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Bolus Administration of Esmolol Attenuates Hemodynamic Effects in Adults Undergoing Laryngoscopy and Endotracheal Intubation: Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Endotracheal intubation by direct laryngoscopy often elicits a reflex response from the sympathetic nervous system that triggers tachycardia and hypertension. Studies that address the use of esmolol in this context show great heterogeneity, making difficult its applicability in clinical practice. Thus, we evaluated the effect of bolus administration of esmolol on heart rate and blood pressure in adult patients undergoing general anesthesia in elective surgeries. Meta-analysis of randomized, double-blind clinical trials with adults undergoing laryngoscopy/endotracheal intubation for elective procedures under general anesthesia using esmolol or saline. English-language articles in PubMed and ClinicalKey databases with terms such as esmolol, laryngoscopy, endotracheal intubation, hypertension, and tachycardia were included. Duplicate articles, which used esmolol in continuous infusion, without a control group, without results in mean and standard deviation formats were excluded. A random effects model was adopted with DerSimonian-Laird tests and weighted mean difference (WMD) calculation for continuous variables, with their respective 95% confidence intervals (95%CI). Of the 287 studies identified, 13 were selected, accounting for 893 patients (447 in the esmolol group and 446 controls). The use of esmolol was considered a protective factor in decreasing heart rate (DMP = -15.66; 95% CI -18.06 to -13.27 and $p < 0.001$) and mean arterial pressure (DMP = -12.12; 95% CI -18.32 to -5.92 and $p < 0.001$) during laryngoscopy and endotracheal intubation.

Esmolol reduces the sympathetic autonomic response of adults undergoing laryngoscopy and endotracheal intubation.

KEYWORDS: Esmolol; Laryngoscopy; Endotracheal intubation; Hypertension; Tachycardia; Meta-analysis.

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INTRODUCTION

In the perioperative context or in emergency care, endotracheal intubation establishes a definitive airway, provides protection against aspiration of gastric contents, and allows ventilation with higher pressures than other devices, such as the face or laryngeal mask.[1] The most used technique for endotracheal intubation is direct laryngoscopy under continuous observation.[1]

The glottis is highly innervated and stimulation by the laryngoscopy maneuver or tracheal tube insertion can elicit an intense sympathetic nervous system response on the cardiovascular system, resulting in arterial hypertension and tachycardia.[2] The combination of these factors can create an imbalance between supply and demand. of oxygen by the myocardium, with the possibility of ischemia, arrhythmias and infarction. These effects may be exaggerated if anesthesia is established by the rapid sequence induction method.[3]

In anesthetic induction, different types of drugs, such as opioids, alpha2-agonists, local anesthetics, beta-blockers and calcium antagonists are used with the aim of inhibiting the afferent and/or efferent pathways responsible for the hemodynamic response to tracheal intubation.[4] However , the ideal combinations for different types of patients and in different situations has always been under debate.

A promising approach to decreasing cardiac responses to increased sympathetic stimulation is the use of beta-adrenergic antagonists.[3] Esmolol, a water-soluble, ultra-short-acting, cardioselective beta-blocker, has a rapid negative chronotropic effect after intravenous administration and a short duration of action (alpha distribution half-life = 2 minutes, beta elimination half-life = 9 minutes).[3] This pharmacokinetic profile is ideal for attenuating transient cardiovascular responses to laryngoscopy and tracheal intubation.[3] In addition, it avoids complications commonly associated with the use of opioids, such as excessive sedation and prolongation of arousal, apnea secondary to chest wall stiffness or respiratory depression, and postoperative nausea and vomiting, which prolong hospital stay.[4] Although through a mechanism still unknown, clinical studies suggest that beta1-adrenergic receptor antagonists play a role in pain modulation.[5]

Albeit administration via continuous infusion has been considered more effective than bolus[6], it must be taken into account that the former requires additional preparation time and effort.[7] Furthermore, since the sympathetic response to laryngoscopy is a transient and brief occurrence, the continuous administration of esmolol is not always indicated. Therefore, when there is a need to quickly perform hemodynamic control, a bolus dose is suggested due to a faster onset of action.[7]

The objective of this meta-analysis was to evaluate the efficacy of bolus administration of esmolol in reducing heart rate and arterial hypertension that occur in adults undergoing endotracheal intubation by direct laryngoscopy.

