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Use of esmolol to treat postoperative arterial hypertension in patients with ischemic heart disease

S. Musayev
EGE Hospital, Baku, Azerbaijan

The objective: **to evaluation of the efficacy and safety of β-adrenoblocker esmolol to treat postoperative arterial hypertension (PAH) in patients with ischemic heart disease.**
***Materials and methods*. The study included 30 patients (45–78 years, mean age – 60.5 ± 17.3 years) who underwent coronary artery bypass grafting surgery with continuous blood purification. PAH developed during the first post-operative hours, and all patients were ventilated under sedation with a RASS (Richmond Agitation-Sedation Scale) score 2–4. All patients had arterial hypertension and were on constant antihypertensive therapy. Esmolol was administered intravenously as a bolus push 20 mg within a minute. When required, injection was repeated in 5 minutes until full required effect. For intraoperative treatment of hypertension 80 mg bolus within 30 seconds was injected followed by 150 mg/kg/min infusion when required. Postoperative dosage was administered similarly.**
***Results*. Esmolol treatment was efficient in 82.6% of cases. Most often, the target level of arterial pressure was achieved at doses of 40 and 60 mg in 20% and 36.7% of cases, respectively. Antihypertensive effect maintained within 24 hours after injection. Esmolol caused moderate reduction of heart rate (by 4–7%), making it possible to use in case of hypertension without tachycardia. The drug was well tolerated and demonstrated a favorable safety profile with no side observed effects.**
***Conclusions*. Use of esmolol demonstrated high efficacy and safety in management of PAH in cardiac surgery patients.**
Keywords: *postoperative arterial hypertension, ischemic heart disease, esmolol.*

Застосування есмололу для лікування післяопераційної артеріальної гіпертензії у пацієнтів з ішемічною хворобою серця

S. Musayev

Мета дослідження: оцінити ефективність і безпечність β-адреноблокатора есмололу для лікування післяопераційної артеріальної гіпертензії (ПАГ) у пацієнтів з ішемічною хворобою серця.
***Матеріали та методи*.** У дослідження включено 30 пацієнтів (віком 45–78 років, середній вік – 60,5 ± 17,3 року), яким було проведено аорто-коронарне шунтування з використанням штучного кровообігу. ПАГ розвинулася в перші години після операції. Усі пацієнти перебували на штучній вентиляції легень із седацією за шкалою RASS (Richmond Agitation-Sedation Scale) на рівні 2–4. У всіх пацієнтів діагностовано артеріальну гіпертензію, і вони отримували постійну антигіпертензивну терапію. Есмолол уводили внутрішньовенно болюсно по 20 мг протягом 1 хв. У разі необхідності ін'єкцію повторювали через 5 хв до досягнення необхідного ефекту. Для інтраопераційного контролю артеріального тиску вводили болюс 80 мг протягом 30 с; після цього, якщо виникала потреба, інфузійно призначали дозу 150 мг/кг/хв. Післяопераційне дозування здійснювали за аналогічною схемою.
***Результати*.** Лікування есмололом виявилося ефективним у 82,6% випадків. Найчастіше цільового рівня артеріального тиску досягали при дозах 40 та 60 мг у 20% та 36,7% випадків відповідно. Антигіпертензивний ефект зберігався протягом 24 год після ін'єкції. Есмолол спричиняв помірне зниження частоти серцевих скорочень (на 4–7%), що дозволяло застосовувати його при гіпертензії без супутньої тахікардії. Препарат добре переносився, побічних ефектів не зафіксовано.
***Висновки*.** Застосування есмололу показало високу ефективність і безпечність у лікуванні ПАГ у пацієнтів кардіохірургічного профілю.
Ключові слова: *післяопераційна артеріальна гіпертензія, ішемічна хвороба серця, есмолол.*

Postoperative arterial hypertension (PAH) remains a major problem after cardiac surgery, particularly among patients with coronary artery disease. PAH significantly increases the risk of life-threatening complications, including mortality. The results of the ECLIPSE study demonstrated a strong correlation between the severity and duration of elevated blood pressure (BP) following cardiac surgery with the likelihood of in-hospital mortality [1]. A 2011 Eurostat analysis involving 790 patients undergoing various surgical procedures found that approximately 29% developed PAH in the postoperative period. Of these patients, with 59% of those patients having a previous history of chronic hypertension. Notably, PAH was most commonly observed after cardiac surgery (up to 40% of cases), while the remaining cases were reported after abdominal, orthopedic and vascular surgeries [2]. According to the results of a number of studies published in the available literature [3], approximately one-quarter of patients with previous arterial hypertension experience a postoperative increase in BP. Moreover, even in people with previously normal BP, intraoperative cardiac changes in the form of an increase in systolic pressure

