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Research Article

EFFICACY OF INTRAVENOUS ESMOLOL WITH INTRANASAL NITROGLYCERINE SPRAY GIVEN BEFORE ENDOTRACHEAL EXTUBATION ON THE ATTENUATION OF PRESSOR RESPONSE: A COMPARATIVE STUDY

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ABSTRACT

Objectives: The aim of the study was to compare the effects of intravenous esmolol and intranasal nitroglycerine spray on attenuation of extubation pressor response in terms of hemodynamic parameters and to compare the adverse effects, if any, of either drug.

Methods: This was a randomized comparative study conducted in a tertiary care medical college in which 64 patients of ASA Grade I with age between 18 and 60 years, including both males and females undergoing elective non cardiac surgeries under general anesthesia with orotracheal intubation were included in this study on the basis of a predefined inclusion and exclusion criteria. Patients were divided into two groups (Depending on whether they received Intravenous Esmolol or NTG spray) of 32 patients each. Attenuation of extubation pressor response in terms of hemodynamic parameters (systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP], heart rate, and rate pressure product) were recorded and compared before induction, during surgery and postoperatively up to 10 min after surgery.

Results: The gender distribution was comparable in both the groups. The mean age of patients in Group A and Group B was found to be 36.90±10.12 and 35.20±11.32 years, respectively. The mean age of both the groups was found to be comparable with no statistically significant difference. Both the study groups were comparable in base line parameters with no significant difference seen in mean age, mean heart rate, mean SBP and DBP, MAP, anesthesia time, and surgery time. Both drugs controlled the blood pressure changes effectively; however, NTG group had a better control of systolic as well as DBP. Heart rate was better controlled in esmolol group.

Conclusion: Intranasal nitro-glycerine and intravenous esmolol before tracheal extubation in ASA Grade I patients are simple, effective, and practical methods of blunting cardiovascular responses to tracheal extubation.

Keywords: Extubation, Hemodynamic parameters, Nitroglycerine, Esmolol, Rate pressure product.

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INTRODUCTION

Endotracheal extubation is one of the frequently performed procedures in the practice of anesthesia. It is the translaryngeal removal of the endotracheal tube from trachea through nose or mouth. Post-operative extubation of trachea is an important event in the course of general anesthesia which causes significant increase in arterial blood pressure and heart rate [1]. These hemodynamic reflexes reflect sympatho-adrenal reflex stimulation (i.e., epi-pharyngeal and laryngo-pharyngeal stimulation) with concomitant increase in plasma levels of catecholamines and activation of α and β adrenergic receptors. This increase in blood pressure and heart rate are transitory, variable, and unpredictable. Many investigators have documented that tracheal extubation causes a modest and transient increase in the heart rate and blood pressure [2].

It has also been observed that respiratory complications after tracheal extubation are 3 times more common than complications occurring during tracheal intubation and induction of anesthesia. There is a greater incidence of postoperative complications such as excessive coughing, irritability, desaturation, and airway obstruction during tracheal extubation than intubation. Normally these responses are transient in nature hence well tolerated by normotensive healthy subjects [3].

Although the exact mechanism responsible for these hemodynamic responses is unknown, these changes may be associated with release of catecholamine occurring during this stressful period. Acute hemodynamic changes during extubation can lead to dangerous arrhythmias, myocardial ischemia, acute cardiac failure, pulmonary edema or cerebrovascular hemorrhage in susceptible individuals [4]. These adverse events are more common in patients with significant comorbid conditions. Various strategies such as extubation in deeper planes of anesthesia, avoiding or reducing duration of laryngoscopy before extubation, use of topical airway anesthesia with lignocaine and pre-treatment with intravenous beta blockers are used to reduce incidence of these adverse events [5]. However, only a handful of them have been proved beneficial in preventing these adverse responses. The reason being, this response is multifactorial and is due to a combination of factors such as pain of the wound, emergence from anesthesia, use of drugs to antagonize neuromuscular block and tracheal irritation. For the same reasons drugs which are used effectively to prevent intubation response can only partially prevent the extubation response or cannot be used at all at the time of extubation. Hence, the dosage and timing of the drug are most important during extubation [6].

