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Original Article

Esmolol Infusion in Pediatric Intensive Care; 2 Years Retrospective Review

Çocuk Yoğun Bakımda Esmolol İnfüzyonları; 2 Yıllık Retrospektif İnceleme

Gülhan Atakul, Ahmet Gönüllü, Özlem Saraç Sandal, Pınar Hepduman, Ferhat Sarı, Gökhan Ceylan, Utku Karaarslan, Hasan Ağın

University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Pediatric Intensive Care Unit, İzmir, Turkey

ABSTRACT

Objective: Esmolol is an exceptionally effective cardio-selective β (1)-receptor blocking agent that demonstrates a swift onset and a brief duration of action. Our goal in this research was to delve into the utilization of esmolol, a potent intravenous beta blocker agent, among pediatric patients in the intensive care unit who possess various medical conditions.

Method: Our research conducted over a span of two years between December 2020 and 2022, took place at the pediatric intensive care unit (PICU). The demographics, primary diagnoses, intensive care admission diagnoses, blood pressure levels, indications for starting esmolol, echocardiographic imaging findings of patients using esmolol infusion, esmolol doses, duration of use, reason for discontinuation, need for mechanical ventilation, use of inotropes, and pediatric risk of mortality score IV scores of patients using esmolol infusion were recorded in the data set.

Results: The lowest starting dose of esmolol infusion (n=37) was determined as 25 mcg/kg/min and the highest dose as 250 mcg/kg/min. The median age of the deceased patients was significantly high. Additionally, the esmolol infusion doses of the surviving patients were higher. In the surviving patients, the median esmolol dose was found to be significantly higher, while the median age was significantly lower.

Conclusion: The use of esmolol through intravenous infusion in PICUs requires careful consideration and monitoring of the patient's hemodynamic and clinical parameters. Our experience has shown that esmolol can effectively regulate heart rate at low dosages.

Keywords: Esmolol, pediatric intensive care, tachycardia

ÖZ

Amaç: Esmolol, hızlı bir başlangıç ve kısa bir etki süresi ile etkili bir kardiyo-selektif β (1)-reseptör bloke edici ajandır. Bu araştırmadaki amacımız, güçlü bir intravenöz beta bloker ajan olan esmololün çeşitli tıbbi rahatsızlıkları olan yoğun bakım ünitesindeki pediatrik hastalarda kullanımını araştırmaktı.

Yöntem: Aralık 2020 ile 2022 yılları arasında iki yıllık bir sürede yürütülen araştırmamız çocuk yoğun bakım ünitesinde (ÇYBÜ) gerçekleştirildi. Esmolol infüzyonu kullanan hastaların demografik özellikleri, temel tanıları, yoğun bakıma yatış tanıları, kan basıncı düzeyleri, esmolol başlama endikasyonları, ekokardiyografik görüntüleme bulguları, esmolol dozları, kullanım süreleri, bırakma nedenleri, mekanik ventilasyon ihtiyacı, inotrop kullanımı ve esmolol infüzyonu kullanan hastaların pediatric risk of mortality score IV skorları veri setine kaydedildi.

Bulgular: Esmolol infüzyonunun en düşük başlangıç dozu (n=37) 25 mcg/kg/dk, en yüksek dozu ise 250 mcg/kg/dk olarak belirlendi. Ölen hastaların ortanca yaşı anlamlı derecede yüksekti. Ayrıca hayatta kalan hastaların esmolol infüzyon dozları daha yüksekti. Hayatta kalan hastalarda ortanca esmolol dozu anlamlı derecede yüksek, ortanca yaş ise anlamlı derecede düşük bulundu.

Sonuç: ÇYBÜ'lerde intravenöz infüzyon yoluyla esmolol kullanımı, hastanın hemodinamik ve klinik parametrelerinin dikkatli bir şekilde değerlendirilmesini ve izlenmesini gerektirir. Deneyimlerimiz esmololün düşük dozlarda kalp atış hızını etkili bir şekilde düzenleyebildiğini göstermiştir.

