DEXMEDETOMIDINE VERSUS MAGNESIUM SULPHATE OR LIDOCAINE FOR BLUNTING STRESS RESPONSE TO DIRECT LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION IN ABDOMINAL SURGERIES.

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ABSTRACT

Back ground: Direct laryngoscopy and endotracheal intubation frequently induces a cardiovascular stress response characterized by hypertension and tachycardia and also hormonal stress response characterized by increased secretion of pituitary hormones.

The present study was undertaken to compare the efficacy of intravenous dexmedetomidine, lidocaine and magnesium sulphate in attenuating the stress response to direct laryngoscopy and endotracheal intubation.

Subjects and Methods: The current **prospective randomized clinical study** was performed in Zagazig University hospitals. A total of 87 patients posted for elective abdominal surgeries under general anesthesia were enrolled in the study. Patients were randomly divided into three groups, group-D (dexmedetomidine group), group-L (lidocaine group) and group-M (magnesium sulphate group) with 29 patients in each group.

Group-D was given 1mcg/kg dexmedetomidine , Group-M was given 30mg/kg of magnesium sulphate and Group-L was given 1.5mg/kg lidocaine all the study drugs were given by IV infusions over a period of 10 minutes before induction of anesthesia which was standardized for all patients. The three groups were observed for changes in hemodynamic parameters at preinfusion of the study drug and preinduction of the anesthesia and 1, 3,5,10 minutes post intubation, blood glucose and cortisol level were measured at preinfusion and 10 min after intubation, Ramsay sedation score and postoperative pain were assessed at preinduction period and 1 hour postoperatively.

Results: It was observed that both dexmedetomidine and magnesium sulphate attenuated the rise in the mean arterial blood pressure significantly, but lidocaine failed to attenuate it.Also dexmedetomidine only decreased the changes in the mean heart rate , serum cortisol, serum glucose level, Ramsay sedation score and postoperative pain significantly.

Conclusion: This study seems to prove that dexmedetomidine and magnesium sulphate play an important role in blunting the stress response resulting from direct laryngoscopy and intubation.

Key Words: Dexmedetomidine, magnesium sulphate ,lidocaine, stress response, laryngoscopy , hemodynamic parameters.

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INTRODUCTION

Direct laryngoscopy and endotracheal intubation frequently induces a cardiovascular stress response in the form of hypertension and tachycardia due to reflex sympathetic simulation and also hormonal stress response characterized by increased secretion of pituitary hormones[1].Numerous drugs like opioids, calcium channel blockers, beta blockers, alpha 2 agonists, magnesium sulphate, local anesthetics etc. have been used to blunt it[2]. Several studies have looked at the efficacy of intravenous lidocaine as an agent to blunt the hemodynamic response to laryngoscopy and intubation [3]. Magnesium has been described as the physiological calcium antagonist because it competes with calcium for membrane channels and can modify many calcium-mediated responses. The ability of magnesium ions to inhibit the release of catecholamines from both the adrenal gland and peripheral adrenergic nerve terminals has been known for over 25 years and is now well established[4]. Dexmedetomidine is an alpha-2 adrenergic agonist having a strong affinity for alpha-2 adrenoceptors. Pretreatment with dexmedetomidine attenuates hemodynamic response to laryngoscopy and intubation. Apha 2-adrenoceptor agonists are being progressively more used in critical care and anesthesia. Beside sedation and analgesia, they also decrease sympathetic tone and attenuate the stress responses to anesthesia and surgery [5]. The present study was undertaken to detect which is the most effective intravenous premedication dexmedetomidine, lidocaine or magnesium sulphate in attenuating the stress response to laryngoscopy and intubation in patients under general anesthesia for abdominal surgeries.

SUBJECTS AND METHODS

After approval of the research ethics committee, this prospective, randomized, controlled, single-blinded clinical study was conducted in Zagazig University Hospitals from 5/2016 to 5/2018 on eighty seven patients who were scheduled to undergo elective abdominal surgeries under general anesthesia.

Written informed consents were obtained from all the patients in the study.

A sample size of 87 American Society of Anesthesiologists (ASA) physical status I and II patients aged between 21 and 50 years undergoing elective abdominal surgery were enrolled in the study. Patients with hypertension, dysrhythmia,diabetes mellitus, obesity, anticipated difficult airway and history of using any opioid or sedative within 48 hours prior to surgery were excluded from the study.All patients included in the study were visited the day before surgery to fulfill the inclusion criteria and they were kept nil orally 6-8 hours before surgery.