Esmolol is a selective β_1 antagonist with a very short duration of action and it has very little if any sympathomimetic action and it lacks membrane stabilizing action. Esmolol is administered intravenous and used when β blockade of short duration is desired or in critically ill patient in whom adverse effect of bradycardia, heart failure, or hypotension may necessitate rapid withdrawal of the drug [7]. Many authors used different doses of esmolol (1, 1.5, and 2 mg/kg) and observed that all three doses were effective in controlling heart rate but

1 mg/kg was insufficient to control increase in systolic blood pressure (SBP), higher doses controlled both SBP and heart rate. It is also found that 2 mg/kg dose had produced significant decrease in heart rate [8].

Nitroglycerine, a well-known vasodilator and coronary vasodilator used intravenously to prevent pressor response to intubation. Intravenous route is useful for rapid action but preparation standardization and stabilization of such solution is problematic and can become expensive. Intranasal route of administration provides a safe, rapid, convenient route with reliability in its effect, ready availability, ease of application, and high stability during anesthesia. Furthermore, presence of surgical drapes, endotracheal tube, oral airway, temperature probe renders topical or sublingual administration of nitroglycerine difficult. In addition, atropine or other antisialagogue given as premedication may decrease dissolution and absorption of sublingual tablet [9].

We undertook this study to compare the attenuation of hemodynamic response to extubation by intravenous esmolol (1.5 mg/kg) and intranasal nitroglycerine spray (0.4 mg spray in each nostril) before extubation in patients undergoing various surgeries and also to find complications if any.

Aims and objectives

The objectives are as follows:

1. To compare the effects of intravenous esmolol and intranasal nitroglycerine spray on attenuation of extubation pressor response in terms of hemodynamic parameters.
2. To compare the adverse effects, if any, of either drug.

METHODS

This was a randomized comparative study conducted in a tertiary care medical college after due approval from the institutional Ethics Committee for Academic Research Projects (ECARP). 64 patients of ASA Grade I with age between 18 and 60 years, including both males and females undergoing elective non cardiac surgeries under general anesthesia with orotracheal intubation were included in this study on the basis of a predefined inclusion and exclusion criteria.

32 patients in each group were selected on the basis of envelop based randomization by systematic random sampling. Sample size calculation was done on the basis of pilot study on hemodynamic changes during endotracheal extubation. Keeping power (1-Beta error) at 80% and confidence interval (1-alphaerror) at 95%, the minimum sample size required in each group was 30 patients; therefore, we included 32 patients (more than minimum required number of cases). The patients were divided into two groups.

Group A = Esmolol group (1.5 mg/kg intravenous given after reversal and 2 min before extubation)

Group B = NTG group (NTG 0.8 mg intranasal sprayed 0.4 mg into each nostril, after reversal and 2 min before extubation.)

Pre-anesthetic evaluation including history and clinical examination was done on the evening before surgery. Mallampatti grading was done to rule out possibility of difficult intubation. Routine investigations including complete blood count, blood sugar, coagulation profile, liver function tests, kidney function tests, X-ray chest PA view, and ECG were done and noted. Patients were kept nil per orally at least 6 h before surgery. On the day of surgery patients were connected to multi parameter monitor for monitoring pulse, SPO_2, ECG, NIBP, $ETCO_2$, and temperature. Baseline blood pressure and heart rate were recorded. Intravenous access was achieved with 18G Intravenous cannula and IV fluid (Ringer's lactate) started.

Premedication

Inj. Midazolam 0.05 mg/kg IV, Inj. fentanyl 2 mcg/kg IV, Inj. ondansetron 0.15 mg/kg IV, Glycopyrrolate 0.004 mg/kg IV.

Induction of anesthesia

General anesthesia was induced after preoxygenation for 3 min with Inj Thiopentone 5 mg/kg, and muscle relaxation was facilitated with Inj.vecuronium 0.1 mg/kg after confirming bag and mask ventilation. Patients were then intubated with proper sized cuffed endotracheal tube after a short duration of laryngoscopy (<15 s). Those patients who required multiple attempts for intubation and duration of laryngoscopy more than 15 s were excluded from study. Patients were ventilated using a 40: 60 mixture of oxygen and nitrous oxide using Bain's circuit and controlled ventilation at flow rates of 100 ml/kg/min. Muscle relaxation was maintained using IV vecuronium in increments of 0.02 mg/kg. Sevoflurane was used as an inhalation agent for maintenance (between 1 and 2% dial setting) to maintain a target heart rate and SBP of ± 20% from base line. At the end of surgery, nitrous oxide and sevoflurane were switched off.

