*Acta Anaesthesiol Scand 2001; **45**: 1011–1022*
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
ISSN 0001-5172

Assessment of the efficacy of esmolol on the haemodynamic changes induced by laryngoscopy and tracheal intubation: A meta-analysis

E. FIGUEREDO and E. M. GARCIA-FUENTES
Department of Anaesthesia, Torrecardenas Hospital, Almería, Spain

Background: Adrenergic stress response induced by laryngoscopy and tracheal intubation (LTI) appears to be attenuated by esmolol, but its potential clinical benefits have not been fully weighed against possible adverse effects.
Methods: A systematic search up to May 2000 was performed using MEDLINE, EMBASE, LILACS, Cochrane library, manual searching and bibliographies in all languages. All randomised comparisons of esmolol with placebo on the haemodynamic changes elicited by LTI were obtained. Trials were included in the present meta-analysis if they recorded heart rate (HR), systolic pressure (SBP), mean arterial pressure (MAP) or diastolic pressure (DBP) at three different stages: pre-induction, immediately prior to intubation, and in the post-intubation period. Weighted mean differences (WMD) and 95% confidence intervals (CI) of the changes in the haemodynamic variables between treatment and placebo groups were calculated.
Results: Of 72 publications identified, 38 randomised controlled trials containing a total of 2009 patients were finally included. Eleven different regimens and doses of esmolol demonstrated effectiveness in the attenuation of HR and BP after LTI in a dose-dependent manner. The most effective regimen was a loading dose of 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over 4 min followed by continuous infusion dose of 200–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [WMD: 20.2 bpm (95% CI: 15.6 to 24.7)]. High bolus dose (200 mg) of esmolol produced a considerable decrease in DBP [WMD 10.1 mmHg (95% CI: 7.3 to 12.8)].
Conclusion: Esmolol is effective, in a dose-dependent manner, in the attenuation of the adrenergic response to LTI. To minimise its adverse effects it should be administered, when considered clinically appropriate, as a continuous infusion regimen.

Received 17 December 2000, accepted for publication 5 May 2001

Key words: Anesthesia: induction; complications: hypertension; tachycardia; intubation, tracheal: cardiovascular responses; sympathetic nervous system: beta adrenergic antagonists, esmolol.

IT HAS BEEN established reasonably well that laryngoscopy and tracheal intubation (LTI) manoeuvres induce marked increases in heart rate (HR) and blood pressure (BP) (1) which, in combination, result in an unfavourable supply–demand balance of myocardial oxygen. The degree of reflex response to laryngeal stimulation appears to vary with the depth of anaesthesia (2), the duration (3) and difficulties encountered during LTI (4, 5) as well as on patient-dependent variables including age and history of diabetes or cardiovascular disease (6, 7).

The haemodynamic changes are, generally, transitory and without sequelae. However, in patients with pre-existing coronary artery disease (CAD), hypertension or cerebrovascular disease an increase in these circulatory parameters may precipitate myocardial ischaemia, arrhythmias and, even, infarction and cerebral haemorrhage (8, 9).

The quest for an effective blockade of these responses has included the use of topical and systemic lidocaine, vasodilators, α- or β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, opiates and inhaled anaesthetic agents.

Since tachycardia appears to be associated more frequently with myocardial ischaemia than does hypertension (10), one interesting approach towards attenuating cardiac responses to laryngeal stimulation is the use of β-adrenergic antagonists. However, whilst attenuation of the pressor response to LTI is desirable, excessive negative chronotropic and inotropic action of the β-receptor blockers may reduce coronary perfusion and precipitate heart failure in susceptible patients (11).

Among the β-adrenergic antagonists, esmolol (methyl 3–4-[2-hydroxy-3-(isopropylamino) propoxyphenyl] propionate hydrochloride) has been shown to be an attractive option because of its β-1 (cardio-selective) adrenergic receptor blocking properties and its

ultra-short duration of action (alpha distribution half-life of 2 min; beta elimination half-life of 9 min) (12, 13).

To date, several studies have assessed the effectiveness of esmolol in blunting the haemodynamic alterations induced by LTI. However, no consensus has been reached regarding the optimum dose nor the mode and timing of its delivery. In the present study we attempted to quantify, using meta-analyses, the effectiveness of the different regimens and doses of esmolol used, as well as the grade of hypotension and bradycardia that can be produced when used in conjunction with anaesthesia induction agents.

Material and methods

Systematic search

We searched MEDLINE (MEDlars onLINE, produced by the National Library of Medicine, USA. -http://www.ncbi.nlm.nih.gov/PubMed/-), EMBASE (Excerpta Medica database, produced by Elsevier Science Publisher, Amsterdam, Holland. Software Spirs: SilverPlatte. -http://www.silverplatter.com/catalog/elan.htm-) and LILACS (Latin American and Caribbean Health Science Literature database, controlled by the Pan American Health Organization [PAHO/WHO]. -http://www.bireme.br/abd/E/elilacs.htm-) (all after the year 1982) and Cochrane Library (issue 1, 2000) for studies that tested the effect of esmolol relative to that of placebo in the control of haemodynamic alterations induced by LTI. Broad free text searches with no restriction on language were undertaken using the terms "esmolol" and "laryngoscopy" and/or "intubation". The last electronic database search was performed in May 2000. Additional full text or abstracts of trials were identified from reference lists of retrieved reports and review articles on esmolol and haemodynamic alterations induced by LTI. A manual search of scientific abstracts from relevant meetings published in major anaesthesiology journals was also performed.