METHODS

Meta-analysis of clinical trials on the use of esmolol to reduce heart rate and arterial hypertension resulting from endotracheal intubation for general anesthesia in adult patients. PRISMA[8] guidelines were followed for reporting systematic review and meta-analysis of randomized clinical trials.

Articles in English published until December 31, 2019 in the following databases were included: in PubMed, they were selected using the keywords esmolol, laryngoscopy, endotracheal intubation, hypertension and tachycardia, separated by AND and OR interlocutors, with the following search strategies: (1) (((((esmolol) AND laryngoscopy) OR endotracheal intubation) AND Clinical Trial[ptyp])) AND hypertension, filters: humans, clinical trials; and (2) ((((((esmolol)) AND (laryngoscopy OR endotracheal intubation)) AND tachycardia) AND Clinical Trial[ptyp] AND Humans[Mesh]). In ClinicalKey, the adopted search was “esmolol AND laryngoscopy”, and filters of full articles and randomized controlled trials were marked. Subsequently, a manual analysis of the references of studies that met the inclusion criteria and search in the gray literature were performed, aiming to increase the number of studies originals not previously found.

Randomized, double-blind clinical trials with adult patients undergoing general anesthesia for elective surgery, which used bolus administration of esmolol and saline control before laryngoscopy and endotracheal intubation, were included. Duplicate articles, those that administered esmolol in continuous infusion, that did not have a saline control group and those that did not present the results in the format of mean and standard deviation were excluded.

Two independent researchers performed a preliminary assessment of titles/abstracts and data extraction. For those selected, a complete reading of the text was used in compliance with the inclusion and exclusion criteria. In case of disagreement, a third researcher made the final appraisal. Data regarding patients, anesthesia and outcomes were recorded in a standardized form developed by the authors. For this study, heart rate (HR), mean arterial pressure (MAP) and double product (DP) were the outcomes evaluated in the period between laryngoscopy and up to 5 minutes after endotracheal intubation. Double product, the result of multiplying systolic blood pressure (SBP) by heart rate, reflects cardiac work and myocardial oxygen consumption.[9] Among the various values presented in this time interval, the highest average observed in the control group (saline) was used, comparing it with the corresponding mean of the esmolol group. Therefore, the effectiveness of the drug was evaluated when it was most needed. Regarding the articles that studied different doses of esmolol within the same research, the effect of each dose compared to the control group was included, justifying the repetition of articles in the statistical analysis, differentiated by the letters (A) and (B).

Sensitivity analysis was designed to explore sources of heterogeneity across studies, when it existed. Statistical heterogeneity was calculated using chi-square method (χ^2) and Higgins test (I^2).[10] We considered the presence of heterogeneity if $p < 0.05$ and $I^2 \geq 50\%$. The odds ratio (OR), with a 95% confidence interval (95% CI), was used for the weighted mean difference (WMD). After qualitative analysis of the studies and statistical heterogeneity, the random effects model was adopted using the DerSimonian-Laird method and statistical analysis using the Comprehensive Meta-analyses® software v.3.3.[11] Evaluation of potential publication bias was performed using the visual analysis of the funnel plot and the Begg[12] and Egger[13] tests. Statistical significance of 5% was adopted.

RESULTS

Initially, a total of 287 studies were identified, 234 in PubMed and 53 in Clinicalkey, of which 13 articles [3,14-25] were selected to compose this meta-analysis, as shown in Figure 1.