At the end of surgery, residual neuromuscular blockade was reversed using Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 0.008 mg/kg given slowly intravenously after observing spontaneous respiratory efforts by patient. Heart rate, SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) were noted at pre-reversal stage (i.e., at end of surgery). After giving reversal agent slowly and 2 min before extubation Group A received Esmolol 1.5 mg/kg intravenously and Group B received intranasal NTG spray 0.8 mg, that is, 0.4 mg in each nostril. Heart rate, SBP, DBP, and MAP were noted just before administration of study drugs. Patients were given 100% oxygen between injection of drug and tracheal extubation. After oropharyngeal suction the endotracheal tube was gently withdrawn on fulfilling extubation criteria. Hemodynamic parameters were noted at pre-reversal stage, before administration of study drug and at the time of extubation (T-0) and one (T-1), three (T-3), five (T-5), and ten (T-10) min after extubation.

Inclusion criteria

The following criteria were included in the study:

1. Patients posted for elective non-cardiac surgery under general anesthesia
2. Age between 18 and 60 years
3. ASA physical status I
4. Mallampatti class 1 and 2
5. Weight between 40 and 80 kg.

Exclusion criteria

The following criteria were excluded from the study:

1. Patient's refusal to give consent.
2. Patients posted for emergency surgeries
3. Patients with significant so-morbid conditions.
4. Patients with difficult airways
5. Patients with known allergy to either of the study drug.

RESULTS

Total number of males in Group A and Group B were 17 (53.13%) and 12 (37.50%), respectively, whereas number of females in Group A and Group B were 15 (46.88%) and 20 (62.50%). The gender distribution among both the groups was found to be comparable with no statistically significant difference ($p>0.05$) (Fig. 1).

The mean age was compared in both the groups. Mean age of patients in Group A and Group B was found to be 36.90±10.12 and 35.20±11.32 years, respectively. The mean age of both the groups was found to be comparable with no statistically significant difference (Table 1).

Both the study groups were comparable in base line parameters with no significant difference seen in mean age, mean heart rate, mean SBP and DBP, MAP, anesthesia time, and surgery time (Table 2).

The comparison of heart rate in both the groups showed that in esmolol group, mean basal heart rate was 74.9 beats/min. The mean heart rate at extubation was 76.3 beats/min, a rise of 1–2 beats from basal. During

the follow-up after esmolol administration, a rise of 1–2 beats/min was observed at 1, 3, and 5 min. At 10th min, the mean heart rate was almost equal to pre-reversal value of 80 beats/min. In the NTG group, the base line heart rate was 75.6 beats/min, which increased to 115.9 beats/min at extubation, a rise of 40 beats/min. During the follow-up it decreased at 1, 3, and 5 min and was 100.4 at 10th min of drug administration. In the NTG group at 10th min the rise of 20 beats/min was observed from the pre reversal value of 80.6 bpm. On comparing the heart rate in esmolol and NTG group, the heart rate was lower and effectively controlled in esmolol group while higher and not controlled in NTG group at 0, 1, 3, 5, and 10 min. On applying the statistical test this difference was found to be significant with a $p<0.05$.

In the esmolol group, the basal SBP was 116 mm of Hg, which increased to 136 mm of Hg at pre-reversal stage. After esmolol administration the systolic BP reduced from 140 mm of Hg before drug administration to 127 mm of Hg, at extubation. During follow-up SBP was 129, 128, and 129 mm Hg at 1, 3, and 5 min, respectively. At 10th min SBP was 130 mm Hg, 14 mm of Hg higher than basal SBP but almost close to pre reversal SBP. In the NTG group, the basal SBP was 117 mm of Hg, which increased to 135 mm of Hg at pre-reversal stage. In the NTG group, there was rapid fall in SBP from 141 mmHg (before drug administration stage) to 116 mmHg at extubation. During follow-up, SBP was 117, 118, and 119 mm Hg at 1, 3, and 5 min, respectively. At 10th min SBP was 120 mm Hg which was almost close to basal BP. The statistical analysis showed that SBP was more effectively controlled in NTG group in comparison with Esmolol group at 0, 1, 3, 5, and 10 min and this difference as statistically significant with a $p<0.05$. However, in both groups, SBP never varied by >20% from basal SBP. The statistical analysis showed that DBP was more effectively controlled in NTG group in comparison with esmolol group at 0, 1, 3, 5, and 10 min and this difference was statistically significant with $p<0.05$. However, in both groups, DBP never varied by >20%.