When the published data were incomplete, we attempted to contact the corresponding authors of the studies for verification and/or updates. When the same study had been presented as an abstract as well as an original article we included only the data from the full report in the present meta-analysis.

Inclusion criteria and principal outcomes

The criteria for inclusion into the meta-analyses were: randomised, placebo-controlled studies that contained data on any of the following four haemodynamic variables: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR). It was considered a requisite that the studies contained baseline values of the above variables as well as at least another two additional values; the first within the period between the administration of esmolol or placebo and the laryngoscopy and the other within 5 min subsequent to the endotracheal intubation. Randomisation was only assumed when so stated in the report.

Data extraction and statistical analyses

The reports were independently read by the present investigators and the following data extracted on each group of patients (esmolol – placebo): 1. the baseline value of the variable analysed (SBP, MAP, DBP, HR); 2. the minimum values of the variable after the administration of esmolol; and 3. the maximum values reached following tracheal intubation. The numbers were extracted directly from the text or from the tables of results of the studies. When the results were presented in figure format, they were enlarged up to A3 paper size to obtain an improved precision for manual calculation of the values. In these figures the measured and calculated absolute values were obtained together with the standard deviations (SD) of the variables by comparison with the graduated scale of the figure.

Other data extracted from each study were: sequence in which the induction agents and esmolol were administered, physical status of the patients (ASA classification), treatment groups, inclusion of opiates in the anaesthetic protocol, exclusion criteria and the description of the adverse effects.

When in the original study estimations of the dispersion of the results were presented as standard error of the mean (SEM), these were transformed into SD by applying the formula: SD=SEM multiplied by the square root of n.

For each variable in each of the study groups of patients from each individual study the following were calculated: a) the percentage difference (increase) between the maximum observed value and the baseline value (% difference=Mv−bv) using the following formula: maximum observed value $\times 100$/baseline value; and b) the percentage difference (decrease) between the baseline value and the minimum observed value (% difference=bv−mv) using the formula: minimum observed value $\times 100$/baseline value.

To obtain a global assessment of the effectiveness of esmolol in modifying each of the variables associated with LTI, the percentage increase of each variable in all the studies combined were averaged using a correction factor based on the numbers of patients in each study:

$$\%\ \text{diff. Mv}-\text{bv}_{\text{global}} = \sum (\%\ \text{diff. Mv}-\text{bv}_a \times n_a + \%\ \text{diff. Mv}-\text{bv}_b \times n_b + \ldots + \%\ \text{diff. Mv}-\text{bv}_x \times n_x)/n_{\text{total}}$$

where:

$\%$ diff. Mv$-$bv$_{global}$=percentage difference between the maximum values observed and the baseline values,
$\%$ diff. $\%$ Mv$-$bv$_x$=percentage difference between the maximum value observed and the baseline value of study "x",
n_x=number of patients (esmolol or placebo group) of study "x", and
n_{total}=total number of patients (esmolol or placebo) in all the studies.

To quantify the decrease in the values of the variables caused by the association "esmolol-anaesthetic inductor", the percentages of decrease were averaged in all of the studies with a formula similar to the one above but replacing "% diff. Mv$-$bv" with "% diff. bv$-$mv".

The studies were further assessed with respect to whether or not opiates had been concomitantly prescribed.

The meta-analysis was applied in each of the variables only when three or more studies evaluated the same doses and/or regimen of administration compared with placebo. Additionally, a meta-analysis was performed to compare the most frequently used doses of esmolol (100 vs 200 mg bolus dose). All outcome variables were continuous.

The meta-analyses were performed with the Revman 4.0.4. statistical program. When the chi-squared test for homogeneity between the results showed positive ($P>0.2$), the variables were analysed with the fixed effect model and, if negative ($P<0.2$), with the randomised effect model. Results are reported as weighted mean differences (WMD) with 95% confidence intervals (CI) of the changes in the haemodynamic variables between treatment and placebo groups.

Results

Included and excluded trials

We retrieved 72 trials but only 38 met our inclusion criteria (Table 1) (14–51). Of these, four were abstracts (20, 25, 27, 35) and five of the articles included in the overall analyses were excluded from the meta-analysis of sub-groups because we did not encounter a minimum of three studies evaluating the same dose and/or parameters (23, 39, 46, 47, 49). Eight abstracts (52–59) were subsequently published as full articles (14, 18, 24, 26, 34, 36, 38, 51) and, consequently, were excluded from the present meta-analysis. Seven studies had to be excluded because there had not been any statement indicating that the study-subjects had been randomised (60–66). For various methodological reasons 10 trials needed to be excluded because they did not fulfil the design criteria of our study (67–76). We contacted 12 corresponding authors by letter or e-mail to clarify the data from their published studies. Three responded positively and the other nine studies were excluded because we were unable to contact the authors or the data we solicited were not forthcoming (77–85).