by 20–40 mmHg and an increase in heart rate (HR) by 15–25 beats per minute (bpm) may be observed during anesthesia. These changes are even more pronounced in patients with untreated uncontrolled hypertension in the preoperative period. It is obvious that uncontrolled hypertensive episodes occurring during or after surgical procedures significantly increase the risk of cardiovascular complications and mortality [4, 5]. According to the current guidelines of the European Society of Hypertension and the European Society of Cardiology, the therapeutic approach to the treatment of PAH largely reflects the strategies for the treatment of hypertensive crises [6, 7]. Given that a significant proportion of postoperative patients are on mechanical ventilation, intravenous drugs are generally preferred over other routes of administration. From this perspective, antihypertensive agents should ideally act and provide maximum effect within a short period of time. In addition, it is important to provide rapid dose titration with minimal side effects [8]. Although modern anesthesiology has at its disposal various pharmacological options for controlling elevated postoperative BP, it cannot be emphasized enough that many drugs have limitations due to lack of sufficient effectiveness or occurrence of undesirable side effects.

In light of these issues, our study aimed to evaluate the efficacy and safety of esmolol, a short-acting β1-adrenergic receptor blocker, for the control of PAH in patients after cardiac surgery.

The objective of the study was to evaluate the clinical efficacy of esmolol in reducing systolic and diastolic BP and in minimizing the need for additional antihypertensive therapy, and to evaluate the safety profile of esmolol, paying particular attention to the incidence of cardiovascular adverse events (including hypotension, bradycardia, atrioventricular conduction abnormalities, bundle branch block, supraventricular and ventricular arrhythmias, and myocardial contractility disorders), allergic reactions, bronchospasm, and other non-cardiac adverse events.

MATERIALS AND METHODS

The study included 30 patients (age range 45–78 years; mean age 60.5 ± 17.3 years) in the postoperative period after cardiac surgery with and without artificial circulation. Patients distribution depending on the type of surgery, gender, age, and the effectiveness of different doses of esmolol, is shown in Table 1.

According to our observations, all patients developed hypertension in the early post-op period while they remained on mechanical ventilation and sedation, with a Richmond Agitation-Sedation Scale (RASS) score of 2 to 4. Each patient had a documented history of chronic hypertension and had been receiving continuous antihypertensive treatment before surgery, which included ACE (Angiotensin-converting enzyme) inhibitors, diuretics, and calcium channel blockers. Preoperative fluid balance was adequately optimized to ensure adequate intravascular volume status. Esmolol was administered intravenously in an initial bolus dose of 20 mg (equivalent to 2 mL of a 1% solution with a concentration of 10 mg/mL) over one minute. If necessary, repeated bolus injections were administered at five-minute intervals until a satisfactory therapeutic effect was achieved. The maximum cumulative administered dose did not exceed 100 mg (10 mL of a 1% solution).

Table 1

Patient distribution by type of surgery and ischemic time

Parameters	Number of patients (n = 30)
Age, years	60.5 ± 17.3
Weight, kg	65.9 ± 11.8
Arterial hypertension, abs. (%)	29 (96.7)
Myocardial revascularization, abs. (%)	10 (33.3)
Concomitant valvular surgery, abs. (%)	6 (20)
Aorta and its brunches surgery, abs. (%)	3 (10)
Complex surgeries, abs. (%)	11 (36.7)
Ischemic time, min	93.0 ± 61.9

Hemodynamic monitoring was performed using bedside CARESCAPE Monitor B650 systems (GE Healthcare, USA). BP measurements were taken invasively via radial artery catheter. The parameters required for the study: BP, as well as HR were documented before and after esmolol administration at five-minute intervals for the first 60 minutes. Additional measurements were taken at 12 and 24 hours after the first dose. The target BP, with minimal risk of complications development was defined in our study as 140/90 mmHg. The effective dose of esmolol was defined as the dose that achieved the target BP as quickly as possible in the early postoperative period and maintained it stable for 12 and 24 hours.

A 12-lead electrocardiogram was performed at baseline (before the start of drug administration) and then at 30 minutes, 1, 12 and 24 hours after the start of therapy. Statistical processing of the obtained data was performed using the Statistica 6.0 software package for Windows. Mean values with standard deviations (SD) were determined. When assessing the dynamics of the controlled parameters, statistical analysis was used for dependent (paired) samples. Changes were considered statistically significant when the corresponding changes in BP and HR demonstrated reliable differences.

