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Blood Pressure, Heart Rate and Arrhythmia Control in the Perioperative Setting by the Short-Acting Beta Blocker Esmolol – A Review

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ABSTRACT

Background: *Patients who undergo surgery, especially with preexisting high cardiovascular risk and high-risk surgery, are vulnerable for developing myocardial ischemia or tachyarrhythmias through sympathetic stimulation during anesthesia. Aim of this systematic review is a summary of the evidence from all randomized controlled trials on the efficacy and safety of the short acting β_1-selective adrenoreceptor blocker esmolol in the prevention and treatment of tachyarrhythmias and critical rises in blood pressure to avoid myocardial ischemia.*

Methods and Findings: *We examined the effect of esmolol in three different settings and included 5765 participants from 110 trials in our meta-analysis. We searched Medline, Embase, the Cochrane Library and hand-searched until January 2012 with an update through additionally search via PubMed to 2017 for articles published in English and German language. Esmolol reduces blood pressure and heart rate significantly in comparison to placebo with better effects in controlling heart rate than heart rhythm. In comparison to other active drugs there are no significant benefits for esmolol in lowering blood pressure, heart rate or control of rhythm. Adverse effects of esmolol as hypotension, bradycardia*

Conclusion: *Esmolol shows reduction in myocardial ischemia in patients with cardiac disease, and with respect to adverse effects and careful titration we recommend esmolol to prevent and treat crisis of blood pressure and heart rate. In healthy patients the perioperative use of esmolol or other active drugs need to document its beneficial effect, further studies are necessary.*

KEYWORDS: *esmolol; tachycardia; hypertension; beta(-)blocker; tachyarrhythmias*

INTRODUCTION

Surgery and perioperative anesthetic maneuvers like intubation and extubation stimulate sympathetic activity with the consequence of an increase in heart rate and blood pressure and – as result – of the risk of myocardial ischemia and supraventricular tachycardias like atrial fibrillation/flutter, especially in patients with preexisting heart disease. The stress of surgery and anesthesia may trigger this myocardial ischemia and these arrhythmias by an increase in myocardial oxygen demand, driven by the sympathetically mediated increase in heart rate and in blood pressure. From a pathophysiological rationale perioperative risk reduction can be achieved by suppressing the overshooting sympathetic tone by betablockers. Two approaches can be achieved to reach this goal:

a) The "preventive approach" is to continue betablocker medication in the perioperative setting in patients currently receiving this medication or to start preoperative betablocker medication in patients with myocardial ischemia, high cardiovascular risk load or scheduled for high-risk surgery.[1, 2]

b) The "therapeutic approach" is the acute treatment of hypertensive emergency, inadaequately high heart rate and supraventricular tachycardias in the perioperative arena by betablockers or other agents. Betablockers displace norepinephrine and epinephrine fromβ-adrenoreceptors of the heart, thereby attenuating the positive inotropic, chronotropic, bathmotropic and dromotropic effects of the sympathetic and endocrine stimulation.There are several critical stages in time, in which there are these strong hemodynamic changes triggered by the rise in sympathetic tone, depending on the type, duration and course of surgery and anesthesia. They include laryngoscopy, intubation, the first skin incision, the insertion of different surgical instruments, the transection of different anatomical structures (preparation) and other surgical stimuli.

In perioperative emergency situations, due to overshooting sympathetic activity, a short-acting betablocker for dampening of sympathetic activity would be the drug of choice from a pharmacokinetic point of view: the heart rate and blood pressure lowering effect starts immediately after intravenous application of the drug, plasma concentration is kept constant by titrated infusion of the beta blocker, and drug action ebbs away very quickly after stopping drug infusion.[3]

Esmololis such a fast-acting β_1-selective adrenoreceptor blocker with rapid onset within two minutes, a very short duration of action (elimination half-life:nine min, full recovery after 18 to 30 min), an effective controllability and no relevant adverse events at recommended therapeutic dosages.[4, 5]

This systematic review investigates the benefits and harms of esmolol in prevention and treatment of supraventricular tachyarrhythmias and critical rises in blood pressure during anesthesia and surgical interventions.

METHODS

Eligibility Criteria

Only randomized controlled trials (RCT) that evaluated efficacy and safety of esmolol were eligible for inclusion in this review. The review considered all trials in three different peri-operative settings:

1. Perioperative treatmentand emergency therapy of supraventricular tachyarrhythmias
2. Prevention and treatment of increased blood pressure during intubation and extubation
3. Prevention and treatment of increased blood pressure during surgery or interventions like electroconvulsive therapy

Systematic Search

We searched Medline, Embase and the Cochrane Library until January 2012for articles published in English and German language (appendix 1). We also searched in registries of on-going trials, hand-searched annual conference proceedings of cardiologic and anesthesia societies (2000-2012),contacted the manufacturer of esmolol (Baxter Germany GmbH) and scanned reference lists of eligible trials. We contacted first authors of eligible trials to obtain further information. In January2017 we updated our latest results up to 01.01.2017with an additionally search via PubMed.

Trial Selection, Classification of Strategies and Quality Assessment

All steps were done by at least two independent authors. We screened all trials identified using the search strategy by title, keywords and abstract and carefully read and discussed full-text versions of potential relevant trialswith respect toour inclusion criteria.

We extracted general information of all included trials, trial characteristics including trial design, timing and follow-up, information describing participants, intervention and primary and secondary outcomes per treatment group. Primary endpoints varied in the indications for esmolol use. The success of treatment with esmolol in emergency or perioperativetreatmentofsupraventriculartachyarrhythmias was measured either as decrease in frequency below 100bpm,as reduction in initial heart rate by about 20 %,oras conversion to sinus rhythm. This information was extracted and analyzed as primary endpoint. The control and decrease of high blood pressure was the main aim of the treatment with esmolol in participants under general anesthesia and generally during surgery. Therefore, in this setting systolic blood pressure or mean arterial pressure were used as primary endpoint.

Finally, we assessed the internal validity of eligible trials according to the Cochrane Collaboration risk of bias tool.[6] Disagreements were resolved by discussion until consensus was obtained. Risk of bias was judged as high, low or unclear in six specific domains. These domains describe bias in random sequence generation, allocation concealment, blinding of participants, physician and outcome assessors, documentation of incomplete outcome data with causes and selective reporting, baseline comparability between treatment groups and the frequency of cross-over. Publication bias was assessed visually using funnel plots.

Meta-Analysis

We used RevMan 5© for the meta-analysis. Effect measures are presented as relative risks (RRs) and mean difference (MD) with their 95 % confidence intervals (CI). Outcome was recorded so that a RR greater than one and negative MD indicated a beneficial effect with more successful control of supraventricular tachyarrhythmias or smaller rise in blood pressure in the treatment group with esmolol. If more than one measurement was reported, the treatment effects on the maximal increase were estimated. Intervention arms with different esmolol dosages and control arms with various other effective drugs were pooled.

We used the random-effects model for meta-analysis of the relevant trials. Statistical heterogeneity between trials was quantified into categories of small, moderate, substantial and considerable heterogeneity on the basis of an I^2 statistic.[6]We decided not to pool studies with considerable heterogeneity (I^2>60 %). In all of the three settings we differentiated the comparison of esmolol to placebo and to other effective drugs. Patients were allocated pursuant their different interventions specially modes of cardiac surgery or between cardiac healthy and pre-stressed participants.

RESULTS

Results of the Search

Having used the above search strategies to identify potentially

relevant articles, we identified a total of 1540 records and assessed 257 regarding in- and exclusion criteria. Of these, 221 trials met our pre-defined inclusion criteria. Altogether 16trials investigated esmolol for treatment of supraventricular tachyarrhythmias and tachycardias, 60trials during intubation or extubation in operative interventions and 52trials during surgical interventions. Altogether seven trials were used in more than one topic(figure 1).