Of the 38 studies finally included, 16 evaluated at least two different doses of esmolol versus placebo (18, 20, 21, 25, 26, 29, 34, 35, 38, 40–43, 49–51). In 14 studies esmolol was compared with placebo as well as with an alternative therapeutic agent (14, 15, 17, 19, 21, 23–26, 28, 29, 36, 44, 47). Eleven different esmolol regimens were tested including intravenous bolus, infusion or combination of both as well as fixed doses (full milligrams) and variable doses (micrograms per kilogram body weight). The most frequently used regimens were intravenous bolus doses of 100 mg and 200 mg. The study by Kapnoudhis et al. (25), despite not including a placebo group, was included in the present analysis only to compare the 100 vs 200 mg dose of esmolol.

We analysed data from 2009 patients of whom 981 had received esmolol, 632 received placebo and the rest (n=396) had received alternative therapeutic agents [mostly opiates (17, 19, 21, 23–25, 28, 29, 36) or lidocaine (19, 23, 26, 44, 47)]. The average trial size was 53 patients (range 12 to 200).

Global analyses

SBP was evaluated in 28 studies (Table 1). The mean baseline value for the groups treated with esmolol was 140 mmHg (range 114–185) (16, 26) and, for the placebo groups, 138 mmHg (range 117–171) (15, 16). Following anaesthesia induction, the SBP values decreased (with respect to the baseline values) by 6.1% in the 525 patients of the placebo groups. The patients of the groups in whom esmolol had been administered (n=782) had a decrease of 13.8%. The maximum decrease observed in one study (mean values of all the patients included in the said study) was 20% in the placebo group (31) while in the patients treated with esmolol the decrease in the SBP reached, in some studies, 35% (15). Following LTI, the SBP increased by 26.3% in patients in the placebo group compared to

Table 1

Characteristics of the studies included in the meta-analysis.

Author	Analysed parameters[a]	Mode of administration (bolus – infusion)	Time of administration[b] (before – after)	Patients esmolol n	Patients placebo n	Total patients n	Exclusion criteria	Opiates[c]	Adverse effects
Atlee JL et al. (14)	S-D-M	Bolus	Before	34	35	132	Yes	Yes	Yes
Ayuso A et al. (15)	S-D	Infusion		10	10	30	Yes	Yes	Yes
Cuchiara RF et al. (16)	S-HR	Infusion		32	30	62	Yes	No	Yes
Ebert JP et al. (17)	S-D-HR	Infusion		20	20	60	Yes	O-g	Yes
Ebert TJ et al. (18)	S-D-HR	Bolus	Before	20	12	32	No	No	No
Feng C et al. (19)	S-HR	Bolus	Before	20	20	80	Yes	O-g	Yes
Gardaz JP et al. (20)	M-HR	Bolus	After	40	20	60	No	Yes	Yes
Gaubatz MCL et al. (21)	S-D-HR	Bolus	Before	22	11	44	Yes	O-g	Yes
Girard D et al. (22)	M-HR	Infusion		11	9	20	Yes	Yes	No
Helfman SM et al. (23)	S-HR	Bolus	After	20	20	80	Yes	O-g	Yes
Johansen JW et al. (24)	S-D-M-HR	b + i	Before	20	20	10	Yes	O-g	No
Kapnoudhis P et al. (25)	D-M	Bolus	Before	45	0	45	Yes	O-g	Yes
Kindler CH et al. (26)	S-HR	Bolus	After	15	15	90	Yes	Yes	Yes
Korenaga GM et al. (27)	S-HR	Infusion		12	10	22	Yes	Yes	No
Korpinen R et al. (28)	S-D-HR	Bolus	Before	15	15	60	Yes	O-g	Yes
Korpinen R et al. (29)	S-D-HR	Bolus	Before	29	15	59	Yes	O-g	Yes
Korpinen R et al. (39)	S-HR	b + i	Before	20	20	40	No	Yes	Yes
Korpinen R et al. (31)	S-D-HR	b + i	Before	20	20	40	Yes	Yes	Yes
Kovac AL et al. (32)	M-HR	Bolus	Before	10	10	20	Yes	Yes	Yes
Liu PL et al. (33)	S-M-HR	Infusion		16	14	30	Yes	No	Yes
Miller DR et al. (34)	M-HR	Bolus	Before	30	15	45	Yes	Yes	Yes
Miller DR et al. (35)	M-HR	Bolus	Before	20	10	30	Yes	Yes	Yes
Newsome LR et al. (36)	M-HR	Infusion		10	10	30	Yes	O-g	Yes
Nicolson SC et al. (37)	M-HR	Infusion		17	17	34	Yes	Yes	Yes
Parnass SM et al. (38)	S-HR	Bolus	Before	20	10	30	Yes	Yes	Yes
Ramanathan J et al. (39)	M	Infusion		6	6	12	Yes	No	No
Sandler AN et al. (40)	S-D-M-HR	Bolus	After	30	15	45	Yes	No	Yes
Sharma S et al. (41)	S-D-M-HR	Bolus	Before	30	15	45	Yes	Yes	Yes
Sharma S et al. (42)	S-HR	Bolus	Before	49	24	73	Yes	No	Yes
Sheppard S et al. (43)	S-HR	Bolus	Before	30	14	44	Yes	No	Yes
Singh H et al. (44)	M-HR	Bolus	After	10	10	40	Yes	No	Yes
Thompson JP et al. (45)	S-D-HR	Bolus	After	10	10	20	Yes	No	Yes
Van den Berg A et al. (46)	S-HR	Bolus	After	40	40	80	Yes	No	Yes
Van den Berg A (47)	S-D-M-HR	Bolus	After	20	20	80	Yes	No	No
Vucevic M et al. (48)	S-HR	Infusion		15	15	30	No	No	Yes
Wang S et al. (49)	S-M-HR	Bolus	After	150	50	200	Yes	Yes	Yes
Yuan L et al. (50)	S-HR	Bolus	Before	15	15	45	No	No	Yes
Zsigmond EK et al. (51)	S-D-HR	Infusion		8	10	40	Yes	Yes	Yes

[a] S=systolic blood pressure; D=diastolic blood pressure; M=mean arterial pressure; HR=heart rate.
[b] Time at which the bolus esmolol was administered relative to the inductor agent.
[c] Opiates administered to the patients. O-g=opiates administered to patients included in other groups.