Inclusion criteria:
- adult patients (age > 18 years) presenting with PAH;
- male and non-pregnant, non-lactating female participants.

Exclusion criteria:
- known hypersensitivity or intolerance to esmolol;
- concurrent use of monoamine oxidase inhibitors;
- evidence of hypovolemia;
- diagnosed bronchial asthma or chronic obstructive pulmonary disease (COPD);
- presence of bradycardia or atrioventricular block of I–III degree;
- ongoing postoperative hemorrhage (defined as drainage exceeding 1.5 mL/kg/min);
- decompensated chronic heart failure or cardiogenic shock.

RESULTS AND DISCUSSION

To achieve the target BP, the following cumulative doses of esmolol were required: 20 mg in 2 patients (6.7%), 40 mg in 6 patients (20%), 60 mg in 11 patients (36.7%), 80 mg in 3 patients (10%), and the maximum dose of 100 mg in another 3 patients (10%). In 5 cases (16.7%), esmolol administration at the maximum tolerated dose (100 mg) did not produce a sufficient response, which required the use of antihypertensive agents of other pharmacological classes. In these cases, nifedipine (a calcium channel blocker) was administered at a continuous infusion rate of 0.3–0.5 mg/h.

The baseline systolic BP (SBP) for all patients averaged 169 ± 2 mmHg, while the mean diastolic BP (DBP) was 94 ± 2 mmHg. The most significant antihypertensive effect was recorded at 60 minutes after the initiation of therapy, with SBP decreased to 135 ± 3 mmHg, corresponding with a 21% reduction from baseline. Similarly, DBP decreased to 78 ± 2 mmHg, representing a 17% drop. Statistically significant reductions in both SBP and DBP were maintained at 1 hour, and further observed at the 12- and 24-hour marks following initial administration. By the end of the first postoperative day, systolic and diastolic pressures had decreased by 28% and 25%, respectively, compared to initial values (refer to Table 2).

Regarding the HR, the early postoperative reduction was modest but reached statistical significance. At 60 minutes post-administration, HR decreased from 79.3 ± 1.7 bpm to 76.1 ± 1.7 bpm ($p = 0.0187$). Further reductions were observed at 12 and 24 hours, with HR 73.9 ± 1.9 bpm and 73.5 ± 1.7 bpm, respectively. These differences were statistically significant when compared to baseline ($p = 0.002$ and $p = 0.0009$, respectively) (see Table 2).

After the drug administration, SBP decreased by 21%, DBP by 17%, HR by 4%. Taking into account that esmolol has a moderate negative chronotropic effect (in most cases manifested by decrease in HR by 4–7%), it is believed that it expands the possibilities of its use. Thus, this property supports its use in the treatment of patients with arterial hypertension not accompanied by tachycardia. During dynamic observation, it was noted that after 12 hours these indicators were lower than the initial ones by 27, 24 and 7%, respectively. Monitoring of the indicators showed that after 24 hours the decrease was by 28, 25 and 7%, respectively.

Thus, our results demonstrated that administration of a titrated and adjusted effective doses of the esmolol, it provided a stable decrease in BP for 24 hours, which was accompanied by a moderate negative chronotropic effect. It should be noted that no adverse events associated with the drug were reported in any patient.

Postoperative hypertension refers to a transient, acute increase in BP that typically occurs within 30–90 minutes after surgery. It is diagnosed when SBP exceeds 160 mmHg or diastolic pressure increases above 90 mmHg. PAH typically persists for 4–8 hours [9]. Several factors are thought to be responsible for PAH, including arousal (common during recovery from general anesthesia), pain, postoperative shivering, and increased sympathetic nervous system activity due to cardiopulmonary bypass. The increase in BP may result from increased plasma concentrations of catecholamines (epinephrine and norepinephrine), angiotensin II, and vasopressin due to stimulation of the neuroendocrine system by the above-mentioned factors [10]. Fluid imbalance, both within and outside the vascular compartment, commonly occur during and after surgery, further exacerbate PAH. It should not be forgotten that hemostatic balance can also be altered by surgical stress. The latter promotes prothrombotic activity and increases fibrinogen and other coagulation factors. This results in platelet activation and aggregation, which can lead to thrombotic events such as graft thrombosis, myocardial infarction, and heart failure [11]. Increased BP after surgery creates additional stress on the heart, which significantly increases the likelihood of bleeding from vascular anastomoses. In some cases, such bleeding can be life-threatening, as it is accompanied by critical blood loss [12, 13].