Since defining that different doses of esmolol could be included in this study, publications that used two different dosages were cited twice. Thus, the 13 initial studies became 20, accounting for 893 patients; 447 in the intervention group and 446 in the control group, with their characteristics shown in Table 1

Table I. **Description of selected studies.**

Study	Study details	n	Age (years)	PS (ASA)	Procedure type
Singh 2013[13]	Esmolol 2mg/kg	40	18-65	I-II	Elective non-cardiac surgeries
	Saline	40			
Shrestha 2011[14]	Esmolol 1,5mg/kg	18	18-65	I-II	Elective surgeries
	Saline	18			
Gupta 2011[15]	Esmolol 2mg/kg	30	15-55	I-II	Elective surgeries
	Saline	30			
Singh 2010[16]	Esmolol 0,5mg/kg	25	18-45	I-II	Elective surgeries
	Saline	25			
Yavascaoglu 2007[17]	Esmolol 0,5mg/kg	20	18-60	I-II	Elective non-ophthalmic surgeries
	Saline	20			
Louizos 2007(A)[18]	Esmolol 2mg/kg	55	NS	I-III	Laryngeal microsurgery
	Saline	53			
Louizos 2007(B)[18]	Esmolol 1,0mg/kg	54	NS	I-III	Laryngeal microsurgery
	Saline	53			
Bensky 2000(A)[19]	Esmolol 0,4mg/kg	21	18-60	I-II	NS
	Saline	20			
Bensky 2000(B)[19]	Esmolol 0,2mg/kg	20	18-60	I-II	NS
	Saline	20			
Atlee 2000[20]	Esmolol 1,0mg/kg	34	18-86	I-III	NS
	Saline	35			
Kindler 1996(A)[21]	Esmolol 2mg/kg	15	17-70	I-II	Elective gynecological surgeries
	Saline	15			
Kindler 1996(B)[21]	Esmolol 1,0mg/kg	15	17-70	I-II	Elective gynecological surgeries
	Saline	15			
Sharma 1996(A)[22]	Esmolol 200mg	15	NS	II	Elective abdominal surgeries
	Saline	15			
Sharma 1996(B)[22]	Esmolol 100mg	15	NS	II	Elective abdominal surgeries
	Saline	15			
Parnass 1990(A)[23]	Esmolol 200mg	10	NS	II-III	NS
	Saline	10			
Parnass 1990(B)[23]	Esmolol 100mg	10	NS	II-III	NS
	Saline	10			
Sheppard 1990(A)[24]	Esmolol 200mg	15	NS	I-II	Elective non-cardiac surgeries
	Saline	14			
Sheppard 1990(B)[24]	Esmolol 100mg	15	NS	I-II	Elective non-cardiac surgeries
	Saline	14			
Ebert 1990(A)[3]	Esmolol 200mg	10	20-55	I-II	Elective surgeries
	Saline	12			
Ebert 1990(B)[3]	Esmolol 100mg	10	20-55	I-II	Elective surgeries
	Saline	12			
Total		893			

Legend: NS – not specified; PS (ASA) – Physical status (American Society of Anesthesiologists).

Four studies were carried out in the United States[3,20,21,24], three in India[16,17,23] and the others in Canada[25], Ghana[14], Nepal[15], Turkey[18], Greece[19] and Switzerland[22].

The dose of esmolol ranged from 0.2 to 2.0 mg/kg in some studies; others used full doses of 100 or 200 mg. The time interval between esmolol administration and endotracheal intubation ranged from 1.5 to 2.0 minutes.

