Beta-Blocking Agents and Electroconvulsive Therapy

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Abstract: In this review we want to summarize the results of the placebo-controlled randomized clinical trials with beta-blocking adrenergic agents during electroconvulsive therapy (ECT), and review the effect on seizure duration and cardiovascular variables. We searched for studies in the electronic databases Medline. Keywords combined in the search were: "beta-adrenergic blocking agents" and "electroconvulsive therapy". The only limitation specified in the search was that the publications should include only randomized controlled trials.

Esmolol **and other beta-blocking adrenergic agents** can have a significant effect on seizure duration during ECT, it shortens seizure duration, and this effect is probably dose dependent. **Therefore routine administration is not recommended.**

Since the relation between seizure duration and efficacy of ECT is dependent on electrode placement it seems advisable to use bilateral electrode placement with patients with cardiovascular risk factors and **an indication for** use of esmolol during every session before seizure induction.

In the absence of cardiovascular risk factors but with prolonging hypertension or tachycardia during ECT sessions, esmolol also is again preferred. Labetalol is an alternative although, especially in high dose, the longer half-life can be considered as a disadvantage. Experiences with landiolol are limited.

Key Words: Electroconvulsive therapy, beta-adrenergic blocking agents, anesthesia, esmolol, labetalol, landiolol, nicardipine, urapidil, depressive disorder.

INTRODUCTION

Electroconvulsive therapy (ECT) is a widely used and effective treatment for severe depression, especially when alternative methods of treatment have failed [1]. It is generally considered to be a low-risk procedure. However, ECT is accompanied by a cardiovascular response that can be dangerous in patients with cardiovascular disease. This response consists of an initial parasympathetic and a subsequent sympathetic reaction. During the electrical stimulus there is an immediate, brief and intense parasympathetic activity, which may cause a transient sinus bradycardia or, rarely, asystole. In some treatment centers, atropine or glycopyrrolate are given before induction of anesthesia to attenuate this vagal effect [2]. This transient vagal discharge is followed by a sympathetic discharge, amplified by adrenal release, which is responsible for the tachycardia and the hypertension observed after the stimulation [3].

Pretreatment screening and adequate management of cardiovascular risk factors remain the most important methods of preventing cardiovascular complications caused by ECT. In addition, attenuation of the cardiovascular response during ECT can be important in patients with cardiovascular disease or patients with prolonging hypertension and tachycardia during an ECT session.

Many antihypertensive drugs have been administered in an attempt to attenuate the acute autonomic response to ECT. Previously diazoxide, hydralazine, propanolol, nitroglycerine ointment and clonidine have been used; however, the duration of action of these agents is longer than the ECT procedure and anesthesia time. Sodium nitroprusside has a short half-life, but reflex tachycardia and persistent hypotension after ECT makes this drug less useful [4].

Recently mostly beta-adrenergic blocking agents with short half-lives, especially esmolol, were studied. However, problems such as decrease in seizure duration, prolonged cardiovascular depression, and excessive hypotension have been reported [5-7] . In addition the use of drugs with beta-blockade activity is limited because it is contraindicated in patients with significant ventricular dysfunction, conduction abnormalities, or bronchospastic disease.

In this review we want to summarize the results of the randomized clinical trials with beta-blocking adrenergic agents during ECT compared to placebo, and review the effect on seizure duration and cardiovascular variables.

Seizure duration is one of the variables used to assess the adequacy of convulsions, and reduction in seizure duration may interfere with therapeutic efficacy. However, the relation between therapeutic efficacy and seizure characteristics has recently proved to be more complicated than originally thought. In recent years it has become evident that seizure duration has little bearing on efficacy [8]. However, when seizure duration is less than 15 seconds in both motor and EEG manifestations, the likelihood is high that the seizure

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was limited by insufficient electrical stimulation and that the treatment was inadequate [9]. In unilateral ECT, electrical doses far higher than seizure threshold also determine efficacy [10]. With bilateral ECT seizure duration is related to efficacy as explained previously.