9.1% in patients treated with the various regimens of esmolol.

DBP was evaluated in 14 studies (Table 1). The mean baseline value for the groups treated with esmolol was 76.6 mmHg (range 64–90) (21, 34) and, for the placebo groups, 77.2 mmHg (range 68–93) (18, 34). Following anaesthesia induction, DBP values decreased by 3.4% in the 228 patients in the placebo groups and by 6.8% in the 297 patients in the esmolol groups. After LTI, the DBP increased by 34.2% in the patients in the placebo groups compared to 22.8% in the patients treated with esmolol.

MAP was evaluated in 16 studies (Table 1). The mean baseline value was 95.9 mmHg (range 73–119) (34, 48) and 94.5 mmHg (range 78–116) (48, 51) for the placebo and esmolol groups, respectively. Following anaesthesia induction, MAP values decreased by 2.6% in the 276 patients of the placebo groups and by 10.1% in the 454 patients in the groups treated with esmolol. After LTI, MAP increased by 21.4% in the patients of the placebo groups compared to 10.6% in the esmolol patient groups.

HR was evaluated in 36 studies (Table 1) that had included 626 patients in placebo groups and 930 patients treated with esmolol. The mean baseline values of HR were 77.7 bpm (range 58–103) (22, 34) and 78.1 bpm (range 64–111) (22, 34) for the placebo and esmolol groups, respectively. After anaesthetic induction,

Table 2

Percentage change relative to baseline. Comparison between studies with and without additional opiate administration.

	Placebo		Esmolol	
	With opiate %	Without opiates %	With opiate %	Without opiates %
SBP decrease	−8.4	−5.8	−16	−13.5
SBP increase	19.6	32.2	4.5	13.3
DBP decrease	−7.7	−1.3	−11.4	−9.2
DBP increase	26.4	45.6	13.4	33.7
MAP decrease	−5.5	2.1	−11.6	−7.8
MAP increase	17.4	31.2	6.7	19.6
HR decrease	2.7	11.9	−9.4	0.1
HR increase	22.6	39.2	4.5	15.4

References of studies included in the analyses:
With opiates: SBP=14, 15, 26–31, 38, 42, 49, 51; DBP=14, 15, 28, 29, 31, 42, 51; MAP=14, 20, 22, 32, 34–37, 42, 49; HR=14, 15, 20, 22, 26–32, 34–38, 42, 49, 51.
Without opiates: SBP=16, 18, 19, 23, 24, 33, 39–41, 43, 45, 48, 50; DBP=18, 24, 40, 45, 47; MAP=24, 33, 39, 40, 44, 47; HR=16, 18, 19, 23, 24, 33, 40, 41, 43–48, 50.

the minimum value of HR for the placebo groups was higher than the baseline value by 7.2% while, for the esmolol group, the minimum value was 4.2% lower than the baseline value. LTI occasioned an increase in HR of 29.6% in the patients of the placebo groups compared to 9.3% in the patients treated with esmolol.

In six of the 38 studies, patients with CAD or with elevated cardiovascular disease risk had been included (16, 17, 22, 35–37). The percentage change in HR relative to baseline values in the patients of both groups (esmolol and placebo) in these studies were similar to those observed in the rest of the studies (minimum value: esmolol=−2% and placebo=+4.8%; maximum value: esmolol=+6.7% and placebo=+23%).

Table 2 contains the percentage changes in the different variables in the 19 studies in which opiates had been administered either as pre-medication or during the induction period [esmolol n=526; placebo n=316] (14, 15, 20, 26–32, 34–38, 42, 49, 51) compared to the 16 studies [esmolol n=368; placebo n=285] (16, 18, 23, 24, 33, 39–41, 43–48, 50) in which the patients did not receive opiates. Two studies were excluded (17, 21) because the administered opiates had not been a systematic aspect of the study protocol. In nine studies the effectiveness of esmolol 100 mg (n=149) was compared with the 200 mg dose (n=145) (18, 20, 25, 38, 40–43, 50). Table 3 summarises the baseline values of SBP, DBP and HR and the corresponding percentage changes.

With respect to the administration of esmolol "before or after" the induction agents, no significant differences were observed between the two alternatives with respect to any of the variables assessed.

Sub-group meta-analyses

Tables 4 and 5 contain the results of each of the meta-analyses comparing: 1) the minimum values observed following the administration of esmolol or placebo (WMD decrease); and 2) the maximum values of both groups after the intubation procedure (WMD increase). There were no differences between the baseline values of the placebo and the esmolol groups with the exception of the meta-analysis that compared DBP between esmolol 200 mg and placebo. The baseline values of the patients of the placebo groups were observed to be higher ($P=0.01$).