Heart rate was evaluated in 20 studies[3,14-25] and the use of esmolol was considered a protective factor as it provided a HR reduction of 15.66 bpm (95% CI: 13.27 to 18.06 and $p < 0.001$) in comparison with the control, as shown in Figure 2. The analysis by dose subgroups showed no change in the effect and highlighted its dose-dependent characteristic, 200 mg: WMD = -19.83 bpm (95% CI -24.85 a - 14.81 and $p < 0.001$); 2 mg/kg: WMD = -17.91 (95% CI -21.41 to -14.41 and $p < 0.001$); 100 mg: WMD = -14.84 (95% CI -19.99 to -9.69 and $p < 0.001$); 1 mg/kg: WMD = -12.99; (95% CI -15.00 to -10.98 and $p < 0.001$); 0.4–0.5 mg/kg: WMD = -11.31 (95% CI -18.56 to -4.07 and $p = 0.002$).

The use of esmolol also significantly reduced MAP (WMD = -12.12; 95% CI -18.32 to -5.92 and $p < 0.001$) (Figure 3). Subgroup analysis maintained the effect for doses equal to or greater than 1 mg/kg (WMD = -13.75; 95% CI -21.68 to -5.82 and $p = 0.001$); the doses ranging from 0.4 to 0.5 mg/kg had no effect on blood pressure control (WMD = -9.59; 95% CI -27.29 to 8.10 and $p = 0.288$).

In the evaluation of the double product, it can be inferred that myocardial oxygen consumption was significantly reduced in the group that used esmolol (WMD = -3,441.01; 95% CI -4,755.21 to -2,126.82 and $p < 0.001$) (Figure 4).

Of the 13 studies included, eight[15-17,19,20,22,24,25] reported that patients using medications with cardiovascular action, including other beta-blockers or antihypertensives, were excluded. The total number of patients not using these drugs represented 67.20% of the sample (n = 600). Three studies[3,14,18] contributing with 164 patients (18.36%) did not specifically mention the inclusion/exclusion of such a confounding factor. Only two studies[21,23], with 129 patients (14.44%), are known to include the use of drugs that could interfere with the results. Thus, it was considered that there was no significant interference of drugs with cardiovascular action on the evaluated effect.

The adverse effects reported in the groups that used esmolol were: four patients with tachycardia[19,25], three with arterial hypertension[25], one with bradycardia[15] and one with bronchospasm[19].

Based on the analysis of the funnel plot (Figure 5), there is relative symmetry between the studies, which suggests that there is no publication bias, confirmed by the Begg ($p = 0.74$) and Egger ($p = 0.36$) tests.

DISCUSSION

This meta-analysis is composed of 13 randomized clinical trials, published between 1990 and 2013, that evaluated the effect of esmolol administered as a bolus dose on heart rate and blood pressure in adults undergoing laryngoscopy and endotracheal intubation in the induction phase of general anesthesia.

Tachycardia and arterial hypertension caused by laryngoscopy, when exaggerated, can cause serious complications, such as acute myocardial infarction and arrhythmias.[3] The pharmacokinetic profile of esmolol is ideal for attenuating transient cardiovascular responses and places it as a drug option to be used to reduce these effects.[3] In addition, it does not cause sedation or respiratory depression.[4]

Tachycardia has a double deleterious effect by increasing myocardial oxygen consumption while decreasing coronary flow time.[3] This meta-analysis found that, during the period between laryngoscopy and five minutes after endotracheal intubation, the effect of a bolus dose of esmolol on HR demonstrated to be able to reduce it by at least 13.27 bpm. It can also be noted that the increase in dosage is accompanied by a greater reduction in HR. A previous study showed that the HR variation reduced from 29.6% in the placebo group to 9.3% in the esmolol group, confirming that its dose-dependent effect was able to alleviate intubation-induced tachycardia and, as such, reduce the risk of deleterious consequences on the myocardium.[26]