Anahtar kelimeler: Esmolol, çocuk yoğun bakım, taşikardi

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Corresponding Author
Gülhan Atakul,
University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Pediatric Intensive Care Unit, İzmir, Turkey
gulhanatakul@gmail.com
ORCID: 0000-0002-3832-9691

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INTRODUCTION

In pediatric intensive care units (PICUs), monitoring the vital signs of patients is an essential component of the treatment process, particularly when it is conducted in conjunction with a multisystem examination. This is especially true for patients who are at risk for complications related to their cardiac function, which can be adversely affected by primary cardiac diseases

or secondary involvement in other medical conditions. Arrhythmias are a common concern in cases of primary cardiac disease, as they can have serious consequences for the patient's overall health. However, the need for treatment methods that aim to correct the patient's hemodynamics may also arise in cases where the patient is experiencing clinical conditions that could negatively impact their cardiac function, such as septic shock caused by severe infections. Therefore, it is imperative that the vital signs and cardiac function of these patients are carefully monitored and monitored in order to ensure that appropriate treatment is provided in a timely manner.

Esmolol is an exceptionally effective cardio-selective β1-receptor blocking agent that demonstrates a swift onset and a brief duration of action[1]. Despite the potential for an increased risk of hypotension, its effect can be swiftly reversed. Its elimination half-life is shorter in newborns and infants compared to children of the pediatric age group (>2 years). Esmolol has been demonstrated to be highly effective in controlling abnormal and elevated hemodynamic parameters in patients suffering from supraventricular tachyarrhythmia, hypertension, and tachycardia, with a noticeable reduction in these conditions seen in conjunction with its use. Infusions of esmolol have also been shown to be beneficial in the acute treatment of cardiac arrhythmias and hypertension in children[2]. In recent years, it has also been utilized in the termination of supraventricular arrhythmias in postoperative cardiac patients for the control of hypertension following cardiac surgery, as well as in the regulation of tachycardia and hyperdynamic profile in cases of sepsis and septic shock[3].

Our goal in this research was to delve into the utilization of esmolol, a potent intravenous beta blocker agent, among pediatric patients in the intensive care unit who possess various medical conditions. By scrutinizing the literature from a pediatric standpoint, we discovered that esmolol has been studied for its pharmacokinetic and therapeutic effects, as well as its use post-cardiac surgery[4,5]. However, we sought to share our own observations and experiences with esmolol in a general pediatric intensive care setting, where patients may present with a range of diagnoses. Thus, we conducted a retrospective analysis on the indications, methods of use, and outcomes of esmolol infusions in the patients we monitored.

MATERIALS and METHODS

Our research project, conducted over a span of two years between December 2020 and December 2022, took place at the PICU. The study involved the examination of the medical records of the patients who were hospitalized during this period, with a focus on the use of intravenous esmolol. All of the relevant clinical notes and treatment orders were carefully reviewed and analyzed in order to gain a comprehensive understanding of the effectiveness of these medications in the treatment of the hospitalized patients. Overall, our research aims to provide valuable insights and recommendations for the use of esmolol in pediatric intensive care settings.

The demographic data, primary diagnoses, intensive care admission diagnoses, blood pressure levels, indications for starting esmolol, echocardiographic imaging findings (if any) of patients using esmolol infusion, esmolol doses (with the highest dose used for each patient noted), duration of use, reason for discontinuation, need for mechanical ventilation, use of inotropes, and pediatric risk of mortality score IV scores of patients using esmolol infusion were recorded in the data set. Each inotrope was grouped separately. Echocardiography results were recorded but patients with multiple findings were not grouped and were not included in statistical analysis due to the presence of multiple findings.

Statistical Analysis

The statistical analysis of the data was performed by the SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics of categorical and numerical data were performed. The distribution of numerical data was evaluated using the Shapiro-Wilk test, histogram, and plot graphics. Non-parametric tests were used due to the non-normal distribution and the median interquartile range values were given.

The study was approved by the Ethics Committee of Health Sciences University of Turkey Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital (protocol no: 813, date: 09.02.2023) and written informed consent was obtained from the parents of all participating subjects.