The best results for the control of HR after LTI were obtained with a loading dose of 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over 4 min and continued with an infusion of 200–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$. With this schedule, HR decreased by 20.2 beats per min (95% CI: 15.6 to 24.7) compared with placebo (Table 4). The greatest decreases in blood pressure before LTI were observed (Table 5) with the bolus dose of 200 mg [SBP: 18 mmHg (95% CI=14.4 to 21.5); MAP: 10.2 mmHg (95% CI=3.1 to 17.2) and DBP: 10.1 mmHg (95% CI=7.3 to 12.8)].

When the studies comparing doses of 100 vs 200 mg were assessed, the values of all the variables were, as can be expected, lower following the administration of the higher dose ($P<0.01$). Hence, the benefit ob-

Table 3

Percentage change relative to baseline values. Comparison between 100 mg and 200 mg doses of esmolol.

	Systolic blood pressure		Diastolic blood pressure		Heart rate	
Dose (mg)	100	200	100	200	100	200
Patients (n)	105	104	64	61	125	124
Baseline values	138.4 mmHg	139.6 mmHg	77.5 mmHg	77 mmHg	78 bpm	72.2 bpm
Decrease from baseline (%)	−12.1	−16.7	−7.5	−12.5	2.2	−0.6
Increase from baseline (%)	18.1	13.3	32.2	20.5	17.4	10.6
N° of studies (References)	7 (18, 38, 40–43, 50)		4 (18, 20, 40, 41)		8 (18, 20, 38, 40–43, 50)	

Table 4

Pooled analyses of different doses of esmolol and administration regimens versus placebo: heart rate evaluation.

Dose and mode of administration	Time of measurement[a]	Method[b]	Z value	*P* value	WMD (95% CI)[c] beats per minute	References
100 mg (bolus)	Before LTI	F	4.6	0.00001	−6.4 (−9.1; −3.6)	18,20,38,40–43,50
	After LTI	R	4.97	0.00001	−13.7 (−19.1; −8.3)	
200 mg (bolus)	Before LTI	R	4.74	0.00001	−8.5 (−12; −5)	18,20,29,34,35,38,40–43,50
	After LTI	R	8.07	0.00001	−18 (−22.4; −13.6)	
1 mg/kg (bolus)	Before LTI	F	2.93	0.003	−6.5 (−10.9; 2.2)	14,21,26
	After LTI	R	2.96	0.003	−12 (−19.9; −4)	
1.5 mg/kg (bolus)	Before LTI	R	1.24	0.2	−6.2 (−16.1; 3.6)	32,34,35,45
	After LTI	R	2.57	0.01	−11.2 (−19.8; −2.7)	
2 mg/kg (bolus)	Before LTI	F	4.14	0.00004	−7.4 (−10.9; −3.9)	19,26,28,29
	After LTI	F	7.81	0.00001	−17.8 (−22.2; 13.3)	
3 mg/kg (bolus)	Before LTI	R	1.43	0.15	−8.4 (−19.8; 3.1)	29,34,35
	After LTI	F	4.17	0.00003	−12.6 (−18.5; −6.6)	
500 μg/kg min (1 min) + continuous infusion of 100–300 μg/kg min	Before LTI	R	1.64	0.1	−13.4 (−29.4; 2.6)	15,37,51
	After LTI	R	4.09	0.00004	−19.3 (−28.6; −10.1)	
500 μg/kg min (2 min) + continuous infusion of 200–300 μg/kg min	Before LTI	R	1.95	0.05	−12.1 (−24.3; 0.1)	22,36,48,51
	After LTI	R	3.81	0.00001	−14.6 (−22.1; −7.1)	
500 μg/kg min (4 min) + continuous infusion of 200–300 μg/kg min	Before LTI	F	6.28	0.00001	−16.5 (−21.7; −11.4)	16,17,27,33,51
	After LTI	F	8.69	0.00001	−20.2 (−24.7; −15.6)	
1 mg (bolus) + continuous infusion of 200–300 μg/kg min	Before LTI	F	2.36	0.02	−5.1 (−9.3; −0.9)	24,30,31
	After LTI	R	2.87	0.004	−13.8 (−23.3; −4.8)	

[a] Before LTI=comparison of the minimum observed values between the esmolol and placebo groups before laryngoscopy and tracheal intubation; After LTI=comparison of the maximum observed values between the esmolol and placebo groups after laryngoscopy and tracheal intubation.
[b] Model of statistical analysis employed in each meta-analysis. F=fixed effect model; R=randomised effect model.
[c] WMD (95% CI)=Weighted mean difference (95% confidence interval) between esmolol and placebo.

tained from 200 mg with respect to the better control of HR following LTI (Fig. 1) would be counter-balanced by the prejudicial decrease in the BP values prior to LTI (Fig. 2).