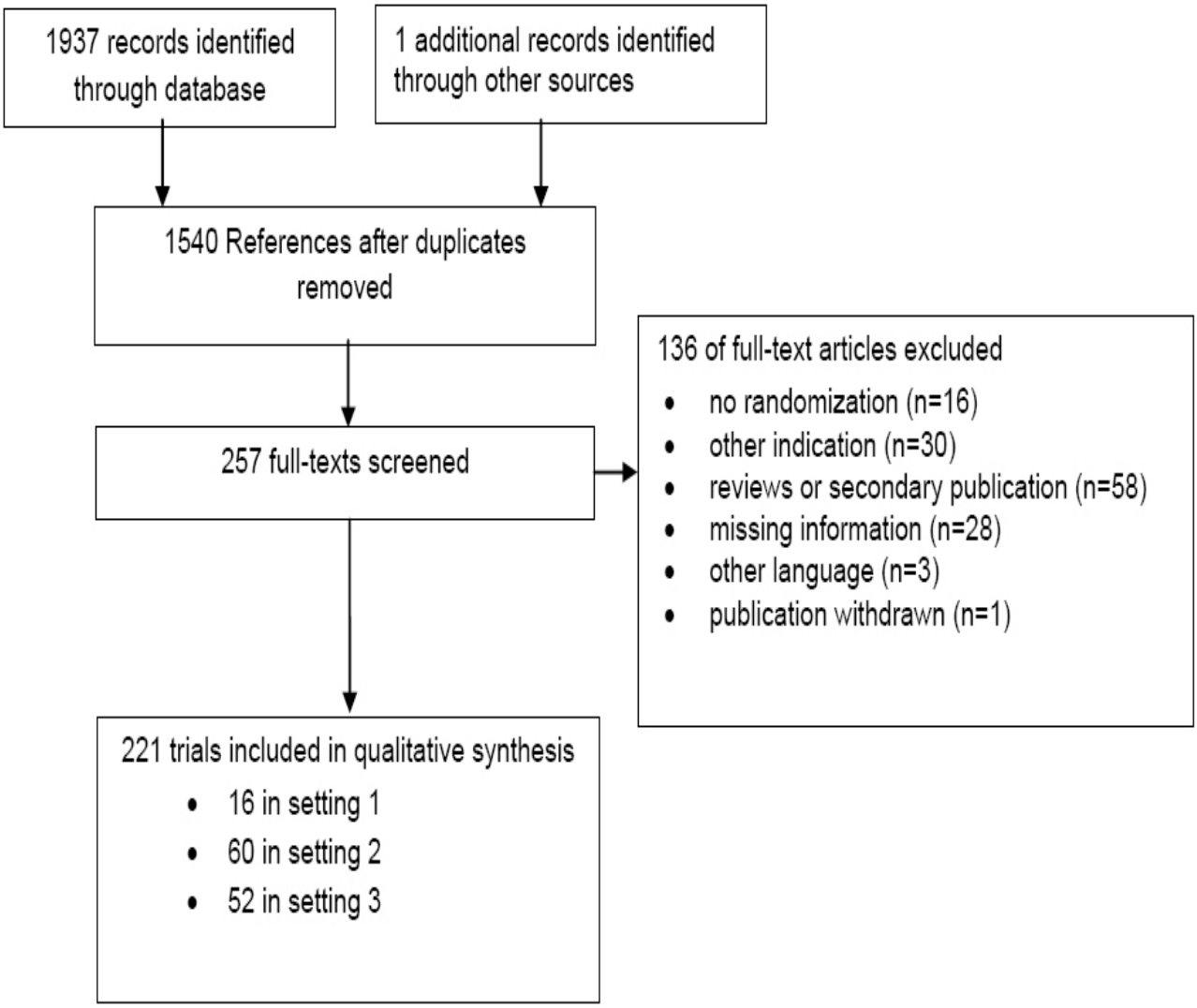

Figure 1. PRISMA flow chart

Included Trials

Altogether 16 trials evaluated the effect of esmolol for control and treatment of supraventricular tachyarrhythmias and tachycardia (setting one). Information on our pre-defined primary or secondary endpoints were available from 14 trials with a total of 692 participants. Altogether seven trials were exclusively performed in the intra- and postoperative setting, four trials describe the use of esmolol independent from the operative setting and threetrials included both. Only one trial included more than two treatment arms. Three trials were multicenter trials[7–9] and two trials used a cross-over design[7, 10].

Eight trials compared esmolol to placebo[7, 10–16], four to diltiazem[15, 17–19] and each one to propranolol[8], acebutolol[20], verapamil[9]or ibutilide-monotherapy[11]. Some trials included only participants with a trial fibrillation or a trial flutter[9, 11, 15, 18, 19], supraventricular tachyarrhythmias[7, 8, 10, 17] or intra- or postoperative tachycardia[12, 13, 13, 14, 16, 20]. Trials were mostly conducted in the USA, as well in Germany, Greece, England and India. All trials included only participants over 18 years with an average age of 60 years with a higher proportion of man (between 32 and 100 %).

Sixty trials evaluated the effect of esmolol under intubation or extubation during operative interventions (setting two). Of them,50trials with 3,446 participants reported information on the primary or secondary endpoint and were included into meta-analyses. Participants in 36 trials underwent elective surgery. The remaining 14 trials included a variety of surgeries (five with coronary artery bypass grafting). A total of 22 trials had three, nine[21–29] had four and one[30] had six treatment arms. Only one trial[31] was a multicenter trial.

Fourty-two trials compared esmolol to placebo and eight to opioids as alfentanil[32–34], local anaesthetic drugs as lidocaine[35–37], hypnotics as propofol[35], calcium channel blockers as nicardipine[38] or α_2-receptor-agonists as clonidine[32, 39]. Trials were predominantly conducted in Western Hemisphere (USA, Great Britain, Canada, Finland, Switzerland), ten trials were conducted in India, four in Turkey and two in Taiwan. The mean patient age varied between 15 and 85 years. Only two trials included participants under 18 years of age.[30,40] Altogether 51% of participants were male, two trials included only female [30,41] and two other trials only male participants[12,28]. ASA (American Society of An anesthesiologists) scores varied from ASA I/II in 31trials (62%) and ASA III/IV[42, 43] in 12 studies (24%) due to differences in inclusion and exclusion criteria.

Fifty-two trials investigated the efficacy of esmolol during surgical interventions (setting three) and 46 trials of them which included 1,627 patients were included in meta-analyses. A total of 16 trials[13, 14, 20, 43–55] including 486 participants with cardiac surgeries and 21 trials including 929 participants with another surgical procedure were performed[12, 16, 56–74]. Of them, , four trials[57, 59, 60, 63] with 104 participants were performed having a forced controlled hypotension during the surgical procedure and 212 participants in nine trials underwent electroconvulsive therapy.[75–83] Totally 36 trials were carried out with a parallel-group design and ten trials used a cross-over design. In 14 trials, there were more than two treatment arms. Only one trial was a multi-center trial.[62]

In the subgroup of cardiac surgery, eleven trials[13, 14, 43, 45–47, 49–52, 55] compared an intervention group with esmolol to placebo, three [44, 48, 54] to sodium nitroprusside, one [53] to diltiazem, and one[20] to acebutolol. In terms of non cardiac surgeries, ten trials[12, 16, 56, 58, 66–68, 70, 72, 74] compared an intervention group with esmolol to placebo, two trials respectively to labetalol[61, 65] or sodium nitroprusside,[62, 73] and one trial each to atenolol[73], remifentanil[69], alfentanil[64], thiopental[64], xylocaine[64], magnesium sulfate[67], lidocaine[67], dexmedetomidine[71] and nitroglycerine[67]. In the non-cardiac surgeries with controlled hypotension, participants with esmolol were compared to sodium nitroprusside[57, 59, 60, 63] or isoflurane[59]. Participants with electroconvulsive therapy received during electroconvulsive therapy sessions either esmolol vs. placebo[75–78, 81–83], labetalol[80, 81, 83], fentanyl[81], lidocaine[81] or nitroglycerine[78]. Most trials were conducted in USA, Germany, Canada, Finland and Spain. The range of age of participants with cardiac surgery varied between 18 and 68 years, participants with non-cardiac surgery were between 25 and 78 years of age, participants with electroconvulsive therapy were older, with ages between 42 and 73 years. Participants with non-cardiac surgery with controlled hypotension had the lowest age between 22 and 42 years, which is probably due to the increased risk of complications in a forced hypotension during surgery. In only four trials[54, 55, 60, 74] children (two months to 18 years) were included in the trial and only one trial[71] defined a maximum age of 60 years. Only 20 trials provide information on gender distribution. Altogether 76 % of participants in the included trials on cardiac surgery were male, 5 3% in non-cardiac surgery, 34 % in electroconvulsive therapy and 55 % in non-cardiac operations with controlled hypotension. One trial included only female participants during gynecological procedures[70].

