring:

Monitoring equipments were attached to the patient including non-invasive arterial Blood pressure, oxygen saturation, 5 leads electrocardiogram leads connected & end tidal carbon dioxide.

Anesthetic Technique:

On arrival to the operating theater, IV line were established and all patients received the same induction agents (propofol 2mg/kg, atracurim 0.5mg/kg).

Before intubation by 3 minutes patients in:

Group I received 1.5mg/kg lidocaine,

Group II received 30mg/kg magnesium sulphate.

Group III received 0.1mg/kg verapamil.

According to a closed envelop technique.

Data collection:

1. **Patient hemodynamics**
   - Heart rate
   - Systemic blood pressure (systolic, diastolic & mean)

M1	Pre-induction
M2	Pre-intubation
M3	Immediate post-intubation
M4	5 min post-intubation

2. **Incidence of complications:**

Complications during or after the intubation: Such as arrhythmia & allergy to drugs were recorded.

- **Statistical Analysis**

The data was collected and analyzed using SPSS version 25. The number and percentage were calculated for the nominal variables, while the min, max, mean and standard deviation were calculated for describing the numerical variables. For testing the significance of the mean difference between groups, the independent-sample t-test, ANOVA and the least significant difference (LSD) were used.

3. Results

Table 1: Demographic statistics

	N	%
Female	37	49.3
Male	38	50.7
ASA1	55	73.3
ASA2	20	26.7

Table 2: The ASA classification in the groups

Group	ASA I		ASA II		Total
Magnesium	18	72.00%	7	28.00%	25
Verapamil	19	76.00%	6	24.00%	25
Lidocaine	18	72.00%	7	28.00%	25
Total	55	73.33%	20	26.67%	75

Table 3: Comparison between the 3 different groups regarding the heart rate in pre-intubation measure (M2)

HR at M2	N	Mean	SD	Minimum	Maximum	F	p-value
Magnesium	25	93.84	6.18	84	100	22.297	0.000**
Verapamil	25	82.04	8.50	67	93		
Lidocaine	25	81.04	7.75	65	92		

There is highly significant difference between the different groups in pre-intubation heart rate measure as heart rate is higher in magnesium group than other groups.

Table 4: Multiple comparison between the different groups to detect the reason of the significance difference in HR at M2

HR at M2		**p-value**
Magnesium	**verapamil**	0.000**
Magnesium	**lidocaine**	0.000**
Verapamil	**lidocaine**	0.640

Multiple comparison showed that magnesium group is the cause of that significant difference.

Table 5: Comparison between the 3 different groups regarding the heart rate in immediate post-intubation measure (M3)

HR at M3	N	Mean	SD	Minimum	Maximum	F	p-value
Magnesium	25	101.00	9.59	84	117	13.958	0.000**
Verapamil	25	92.72	8.13	77	105		
Lidocaine	25	87.40	9.71	68	100		

There is highly significant difference between the different groups in immediate post-intubation heart rate measure as heart rate is higher in magnesium group than other groups.

Table 6: Multiple comparison between the different groups to detect the reason of the significance difference in HR at M3

HR at M3		**p-value**
Magnesium	**Verapamil**	0.002**
Magnesium	**Lidocaine**	0.000**
Verapamil	**Lidocaine**	0.054

Multiple comparison showed that magnesium group is the cause of that significant difference.

Table 7: Comparison between the 3 different groups regarding the heart rate in 5 min post-intubation measure (M4)

HR at M4	N	Mean	SD	Minimum	Maximum	F	p-value
Magnesium	25	91.76	13.42	63	107	8.073	0.001**
Verapamil	25	85.64	9.62	66	97		
Lidocaine	25	79.72	8.01	63	90		

There is highly significant difference between the different groups in 5 min post-intubation heart rate measure as heart rate is higher in magnesium group than other groups.

Table 8: Multiple comparison between the different groups to detect the reason of the significance difference in HR at M4

HR at M4		**p-value**
Magnesium	**Verapamil**	0.045*
Magnesium	**Lidocaine**	0.000**
Verapamil	**Lidocaine**	0.052

Multiple comparison showed that magnesium group is the cause of that significant difference.

Table 9: Comparison between the 3 different groups regarding the difference in systolic blood pressure between the first (M1) and third measures (M3)

sysdf31	N	Mean	SD	Minimum	Maximum	F	p-value
Magnesium	25	15.88%	9.65	2.00	35.00	3.757	0.028*
Verapamil	25	9.08%	13.29	-8.00	34.00		
Lidocaine	25	15.36%	4.03	9.00	21.00		

There is significant difference between the different groups regarding difference between M1 & M3 as difference in systolic blood pressure is lower in verapamil group than other groups. Change in all groups is less than 20%.