Conflicting results of the influence of beta-adrenergic blocking agents on seizure duration have been published. In this review we examine the placebo-controlled trials in which the effect of beta-adrenergic blocking agents on seizure duration and cardiovascular parameters during ECT is one of the outcome criteria. Method

We searched for studies in the electronic databases Medline, and included all published articles irrespective of the language. Keywords combined in the search were: "beta-adrenergic blocking agents" and "electroconvulsive therapy". The only limitation in the search was that the publication type had to be randomized controlled trials. Data on seizure duration or cardiovascular parameters had to be presented, all trials had to be placebo-controlled and of comparable design. All publications were reviewed by two authors (WvdB, THNG). When results differed, consensus was reached between both authors. If different dosages of beta-adrenergic blocking agents in comparison with placebo were used in a trial, each dosage was considered as a separate trial. Results

Our search strategy resulted in 20 publications. Two publications were not about beta-adrenergic blocking agents and the effect on seizure duration but explored the response of the psychiatric disorder to the addition of beta-adrenergic blocking to ECT or the usual treatment of schizophrenia [11, 12]. Another publication reported on the effects (of among others beta-blocking agents on neuroendocrine hormones and could not be used for the current review [13]. Several other publications did not mention the absolute duration of the seizure or did not include this outcome criterion [14-17]. In one study interaction between nicardipine and labetalol was studied, but no absolute seizure duration was reported between sessions with or without labetalol addition [6]. One study reported on the effect of esmolol on the bisprectal index scale (BIS) [18]. In that study the effect of a single esmolol dose on the BIS was assessed. A bolus of esmolol 80 mg was given to 30 healthy male patients after induction of anesthesia using propofol, with either fentanyl or placebo. Anesthesia was maintained using propofol to keep the BIS value between 55 and 60. The result suggests that a single dose of esmolol affects the systolic blood pressure (SBP) and heart rate (HR) but does not affect the BIS value. How esmolol affects the seizure duration and EEG changes remains unclear. In a recent trial with nicardipine, the use of labetalol was an outcome criterion [19].

Of the remaining publications eight were a comparison between esmolol and placebo, two on labetalol [15, 17] and one on landiolol compared to placebo [20].

ESMOLOL

Five publications used esmolol as infusion sometimes combined with a starting bolus [21-25]; three trials administered solely a bolus [5, 7, 26]. For the trials with infusion treatment with or without a starting bolus the total dosage

used was calculated with the mean weight of patients and the duration of the infusion; these calculations are given in Table **1**. One publication did not mention the average weight of the patients; weight was calculated by calculating the mean weights of all other trials and using the mean for this trial [24]. Another publication did not mention the mean weight but this could be derived from data on the dosages used for anesthetic and muscle relaxation [25]. For the trials with bolus treatment the bolus dosage to mean weight is calculated as way of comparison between these trials; these data are also shown in Table **1**.

Tables **2** present data on number of patients, number of sessions per patient, dosages and seizure duration and significant effects of esmolol in comparison with placebo, on the cardiovascular variables for each trial.

Esmolol significantly reduces seizure duration as measured with the cuff method in all infusion trials except one [23]. The cuff method consists of inflating a blood pressure cuff above the right knee to 300 mm Hg, before the administration of succinylcholine; because there is no neuromuscular block in the right lower leg, duration of the convulsion can be timed clinically. In all infusion trials cardiovascular variables were significantly attenuated by esmolol, diastolic blood pressure was attenuated only with a high dose of esmolol [22]. In trials using bolus administration the effect on seizure duration are inconclusive, cardiovascular variables are significantly attenuated in all trials.

LABETALOL

Labetalol is studied in five trials [6, 15, 17, 19, 27]. The first study included 11 patients (average age 70.3 years) identified as American Society for Anesthesiologists (ASA) physical class status II, III and IV, all with a concurrent medical disease with a refractory affective disorder [15]. As compared with placebo, labetalol blunted the increase in mean arterial pressure (MAP) and HR. Moreover, the frequency of atrial arrythmias and premature ventricular contractions were also significantly reduced with labetalol. Seizure duration was not measured in this trial [15].

In the next study, nicardipine, a dihydropyridine calcium antagonist was studied for hemodynamic changes during ECT [6]. Nicardipine was administered in three different dosages; with each dosage 10 mg of labetalol was administered. Nicardipine 2.5 mg bolus i.v. in combination with labetalol 10 mg i.v. administered 4 minutes for induction of anesthesia was the most effective combination in attenuating the acute hypertensive response during ECT. Seizure duration was not adversely affected. The hypotensive effect of nicardipine was accompanied by tachycardia, implying that nicardapine must be administered in combination with a beta-adrenergic blocking agent to minimize the nicardipine induced increase in HR [6].