RESULTS

In our study, the data of 37 patients were analyzed. Demographic data and patient characteristics of these patients are given in Table 1. The lowest starting dose of esmolol infusion was determined as 25 mcg/kg/min and the highest dose as 250 mcg/kg/min. Upon starting esmolol, it was determined that cardiology consultation was requested for 32 (86%) of the total 37 patients and

Table 1. Demographic data, diagnosis, PRISM IV score and esmolol variables of patients using esmolol	
Demographics	**n=37**
Gender	**n (%)**
Male/female	23 (62.2)/14 (37.8)
Age	**Median; (IQR)**
Months	41; (116)
Primary diagnosis of patients	**n (%)**
Norological disease	8 (21.6)
Hematological disease	7 (18.9)
Cardiovascular disease	5 (13.5)
Nephrological disease	4 (10.8)
Metabolic disease	7 (18.9)
Immunological disease	2 (5.4)
Gastroenterological disease	2 (5.4)
Without chronic disease	2 (5.4)
PICU admission diagnoses	**n (%)**
Hypertension	1 (2.7)
Respiratory failure	8 (21.6)
Cardiac failure	2 (5.4)
Septic shock	16 (43.2)
Metabolic crisis	1 (2.7)
MIS-C	1 (2.7)
Acute renal failure	1 (2.7)
Post-CPR	5 (13.5)
Change of consciousness	2 (5.4)
Blood pressures	**Median; (IQR)**
Systolic blood pressure	90 (15)
Diastolic blood pressure	55 (11)
Mean arteriel pressure	69 (13)
Indications	**n (%)**
Hypertension	3 (8.1)
Sinus tachycardia	25 (67.6)
Supraventrcular tachycardia	8 (21.6)
Ventricular tachycardia	1 (2.7)
Esmolol	**Median; (IQR)**
Maximum dosage (mcg/kg/min)	50 (37.5)
Infusion time (hour)	17 (63)
Reason for discontinuation	**Median; (IQR)**
Bradycardia	1 (2.7)
Normocardia	17 (45.9)
Normotension	5 (13.5)
Atrial flutter	1 (2.7)
Medication change	3 (8.1)
Hypotension	2 (5.4)
Exitus (during medication)	8 (21.6)
Mortality scores	**Median; (IQR)**
PRISM IV	9 (11.5)
PRISM IV (%)	4.62 (17.11)

PRISM IV: Pediatric risk of mortality score IV, MIS-C: Multisystem inflammatory syndrome in children, CPR: Cardiopulmonary resuscitation, IQR: Interquartile range, PICU: Pediatric intensive care unit

echocardiographic evaluation was performed. In the echocardiographic imaging of these patients, it was seen that 8 (25%) of them had normal findings. In the other patients (75%), findings such as valve insufficiencies and stenoses, operated or non-operated congenital heart defects, pericardial effusion, pulmonary hypertension, and hypertrophic cardiomyopathy were detected.

The relationship between esmolol dose, duration of use, heart rate and ejection fraction, and inotropic use, and mechanical ventilation is given in (Table 2.) The number of patients using dobutamine and milrinon was too small for statistical analysis. The relationship between the presence of mortality and esmolol dose, duration of use, age, and blood pressure values was investigated. The median age of the deceased patients was significantly high. Additionally, the esmolol infusion doses of the surviving patients were higher (Table 3).

All of the exitus cases were accompanied by underlying chronic diseases, while 7 of them were being followed with a diagnosis of septic shock and 1 with a diagnosis of septic shock and acute respiratory distress syndrome. Two cases were receiving esmolol due to supraventricular tachycardia, while the others were receiving it due to sinus tachycardia. In the surviving patients, the median esmolol dose was found to be significantly higher, while the median age was significantly lower. The reasons for ceasing esmolol were evaluated according to the use of noradrenaline or adrenaline. The median values for esmolol use were significantly higher and age median values were significantly lower in surviving patients (Table 4).

DISCUSSION

Our PICU serves as a center of medical expertise where we treat a wide range of critical illnesses, excluding trauma cases. Given the delicate nature of critical patients, we often must implement cardiac support therapies to address any issues that may arise and impact hemodynamics. We use most frequently employed methods for this purpose include inotropic treatments, fluid therapy, and treatments targeted towards arrhythmias in our intensive care unit. Our studies have shown that the patients admitted to our intensive care unit frequently suffer from chronic diseases, with neurological, metabolic, and hematological ailments being among the most prominent.