Table 10: Multiple comparison between the different groups to detect the reason of the significance difference between M1 & M3

sysdf31		**p-value**
Magnesium	**verapamil**	0.016*
Magnesium	**lidocaine**	0.851
Verapamil	**lidocaine**	0.026*

Multiple comparison showed that verapamil group is the cause of that significant difference.

Table 11: Comparison between the 3 different groups regarding the difference in heart rate between the first (M1) and second measures (M2)

ratedf21	N	Mean	SD	Minimum	Maximum	F	p-value
Magnesium	25	11.16%	5.23	3.00	20.00	12.628	0.000**
Verapamil	25	-3.32%	15.45	-24.00	21.00		
Lidocaine	25	0.12%	8.59	-22.00	14.00		

There is highly significant difference between the different groups regarding difference between M1 & M2 as difference in heart rate is higher in magnesium group than other groups. Change in all groups is less than 20%.

Table 12: Multiple comparison between the different groups to detect the reason of the significance difference between M1 & M2 in HR

ratedf21		**p-value**
Magnesium	**Verapamil**	0.000**
Magnesium	**Lidocaine**	0.000**
Verapamil	**Lidocaine**	0.257

Multiple comparison showed that magnesium group is the cause of that significant difference.

Table 13: Comparison between the 3 different groups regarding the difference in heart rate between the first (M1) and third measures (M3)

ratedf31	N	Mean	SD	Minimum	Maximum	F	p-value
Magnesium	25	18.32%	7.81	5.00	30.00	10.946	0.000**
Verapamil	25	7.36%	11.74	-14.00	24.00		
Lidocaine	25	6.48%	9.96	-19.00	13.00		

There is highly significant difference between the different groups regarding difference between M1 & M3 as difference in heart rate is higher in magnesium group than other groups. Change in all groups is less than 20%.

Table 14: Multiple comparison between the different groups to detect the reason of the significance difference between M1 & M3 in HR

ratedf31		**p-value**
Magnesium	**Verapamil**	0.000**
Magnesium	**Lidocaine**	0.000**
Verapamil	**Lidocaine**	0.756

Multiple comparison showed that magnesium group is the cause of that significant difference as difference.

Table 15: Comparison between the 3 different groups regarding the difference in heart rate between the first (M1) and fourth measures (M4)

ratedf41	N	Mean	SD	Minimum	Maximum	F	p-value
Magnesium	25	9.08%	11.10	-12.00	29.00	5.708	0.005**
Verapamil	25	0.28%	14.06	-25.00	24.00		
Lidocaine	25	-1.20%	9.22	-24.00	8.00		

There is highly significant difference between the different groups regarding difference between M1 & M4 as difference in heart rate is higher in magnesium group than other groups. Change in all groups is less than 20%.

Table 16: Multiple comparison between the different groups to detect the reason of the significance difference between M1 & M4 in HR

ratedf41		p-value
Magnesium	**Verapamil**	0.009**
Magnesium	**Lidocaine**	0.003**
Verapamil	**Lidocaine**	0.654

Multiple comparison showed that magnesium group is the cause of that significant difference.

4. Discussion

Hemodynamic response to laryngoscopy and intubation is well established. Hypertension and tachycardia have been reported since 1950 during intubation under anesthesia. Increase in blood pressure and heart rate occurs most commonly from reflex sympathetic discharge in response to laryngotracheal stimulation, which in turn leads to increased plasma catecholamines concentration. This effect can cause acute hemodynamic instabilities such as increasing in pulmonary artery and capillary wedge pressure. Hemodynamic instability is defined as a state, which requires for circulatory or mechanical support to maintain a normal blood pressure or cardiac output. The changes in hemodynamic parameters >20% of basal value for each patient is usually considered as abnormal. Hemodynamic instability could cause many hazards complications. These complications cause significant adverse effects especially in patients with heart diseases and pulmonary disorders. These changes may be fatal in patients with heart disease and high blood pressure. During recovery from anesthesia hypertension may occur provoking post-operative complications like bleeding, increased intracranial and intraocular pressure.

Various methods to attenuate those responses have been tried. One of these methods is using pharmacological agents. Various pharmacological agents have been used to prevent these effects consisting deep anaesthesia, topical anesthesia, use of ganglionic blockers, adrenoreceptor blockers, narcotics, calcium channel blockers, sodium channel blockers, vasodilators, Magnesium sulphate and paracetamol.

The present clinical study was undertaken to evaluate the effect of lidocaine, magnesium sulphate and verapamil. Study was done in three groups (25 each group). In group I patients received lidocaine, group II patients received magnesium sulphate and in group III patients received verapamil. Findings of each groups are discussed in comparison with their pre-operative values at different time intervals with regard to heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure.