Risk of Bias in included Trials

In only 16 of the 221 trials, the method of randomization was reported in the text. Treatment allocation of clusters or participants was described as concealed in 22 trials. A total of 73 trials were double-blinded, outcome assessment was blinded in eight additional trials. In 97 trials, the analysis was done by intention-to-treat. Total numbers of drop-outs were low (<10 %) and their causes were given per group. Pre-planned primary endpoints were adequately reported in 18 trials. Other Risk of bias was evident in 66 trials. These sources of bias included the intake of other interventions that may influence the effect of esmolol as additional antihypertensive or an aesthetic drugs[8, 9, 17, 18, 21, 23, 31, 32, 34, 55, 74, 84–88] or long-term medication[12, 23, 31, 36, 42, 89]. Most included trials were conducted as single-center trials with less than 20 participants per intervention group. Especially in trials published before the CONSORT statement[90] demographic and clinical characteristics of participants were not adequately described.

Effects of Intervention

Perioperative treatment and emergency therapy of supraventricular tachyarrhythmias

In comparison to placebo four trials[7, 10, 11, 15], including a total of 197 participants, showed a higher rate of successful conversion to sinus rhythm with esmolol (Risk Ratio (RR) 1.24; 95 % CI 0.76 to 2.03) with moderate heterogeneity between treatment effects of individual trials (I^2=40%) (figure 2). Two trials[7, 10] with 79 participants demonstrated a higher success rate on the combined outcome (conversion to sinus rhythm or decreased heart rate) with esmolol compared to placebo (RR 12.37; 95 % CI 3.67 to 41.64).

Another group of six trials[8, 9, 15, 17–19] (322 participants) documented a non-significant benefit of esmolol in comparison to other effective drugs with more successful conversions and one trial[8] stated no relevant difference between esmolol and propranolol (table 1). Two[9, 18] of the mentioned six trials reported absolute values. Esmolol reduced heart rate from 134±19 bpm to 91±14 bpm compared to diltiazem with a reduction from 144±17 bpm to 79±9 bpm.[18] In comparison to verapamil with reductions from 142±4 bpm to 98±3 bpm, heart rate in the esmolol group decreased from 139±4 bpm to 106±3 bpm.[9]

Table 1. Conversion to sinus rhythm and combined endpoint conversion to sinus rhythm or decreased heart rate (bpm) with subgroup analyses for the comparison of esmolol vs. other drugs.*CI – Confidence Interval*

Study	Comparative drug	Esmolol		Control (comparative drug)		Risk Ratio
1.1 conversion to sinus rhythm		events	total	events	total	Mantel-Haenszel, Random, 95% CI
Balser 1998	diltiazem	20	34	10	30	1.76 [0.99, 3.15]
Hassan 2007	diltiazem	10	26	10	24	0.92 [0.47, 1.82]
Mooss 2000	diltiazem	12	15	10	15	1.20 [0.77, 1.86]
Morganroth 1985	propranolol	7	50	9	55	0.86 [0.34, 2.16]
Platia 1989	verapamil	7	21	2	24	4.00 [0.93, 17.19]
Sticherling 2002	diltiazem	10	15	3	13	2.89 [1.01, 8.30]
Subtotal (95% CI)		**66**	**161**	**44**	**161**	**1.40 [0.96, 2.03]**
1.2 conversion to sinus rhythm or decreased heart rate						
Morganroth 1985	propranolol	36	50	38	55	1.04 [0.81, 1.33]
Total (95% CI)		**102**	**211**	**82**	**216**	**1.27 [0.95, 1.70]**

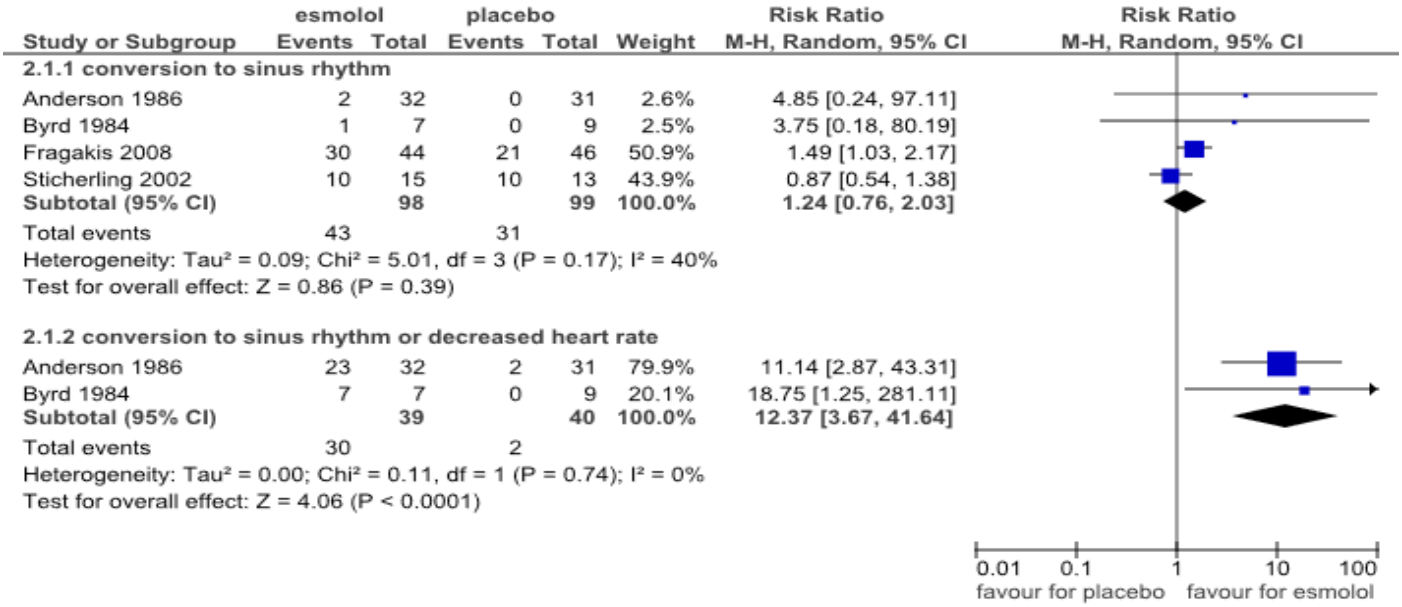

Figure 2. Conversion to sinus rhythm and combined endpoint (conversion to sinus rhythm or decreased heart rate) by esmolol vs. placebo in perioperative treatment and emergency therapy of supraventricular tachyarrhythmias

Prevention and treatment of increased blood pressure under general anesthesia during intubation and extubation_

Summarizing treatment effects on MAP of seven trials including 301 participants during intubation[21, 28, 41, 87, 91–93]resulted in a lowering of the maximal MAP by 10.1 mmHg (95 %CI 4.8 to 15.4) with esmolol compared to placebo with substantial heterogeneity (I^2=56 %) (figure 3). Two[92, 93] of the trails showed a change in absolute values. MAP decreased after administered study drug (before laryngoscopy) from 88±12 mmHg to 77±14 mmHg[92]and from 100±11 mmHg to 76±18 mmHg[93]by esmolol compared to placebo with reduction from 86±14 mmHg to 79±15 mmHg[92] and 94±11 mmHg to 73±12 mmHg[93].