In addition to cardiac complications, a hypertensive spike secondary to laryngoscopy/endotracheal intubation may increase intracranial pressure and cause irreversible damage during anesthetic induction.[27] In this context, some authors have suggested that small doses of esmolol (0.2 or 0.4 mg/ kg) could block the increase in HR and BP [20], while others reported that 1.5 mg/kg attenuated tachycardia[28], but with no effect on MAP. This meta-analysis shows that esmolol has a significant role in blood pressure reduction, depending on the dose used. While doses equal to or greater than 1mg/kg were able to control the increase in MAP, and doses of 0.4–0.5 mg/kg were not effective in controlling blood pressure. It could be noted that the lowest dose used in the studies (0.4 to 0.5 mg/kg) proved to be effective in reducing HR without this effect being observed in the attenuation of arterial hypertension. This is a predictable fact, since the main characteristic of a beta-blocker is its negative chronotropic effect.[26]

It is known that the double product, determined by HR and SBP, is correlated with global myocardial oxygen consumption and its increase may predispose to an increased risk of ischemia in patients with coronary artery disease.[29] Therefore, the significant reduction of DP by esmolol in relation to the control group accounts for its important role in the protection of the cardiac muscle.

It is worth mentioning that hypotension and bradycardia are equally deleterious, since they can reduce cardiac output and global oxygen supply. Perioperative arterial hypotension is related to an increase in acute myocardial infarction, acute renal failure and mortality up to

30 days after surgery.[30,31] During laparoscopic surgeries, bradycardia associated with pneumoperitoneum can lead to cardiac arrest, especially in previously healthy patients and athletes.[32] Therefore, the dose of esmolol should be sufficient to avoid hypertension and tachycardia at the time of induction, without causing persisting hypotension and bradycardia.

The rare reports of complications demonstrate the safety of the dosages used in the studies, but their results are restricted to adult patients undergoing elective surgeries and cannot be extrapolated to extremes of age and/or emergency surgeries. It is suggested that the dose should be individualized considering the particularities of each case.

The quality of a meta-analysis depends on the selection of relevant studies, detection bias and heterogeneity.[33] Despite the different strategies adopted in this study to minimize possible biases, these cannot be ruled out. A grading scale of possible risks of bias was not used. However, only double-blind, randomized clinical trials that met the defined characteristics (PICOS method) were included. Other large databases were not searched due to access difficulties, which could induce the occurrence of selection bias in this study. To overcome this limitation, the used method included a search in two distinguished databases associated with a manual search of references and in the gray literature. Differences between esmolol doses, medications used in anesthetic induction, data collection, types of surgeries and patient profiles are some factors that can be listed as possible causes of the high heterogeneity found and that justify the use of the random effects model used. On the other hand, publication bias was ruled out by three different methods.

This meta-analysis contributes to show that esmolol is reliably capable of providing cardiovascular protection by reducing heart rate and blood pressure during the laryngoscopy maneuver in adults, even when administered as a bolus dose, and not only as a continuous infusion.

CONCLUSION

The bolus administration of esmolol had a significant effect in reducing the chronotropic and pressure response up to the fifth minute after laryngoscopy for endotracheal intubation.

Conflict of interest

The authors declare no conflicts of interest.