Patients were randomly divided into three groups according the study drug used: **group D, group L, and group M** with 29 patients in each group.

Group D was given dexmedetomidine 1mcg/kg diluted in 100 ml of normal saline IV infusion over a period of 10 min and the infusion was completed 10 min before induction. Group M was given 30mg/kg of magnesium sulphate diluted in 100 ml of normal saline IV infusion over a period of 10 min and the infusion was completed 10 min before induction. Group L was given 1.5mg/kg lidocaine diluted in 100 ml of normal saline IV infusion over a period of 10 min and the infusion was completed 10 min before induction, in addition to the standardized anesthetic protocol and group L considered as the control group.

On arrival to the operating room canula was inserted, routine monitors were applied for recording base line: heart rate (HR), mean arterial blood pressure and oxygen saturation values.Blood sample was obtained to check serum glucose and cortisol preinfusion and ten minutes after intubation.

The anesthetic protocol was standardized in all the study groups ,after preoxygenation for 3 minutes, all patients received Propofol 2mg/kg iv and fentanyl 1 mcg/kg iv. Endotracheal intubation was facilitated with 1.5 mg/kg of succinylcholine given IV 1 min prior to laryngoscopy and intubation. Laryngoscopy was performed using Macintosh laryngoscope and trachea was intubated with appropriate size endotracheal tube and connected to end tidal co_2 monitor. After confirmation of bilateral equal air entry, it was connected to mechanical ventilation using isoflurane 2% for maintaining anesthesia and to keep end tidal CO_2 between 35-40 mmHg, muscle relaxation was maintained by initial loading dose of cisatracurium 0.15 mg/kg iv then 0.03 mg/kg iv for maintenance every 20 min, Ringer's solution at a rate 5 ml/kg/hour iv infusion for fluid maintenance.

At the end of the surgery the inhaled gas was off and the patients was reversed with neostigmine 0.05mg/kg and atropine 0.01mg/kg,then extubation was performed after fulfilling the criteria for extubation.

The three groups were observed for changes in hemodynamic parameters i.e. heart rate

(HR) and mean arterial blood pressure at preinfusion , preinduction period and at 1,3,5,10 minutes post intubation, serum glucose and serum cortisol level at preinfusion and 10 min after intubation, Ramsay sedation score and pain at preinduction period and 1 hour post operatively.

Modified Ramsay sedation scale [6]

- 1 = Anxious, agitated, restless.
- 2 = Cooperative, oriented, tranquil.
- 3= Responds to commands only.
- 4 = Brisk response to light or loud noise.
- 5 =Sluggish response to light or loud noise.
- 6 = No response to light or loud noise.

STATISTICAL ANALYSIS

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium).

Kraskall Wallis H test was used to compare between two groups of non-normally distributed variables.

Friedman's test was used to compare repeated measurement of non- normally distributed variables; pairwise comparison with baseline level was done by Wilcoxon signed ranks test.Stuart–Maxwell test (different generalization of McNemar test) was used for testing marginal homogeneity in two repeated measures ordinal data.

All tests were two sided. p-value < 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically insignificant (NS).

RESULTS

As regards to the demographic data including age, gender,ASA, type of the surgery and duration of the surgery there was no significant statistical difference between the three groups (P-value>0.05) (table 1).

Table (1): Demographic data, type and duration of surgery.

Basic characteristics	Group D (n=29) Mean	±SD	Group M (n=29) Mean	±SD	Group L (n=29) Mean	±SD	p-value
Age	42	±7.79	41.72	±8.58	42.20	±7.15	0.944
	No.	%	No.	%	No.	%	
Gender							
Male	8	27.6%	13	44.8%	15	51.7%	>0.05
Female	21	72.4%	16	55.2%	14	48.3%	
ASA							
ASA I	14	48.3%	16	55.2%	15	51.7%	>0.05
ASA II	15	51.7%	13	44.8%	14	48.3%	
Surgery							
Hernia	9	31%	8	27.6%	10	34.5%	>0.05
Renal stone	5	17.2%	6	20.7%	5	17.2%	
Myomectomy	8	27.6%	7	24.1%	7	24.1%	
Hysterectomy	7	24.1%	8	27.6%	7	24.1%	
Duration of the surgery	90±11.78		93±14.1		91±14.27		>0.05

0 p-value ≥ 0.05 is insignificant.