There was no significant difference between the three groups as regard the demographic data (age, weight, height, BMI and gender).

Our results showed that the change in hemodynamics between basal measures regarding blood pressure & heart rate and measures after intubation is less than 20% regarding the three groups. So, the three drugs with selected regimen could be used for attenuation of stress response.

As regard lidocaine, our results showed that there was a decrease in mean blood pressure and slight increase in heart rate after administration of the drug before intubation by about 12.5% and 0.12% respectively. But after intubation, the mean blood pressure and heart rate had increased by 11.84% & 6.48% respectively. After 5 minute intubation, the mean blood pressure and heart rate decreased by 14% & 1.2% respectively.

Lidocaine reduces the rate of rise of phase 0 of action potential by blocking inactivated sodium channels and raising the threshold potential. The duration of action potential and the refractory period are decreased as the repolarization phase 3 is shortened.

Similar to our results, **(Tam et al., 1987)** showed that IV lidocaine at a dose of 1.5 mg/kg given 3 min before intubation offered statistically significant attenuation of increases in mean blood pressure & heart rate. The attenuation of circulatory response to tracheal intubation occurred only when the IV lidocaine was given 3 min before intubation. Intravenous lidocaine may suppress circulatory responses to tracheal intubation by increasing the depth of general anesthesia. Lidocaine also has direct cardiac depressant and peripheral vasodilating effects.

According to **(Wilson et al., 1991)** results, intravenous lignocaine attenuated the pressor but not the chronotropic response to laryngoscopy and tracheal intubation which agree with our results.

(Mendonça et al., 2017) results confirm our study that lidocaine had good efficacy and safety for hemodynamic control during laryngoscopy and intubation, presenting as an option to mitigate the stimulation of upper airway in patients undergoing general anesthesia. Lidocaine has an antagonistic action on sodium channels, NMDA receptors, reduces the release of substance P and has glycinergic action, resulting in decreased airway reactivity.

(Prasad et al., 2015) showed that lidocaine is not effective as stress attenuator. The difference between our results and **(Prasad et al., 2015)** study that we depend on mean difference between the post intubation and the basal readings while **(Prasad et al., 2015)** study depend on maximum deference between the post intubation and the basal readings.

(Miller et al., 1990) showed different results as lignocaine 1.5 mg/kg given IV within 3 min of laryngoscopy failed to attenuate the cardiovascular responses to laryngoscopy and intubation. This may be due to the lidocaine was injected slowly over 30 sec, while in our study, lidocaine was injected as a bolus dose.

As regard magnesium, our results showed that there was a decrease in mean blood pressure and increase in heart rate after administration of the drug before intubation by about 15% and 11.2% respectively. But after intubation, the mean blood pressure and heart rate had increased by 11.4% & 18.3% respectively. After 5 minute intubation, the mean blood pressure and heart rate decreased by 13.5% & 9.1% respectively.

We noticed that magnesium has increased heart rate in all measured data. That effect may be expected that magnesium would slow the HR by inhibiting the calcium mediated depolarizing current in the pacemaker tissue, the effect that has been demonstrated in the isolated animal hearts. However, in the intact animal the ability of magnesium to inhibit the release of acetylcholine from the vagus nerve predominates and, therefore, the overall effect is mild increase in the heart rate as seen in this study. It also may can be physiologically explained by the direct vasodilator effect of this drug.

(Mendonça et al., 2017) results showed that magnesium sulfate is sufficient to attenuate the hemodynamic response to tracheal intubation which confirm our study results. As magnesium sulfate blocks the release of catecholamines from adrenergic nerve terminals and adrenal gland, it has cardio-protective, antiarrhythmic action, and induces coronary and systemic vasodilation by antagonizing calcium ion in vascular smooth muscle.

Also **(Honarmand et al., 2015)** results showed magnesium administered at dosage of 30 mg/kg attenuated the increase in arterial pressure changes after laryngoscopy and endotracheal intubation without significant effect on the HR changes. Magnesium caused vasodilation by sympathetic blockade and inhibition of catecholamine release. IV magnesium administration results in a decrease in systemic vascular resistance. Due to these effects, magnesium inhibited the increase in arterial pressure after laryngoscopy and tracheal intubation. This results are against with our results as heart rate are affected after intubation. That difference may be due to **(Honarmand et al., 2015)** used fentanyl during induction while we didn't used any opioids during induction.