While comparing the rate pressure product, it was low in esmolol group than NTG group at 0, 1, 3, 5, and 10 min after drugs administration and this difference was statistically significant with a $p<0.05$ (Table 3).

DISCUSSION

General anesthesia has almost become synonymous with endotracheal anesthesia. As a matter of fact, the rapid studies made in the specialty of anesthesia can directly be attributed to our ability to manage the airway.

Translaryngeal removal of the endotracheal tube (Endotracheal extubation) is one of the frequently performed procedures in the practice of anesthesia. Tracheal extubation often provokes hypertension and tachycardia as does tracheal intubation due to reflex sympathetic discharge caused by pharyngeal and laryngeal stimulation [10]. This stimulation is associated with increase in plasma epinephrine concentration. These cardiovascular responses to endotracheal extubation are probably of little consequences in healthy individuals, but may be more severe and hazardous in hypertensive patients [11].

These circulatory perturbations occasionally lead to myocardial ischemia, Heart failure, arrhythmias, laryngospasm, bronchospasm, and cerebrovascular accidents due to imbalances between myocardial O_2 demand and supply in susceptible patients.

Tracheal extubation is as hazardous as tracheal intubation and at times is stormy causing severe hypertension, tachycardia, arrhythmias, coughing, laryngospasm, bronchospasm and cerebrovascular accidents more so in patients with hypertension, coronary artery disease and cerebrovascular disease.

Various drugs have been used to attenuate the stress response due to extubation including Esmolol and Nitroglycerine alone or in combination with other drugs, that is, nicardipine and lidocaine. But the author did not find any published research article to compare the effect of esmolol and nitroglycerine in attenuating cardiovascular response following tracheal extubation.

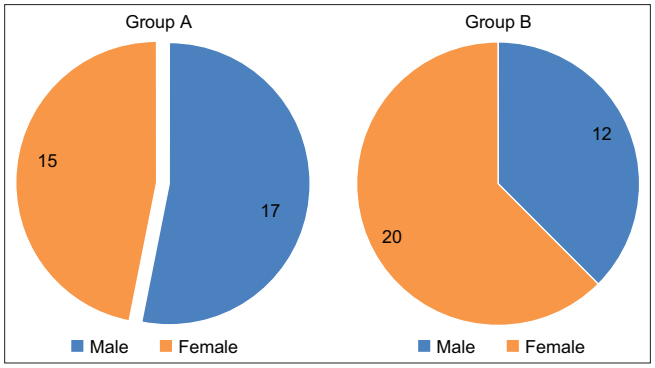

Fig. 1: Gender distribution of the studied cases

Table 1: Comparison of mean age of the studied cases

Age group (years)	Group		χ^2	p-value	Remark
	Esmolol, n (%)	NTG, n (%)			
Up to 20	3 (9.38)	3 (9.38)	4.38	0.357	NS
21–30	7 (21.88)	11 (34.38)			
31–40	11 (34.38)	6 (18.75)			
41–50	10 (31.25)	8 (25.00)			
>50	1 (3.13)	4 (12.50)			
Total	32 (100.00)	32 (100.00)			
Mean age	36.90±10.12	35.20±11.32			

NS: Not significant

Table 2: Baseline data of patients in both the groups

Variable	Group	Mean±SD	p-value	Remark
Age (years)	Esmolol	36.9±10.1	0.53	NS
	NTG	35.2±11.3		
HR	Esmolol	74.9±2.5	0.38	NS
	NTG	75.6±2.6		
SBP	Esmolol	116.3±2.8	0.31	NS
	NTG	116.9±2.6		
DBP	Esmolol	75.6±11.6	0.65	NS
	NTG	75.7±2.5		
MAP	Esmolol	89.2±7.5	0.77	NS
	NTG	88.8±1.8		
Anesthesia time	Esmolol	121.1±24.7	0.44	NS
	NTG	115.3±32.8		
Surgery time	Esmolol	105.8±23.4	0.12	NS
	NTG	94.1±32.7		