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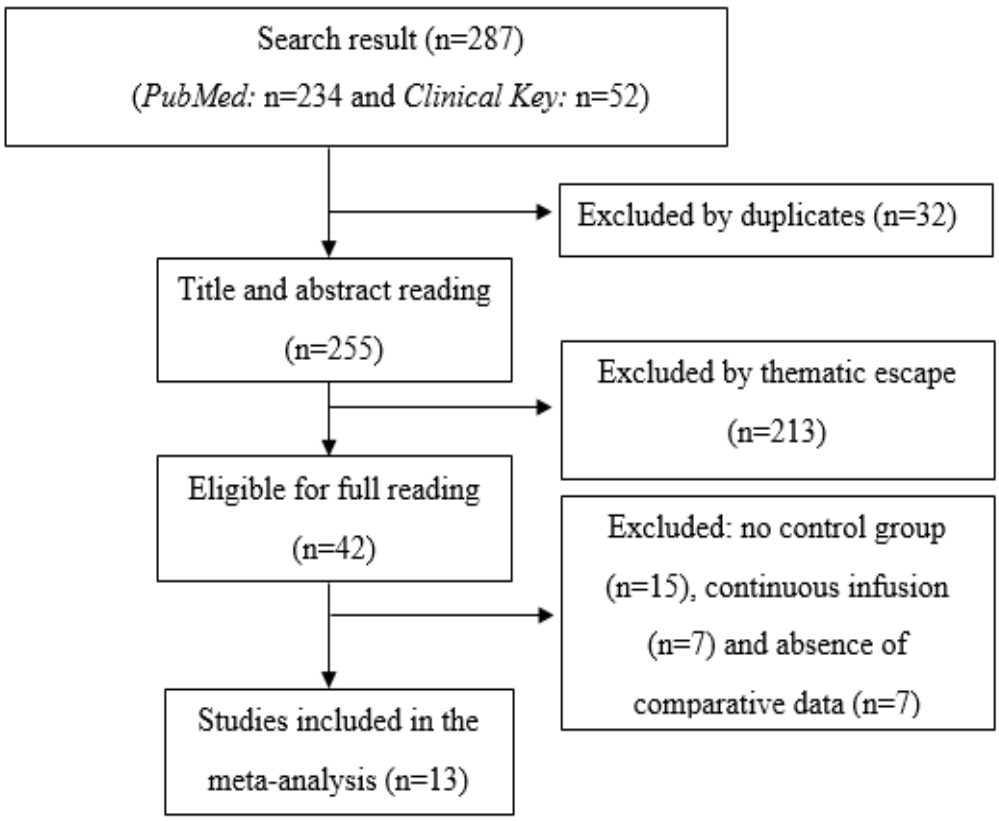
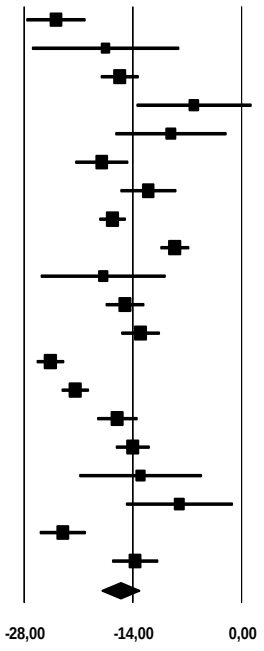


Figure 1. **Study selection diagram.**

Study	Esmolol Mean±SD	n	Saline Mean±SD	n	Weight (%)	Random effects WMD (IC 95%)
Singh 2013[14]	92,20±9,74	40	116,10±7,62	40	5,20	-23,90 (-27,73: -20,06)
Shrestha 2011[15]	83,78±11,99	18	101,28±16,73	18	3,09	-17,50(-27,00: -7,99)
Gupta 2011[16]	91,66±5,01	30	107,33±4,82	30	5,63	-15,67 (-18,15: -13,18)
Singh 2010[17]	108,64±11,41	25	114,76±15,19	25	3,80	-6,12 (-13,56: 1,32)
Yavascaoglu 2007[18]	88,10±8,40	20	97,20±14,10	20	3,89	-9,10 (-16,29: -1,90)
Louizos 2007(A)[19]	68,00±7,00	55	86,00±11,00	53	5,32	-18,00 (-21,46: -14,53)
Louizos 2007(B)[19]	74,00±8,00	54	86,00±11,00	53	5,26	-12,00 (-15,63: -8,36)
Bensky 2000(A)[20]	88,20±2,40	21	104,80±3,30	20	5,80	-16,60 (-18,37: -14,84)
Bensky 2000(B)[20]	96,20±2,80	20	104,80±3,30	20	5,77	-8,60 (-10,49: -6,70)
Atlee 2000[21]	89,20±12,70	34	107,00±20,50	35	3,57	-17,80 (-25,87: -9,72)
Kindler 1996(A)[22]	75,00±3,00	15	90,00±4,00	15	5,62	-15,00 (-17,53: -12,47)
Kindler 1996(B)[22]	77,00±3,00	15	90,00±4,00	15	5,62	-13,00 (-15,53: -10,47)
Sharma 1996(A)[23]	83,60±2,20	15	108,20±2,80	15	5,79	-24,60 (-26,40: -22,79)
Sharma 1996(B)[23]	86,80±2,20	15	108,20±2,80	15	5,79	-21,40 (-23,20: -19,59)
Parnass 1990(A)[24]	88,00±3,00	10	104,00±3,00	10	5,59	-16,00 (-18,63: -13,37)
Parnass 1990(B)[24]	90,00±2,00	10	104,00±3,00	10	5,69	-14,00 (-16,23: -11,76)
Sheppard 1990(A)[25]	86,00±11,90	15	99,00±9,70	14	3,62	-13,00 (-20,93: -5,06)
Sheppard 1990(B)[25]	91,00±9,30	15	99,00±9,70	14	4,00	-8,00 (-14,91: -1,08)
Ebert 1990(A)[3]	88,00±3,00	10	111,00±4,00	12	5,47	-23,00 (-26,00: -19,99)
Ebert 1990(B)[3]	97,30±3,00	10	111,00±4,00	12	5,47	-13,70 (-16,70: -10,69)
Total		447		446	100	-15,66 (-18,06: -13,26)