Discussion

The principal characteristic of a beta-blocker is the negative chronotropic effect. The present study confirms, as expected, the capacity of esmolol to alleviate intubation-induced tachycardia and, as such, to diminish the risk of deleterious consequences on the myocardium. The increment of post-intubation HR was reduced from 29.6% in the placebo groups to 9.3% in the esmolol groups. It is known that tachycardia may impose more stress on the heart than do increases in BP (86), perhaps due to the dual effect of tachycardia in increasing myocardial oxygen consumption while decreasing the diastolic filling and diminishing the time for effective coronary flow (18). It is also known that the sum of tachycardia plus hypertension (rate-pressure product) correlates with global myocardial oxygen consumption and predisposes to an elevated risk of ischaemia in patients with CAD (87). In those patients with intra-cranial hypertension and poor cerebral compliance, an additional increase in BP could have disastrous consequences (9). In the studies analysed here, the effect of esmolol on HR is accompanied by a reduction in the BP values: SBP elevation decreasing from 26.3% to 9.1%, MAP from 21.4% to 10.6% and DBP from 34.2% to 22.8% in placebo vs esmolol groups, respectively.

In non-stimulated anaesthetised patients, administration of esmolol produces a clinically significant reduction in HR, MAP and cardiac output (88). These effects, added to the vasodilator effect of anaesthesia induction agents, produce a depression on haemodynamic variables which could precipitate myocardial ischaemia in susceptible patients (11). Esmolol, in combination with the different induction agents, provoked, in the period immediately pre-intubation, a dose-dependent decrease of 6.8% in DBP and of 10.1% in MAP, in comparison to 3.4% and 2.6% observed in the respective placebo groups. For example, with the bolus dose of 200 mg of esmolol, DBP had decreased, in absolute values, by 10.1 mmHg more than with placebo (Table 5). This important finding must be taken into consideration given that, in some patients, de-

pression of DBP may detrimentally affect myocardial blood flow.

Some authors maintain that better control of the adrenergic response to LTI could be achieved with a combination of a beta-blocking agent together with low doses of an opiate (19, 21, 83, 89). The efficacy of opiates *per se* in blocking cardiovascular responses to LTI, principally in the control of BP, has been demonstrated by several studies (19, 23, 90, 91). Hence, the administration of opiates (in others than the study groups) in trials in which the haemodynamic responses to LTI were evaluated constitute a bias and should be questioned. Nevertheless, in 19 of the 38 studies that we analysed, opiates were used as an integral part of the standard anaesthesia and had been employed without restrictions. In our study, each subgroup was assessed separately and we can corroborate that, in the studies in which opiates had been employed as premedication or in the induction of anaesthesia, the increments in SBP and HR elicited by LTI had been more attenuated while greater decreases in these values were observed in the post-induction period. (Table 2). In the studies in which esmolol had been used in the absence of opiates, the effectiveness of esmolol was noted not only in the control of tachycardia but also in the attenuation of the hypertensive response to the LTI.

Patients with known or suspected ischaemic heart disease are those who most need to be protected from the stresses of intubation (8). However, such individuals are least likely to be found in the control group of a prospective study assessing haemodynamic control during LTI (10). Hence, the efficacy of the different agents used with this objective would be extrapolated from studies assessing healthy patients. However, hypertensive patients, whether treated or not, show greater changes in arterial pressure than normotensive patients of the same age (7, 11) and the validity of such an extrapolation is certainly debatable (10, 92). The scarcity of studies evaluating patients with hypertension or with CAD precluded us sub-dividing this group of studies with respect to the dose of esmolol

Table 5

Pooled analyses of different doses and administration regimens of esmolol versus placebo: blood pressure evaluation.

Parameter	Doses and mode of administration	Time of measurement[a]	Method[b]	Z value	*P* value	WMD (95% CI)[c] mmHg	References
SBP	100 mg (bolus)	Before LTI	F	4.81	0.00001	−9.61 (−13.5; −5.7)	18,38,40–43,50
		After LTI	R	6.28	0.00001	−11.1 (−15.7; −6.5)	
	200 mg (bolus)	Before LTI	F	9.98	0.00001	−18 (−21.5; −14.4)	18,29,38,40–43,50
		After LTI	F	12.16	0.00001	−30.9 (−35.9; −25.9)	
	1 mg/kg (bolus)	Before LTI	R	1.17	0.2	4.9 (−3.3; 13.1)	14,21,26
		After LTI	F	0.87	0.4	4.1 (−5.2; 13.4)	
	2 mg/kg (bolus)	Before LTI	F	2.90	0.004	−7.4 (−12.4; −2.4)	19,26,28,29
		After LTI	R	2.44	0.01	−19.4 (−35.1; −3.8)	
	500 μg/kg min (4 min)+ continuous infusion of 200–300 μg/kg min	Before LTI	F	0.14	0.9	−0.5 (−8.2; 7.1)	16,17,27,33,51
		After LTI	F	5.38	0.00001	−26 (−35.3; −16.5)	
	1 mg (bolus) + continuous infusion of 200–300 μg/kg min	Before LTI	F	2.03	0.04	−6.2 (−12.2; −0.2)	24,30,31
		After LTI	R	1.84	0.07	−19.2 (−39.6; 1.2)	
DBP	100 mg (bolus)	Before LTI	F	3.90	0.0001	−5.4 (−8.1; −2.7)	18,40,41
		After LTI	R	2.14	0.03	−13.2 (−25.2; −1.1)	
	200 mg (bolus)	Before LTI	F	7.19	0.00001	−10.1 (−12.8; −7.3)	18,29,40,41
		After LTI	R	4.23	0.00002	−19.3 (−28.3; −10.4)	
MAP	100 mg (bolus)	Before LTI	F	4.77	0.00001	−6.5 (−9.1; −3.8)	20,40,41
		After LTI	R	2.81	0.005	−16.8 (−28.5; −5.1)	
	200 mg (bolus)	Before LTI	R	2.84	0.005	−10.2 (−17.2; −3.1)	20,34,35,40,41
		After LTI	R	4	0.00006	−19.4 (28.9; −9.9)	
	1.5 mg/kg (bolus)	Before LTI	F	0.65	0.5	−2.1 (−8.6; 4.3)	32,34,35
		After LTI	F	2.65	0.008	−10.7 (18.6; −2.8)	

[a] Before LTI=comparison of the minimum observed values between the esmolol and placebo groups before laryngoscopy and tracheal intubation; After LTI=comparison of the maximum observed values between the esmolol and placebo groups after laryngoscopy and tracheal intubation.