However, four additional trials[32, 34, 37, 39] with 242 participants compared esmolol to other effective drugs as alfentanil and/or clonidine or lidocaine and stated a higher maximal MAP during intubation in patients treated with esmolol (Mean Difference (MD)19.2 mmHg; 95 % CI 4.8 to33.7) (table 2).

A total of 30 trials investigated the efficacy of esmolol on SBP and differentiated between cardiac healthy and cardiac pre-stressed (patients with cardiac disease, high ASA classification, cardiac surgery) participants. Of them, 19 trials with 795cardiac healthy participants demonstrated a clinically relevant lower maximal SBP (MD 18.3 mmHg; 95 % CI 13.7 to 23.0) with esmolol compared to placebo. This result was stated in 12 trials with 1,121 cardiac pre-stressed participants with a MD of 22 mmHg (95 % CI 15.1 to 28.9) (table 3).One trial[31] in this group described a decrease of

maximal SBP by 13±3 mmHg through 100 mg esmolol and by 23±3 mmHg through 200 mg esmolol compared to placebo without any significant change. There is uncertainty on the hemodynamic effects of esmolol compared to lidocaineand alfentanil (table 4).

Esmolol attenuated the rise ofMAP during extubation compared to placebo in two studies[86, 94] with 75 participants (MD -8.1 mmHg (95%CI -18.7 to 2.54) (figure 3) but not significantly. In additional five trials trials[35, 38, 95–97]investigated the rise of SBP during extubation. Three trials[95–97] of them with 210 participants, esmolol lowered - compared to placebo- maximal SBP after extubation by 14.7 mmHg (95% CI 0.2 to 29.3) (table 5). With respect to lowering of SBP during extubation, no significant difference in the effect of esmolol in comparison to lidocaine, propofol and lidocaine is seen (table 5).

Table 2. Maximum of mean blood pressure (MAP) (mmHg) with subgroup analyses for the comparison of esmolol vs. other effective drugs during intubation (IT).*IV- Inverse Variance*; *CI – Confidence Interval*

Study	Comparative drug	Esmolol			Control (comparative drug)			Mean Difference
2.1 MAP during ITN		Mean	SD	total	Mean	SD	total	IV, Random, 95% CI
Fernandez-Galinsky 2004	alfentanil+clonidine	114.1	27.6	16	93.1	17.8	29	21.00 [6.00, 36.00]
Rajbhandar 2014	lidocaine	118.1	18.2	30	116.1	14.6	30	2.00 [-6.35, 10.35]
Smith 1991	alfentanil	115	25	47	88	12.7	50	27.00 [19.03, 34.97]
Zalunardo	clonidine	133	28	20	104	22	20	29.00 [13.39, 44.61]
Total (95% CI)				**113**			**129**	**19.24 [4.79, 33,69]**

Table 3. Maximum of systolic blood pressure (mm Hg) during intubation in cardiac healthy and in cardiac pre-stressed participants, with subgroup analyses for comparison of esmolol vs. placebo. *IV- Inverse Variance*; *CI – Confidence Interval*

Study	Esmolol			Placebo			Mean Difference
3.1 cardiac healthy	Mean	SD	total	Mean	SD	total	IV, Random, 95%CI
Campagni 1999	134	27	15	139	24	13	-5.00 [-23.89, 13.89]
Ebert 1990	161.7	24.8	20	189	15.4	12	-27.30 [-41.23, -13.37]
Feng 1996	155	26.8	20	196	26.8	20	-41.00 [-57.61, -24.39]
Gong 1999	147	25	11	160	30	12	-13.00 [-35.50, 9.50]
Gupta 2009	148.3	10.2	20	167.9	9.6	20	-19.60 [-25.74, -13.46]
Kar 1998	139.3	19.1	20	161.4	20.7	20	-22.10 [-34.44, -9.76]
Kindler 1996	130.5	17.5	30	133	23.2	15	-2.50 [-15.81, 10.81]
Korpinen 1995	158.6	19.1	29	176.7	12.9	15	-18.10 [-27.64, -8.56]
Korpinen 1995a	151	17.2	15	177.8	28	15	-26.80 [-43.43, -10.17]
Levit 2001	151.1	8.9	16	155.6	17.8	14	-4.50 [-14.79, 5.79]
Rathore 2002	155.1	18.8	75	162.5	24.5	25	-7.40 [-17.90, 3.10]
Sharma 1995	158.2	21.3	49	175	18.2	24	-16.80 [-26.21, -7.39]
Sheppard 1990	153	20.8	30	170	19.5	14	-17.00 [-29.64, -4.36]
Singh 2010	158.7	16.8	25	162.4	14.3	25	-3.70 [-12.35, 4.95]
Thompson 1997	140.9	24	10	180	24	10	-39.10 [-60.14, -18.06]
Venkatesha 2002	135.5	6.9	17	150	14	15	-14.50 [-22.31, -6.69]
Vucevic 1992	151	18	15	188	23	15	-37.00 [-51.78, -22.22]
Yuan 1994	159.5	19.4	30	188	15.5	15	-28.50 [-38.97, -18.03]
Zargar 2002	139.2	19.1	20	161.4	20.7	20	-22.20 [-34.54, -9.86]
Subtotal (95% CI)			**467**			**319**	**-18.33 [-22.99, -13.68]**
3.2 cardiac pre-stressed							
Atlee 2000	160.7	31.1	34	148.5	28.7	35	12.20 [-1.93, 26.33]
Cucchiara 1986	189.5	44.7	36	220	43.2	37	-30.50 [-50.67, -10.33]
Ebert 1989	161.5	32.2	20	186.6	42.9	20	-25.10 [-48.61, -1.59]
Gold 1989	128	19.4	15	145	34.9	15	-17.00 [-37.21, 3.21]
Harrison 1987	134.6	12.8	15	136.1	24	15	-1.50 [-15.26, 12.26]

Helfman 1991	153	22.4	20	176	22.4	20	-23.00 [-36.88, -9.12]
Louizoz 2007	119.4	11.5	109	147	20	53	-27.60 [-33.40, -21.80]
Miller 1991	150	50	368	167.8	70.3	180	-17.80 [-29.27, -6.33]
O' Dwyer 1993	119.3	21.2	7	164.7	30.4	7	-45.40 [-72.86, -17.94]
Parnass 1990	164	8.6	20	200	4	10	-36.00 [-40.51, -31.49]
Sharma 1996	140.2	8.9	30	173.2	12.4	15	-33.00 [-40.04, -25.96]
Sharma 2006	132.8	3.7	20	154.1	6.2	20	-21.30 [-24.46, -18.14]
Subtotal (95% CI)			**694**			**427**	**-21.96 [-28.81, -15.11]**
Total (95% CI)			**1161**			**746**	**-19.84 [-23.97, -15.72]**

Table 4. Maximum of systolic blood pressure (mm Hg) in cardiac healthy and in cardiac pre-stressed participants with subgroup analyses for comparison of esmolol vs. other effective drugs during intubation.*IV- Inverse Variance*; *CI – Confidence Interval*

Study	Esmolol			Lidocaine			Mean Difference
4.1 cardiac healthy	Mean	SD	total	Mean	SD	total	IV, Random, 95%CI
Levit 2001	151.1	8.9	16	155.6	17.8	14	-4.50 [-14.79, 5.79]
4.2 cardiac pre-stressed	**Esmolol**			**Alfentanil**			
Maguire 2001	154	30	20	140	28	20	14.00 [-3.98, 31.98]
Total (95% CI)			36			34	3.22 [-14.66, 21.10]