On studying the heart rate it was denoted that the baseline heart rate (preinfusion) had no significant difference between the three groups, while the use of dexmedetomidine in group (D) patients significantly blunt the rise in the mean heart rate either at T1 (1 min after intubation) or the following readings from T3 to T10 (table 2).

Table (2): Comparison between studied groups as regards Heart rate (beat/min).

HR (beat/min)	Group D (n=29) Mean	±SD	Group M (n=29) Mean	±SD	Group L (n=29) Mean	±SD	p_1-value
Preinfusion	92.62	±7.27	93.34	±10.31	92.10	±9.71	0.732*
Preinduction	78.41	±9.01[ab]†	90.75	±12.39	91.03	±9.29†	<0.001*
1 min after intubation(T1)	74.48	±9.02[ab]†	87.89	±12.14[c]†	108.34	±20.65†	<0.001*
3 min after intubation(T3)	69.41	±7.61[ab]†	83.34	±10.20[c]†	100.72	±17.41†	<0.001*
5 min after intubation(T5)	62.86	±4.02[ab]†	79.17	±9.80[c]†	94.24	±16.29	<0.001*
10 min after intubation(T10)	59.17	±2.42[ab]†	75.13	±8.07[c]†	92.20	±16.13	<0.001*
Test§	143.194		128.409		75.402		
p_2-value	<0.001*		<0.001*		<0.001*		

§ Friedman's test. **:p-value <0.05 is significant. *: p-value <0.001 is higly significant.$P_{1:}$ p value between the three groups $P_{2:}$ p value between the same group at different times

a: significant difference between group D and group M. b: significant difference between group D and group L. c: significant difference between group Mand group L. † significant difference when compared to baseline level.

Table (3) shows that the MAP at the preinfusion period of the testing drug had no significant difference between the three groups and there was no statistically significant difference between dexmedetomidine and magnesium sulphate in all the following times (preinduction and from T1-T10) while there was statistically significant difference between dexmedetomidine and magnesium sulphate in comparison to lidocaine in all the following times (preinduction and from T1-T10).

Also, dexmedetomidine and magnesium sulphate not only blunted the rise in the MAP but also shortened the time needed to return to the preinduction values which was reached 5 minutes after intubation in group (D) and group (M) patients while in group (L) patients it was reached after 10 minutes.

Table (3): Comparison between studied groups as regards Mean Arterial blood Pressure(MAP) (mmHg).

MAP (mmHg)	Group D (n=29) Mean	±SD	Group M (n=29) Mean	±SD	Group L (n=29) Mean	±SD	p_1-value
Preinfusion	102.47	±6.79	97.95	±10.54	97.93	±9.77	0.082
Preinduction	82.70	±3.39[b]†	83.44	±5.97[c]†	94.42	±9.05†	<0.001*
1 min after intubation(T1)	92.36	±6.03[b]†	93.56	±7.34[c]†	105.00	±8.95†	<0.001*
3 min after intubation(T3)	87.64	±5.39[b]†	88.50	±6.33[c]†	100.48	±7.00	<0.001*
5 min after intubation(T5)	82.93	±5.05[b]†	84.02	±6.30[c]†	99.26	±7.20	<0.001*
10 min after intubation(T10)	78.33	±5.56[b]†	79.19	±6.55[c]†	98.18	±5.97	<0.001*
Test§	132.022		107.675		47.240		
p_2-value	<0.001*		<0.001*		<0.001*		

.P_1: p value between the three groups P_2: p value between the same group at different times

§ Friedman's test **:p-value <0.05 is significant. *: p-value <0.001 is higly significant. b: significant difference between group D and groupL. c: significant difference between group M and groupL. † significant difference when compared to baseline level.

Table (4) shows that regarding serum cortisol there was no significance difference between the three groups at the preinfusion time.Serum cortisol showed significantly lower levels in group (D) 10 min after intubation as compared to both group (M) and group (L) .

Moreover it was found that the difference between group M and group L in the following sample was statistically non significant.

Table (4): Comparison between studied groups as regards Serum cortisol during different times of the study.