In a more recent study, nicardipine was administered immediately before application of the ECT stimulus after induction of anesthesia for ECT [19]. Bolus injections of 20, 40 and 80 µg/kg nicardipine i.v. were compared with placebo in a randomized double blind cross over study during four ECT sessions in 25 patients. One of the outcome criteria was the need of labetalol during the sessions. Nicardipine 40

Table 1. **Calculation of the Total Dose of Esmolol Administered During Treatment Sessions for Trials Using Infusion and of the Bolus Dosage by Mean Weight**

Publication	Schedule	Duration (min)	Average weight (kg)	Total dosage (mg)	Bolus/Average weight (mg/kg)
Kovac (1990) [21]	80 mg bolus, 24 mg/min infusion	8	64	272	1.25
Howie (1990) [22]	500 µg/kg/min 300 µg/kg/min	4 3	75	292.5	
Howie (1992) [23]	500 µg/kg/min bolus 300 µg/kg/min	8	64	32 +153.6=185.6	
Howie (1992) [23]	500 µg/kg/min bolus 200 µg/kg/min	8	64	32+102.4= 134.4	
Howie (1992) [23]	500 µg/kg/min bolus 100 µg/kg/min	8	64	32+51.2=83.2	
Zvara (1997) [24]	500 µg/kg (1 minute) 200 µg/kg/min	12	66	33+158.4=191.4	
McCall (1997) [25]	500 µg/kg (1 minute) 200 µg/kg/min	11	64.2	32.1+141,2=173.3	
Kovac (1991) [5]	Bolus 100 mg		70		1.4
Kovac (1991) [5]	Bolus 200 mg		70		2.8
Weinger (1991) [13]	Bolus 75.6 mg		75.6		1
Van den Broek (1999) [7]	Bolus 80 mg		63.7		1.25

µg/kg i.v. appeared the optimal dose because it was more effective in controlling the acute hypertensive response than the smaller dose (20 µg/kg) dose and was associated with less increase in HR during the ECT treatment and less decrease in MAP on awakening compared with the 80 µg/kg dose. Nicardipine did not adversely affect the duration of the ECT-induced seizure, regardless of the dose administered. Rescue treatment with labetalol was needed in the group with 40 µg/kg and 80 µg/kg, but significantly less than in the control group [19].

Labetalol was also compared with urapidil, a postsynaptic α-1-adrenergic antagonist and central serotoninergic agonist, in a double-blind placebo-controlled cross over design in which each patient served as their own control [27]. Labetalol (0.2 mg/kg i.v.) and urapidil (25 mg i.v.) was administered prior to succinylcholine. Heart rate decreased 1 minute after ECT and remained lower than HR values recorded at baseline situation with labetalol. In the control and urapidil group HR significantly increased compared to baseline. Both treatment conditions significantly attenuated the hypertensive response in comparison with the control group; neither of the treatments had any influence on seizure duration. Since urapidil was able to reduce the increase in hypertensive response to the ECT stimulus, this drug seems to be a good alternative in patients with contraindication for beta-antagonists [27]. Urapidil has no attenuating effect on heart rate.

In an open study with a randomized block design, 18 patients underwent ECT in each of five experimental states: no drug, esmolol low dose (1.3 mg/kg), esmolol high dose (4.4. mg/kg), labetalol low dose (0.13 mg/kg) or labetalol high dose (0.44 mg/kg) [17]. The drug was administered i.v. immediately prior to methohexital and sucinylcholine. Low and high doses of antihypertensive drugs significantly attenuated SBP (1 and 3 minutes after ECT stimulus), diastolic blood pressure (DBP) (1 minute), and HR (1 and 3 minutes). The antihypertensive drugs in low dose produced a reduction of peak increases in SBP by approximately 50%, whereas after high doses, such increases were nearly eliminated. However, the high dose of labetalol had significant effects on SBP after 5 and 10 minutes. This can be attributed to the longer half-life of labetalol. Therefore esmolol may be preferred if a larger dose of beta-adrenergic blocker is contemplated. Seizure duration was not an outcome criterion in this trial [17].

LANDIOLOL

Landiolol is an ultra-short-acting beta-adrenoreceptor blocker (half-life 3-4 min) created by altering the chemical structure of esmolol to produce a greater degree of cardio-selectivity and more potency. Landiolol (0.1 mg/kg) was studied in 10 patients receiving maintenance ECT once or twice a month at an outpatient psychiatric clinic in a randomized, placebo-controlled, double-blind cross-over study [20].

Table 2. Demographic Variables, Esmolol Dosage and Outcome Measures for Trials Using Infusion Administration and Bolus Administration of Esmolol