SD: Standard deviation, NS: Not significant, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

Esmolol has been used extensively for attenuation of cardiovascular response of tracheal extubation as well as intubation. Dyson *et al*. conducted a study in 1990 to evaluate the effect of Esmolol on cardiovascular responses to extubation. The authors studied three doses of esmolol (1, 1.5, and 2 mg/kg) given as bolus 2 min after reversal of neuromuscular blockade. Heart rate ($p<0.01$), SBP ($p<0.02$), and rate pressure product ($p<0.01$) significantly increased during extubation of control group. All doses of esmolol attenuated the increase of heart rate but 1 mg/kg was insufficient to control the increase in SBP. Doses of 1.5 and 2 mg/kg controlled both SBP and heart rate but larger doses produced significant decrease in heart rate. Hence, they concluded that esmolol attenuates the cardiovascular responses to extubation [8].

Wang *et al*. in 2003 studied effects of different doses of IV Esmolol on cardiovascular responses to tracheal extubation 175 patients were

Table 3: Comparison of hemodynamic parameters in studied groups

Hemodynamic	Group	Mean±SD	p-value	Remark
HR				
Basal	Esmolol	74.9±2.5	0.381	NS
	NTG	75.6±3.4		
Prereversal	Esmolol	80.0±3.6	0.512	NS
	NTG	80.6±2.8		
Before study drug	Esmolol	82.3±2.5	0.921	NS
	NTG	82.3±2.5		
0 min	Esmolol	76.3±3.2	<0.001	HS
	NTG	115.9±3.8		
1 min	Esmolol	77.3±2.4	<0.001	HS
	NTG	114.6±3.7		
3 min	Esmolol	77.2±2.0	<0.001	HS
	NTG	110.9±3.5		
5 min	Esmolol	78.9±1.6	<0.001	HS
	NTG	105.7±2.2		
10 min	Esmolol	79.4±1.5	<0.001	HS
	NTG	100.4±3.3		
SBP				
Basal	Esmolol	116±3	0.309	NS
	NTG	117±3		
Prereversal	Esmolol	136±5	0.767	NS
	NTG	135±4		
Before study drug	Esmolol	140±4	0.301	NS
	NTG	141±2		
0 min	Esmolol	127±5	<0.001	HS
	NTG	116±5		
1 min	Esmolol	129±3	<0.001	HS
	NTG	117±3		
3 min	Esmolol	128±4	<0.001	HS
	NTG	118±4		
5 min	Esmolol	129±4	<0.001	HS
	NTG	119±4		
10 min	Esmolol	130±5	<0.001	HS
	NTG	120±3		
DBP				
Basal	Esmolol	76±11	0.646	NS
	NTG	75±2		
Prereversal	Esmolol	85±4	0.649	NS
	NTG	86±3		
Before study drug	Esmolol	87±3	0.094	NS
	NTG	88±3		
0 min	Esmolol	78±3	<0.001	HS
	NTG	68±3		
1 min	Esmolol	78±4	<0.001	HS
	NTG	67±2		
3 min	Esmolol	80±5	<0.001	HS
	NTG	70±3		
5 min	Esmolol	81±3	<0.001	HS
	NTG	67±2		
10 min	Esmolol	82±4	<0.001	HS
	NTG	74±4		
MAP				
Basal	Esmolol	89±8	0.774	NS
	NTG	89±2		
Prereversal	Esmolol	102±3	0.121	NS
	NTG	103±3		
Before study drug	Esmolol	105±3	0.091	NS
	NTG	106±2		
0 min	Esmolol	95±2	<0.001	HS
	NTG	84±3		
1 min	Esmolol	95±3	<0.001	HS
	NTG	84±1		
3 min	Esmolol	96±4	<0.001	HS
	NTG	86±2		
5 min	Esmolol	93±2	<0.001	HS
	NTG	84±2		
10 min	Esmolol	98±3	<0.001	HS
	NTG	89±2		
RPP				
Basal	Esmolol	8710.0±322.0	0.16	NS
	NTG	8853.7±461.0		
Prereversal	Esmolol	10,870.4±547.9	0.0404	S
	NTG	11,150.3±521.6		
Before study drug	Esmolol	11,518.3±435.1	0.45	NS
	NTG	11,627.3±424.7		
0 min	Esmolol	9677.6±573.0	< 0.0001	HS
	NTG	13,413.3±726.9		
1 min	Esmolol	9936.9±448.1	<0.001	HS
	NTG	13,406.8±613.4		
3 min	Esmolol	9841.8±316.2	<0.001	HS
	NTG	13,206.9±567.2		
5 min	Esmolol	10,153.9±346.4	<0.001	HS
	NTG	12,546.0±463.7		
10 min	Esmolol	10,306.8±409.2	<0.001	HS
	NTG	12031.1±560.9		