[b] Model of statistical analysis employed in each meta-analysis. F=fixed effect model; R=randomised effect model.

[c] WMD (95% CI)=Weighted mean difference (95% confidence interval) between esmolol and placebo.

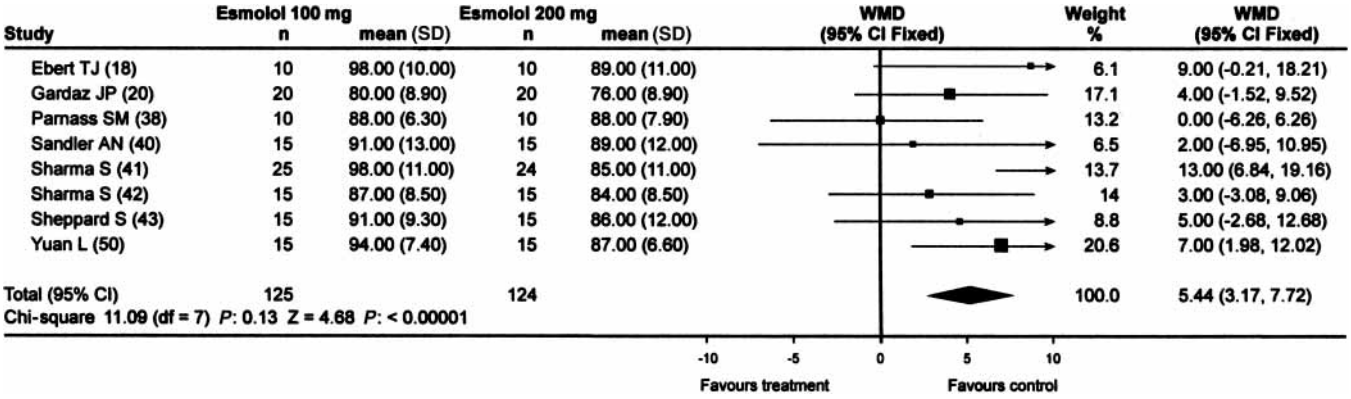

Fig. 1. Heart rate (beats per minute) after tracheal intubation. Weighted mean difference (95% confidence interval) between the groups treated with 100 mg and 200 mg of esmolol. Fixed effects model. Symbol sizes are proportional to the study weight. The ends of the horizontal line denote the 95% CI.

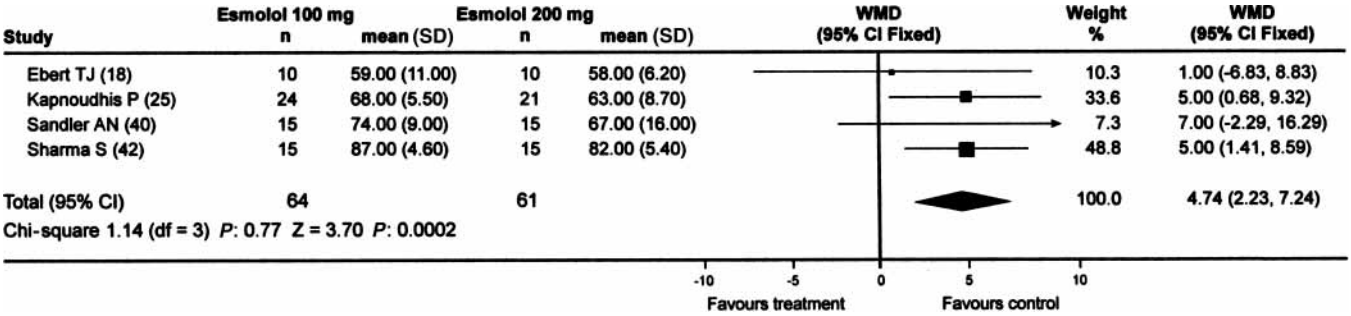

Fig. 2. Diastolic blood pressure (mmHg) prior to laryngoscopy. Weighted mean difference (95% confidence interval) between the groups treated with 100 mg and 200 mg of esmolol. Fixed effects model. Symbol sizes are proportional to the study weight. The ends of the horizontal line denote the 95% CI.

administered. Nevertheless, in the six studies (16, 17, 22, 35–37) that evaluated these types of patients, both the effectiveness of esmolol as well as the magnitude of adverse effects were not ostensibly different from those observed in studies with healthy patients.