Table 2

BP and HR dynamics during first post-operative day

Parameters	Starting	1 h	12 h	24 h
SBP, mmHg	169.2 ± 2.0	134.2 ± 2.7 (–21%)	123.9 ± 1.8 (–27%)	121.8 ± 1.9 (–28%)
DBP, mmHg	93.6 ± 2.5	77.7 ± 2.1 (–17%)	71.2 ± 1.6 (–24%)	69.9 ± 2.3 (–25%)
HR, bpm	79.3 ± 1.7	76.1 ± 1.7 (–4%)	73.9 ± 1.8 (–7%)	73.6 ± 1.7 (–7%)

Various drugs are used for the pharmacological treatment of PAH in patients recovering from cardiac surgery. These include nitrates such as nitroglycerin and sodium nitroprusside, calcium channel blockers (nifedipine, nicardipine, clevidipine), β-blockers (such as esmolol and metoprolol), the combined α- and β-blocker labetalol, and the selective α1-blocker urapidil.

Sodium nitroprusside, a potent vasodilator that affects both the arterial and venous systems. The drug is often used in hypertensive crises, and the fact that its action begins almost immediately after intravenous administration allows its use for precise control of BP. Importantly, its effects disappear within minutes of stopping the infusion, which is also an advantage for precise control. However, this drug has limitations, such as the risk of rebound hypertension upon discontinuation and potential cyanide toxicity due to its metabolic breakdown.

In some cases, such as in patients with hypertension and ischemic heart disease, such as unstable angina, post-coronary artery bypass grafting, or recent myocardial infarction, nitroglycerin is often preferred to sodium nitroprusside. It has a vasodilatory effect, which is accompanied by a marked antianginal effect. However, given that excessive reduction in BP can impair coronary perfusion and worsen myocardial ischemia, it is necessary to carefully monitor BP. In addition, the drug tolerance development should be taken into account, which can occur with prolonged nitroglycerin infusion (more than 24–48 hours), which is accompanied by a decrease in the therapeutic response. Esmolol, a short-acting β1-selective adrenergic blocker, has several advantages in the treatment of PAH, especially in patients who have undergone cardiac surgery. First of all, this is due to the fact that its onset of action occurs within 60–120 seconds and its

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period of action is limited to approximately 10–20 minutes, which allows precise titration and rapid discontinuation in case of adverse effects. The main mechanism of action of esmolol includes negative inotropic and chronotropic effects, which leads to a decrease in cardiac output. In addition, this drug is suitable for use in patients with impaired liver or kidney function. However, there are contraindications: in patients with COPD, bronchial asthma, severe bradycardia, decompensated heart failure. Caution is required when used in combination with other β-blockers [14]. Metoprolol is a cardioselective β1-adrenergic receptor blocker; in addition to antihypertensive properties, it also has antianginal and antiarrhythmic properties, sufficient efficacy and a safety profile, which have been confirmed in various clinical studies [14, 15]. Thus, in patients with stage 2–3 hypertension combined with true polycythemia, treatment with metoprolol led to a significant decrease in average daily systolic and DBP – by 17.4% and 13.2%, respectively – with good tolerability. However, selective β1-blockade is often insufficient to achieve optimal control of postoperative hypertension. Clonidine, a centrally acting α2-adrenergic agonist, is not commonly used to treat PAH in cardiac surgery patients because of its variable hypotensive response and the risk of rebound hypertension upon withdrawal. Another α2-agonist (dexmedetomidine) has been shown to be effective in controlling hypertension associated with emotional arousal, anxiety, or delirium [16]. Its antihypertensive action is based on a decrease in sympathetic outflow, resulting in a decrease in HR and cardiac output, and an increase in parasympathetic (vagal) tone. The central mechanism of action of this drug also involves stimulation of imidazoline I1 receptors [17]. However, the drug requires special caution in elderly patients [18]. This is because it can cause bradycardia and hypotension as the most common side effects.