Study	n	Design	Total dosage (Table 1)	Significant effect on cardiovascular variables	Esmolol		Placebo	
					Cuff (sec)	EEG (sec)	Cuff (sec)	EEG (sec)
Kovac (1990) [21]	17	1 esmolol 1 placebo session	272	HR MAP RPP		39±3		45±3 ns
Howie (1990) [22]	20	4 esmolol 4 placebo	292.5	HR SBP DBP	39±14	67±28	48±18 Sign.	86±41 Sign.
Howie (1992) [23]	20	2 esmolol 2 placebo	185.6	HR SBP DBP MAP	36±14	56±27	42±11 Sign.	67±29 ns
Howie (1992) [23]	20	2 esmolol 2 placebo	134.4	HR SBP MAP	34±14	64±36	42±11 Sign.	67±29 ns
Howie (1992) [23]	20	2 esmolol 2 placebo	83.2	HR SBP MAP	38±11	62±26	42±11 ns	67±29 ns
Zvara (1997) [24]	19	1.94 esmolol 1.78 placebo	191.4	HR SBP MAP	26.4±2.1	50.6±3.0	35.5±7.2 Sign	55.1±4.3 ns
McCall (1997) [25]	18	1.55 esmolol 1.55 placebo	173.3		26.3±8.3	49.7±17.6	33.2±7.2 Sign.	53.3±17.7 ns
Study	n	Design	Bolus dosage/mean weight (mg/kg)	Significant effect on cardiovascular variables	Cuff (sec)	EEG (sec)	Cuff (sec)	EEG (sec)
Kovac (1991) [5]	12	1 esmolol 1 placebo	1.4	HR RPP MAP		44.58±4.61		52.75±4.61 ns
Kovac (1991) [5]	12	1 esmolol 1 placebo	2.8	HR RPP MAP		40.00±3.09		52.75±4.61 Sign.
Weinger (1991) [13]	10	1 esmolol 1 placebo	1	HR RPP SBP		45.8±5.9		56.5±12.5 ns
v.d. Broek (1999) [7]	22	3 esmolol 3 placebo	1.25	HR MAP SBP	38.7	55.1	45.6 Sign.	69.1 Sign.

HR= heart rate, MAP= mean arterial pressure, RPP= rate pressure product, SBP= systolic blood pressure, DBP= diastolic blood pressure. ns=difference between esmolol and placebo not significant. Sign= significant difference between placebo and esmolol.

All patients were using different antidepressive agents during the trial. There was no significant difference in mean motor seizure duration between the placebo and landiolol sessions. Administration of landiolol prevented the increase in SBP at 1-3 minutes after electrical stimulus significantly compared to placebo. Heart rate tended to decrease (but not significantly) after landiolol administration, and was maintained lower than the value in the placebo session until 3 minutes after ECT. This study only evaluated one dose of landiolol and only SBP and HR. Since coronary perfusion occurs during diastole, MAP is considered a better indication of coronary perfusion than SBP. This dosage did not lead to

hypotension or bradycardia. Perhaps a larger dose would also attenuate HR to a significant level.

DISCUSSION

As can be derived from Table **2** in almost all trials except one [23] esmolol significantly shortens seizure duration as measured with the cuff method. With the highest dose with the infusion technique the seizure duration as measured with the EEG was also significantly shorter with esmolol [22]. In all infusion trials cardiovascular variables were significantly attenuated by esmolol. Especially HR, MAP and SBP were attenuated. Diastolic blood pressure was attenuated only in one trial with a high dosage of esmolol [22].

In trials using bolus administration the effects on seizure duration are inconclusive. With a relatively high bolus dosage [5] or relatively more sessions [7] a significant attenuating effect on seizure duration is accomplished by esmolol in comparison with placebo.

A formal quantitative meta-analysis of the effect of esmolol on seizure duration in comparison with placebo could not be performed because in almost all trials the mean difference of seizure duration between esmolol and placebo sessions and its standard error could not be derived. The relevant publications lacked sufficient details on this main study outcome. Exact p-values for differences between conditions are usually not reported. In future studies when beta-blockers are compared with placebo it is important to at least report the mean difference between conditions, with either standard errors or accurate p-values or 95% confidence intervals, in order to enable a subsequent quantative meta-analysis.

Since the effect on seizure duration of esmolol cannot be determined in a systematic manner, and since the relation between seizure duration and efficacy of ECT is dependent on electrode placement, it seems advisable to use bilateral electrode placement with patients with cardiovascular risk factors and use of esmolol. One should take into account the possible negative effect of esmolol on seizure duration in these cases and adhere to the guidelines for ECT that advise at least 10 treatment sessions with bilateral ECT before one can conclude that ECT is not efficacious. Routine administration of esmolol during ECT sessions as a prophylactic measure is not advised [7].

In the absence of cardiovascular risk factors but prolonging hypertension or tachycardia during ECT sessions, esmolol also is preferred. Labetalol is an alternative although (especially in high dose) the longer half-life of labetalol can be considered as a disadvantage. Labetalol is mostly studied as a rescue treatment with nicardipine and in comparison with urapidil. Data comparing labetalol with placebo and effects on seizure duration are scarce.

Experiences with landiolol are limited but the short half-life, greater degree of cardio selectivity and more potency makes it a promising alternative.

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