SD: Standard deviation, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, RPP: Rate pressure product, S: Significant, NS: Not significant, HS: Highly significant

divided into five groups. Before the tracheal extubation, patients received 10 mL saline (control) or IV esmolol 0.5 mg/kg or 1.0 mg/kg or 1.5 mg/kg or 2.0 mg/kg and then the trachea was extubated 2 min later. The author concluded that esmolol of 1.5 mg/kg had not only controlled cardiovascular responses more effectively to the tracheal extubation but also had no side-effects. However, 2 mg/kg dose showed significant postoperative bradycardia [12].

Kovac *et al*. conducted a study to evaluate the effectiveness of intravenous nicardipine versus esmolol in attenuating the hemodynamic response to anesthesia emergence and extubation. The author concluded that 1.5 mg/kg esmolol was more effective in attenuating heart rate response to extubation [13].

Intranasal nitroglycerine has been used to attenuate stress response to intubation as well as extubation. Fassoulaki *et al*. described that intranasal NTG have advantage over Intravenous nitro-glycerine that it is easy to prepare, standardization, and stabilization [14]. The doses used for intranasal NTG spray varies from 0.3 mg as used by Iwasaka *et al*. [15], 0.8, 2 mg used by Dich-Nielsen *et al*. [16] and 0.8 mg as used by Grover *et al*. [17].

The present study has shown that both systolic and DBP was well controlled by intranasal NTG spray and esmolol infusion as no case of hypotension or hypertension was noted in the both groups. Although the fall in BP after administrating, the drug was more in intranasal NTG group as compared with the esmolol group and this difference was found to be highly significant. During the study it was seen that, the mean heart rate was significantly more in NTG group than esmolol group at 0, 1, 3, 5, and 10 min. The raised heart rate in NTG group can be explained by the fact that it is a vasodilator and tachycardia is a known side effect.

This finding emphasizes that both esmolol and NTG are able to control SBP, DBP, and MAP effectively but esmolol gives better control of heart rate during tracheal extubation than NTG.

Tracheal extubation and emergence from anesthesia may cause dangerous increase in myocardial oxygen demand in patients with coronary artery disease or at risk of developing it [18]. During this study, rate pressure product was high in NTG group as compared to Esmolol group, thus NTG should be cautiously used in coronary artery disease patients [19].

Limitation of the study

We only studied cases undergoing elective non cardiac surgeries and belonging to ASA Grade I and.Inclusion of ASA Grade II and above would

have helped in determining outcome in patients who have associated hemodynamic instability.

CONCLUSION

Giving intranasal nitro-glycerine and intravenous esmolol before tracheal extubation in ASA Grade I is a simple, effective, and practical method of blunting cardiovascular responses to tracheal extubation. Both drugs controlled the blood pressure changes effectively; however, NTG group had a better control of systolic as well as DBP. Heart rate was better controlled in esmolol group. Moreover, rate pressure product was high in NTG group making it unsuitable for patients suffering or at risk of coronary artery disease.

AUTHORS CONTRIBUTION

MK - Concept and design of the study, interpreted the results, prepared first draft of manuscript, and critical revision of the manuscript; VK - Statistically analyzed and interpreted, reviewed the literature, and manuscript preparation; SM - Design of the study, statistically analyses and interpreted, preparation of manuscript, and revision of the manuscript; and PJ - Statisticaly analysis and overall co-ordination of study.

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CONFLICTS OF INTERESTS

None.

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