Table 5. Maximum of systolic blood pressure (mmHg)with subgroup analyses for the comparison of esmolol vs. placebo and esmolol vs. other effective drugs during extubation (ET).*IV- Inverse Variance*; *CI – Confidence Interval*

Study	Comparative drug	Esmolol			Control (comparative drug)			Mean Difference
5.1 SBP during ET		Mean	SD	total	Mean	SD	total	IV, Random, 95% CI
Arar 2007	placebo	144.3	18.1	40	166.7	17.2	40	-22.40 [-30.14, -14.66]
Kurian 2001	placebo	115	3.89	31	119.1	3.3	37	-4.10 [-5.83, -2.37]
Schäffer 1994	placebo	160.2	25.5	40	180	30.4	22	-19.80 [-34.76, -4.84]
Subtotal (95% CI)				**111**			**99**	**-14.71 [-29.25, -0.17]**
Chhabra 2003	lidocaine + propofol	133	17.6	30	138.4	16	60	-5.40 [-12.89, 2.09]
Kovac 2007	nicardipine	147.5	24.9	11	140	16.6	11	7.50 [-10.18, 25.18]
Total (95% CI)				**152**			**170**	**-9.38 [-18.16, -0.60]**

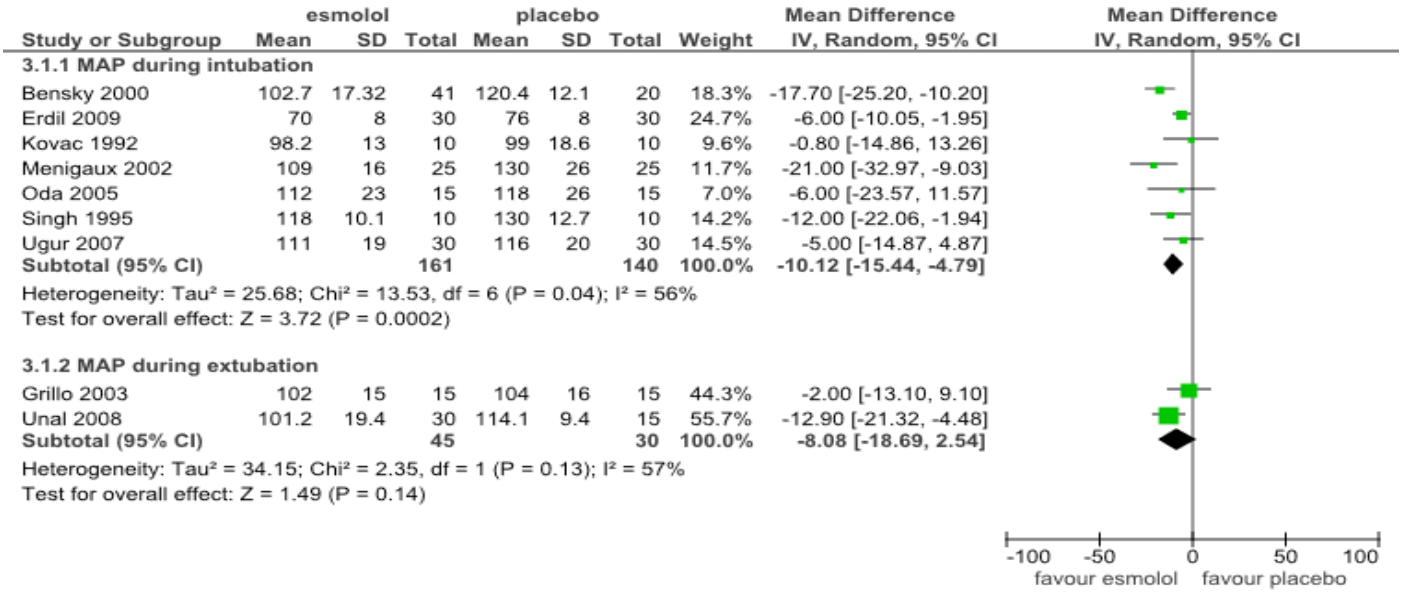

Figure 3. Maximalmean blood pressure (MAP) (mmHg) for the comparison of esmolol vs. placebo during intubation and extubation

Prevention and treatment of increased blood pressure during surgery or surgery like interventions

The efficacy of esmolol was compared during cardiac and non-cardiac surgeries, non-cardiac surgery with controlled hypotension and electroconvulsive therapy in46trialswith a total of1,647participants.

During cardiac surgery, eight trials[45–47, 49–52] with 241 participants stated lower maximal MAP values with esmolol compared to placebo (MD -4.1 mmHg; 95 % CI -7.1 to -1.0). There is uncertainty whether esmolol is more efficient than other effective drugs as diltiazem or acebutolol[20, 53](table 6).

A total of fourtrials[13, 14, 43, 47]with 130participants having cardiac surgery predominantly showed a lower maximal SBP in the esmolol group in comparison to the placebo group with considerable heterogeneity between groups. Three additional trials[44, 48, 54]with 75 participants having cardiac surgery stated a small, clinically non-relevant benefit between patients treated with esmolol and sodium nitroprusside (table 7).

During non-cardiac surgery, six trials[56, 58, 67, 68, 70, 74] with 290 participants demonstrated considerable heterogenic treatment effects on maximal MAP between esmolol and placebo (MD -11.8 mmHg; 95 % CI -23.9 to 0.34)with considerable heterogeneity between trials (I^2=95 %). Five trials[62, 64, 67, 71, 73], including a total of 292 participants, compared esmolol to other effective drugs with similar maximal MAP (MD 1.8 mmHg; 95 %CI 0.3 to 3.3) (table 6).

Seventrialswith263participantscompared the efficacy of esmolol with placebo on them aximal SBP[12, 16, 58, 65–67, 72]and demonstrated clinically relevant advantages of esmolol with substantial heterogeneity between trials (I^2=91%) (table 7). Finally, five trials[61, 64, 65, 67, 69] including 215 participants stated no clinically relevant differences between esmolol and other effective drugs on maximal SBP (MD 2.1 mmHg; 95 % CI -1.4 to 5.7) (table 7).

During non-cardiac surgery with controlled hypotension, four trials including 104 participants[75–77,79,82]stated comparable effects on maximal MAP values between esmolol and other effective treatment (MD -0.46 mmHg; 95 % CI -3.2 to 2.3) with substantial heterogeneity between trials (I^2=65 %). Three trials[57, 59, 63] with 74 participants compared the efficacy of esmolol with other effective drugs and showed lower maximal SBP (MD -3.8 mmHg; 95 % CI -6.9 to -0.7) by esmolol with small heterogeneity between trials (I^2=0 %) (table 7). During electroconvulsive therapy, eight trials[75, 77–83] with 371 participants demonstrated clinically relevant lower SBP under esmolol compared to placebo with considerable heterogeneity between trials (I^2=87 %). No relevant differences were found in four trials[78, 80, 81, 83] with 192 participants in comparison of esmolol with other effective drugs (MD 2.7 mmHg; 95 % CI -3.1 to 8.5) (table7).