One of the drugs with antihypertensive action – urapidil – combines peripheral α1-adrenergic antagonism with central agonist activity on serotonin 5-HT1A receptors. In the study by W. Yang et al. [19], urapidil demonstrated effectiveness in reducing postoperative hypertension after myocardial revascularization. However, there is a dangerous hypotensive effect, which was recorded in a third of patients after one hour of continuous infusion. Nifedipine, a calcium channel blocker, has vasodilatory, antianginal, and hypotensive properties. Despite its effectiveness in the treatment of hypertension and angina, its use is limited by the high incidence of side effects, including reflex tachycardia, arrhythmia, excessive hypotension, cerebral hypoperfusion, hepatic and renal dysfunction, and peripheral circulatory disorders. In addition, its intravenous formula contains ethanol, which requires careful administration [20]. There are comparative studies that evaluated isradipine and nifedipine in patients with PAH after myocardial revascularization. In this case, nifedipine caused a delayed hypotensive response (usually after 30 minutes) and required dosages 5–7 times higher than standard recommendations (on average 19.8 mg over 3 hours), which often led to arrhythmias and conduction disturbances, while isradipine has a more favorable profile: rapid onset (within 5–10 minutes), good dose control and minimal risk of hypertension recurrence. Moreover, there is another danger with nifedipine: the therapeutic effect of nifedipine often decreased when switching to a maintenance dose, and recurrent episodes of hypertension were observed in about half of the patients [21]. Labetalol, with its dual action as an α1-adrenergic blocker and nonselective β-blocker, is also used in the treatment of PAH. The drug is metabolized in the liver and exerts effects lasting up to 4 hours, making it suitable for continuous infusion. Bolus doses of 1–2 mg/kg can rapidly decrease BP. However, labetalol is contraindicated in individuals with sinus bradycardia, bronchial asthma, or conduction disorders [22, 23]. Our findings suggest that esmolol, a β1-selective adrenergic blocker, is an effective option for controlling postoperative hypertension in patients after cardiac surgery, which supports the above findings. In our study, the most effective therapeutic responses were observed at doses of 40 mg and 60 mg, which normalized BP in 20% and 36.7% of patients, respectively. Lower (20 mg) and higher (80 mg and 100 mg) doses were effective in 6.7%, 10% and 10% of cases, respectively. The positive effect was also in the fact that BP control was achieved in 83.4% of patients with esmolol monotherapy. In the remaining 16.6%, the target pressure was achieved with the addition of nifedipine. However, the required dose of nifedipine was significantly lower than used for monotherapy [15, 24]. Another positive result of our study is that the antihypertensive effect of esmolol remained stable for 24 hours after administration. Patients with pre-existing hypovolemia, bradycardia, or cardiac conduction disturbances were excluded from esmolol therapy, which probably contributed to the absence of complications and side effects. It should be noted that the drug demonstrated excellent tolerability, which serves as an indicator of its favorable safety profile. These findings are in line with the results of multiple clinical investigations conducted within the russian federation. Notably, the ALBATROS study, an open-label, randomized, multicenter trial, assessed the efficacy of intravenous esmolol versus enalapril in managing uncomplicated hypertensive crises [25]. The study included participation from eleven clinical centers across russia. Both treatment arms showed significant reductions in SBP and DBP. Esmolol, when titrated in doses ranging from 10 to 70 mg, achieved BP stabilization in 90% of patients experiencing hypertensive episodes. Similar results were obtained in another clinical study. That study evaluated the parameters of 83 patients treated for hypertensive crises by moscow emergency medical teams. Among the patients examined, esmolol not only proved effective in uncomplicated hypertensive episodes, but also demonstrated clinical utility in the treatment of crisis-related complications, including acute cerebrovascular events, acute coronary syndrome, and various tachyarrhythmias [25]. In one of our previous studies, we obtained similar results, which confirms our tactics in relation to patients with PAH [26].

CONCLUSIONS

1. In cardiac surgery patients, the use of the β-blocker esmolol to relieve PAH provides a reliable reduction in

SBP (by 22%) and DBP (by 17%). The period of maintaining the target BP level is 24 hours. The most effective doses are 40 and 60 mg, allowing to achieve the target BP level in the largest number of patients – 20% and 36.7%, respectively.

2. The drug is characterized by good tolerability and a safety profile in this cohort of patients (absence of side effects).

Thus, clinical evaluation of the antihypertensive effect of esmolol in reducing BP has shown that it is effective in stabilizing BP in patients with postoperative hypertension. The titration principle is recommended, which allows selecting an effective and safe individual dose of the drug, ensures safety and efficacy for intravenous administration of esmolol in patients with post-operative arterial hypertension.

Information about the author

Musayev Seymur – Doctor of Philosophy, Cardiovascular Surgeon, EGE Hospital, Baku, Azerbaijan. *E-mail: mic_amu@mail.ru*

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