Serum cortisol	Group D (n=29) Mean	±SD	Group M (n=29) Mean	±SD	Group L (n=29) Mean	±SD	p_1-value
Preinfusion	22.06	±3.18	23.94	±4.38	22.13	±3.52	0.114
10 min after intubation	25.86	±3.34[ab]	36.43	±5.85	37.33	±5.64	<0.001*
Test§	-4.703		-4.709		-4.704		
p_2-value	<0.001*		<0.001*		<0.001*		

§ Wilcoxon signed ranks test. **: p-value <0.05 is significant *:p-value <0.001 is higly significant. a: significant difference between group D and group M. b: significant difference between group D and group L. . P_1: p value between the three groups P_2: p value between the same group at different times

Table (5) shows that regarding blood glucose level there was no significance difference between the three groups (D, M, L) AND 10 minutes after intubation.

Table (5): Comparison between studied groups as regard fasting blood glucose (mg/dl).

fasting blood glucose (mg/dl)	Group D (n=29)		Group M (n=29)		Group L (n=29)		p_1-value
	Mean	±SD	Mean	±SD	Mean	±SD	
Preinfusion	144.03	±7.84	143.62	±14.40	145.44	±12.75	0.947
10 min after intubation	148.06	±10.85	149.58	±13.48	150.10	±13.05	0.913
Test	2.126		-3.423		-4.638		
p_2-value	0.042**		0.001*		<0.001*		

** p-value <0.05 is significant *p-value <0.001 is higly significant. P_1: p value between the three groups P_2: p value between the same group at different times

Table (6) and table (7) show that regarding Ramsay sedation score at the preinfusion period there was no significant difference between the three groups while at the preinduction period (after infusion of the study drug) most of the patients in group D (82.8%) had sedation score 3 (responds to commands only), while in group M and group L most of the patients had sedation score 2 (cooperative, oriented, tranquil); group M (86.2%) group L (96.6%). So it was denoted that there is a significant difference between group D in comparison to group M and group L in the preinduction period. Although dexmedetomidine had the upper hand in sedation durig preinduction period, there was no significant difference between the three groups one hour postoperatively.

Table (6): Comparison between studied groups as regards Ramsay sedation score.

Ramsay score	Group D (n=29)		Group M (n=29)		Group L (n=29)		p_1-value
	Mean	±SD	Mean	±SD	Mean	±SD	
preinfusion period	2		2		2		>0.05
just before induction	3.10	±0.40[ab]	2.13	±0.35	1.96	±0.18	<0.001*
1 hr post- operatively	1.62	±0.49	1.37	±0.49	1.41	±0.50	0.141
Test§	-4.750		-4.300		-4.000		
p_2-value	<0.001*		<0.001*		<0.001*		

§ Wilcoxon signed ranks test. * *:p-value <0.05 is significant *: p-value <0.001 is higly significant. a: significant difference between group D and group M b: significant difference between group D and group L. .P_1: p value between the three groups P_2: p value between the same group at different times

Table (7): Comparison between studied groups as regardS Ramsay sedation score.

Ramsay score	Group D (n=29) No.	%	Group M (n=29) No.	%	Group L (n=29) No.	%	p_1-value
preinfusion period							
2	29		29		29		>0.05
just before induction							
1	0	0%[ab]	0	0%	1	3.4%	<0.001*
2	1	3.4%	25	86.2%	28	96.6%	
3	24	82.8%	4	13.8%	0	0%	
4	4	13.8%	0	0%	0	0%	
1 hr post- operatively							
1	11	37.9%	18	62.1%	17	58.6%	0.138
2	18	62.1%	11	37.9%	12	41.4%	
Test	28.000§		19.059§		14.063¶		
p_2-value	<0.001*		<0.001*		<0.001*		

§ Stuart Maxwell test **:p-value <0.05 is significant *: p-value <0.001 is higly significant. McNemar's test. a: significant difference between group D and group M, b: significant difference between group D and group L, c: significant difference between group M and group L. .$P_{1:}$ p value between the three groups $P_{2:}$ p value between the same group at different times

Table (8) shows that regarding Visual analogue pain scale at the basal period (before infusion of the testing drug) there was no significant differences. While 1hour postoperatively it was found that there were statistically significant differences between the three groups of the study as VAS was significantly higher in group M and group L when compared with group D.which indicates higher analgesic effect of Dexmedetomidine as compared to either Magnesium or Lidocaine.

Table (8): Comparison between studied groups as regards Visual analogue pain scale.