Table 6. Maximum of mean blood pressure (mmHg)with subgroup analyses for the comparison of esmolol vs. other effective drugs during cardiac and non-cardiac surgery and during electroconvulsive therapy. *IV- Inverse Variance*; *CI – Confidence Interval*

Study	Comperative drug	Esmolol			Control (comperative drug)			Mean Difference
6.1 cardiac surgery		Mean	SD	total	Mean	SD	total	IV, Random, 95% CI
Chauhan 1999	diltiamzem	113	14	30	98	16	30	15.00 [7.39, 22.61]
Kling 1990	acebutolol	74	10	10	82	16	10	-8.00 [-19.69, 3.69]
Subtotal (95% CI)				**40**			**40**	**3.95 [-18.58, 26.47]**
6.2 non- cardiac surgery		Mean	SD	total	Mean	SD	total	IV, Random, 95% CI
Amr 2011	natriumnitro-prussid+ atenolol	69	0.6	24	66	0.4	24	3.00 [2.71, 3.29]
Doblar 1996	alfentanil+ thiopental+ xylocaine	99	18.97	10	103	16.43	30	-4.00 [-17.15, 9.15]
Kol 2009	dexmede-tomidin	65	5	35	63.75	3.21	70	1.25 [-0.57, 3.07]
Shah 1993	natriumnitro-prussid	59	2	10	58	4	9	1.00 [-1.89, 3.89]
van de Berg 1997	magnesium-sulfate+ lidocaine+ nitro-gycerine	85	9	20	86.67	19.05	60	-1.67 [-7.90, 4.56]
Subtotal (95% CI)				**99**			**193**	**1.80 [0.26, 3.34]**
Total (95% CI)				**139**			**233**	**1.97 [-0.31, 4.24]**

Table 7. Maximum of systolic blood pressure (mmHg)with subgroup analyses for the comparison of esmolol vs. placebo and esmolol vs. other effective drugs during cardiac and non-cardiac surgery and during electroconvulsive therapy.IV- Inverse Variance; CI – Confidence Interval

Study	**Comperative drug**	**Esmolol**			**Control (comperativedrug)**			**Mean Difference**
7.1 cardiacsurgery		Mean	SD	total	Mean	SD	total	IV, Random, 95% CI
de Bruijn 1987	placebo	115	18	19	171	31	21	-56.00 [-71.53, -40.47]
Harrison1987	placebo	110.5	10.45	15	110.1	11.62	15	0.40 [-7.51, 8.31]
Reves 1990	placebo	134	15	16	139	21	14	-5.00 [-18.23, 8.23]
Tempe 1999	placebo	124	10	15	138	7	15	-14.00 [-20.18, -7.82]
Dittrich 2003	natriumnitro-prussid	130.5	33.87	6	144.29	29.17	5	-13.79 [-51.05, 23.47]
Gray 1985	natriumnitro-prussid	136	14	12	141	15	12	-5.00 [-16.61, 6.61]
Gray 1987	natriumnitro-prussid	136	12	20	141	13	20	-5.00 [-12.75, 2.75]
Total (95% CI)				**103**			**102**	**-13.02 [-23.96, -2.07]**
7.2 non-cardiacsurgery		Mean	SD	total	Mean	SD	total	IV, Random, 95% CI
Ayuso 1997	placebo	83	23	10	164	20	10	-81.00 [-99.89, -62.11]
Gold 1989	placebo	117	23.24	15	130	19.36	15	-13.00 [-28.31, 2.31]
Korpinen 1997	placebo	113	13.42	20	117	17.89	20	-4.00 [-13.80, 5.80]
Korpinen 1998	placebo	101	13.42	20	111	17.89	20	-10.00 [-19.80, -0.20]
Sandler 1990	placebo	192	26.68	30	217	30	15	-25.00 [-42.93, -7.07]
van de Berg 1997	placebo	115	11	20	111	21	20	4.00 [-6.39, 14.39]
Whirley-Diaz 1991	placebo	123.67	22.57	33	137	15.49	15	-13.33 [-24.32, -2.34]
Ayuso 1997	labetalol	83	23	10	102	29	10	-19.00 [-41.94, 3.94]
Coloma 2001	remifentanil	106	10	27	101	7.5	26	5.00 [0.25, 9.75]
Doblar 1996	alfentanil+ thiopental+ xylocaine	139	25.3	10	144.67	21.98	30	-5.67 [-23.21, 11.87]
Singh 1992	labetalol	171	3.4	11	169	4.7	11	2.00 [-1.43, 5.43]
van de Berg 1997	magnesium-sulfate+ lidocaine+ nitro-gycerine	115	11	20	113.33	26.44	60	1.67 [-6.58, 9.92]

Subtotal (95% CI)				**78**			**137**	**2.14 [-1.43, 5.71]**
Total (95% CI)				**226**			**252**	**-1.10 [-3.35, 1.15]**
7.3 non-cardiac surgery with controlled hypotension								
Boezaart 1995	natriumnitroprussid	71	11.38	10	76.1	16.25	10	-5.10[-17.40, 7.20]
Ornstein 1988	natriumnitroprussid	80.7	4.3	15	83.2	6.3	10	-2.50 [-6.97, 1.97]
Ornstein 1991	natriumnitroprussid	82	6	10	87.05	6.55	19	-5.05 [-9.79, -0.31]
Total (95% CI)					**35**		**39**	**-3.79 [-6.94, -0.65]**
7.4electro-Convulsive therapy		Mean	SD	total	Mean	SD	total	IV, Random, 95% CI
Castelli 1995	placebo	163	21.64	36	208	16.97	18	-45.00 [-55.56, -34.44]
Howie 1990	placebo	118.4	14.5	20	122.6	14.6	20	-4.20 [-13.22, 4.82]
Howie 1992	placebo	146.42	28.74	60	172	34.55	20	-25.58 [-42.38, -8.78]
O'Connor 1996	placebo	175	28	13	190.5	32	13	-15.50 [-38.61, 7.61]
O'Flaherty 1992	placebo	144	9.88	10	148.8	17.23	10	-4.80 [-17.11, 7.51]
Shrestha 2007	placebo	93.33	17.48	30	92.66	14.18	30	0.67 [-7.38, 8.72]
Weinger 1991	placebo	175	34.79	10	196	41.11	10	-21.00 [-54.38, 12.38]
Zvara 1997	placebo	172	60.83	37	188	38.89	34	-16.00 [-39.56, 7.56]
Subtotal (95% CI)				**216**			**155**	**-15.94 [-29.40, -2.48]**
Castelli 1995	labetalol	163	21.64	36	151.5	26.83	36	11.50 [0.24, 22.76]
O'Flaherty 1992	nitro-glycerin	144	9.88	10	143	9.58	10	1.00 [-7.53, 9.53]
Shrestha 2007	labetalol	93.33	17.48	30	93.33	17.48	30	0.00 [-8.85, 8.85]
Weinger 1991	Labetalol+ fentanyl+ lidocaine	175	34.79	10	183	47.5	30	-8.00 [-35.46, 19.46]
Subtotal (95% CI)				**86**			**106**	**2.71 [-3.11, 8.52]**
Total (95% CI)				**302**			**261**	**-9.54 [-19.17, 0.09]**

SIDE EFFECTS

Setting one: Perioperative treatment and emergency therapy of supraventricular tachyarrhythmias

Nine trials[7–11,17–19,98] on emergency or perioperative treatment of supraventricular tachyarrhythmias reported hypotension in 63 out of 288 participants(21.8 %) treated with esmolol compared to 24 out of 156 participants (15.4 %) treated with other effective drugs and in one out of 101 participants treated with placebo. Results from five trials[8, 11, 18, 19, 98] reported bradycardia in one out of 149 participants(0.7 %) with esmolol compared to five out of 102 participants(5 %) with other effective drugs and no participant of the placebo groups. No deaths in any of the patients relating to esmolol treatment were reported.

Setting two: Prevention and treatment of increased blood pressure during intubation and extubation

A total of 14 trials on prevention and treatment of increased blood pressure under general anesthesia during intubation and extubation reported hypotension in 119 out of 647participants (18 %) treated with esmolol compared to 2 out of 20 (10 %) participants treated with another effective drug (alfentanil) and 34 out of 399 (9 %) participants treated with placebo. Bradycardia was observed in nine trials.[12, 22, 31, 84, 92, 93, 96, 99, 100] It was reported in 12 out of 536

(2 %) participants treated with esmolol compared to 6 out of 352 (1.7 %) participants treated with placebo. In five trials[22, 28, 31, 33, 99] hypotension and bradycardia had been treated for stabilization. Change to other effective drugs for lowering blood pressure or heart rate were reported in eleven studies[43, 86, 94–97, 101–106] in which placebo treated participants got more times an intervention. The used drugs were nitroglycerine, glyceroltrinitrate, clonidine, nifedipine, nicardipine, β-blocker und thiopental. Three trials[43, 84, 96] reported myocardial ischemia in 5 out of 98 (5 %) participants treated with esmolol and 15 out of 94 (16 %) participants treated with placebo.