Heterogeneity Test: X^2= 246,75; DF=19 (p < 0,000); I^2=92,30%

Favorable to esmolol

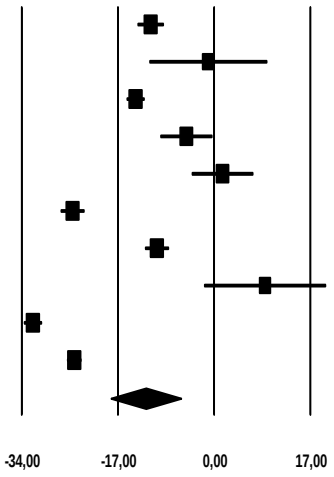
Favorable to saline

Overall effect test: Z= -12,79 (p < 0,001)

Figure 2. Meta-analysis of the effect of esmolol bolus administration on heart rate in adults undergoing laryngoscopy and endotracheal intubation.

Legend: SD – standard deviation; WMD - weighted mean difference.

Study	Esmolol		Saline		Weight	Random effects
	Mean±SD	n	Mean±SD	n	(%)	WMD (IC 95%)
Singh 2013[14]	106,10±4,98	40	117,30±5,90	40	10,56	-11,20 (-13,59: -8,80)
Shrestha 2011[15]	102,72±16,77	18	103,76±15,20	18	8,22	-1,04 (-11,49: 9,41)
Gupta 2011[16]	96,70±3,32	30	110,56±3,24	30	10,64	-13,86 (-15,52: -12, 20)
Singh 2010[17]	117,28±8,53	25	122,18±8,24	25	10,12	-4,90 (-9,54: -0,25)
Yavascaoglu 2007[18]	91,90±7,70	20	90,40±9,90	20	9,89	1,50 (-3,99: 6,99)
Bensky 2000(A)[20]	95,40±4,20	21	120,4±2,70	20	10,59	-25,00 (-27,17: -22,82)
Bensky 2000(B)[20]	110,30±4,10	20	120,40±2,70	20	10,59	-10,10 (-12,25: -7,94)
Atlee 2000[21]	123,10±22,30	34	114,10±23,60	35	8,08	9,00 (-30,59: 19,84)
Sharma 1996(A)[23]	100,00±2,10	15	132,00±2,50	15	10,65	-32,00 (-0,71: -30,34)
Sharma 1996(B)[23]	107,30±0,80	15	132,00±2,50	15	10,67	-24,70 (-0,45: -23,37)
Total		238		238	100	-12,12 (-18,32: -5,92)



Heterogeneity Test:
X^2= 596,04; DF=9 (p < 0,001); I^2=98,49%

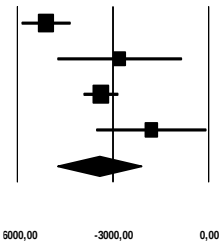
Favorable to esmolol

Favorable to saline

Overall effect test:
Z= -3,83 (p < 0,001)

Figure 3. Meta-analysis of the effect of esmolol bolus administration on mean arterial pressure in adults undergoing laryngoscopy and endotracheal intubation.
Legend: SD – standard deviation; WMD - weighted mean difference.