(Kotwani et al., 2016) results showed magnesium definitely attenuates the effect on heart rate and blood pressure in response to laryngoscopy and intubation which is in agreement with our results. It is clear that although magnesium administration leads to tachycardia and hypotension, but by itself this effect is transient. The actions of magnesium in protecting against the potentially harmful cardiovascular effects of tracheal intubation are not superior to the actions of the potent short acting opiate agents like fentanyl and alfentanil. However, the use of opiates has been associated with muscle rigidity, bradycardia, hypotension, and respiratory depression. In circumstances where these complications may be undesirable, magnesium could be a useful alternative. Magnesium has also been shown to reduce fasciculation and potassium release after succinylcholine and these actions combined with the cardiovascular control that can be achieved by the use of magnesium can be of value.

As regard verapamil, our results showed that there was a decrease in mean blood pressure and in heart rate after administration of the drug before intubation by about 13% and 3.3% respectively. But after intubation, the mean blood pressure and heart rate had increased by 11.4% & 7.4% respectively.

After 5 minute intubation, the mean blood pressure decreased and heart rate increased by 14.9% & 0.3% respectively.

Verapamil as calcium channel blocker agents is known to depress significantly sinoatrial nodal function and causes atrioventricular nodal block. Also, verapamil produces hypotension, which is thought to arise from relaxation of vascular smooth muscle.

(Yaku et al., 1992) results showed that verapamil 0.1 mg/kg attenuated the increases in mean arterial blood pressure after tracheal intubation which confirm our study results. Verapamil was shown to be a putative coronary vasodilator with negative inotropic and chronotropic effects.

Also **(Wig et al., 1994)** results showed that verapamil was effective in attenuating the hypertensive response to laryngoscopy and tracheal intubation, but neither controlled the resulting tachycardia which is against to our results. That difference may be due to **(Wig et al., 1994)** had used succinylcholine, which precurarisation may result in tachycardia and hypertension.

(Mikawa et al., 1996) results showed that verapamil attenuated hypertension associate with tracheal intubation and successfully blunted tachycardia similar to our results. Laryngoscopy and tracheal intubation increase the level of plasma catecholamines. However, verapamil has been shown to reduce the pressor effect of circulating catecholamines on resistance vessels, resulting from inhibition of the calcium influx that accompanies stimulations of α2 receptors, leading to attenuation of the increase in arterial pressure after elevated concentrations of catecholamines.

As a comparison between the lidocaine and verapamil groups, our results showed that there was no significant difference between the two groups regarding any vital parameter had been measured.

As a comparison between lidocaine and magnesium groups, our results showed that there was no significant difference between the two groups regarding blood pressure measures. As regarding heart rate, there is a highly significance between the two groups with increased heart rate in magnesium group in pre-intubation, immediate post-intubation & 5 min post intubation measures. When we assessed the difference between the blood pressure measures with basic readings, we found a highly significant difference in systolic blood pressure difference between the basic and post intubation measure. Also, there was a highly significant difference between the groups regarding heart rate difference between the basic measure and pre-intubation, immediate post-intubation & 5 min post-intubation measures. **(Mendonça et al., 2017)** study showed that lower magnesium sulfate doses are sufficient to attenuate the hemodynamic response to tracheal intubation, with results similar to lidocaine which is against our results. The use of fentanyl in induction in **(Mendonça et al., 2017)** study could be the explanation of that difference.

As a comparison between Magnesium and verapamil groups, our results showed that there was no significant difference between the two groups regarding blood pressure measures. As regarding heart rate, there is a highly significance between the two groups with increased heart rate in verapamil group in pre-intubation, immediate post-intubation & 5 min post intubation measures. When we assessed the difference between the blood pressure measures with basic readings, we found a highly significant difference in systolic blood pressure difference between the basic and post intubation measure. Also, there was a highly significant difference between the groups regarding heart rate difference between the basic measure and pre-intubation, immediate post-intubation & 5 min post-intubation measures.

Calcium channel blockers are preferred because myocardial depression produced is minimized by reduction in after load so that cardiac output remain unchanged. While, it was found that magnesium sulphate fails to attenuate rise in heart rate comparing to verapamil.

We conclude that all three drugs could be used as anti-stress response to tracheal intubation. There is no significant difference between the groups in control blood pressure. Verapamil is the best in controlling heart rate.

Conclusion

Adding lidocaine or magnesium sulphate or verapamil to anesthetic drugs decreased the stress response of intubation. All drugs altered the stress of endotracheal intubation with less than 20% change from basal readings regarding blood pressure and heart rate. There is no significant difference between groups regarding blood pressure. Verapamil is the best to control heart rate effectively while magnesium sulphate is the least to control tachycardia.

Further studies are recommended to apply these drugs for higher scale of population. Higher number of patients may be needed to detect any complications with the drugs. Using small dose of opioids may be needed in future studies for better control of heart rate especially with magnesium sulphate.

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