VAS of pain	Group D (n=29) Mean	±SD	Group M (n=29) Mean	±SD	Group L (n=29) Mean	±SD	p_1-value
Basal before infusion of the testing agent	2.00	±0.80	2.03	±0.82	2.03	±0.77	0.982
1 hr post operatively	3.34	±0.97[ab]	4.03	±0.82	4.31	±0.66	0.001*
Test§	-4.008		-4.503		-4.672		
p_2-value	<0.001*		<0.001*		<0.001*		

§ Wilcoxon signed ranks test.
**: p-value <0.05 is significant *: p-value <0.001 is higly significant.
a: significant difference between group D and group M. b: significant difference between group D and group L. .$P_{1:}$ p value between the three groups $P_{2:}$ p value between the same group at different times

None of the patients of the study had any side effects whether intraoperatively or in PACU that necessitated treatment.

DISCUSSION

Laryngoscopy and endotracheal intubation are considered as the most critical events during general anesthesia as they provoke transient but marked sympathoadrenal response manifesting as hypertension, tachycardia and dysrhythmia. Many drugs have been tried by various physicians for blunting hemodynamic responses to laryngoscopy and intubation but all such maneuvers had their own limitations [1].

A lot of studies were published with different modalities and techniques trying to decrease the effect of this reflex especially in risky patients with comorbidities. Narcotics with different doses, Beta-adrenergic blocking agents like esmolol, opioids, gabapentin, magnesium sulphate, lidocaine and alpha2 agonists like clonidine and dexmedetomidine have been used to attenuate the rise in MAP and HR [7].

On studying heart rate changes we found the use of dexmedetomidine in group (D) patients significantly decreased the changes in the mean heart rate either at the time of intubation (T1) or the following readings from T2 to T10 and this agree with the study of ***Krishna et al.,*** and ***Prasad et al.,***. [1, 3]

On studying changes in the mean arterial blood pressure (MAP) it was shown that dexmedetomidine and magnesium sulphate not only blunt the rise in the MAP but also shorten the time needed to return to the preinduction values which was reached 5 minutes after intubation in group (D) and group (M) patients while in group (L) patients it was reached after 10 minutes and this observation similar to the observation of ***Gunalan et al.,*** [8]and ***Krishna et al.,*** [1]

The α2-agonists including dexmedetomidine decrease central sympathetic outflow by acting like a brake and decreasing intraoperative cardiovascular and endocrine responses due to surgical stimuli and laryngoscopy[9]

On studying the changes in the three groups regarding the changes of the serum cortisol level and blood glucose levels we found out that the rise above the preinfusion level in group (D) is lower than that in group (M) and group (L) 10 minutes after intubation.and this agree with the study of ***Jee et al.*** [10]

On studying changes as regards to Ramsay sedation score at the preinfusion period there was no significant difference between the three group while at the preinduction period (after infusion of the testing agent) it was shown that most of the patients in group D had sedation score 3 (Responds to commands only), while in group M and group L most of the patients had sedation score 2 (Cooperative, oriented, tranquil). Although dexmedetomidine had the upper hand in sedation there was no significant difference between the three groups one hour postoperatively. Several authors have reported that dexmedetomine infusion produces sedation which mimics normal sleep, patients are arousable to verbal commands and this was in agreement to the current study[11].In contrast to this study Harsoor et al.,provided a study to evaluate the effect of intravenous dexmedetomidine infusion during general anesthesia for abdominal surgeries on blood glucose levels and on sevoflurane requirements during anesthesia and dexmedetomidine group showed significant decrease in blood glucose levels[12].

On studying changes in the three groups regarding Visual analogue pain scale we found that it was significantly higher in group M and group L when compared with group D 1hour postoperatively in contrast ***Cho et al.*** found no significant differences in VAS scores between lidocaine and dexmedetomidine groups[13]. Also ***Park et al.*** studied the analgesic effect of perioperative dexmedetomidine infusion during laparoscopic cholecystectomy in comparison to placebo group and found that there were no significant differences in VAS scores between the two groups[14].

Limitation of our study was that the effect was not seen in hypertensive and cardiac patients. It will be more useful to study in high-risk hypertensive and cardiac patients which we didn't do in this study. Also plasma catecholamine levels, which is a point of measuring hemodynamic stress response was not measured in our study as we did not have catecholamine kits in our institute.There was no conflict of interest in this study.

CONCLUSION

We conclude that Dexmedetomidine and magnesium sulphate play an important role in blunting the stress response resulting from direct laryngoscopy and endotracheal intubation in patients undergoing elective abdominal surgeries.

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