Study	Esmolol		Saline		Weight	Random effects
	Mean±SD	n	Mean±SD	n	(%)	WMD (IC 95%)
Singh 2013[14]	12.681,00±1.605,00	40	17.778,00±1.926,00	40	29,35	-5097,00 (-5873,94: -4320,05)
Shrestha 2011[15]	10.879,72±2.539,17	18	13.670,11±3.402,72	18	18,92	-2790,39 (-4751,76: -829,01)
Gupta 2011[16]	12.396,70±941,03	30	15.772,27±1.233,88	30	30,90	-3375,57 (-3930,85: -2820,28)
Singh 2010[17]	16.894,00±3.203,00	25	18.689,00±3.059,00	25	20,82	-1795,00 (-3531,16: -58,83)
Total		113		113	100	-3441,01 (-4755,21: -21,26)



Heterogeneity Test:
X^2= 19,07; DF=3 (p < 0,001); I^2=84,27%

Favorable to esmolol

Favorable to saline

Overall effect test:
Z= -5,13 (p < 0,001)

Figure 4. Meta-analysis of the effect of esmolol bolus administration on the double product of adults undergoing laryngoscopy and endotracheal intubation.
Legend: SD – standard deviation; WMD - weighted mean difference.

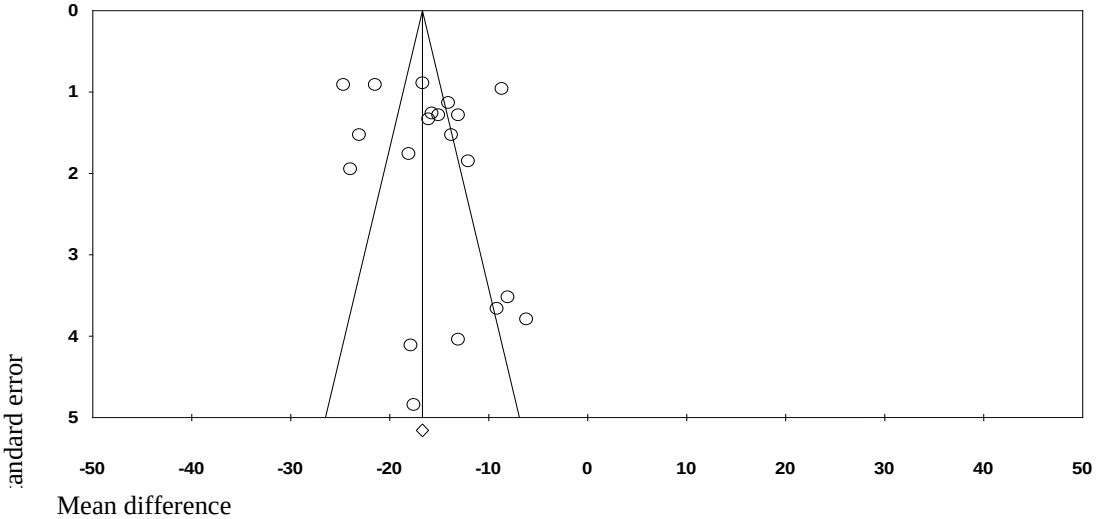


Figure 5. **Funnel plot of the effect of esmolol bolus administration on heart rate in adults undergoing laryngoscopy and orotracheal intubation.**