Increase in HR of 20% above baseline (17) or an absolute value >100/110 beats/min (86, 93) and/or an increase in SBP (>180 mmHg) (19) may be associated with critical increases in myocardial oxygen consumption (17) and, in those patients with risk factors for CAD, may precipitate ischaemic changes (94) which have been associated with post-operative myocardial infarction (95). A few studies on esmolol have evaluated the incidence of ischaemia induced by intubation and the long-term post-operative repercussions (15, 18, 31, 36, 37, 47) but no clear cause–effect relationship can be deduced from them. In some esmolol studies other parameters of cardiac function (cardiac index, systemic vascular resistance, pulmonary artery capillary wedge pressure) have been investigated and the results have suggested that the use of esmolol be limited to those patients with ischaemic heart disease but with good left ventricular function, especially if borderline hypertension is present (37, 51). Healthy patients are not exempt from suffering myocardial ischaemia in situations of increased myocardial oxygen demand (96) but, due to their good adaptability to transient increases in HR and BP, these patients should be excluded from the preventive indications of esmolol (97).

To identify the optimum dose and mode of administration of esmolol, we hypothesised that the best option would be that which showed effectiveness in the attenuation in the values post-intubation ($P<0.05$) while minimising the differences, relative to placebo, in the post-induction values ($P>0.05$). Better results were obtained in blocking the adrenergic response using the higher dose of esmolol while, at the same time, taking on a higher risk of hypotension and bradycardia (q.v. 100 mg vs 200 mg; Fig. 1, 2 and Table 3). Curiously, the bolus dose of 1 $mg \cdot kg^{-1}$ did not result in an effective reduction in SBP. We would interpret this as being due to the study of Atlee et al. (14) (containing the greatest number of patients

within the respective meta-analysis) in which the baseline values of the placebo group (121.9 mmHg) were significantly lower than the baseline values of the esmolol group (142.8 mmHg), thus distorting the data and the interpretation of the results. From the respective meta-analyses (Tables 4 and 5) it can be deduced that the doses of 500 $\mu g \cdot kg^{-1}$ over a period of 1–4 min plus a continuous intravenous infusion of 200–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ are those that best conform to our above hypothesis. Some authors feel that the time required for preparation of an infusion may add a degree of complexity to the induction process (34, 40, 80, 83) but we believe that, in the prevention of an incident of high risk, the election of the best therapeutic option should not be influenced by aspects of convenience.

Given that tachycardia and hypertension are directly related to the duration of the laryngoscopy and the difficulty of intubation (4), an additional indication for the use of esmolol during the process of anaesthesia could be the prospect of a difficult intubation. In some studies the protective effect of a bolus dose of esmolol on the haemodynamic alterations has been observed to be fleeting (26, 80, 85). Hence, in circumstances under which an intubation could be of an unforeseeable duration, a continuous infusion of esmolol would be the appropriate choice. Conversely, for some of the indications in which esmolol is used as a treatment, a more rapid onset of action could be beneficial and a bolus dose would be advisable (98, 99).

Following a bolus administration of esmolol, the median time to peak effect on HR is 1 min and, for BP, 2 min (100). Consequently, for an effective response, the optimal dosing interval prior to intubation should be 2 min. Since the different anaesthetic techniques used were not directly comparable we were not able to determine whether esmolol in bolus dose ought to be administered before or after the anaesthetic induction. Jacque et al. (70) suggested that esmolol should be applied after the anaesthetic induction agents but, in their study, they had allowed a period of 4 min to elapse between the bolus dose of esmolol and the laryngoscopy. We believe that the optimum sequence of administration of the different drugs should be determined based on the knowledge of the pharmacokinetic properties of each of the agents used in the induction. The administration of esmolol by continuous infusion commencing before anaesthesia induction produces a constant plasma concentration and would resolve any such problem.

We admit that the present meta-analysis has important limitations that need to be taken into account in interpreting the results. The studies are difficult to compare because of variations in patient populations, premedications, induction regimens, additional use of opioids, doses and rates of injection of esmolol (and of the other drugs used in the induction of the anaesthesia), intervals between administration and laryngoscopy, duration of LTI manoeuvres and methods of data collection. Additionally, in the majority of the studies, the recorded measurements of BP were obtained using non-invasive techniques and at predetermined fixed times and, hence, the values recorded overestimate the minimum values and underestimate the maximum values reached. Further, we need to stress that the data from each study are the means of quantitative variables (with their respective standard deviations) which, in some patients, meant that these parameters could be, and were, very different from those stated.

We conclude that esmolol is an effective drug to block tachycardia and the SBP increase induced by airway manipulation. However, a dose-dependent risk of hypotension during the induction of anaesthesia is entailed and so its routine use in anaesthesia is not indicated. Its use in specific risk groups remains controversial (10) and, in groups in whom the risk–benefit is difficult to predict, usage needs to be evaluated on an individual basis. To diminish the incidence and seriousness of side-effects we would advise, for those patients in whom it is considered appropriate, the administration of a small loading dose (500 $\mu g \cdot kg^{-1}$) over 4 min followed by a continuous intravenous infusion of between 200 and 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Acknowledgements

We thank Drs JL Atlee, JW Johansen, and S Wang who responded to our enquiries and generously made their data available to us. We thank Dr Ana Soriano for her help in the search of data.

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Address:
Eduardo Figueredo
Ps. Palmeral, 1. Edf. Capri 6-C
Aguadulce
04720 Almería
Spain
e-mail: eduardofigueredo@hotmail.com