Setting three: Prevention and treatment of increased blood pressure during surgery or interventions like electroconvulsive therapy

Hypotension was observed in two trials[44, 48]during cardiac surgery, in five trials during non-cardiac surgery[12, 56, 58, 65, 70] and in three trials[75, 77, 80] during electroconvulsive therapy. During cardiac surgery, hypotension was reported in 2 out of 32 (6 %) participants treated with esmolol and 18/32 (56 %) participants treated with other effective drugs. During non-cardiac surgery, hypotension was reported in 7 out of 159(4 %) participants treated with esmolol, but none of 34 participants treated with other effective drugs and none of 88 participants treated with placebo suffered from hypotension. During electroconvulsive therapy, none of the 152, 36 and 58 participants treated with esmolol, other effective drugs or placebo suffered from hypotension. Bradycardia was observed in five trials during non-cardiac surgery[12, 56, 58, 65, 70] were 6 out of 120(5 %) participants with esmolol, 0 out of 24 participants with other drugs and 1 out of 82 (1 %) participants suffered from bradycardia and in three trials[75, 77, 80] on electroconvulsive therapies with no observation of bradycardia in all participants. Myocardial ischemia was seen in five[13, 43, 45, 47, 50] trials during cardiac surgery. From these 14 % (10 out of 72) of esmolol treated participants in comparison to 24 % (20 out of 82) of placebo treated participants developed myocardial ischemia. One trial[49] reported a participant with myocardial infarction in the placebo group during cardiac surgery.

DISCUSSION

Cardiovascular risk in the perioperative setting

Anesthesia is associated with intraoperative and postoperative hemodynamic risks especially hypertension and tachycardia through intubation, pain, extubation, time of incision and in the postoperative setting as well as hypotension after induction of anesthesiauntil time to incision and before end of surgery.

Hypertension and tachyarrhythmia as intra-and postoperative risk factors

Patients with chronic hypertension and consecutive coronary artery disease have a higher risk in morbidity and mortality in connection with neurosurgery, aortic- and especially cardiac surgery. But also non cardiac surgery is associated with cardiac complications like myocardial ischemia in 25 % of patients[107, 108]. Preoperative hypertension is a stronger risk factor for intraoperative hypertension and tachycardia and is associated with increased risk of death after non cardiac surgery in comparison to normotensive patients (OR 3.8)[107, 108]. Also postoperative hypertension leads to higher risk for bleeding, myocardial infarction and cerebrovascular events in cardiac and non cardiac patients especially in those with preoperative hypertension[107, 108].

For these reasons, it is important that patients with chronic hypertension are well controlled, risks for intra- and postoperative hypertension are avoided, and in case of urgencies patients are rapidly and effectively treated, however, without inducing iatrogenic hypotension[108].

Prevention and Management of intra- and postoperative hemodynamic instabilities

For the "preventive approach" avoiding hypertension, myocardial is chaemia and arrhythmias in the perioperative setting, a large number of randomized controlled trials form the basis for given guideline recommendations.[1]

In contrast emergency treatment of the individual patient with acute perioperative hypertensive crisis, inadequate rise in sinus rhythm or supraventricular tachyarrhythmia, especially a trial fibrillation/flutter, is not based on the quantitative results of large randomized trials, but "only" in a qualitative manner on the rationale that these situations bear the risk of acute coronary syndrome, stroke or death. Treatment of perioperative urgencies through intubation, extubation and pain by surgical incision could be handled with beta blockers, ACE inhibitors, calcium channel blockers and vasodilators[107, 108]. Tachycardic perioperative urgencies are reflected better by an acutely critically ill tachycardic patient at the ICU than by patients with chronic coronary heart disease or systolic heart failure with an in adaequtely high heart rete > 70-75 bmp[109].ICUpatients with >95 bpm for > 12 hrs sustain much more major cardiac events than those in the control group (49 % vs. 13 %)[109]. In 89 critically ill ICU patients with multiple organ dysfunction syndrome (MODS) of cardiac or septic origin, those patients with≥ 90 bpm have a much higher 28-day mortality (HR 2.30) than those with < 90 bpm[110].

In 77 critically ill ICU patients with septic shock, the high heart rate of ≥95 bpm could be effectively reduced by a 4-day period of intravenous esmolol treatment, with a mean reduction of 18 bpm[111], correlating with a lower 28-day mortality (49.4 % vs 80.5%; p<0.001). These findings argue for a prognostic relevance of an inadequately high heart rate in the acutely critically ill ICU patient and for a protective effect of dampening the overshooting sympathetic activity - triggering the rise in heart rate - by short term use with the beta blocker esmolol. Similar data reflecting high blood

pressure values under these conditions are not available yet.

Postoperative hypertension can be prevented causally by normovolemia, normothermia and by avoidance of hypoxia, pain and symptomatically by antihypertensive drugs. Aim of all treatment options is the protection of organ function and a balance between the risk from hypertension and hypoper fusion through antihypertensive treatment[107], with the ideal agent being rapid acting, safe, inexpensive, convenient, predictable and easy to titrate[108].

Esmolol in the perioperative arena

With respect to the use of esmolol in treating overshooting sympathetic activity in surgical patients, our review reports a large number of randomized, though relatively small clinical trials which demonstrate the effectiveness in lowering blood pressure, reducing heart rate and converting supraventricular tachyarrhythmias – especially atrial fibrillation/flutter - in sinus rhythm.In comparison to placebo, esmolol is significantly more effective in all surgical scenarios tested (figures 2, 3, table 3, 5, 7), with lowering blood pressure and heart rate as well as conversion of supraventricular tachycardias into sinus rhythm (figure 2). The latter scenario is generalizable from the perioperative arena to the emergency setting in general. With respect to non-cardiac surgery, our data are in agreement with the meta-analysis of Yu et al (2011)[112], providing convincing evidence for esmolol as effective agent to reduce overshooting sympathetic tone in the perioperative arena. But for the price of: an increased incidence of unplanned hypotension (OR 2.1), but not an increased incidence of significant bradycardia (OR 1.2);interestingly, esmolol decreased the frequency of myocardial ischemia in the 7 evaluating studies (OR 0.17). Our trials reported myocardial ischemia only in cardiac or vascular surgery with cardiac pre-stressed participants (esmolol 9 % vs. placebo 20 %).

Comparing esmolol with other beta-blockers and other agents

Considering current guidelines[1], there are recommendations on the use of beta-blocker for perioperative prophylaxis and treatment of blood pressure, heart rate and frequency control of supraventricular arrhythmias as atrial fibrillation. In clinical practice, esmolol is one of the agents used for these indications, with others being further i.v.-beta-blockers as metoprolol, propranolol, atenolol and the new short-acting landiolol[113, 114], transdermal clonidine, ACE inhibitors as enalapril, calcium channel blocker as verapamil and diltiazem, and in case of severe hypertension[107, 108]labetalol, nitroglycerine and sodium-nitroprusside.

Comparison to beta-blockers

Beta-blockade like metoprolol and bisoprolol protect development of myocardial ischemia during vascular surgery without adverse events like stroke and hypotension[115]. In our meta-analysis, in the trials comparing esmolol with other betablockers, no significant difference in lowering heart rate and blood pressure could be detected, not surprising in view of the identical pharmakodynamic properties. Due to the excellent controllability of the esmolol application, less side effects like hypotension and symptomatic bradycardia could have been expected, but – interestingly - this was also not the case. For landiolol, another short-acting betablocker, with a half-life of 3 minutes and 8-times higherβ_1-selectivity as esmolol, a statistically more effective termination of postoperative a trial fibrillation has been described[116].

Comparison to other drugs

Esmolol has also been compared in its effectiveness with other non-beta blocker (see "Results")without remarkable difference considering blood pressure and heart rate lowering. The use of these substances could be of interest when only heart rate but not blood pressure should be lowered in hypotensive tachycardic patients or only blood pressure but not heart rate should be lowered in hypertensive bradycardic patients. The pacemaker channel inhibitor ivabradine selectively reduces heart rate[117] and the new anti arrhythmic agent vernakalant[118] is now an alternative for cardioversion of arterial fibrillation/flutter[119].

Perioperative beta-blocker action beyond heart rate and blood pressure?

Härkänen et al (2015)[120] evaluated postoperative pain in11 randomized clinical trials including701 adults treated with esmolol (ten trials) or propranolol (one trial). Overall both beta-adrenergic antagonists demonstrated an opioid-sparing efficacy and patients needed less rescue analgesics (32 to 50 % in esmolol group and 72 % in propranolol group) compared to placebo accompanied by lower pain ratings and longer time till rescue drug was given[120]. In patients undergoing intracranial surgery, Asouhidou et al (2015)[121]reported that esmolol showed hemodynamic stability and did not influence bispectral index (BIS) on his own. However, taken together all available study results[32, 92, 93, 121],the effect of esmololon BISneeds further clarification.

Reduction of heart rate and blood pressure or blockage of overshooting sympathetic tone?

Finally, do we need to treat only exaggerated heart rate and blood pressure by any specific agent or must we treat specifically the overshooting sympathetic activity by betablocker in the perioperative arena to avoid complications? Presently, we cannot answer this question, as our review found only trials dealing with treatment of overshooting heart rate and blood pressure and of supraventricular tachyarrhythmias, but not dealing with the prognostic consequences of this hemodynamic derangement. What we know from clinical practice and the mentioned trials above is that intra- and postoperative hemodynamic instabilities are related to cardiovascular complications[108].Specially

preoperative hypertension is associated with higher risk of postoperative death[107, 108]. However, a first step in answering this question will come from heart rate lowering treatment of critically ill ICU patients and inadequately high heart rates either by the beta blocker esmolol[111] or the selective pacemaker channel (funny channel) inhibitor ivabradine[122]. Comparing both studies, esmolol was more effective in heart rat lowering than ivabradine and only esmolol improved hemodynamics and reduced morbidity and mortality. Therefore, dampening the overshooting sympathetic activity to suppress heart rate might be better than pure heart rate reduction in MODS/septic shock patients with inadequately high heart rate, and – as might be speculated - possibly also in patients in the perioperative arena.

Limitations

The quality of evidence in this review was ranged with GRADE-system[123] and limitations are attributable to the limitations of the single trials included in the meta –analysis, inconsistency of treatment effects, imprecision and resulting broad95 % CIand potential publication bias. Inconsistency is caused by differences in sample size, patient characteristics, resulting surgeries and study design. Some trials include patients with pre-existing conditions as hypertension and cardiac long-term medication while others defined these conditions as exclusion criteria. Premedication,especially opioids, cardiac active drugs and different kinds and doses of anesthetics, should be considered critically. All included studies were randomized and most double-blind, some trials used cross-over design with possible interactions.

CONCLUSION

In summary esmolol is an effective drug for intraoperative reduction and prevention of increased heart rate, blood pressureand tachyarrhythmia in patients with cardiac risk with no differences to other beta-blockers. Side effects can be minimized through slow and careful titration of esmolol. Specifically, for intraoperative urgencies the use of esmolol in patients with cardiac risk should be considered. In emergency medicine esmolol is already included for treatment of tachycardia or tachyarrhythmia. Esmolol seems to be very attractive because of the additive characteristics which should be part of future trials with large number of participants and high methodic quality. Considering other active drugs esmolol should be compared to new generation of cardio active drugs.

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APPENDIX

1 Search Strategy

CENTRAL on The Cochrane Library

#1 Esmolol
#2 tachyarrythmias
#3 Arrhythmias, Cardiac
#4 Emergencies/
#5 urgencies
#6 Intraoperative complications
#7 Postoperative complications
#8 Intubation, Intratracheal/ae
#9 Laryngoscopy
#10 hypertensive crisis.mp
#11 hypertension.mp
#12 rate pressure product
#13 (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
#14 (#1 and #13)

Medline (on Ovid)

1. Esmolol.mp
2. tachyarrythmias.mp
3. Arrhythmias, Cardiac.mp. or Arrhythmias, Cardiac/
4. Emergencies.mp. or Emergencies/
5. Adult/ or Hypertension/ or Emergencies/ or Middle Aged/ or urgencies.mp. or Emergency Service, Hospital/ or Aged/
6. Intraoperative complications.mp. or Intraoperative Complications/
7. Postoperative complications.mp. or Postoperative Complications/

8. Intubation, Intratracheal/ae
9. Laryngoscopy.mp. or Laryngoscopy/
10. hypertensive crisis.mp
11. hypertension.mp
12. Middle Aged/ or Oxygen Consumption/ or Coronary Disease/ or Calcium Channel Blockers/ or Hypertension/ or Angina Pectoris/ or Heart Rate/ or Myocardium/ or Blood Pressure/ or rate pressure product.mp. or Adult/
13. or /(2-12)
14. 1 and 13

Embase (on Ovid)

1. Esmolol
2. Milrinone/ or Supraventricular Tachycardia/ or Adverse Drug Reaction/ or Heart/ or Heart Arrhythmia/ or Heart Infarction/ or Amiodarone/ or Tachycardia/ or Heart Ventricle Tachycardia/ or tachyarrythmias.mp. or Drug Therapy/
3. Bradykinin/ or Diuretic Agent/ or Endothelin B Receptor Antagonist/ or Dipeptidyl Carboxypeptidase Inhibitor/ or Ramipril/ or Antiarrhythmic Agent/ or Heart Muscle Ischemia/ or Heart Ventricle Arrhythmia/ or Heart Arrhythmia/ or Arrhythmias, Cardiac.mp. or Heart Infarction/
4. Emergencies/
5. urgencies
6. Intraoperative complications.mp. or Peroperative Complication/
7. Postoperative complications.mp. or Postoperative Complication/
8. Intubation, Intratracheal/ae
9. Laryngoscopy.mp. or Laryngoscopy/
10. hypertensive crisis.mp
11. hypertension.mp
12. Hypertension/ or Blood Pressure/ or Losartan/ or Systolic Blood Pressure/ or Enalapril/ or Diazepam/ or Verapamil/ or Metoprolol Succinate/ or Heart Rate/ or rate pressure product.mp. or Amlodipine Besylate/
13. or /2-12
14. (1 and 13)
15. Randomized Controlled Trial/
16. exp controlled clinical trial/
17. Randomized Controlled Trial/
18. random allocation.af.
19. double blind method$.pt,af.
20. single-blind method$.af.
21. cross-over.mp.
22. Treatment Outcome/ or Scoring System/ or Outcomes Research/ or propensity score.mp. or Statistical Analysis/
23. or / 15-22
24. exp ANIMAL
25. "not human$".af.
26. 25 or 24
27. 23 not 26
28. clinical trial$.pt,af.
29. clinical trial$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
30. (clin$ adj25 trial$).ti,ot,ab.
31. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,pt,ot,ab.
32. placebo$.af.
33. random$.pt,af.
34. research design$.af.
35. or/ 28-34
36. 35 not 26
37. 36 not 27
38. comparative stud$.af.
39. evaluat$ stud$.af.
40. follow up stud$.af.
41. prospective stud$.pt,af.
42. (control$ or prospectiv$ or volunteer$).ti,ot,ab.
43. or/ 38-42
44. 43 not 26
45. 44 not (27 or 37)
46. 27 or 37 or 45
47. 46 and 14

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