Sympathetic-induced tachycardia typically occurs in septic shock patients to compensate for severe

Table 2. Analysis of esmolol, heart rate and ejection fraction variables according to inotrope types and mechanical ventilation use

Treatment variables n (%)	Esmolol dosage (mcg/kg/min) median (IQR)	Esmolol ınfusion time (hour) median (IQR)	Heart rate median (IQR)	Ejection fraction (%) median (IQR)
Inotrop				
Used =29 (78.4)	50 (25)	17 (63)	180 (30)	61 (18)
Unused =8 (21.6)	50 (68.75)	26.5 (60)	167.5 (33)	74 (6.25)
	p=0.506	p=0.897	p=0.281	**p=0.028**
Adrenalin				
Used =17 (45.9)	50 (37.5)	17 (64)	167.5 (28)	63 (20)
Unused =20 (54.1)	50 (43.75)	24 (63)	188 (23)	64 (14)
	p=0.722	p=0.692	p=0.08	p=0.618
Noradrenalin				
Used =26 (70.3)	50 (25)	19.5 (65)	179 (30)	63 (16)
Unused =11 (29.7)	50 (75)	17 (41)	170 (30)	69 (21)
	p=0.738	p=0.441	p=0.618	p=0.75
Dopamin				
Used =10 (27)	37.5 (31.25)	52 (186)	169 (38)	62 (17)
Unused =27 (73)	50 (50)	16 (41)	175 (30)	64 (19.5)
	p=0.502	p=0.028	p=0.692	p=0.768
Dobutamin				
Used =3 (8.1)	25 (25-50)	12 (4-32)	220 (150-230)	54 (50-58)
Unused =34 (91.9)	50 (50)	19.5 (65)	172.5 (30)	65 (19)
	N/A	**N/A**	**N/A**	**N/A**
Milrinon				
Used =2 (5.4)	62.5 (25-100)	18.5 (6-31)	190 (180-200)	65 (16.75)
Unused =35 (94.6)	50 (25)	17 (65)	170 (30)	46 (37-55)
	N/A	**N/A**	**N/A**	**N/A**
Mechanical ventilation				
Used =30 (81.8)	50 (25)	27 (60)	176.5 (30)	62.5 (19)
Unused =7 (18.9)	50 (75)	5 (28)	170 (40)	67 (17.5)
	p=0.314	p=0.111	p=0.891	p=0.876

IQR: Interquartile range, N/A: Not applicable

Table 3. Esmolol dosage, infusion time, age and blood pressure with mortality

Mortality	Age (months) median (IQR)	Esmolol dosage median (IQR)	Infusion time median (IQR)	Heart rate median (IQR)	Systolic blood pressure median (IQR)	Diastolic blood pressure median (IQR)	Mean arterial pressure median (IQR)
Survival	28 (43)	50 (50)	31 (67)	170 (30)	90 (16)	55 (10)	69.97 (11)
Exitus	181 (86)	25 (18.75)	15.5 (25)	176.5 (35)	90 (19)	55 (23)	66.67 (21)
p-value*	**0.001**	**0.044**	0.196	0.867	0.615	0.866	0.81

*Mann-Whitney U test, IQR: Interquartile range

Table 4. Analysis of the reasons for discontinuation of esmolol according to the use of noradrenaline or adrenaline				
Reason of discontinuation	**Noradrenalin n=26 (70.3) n (%)**		**Adrenalin n=17 (45.9) n (%)**	
	Used	**Unused**	**Used**	**Unused**
Bradycardia	0	1 (9.1)	0	1 (5)
Normocardia	12 (46.2)	5 (45.5)	10 (58.8)	7 (35)
Hypotension	2 (7.7)	0	0	2 (10)
Normotension	3 (11.5)	2 (182)	1 (5.9)	4 (20)
Atrial flutter	0	1 (9.1)	0	1 (5)
Medication change	1 (3.8)	2 (18.2)	0	3 (15)
Exitus	8 (30.8)	0	6 (35.3)	2 (10)

hypotension, hypoperfusion, and low cardiac output. Despite successful resuscitation with fluids and vasopressors, according to current clinical guidelines, this high heart rate is often persistent in these patients and usually results from long-term adrenergic stimulation of the heart. This uncontrolled tachycardia has been independently associated with increased mortality risk, so it can be harmful to the patient's condition if not treated properly. Persistent tachycardia is often seen in septic shock patients undergoing resuscitation and is an independent risk factor for increased mortality[6,7]. Almost half of the cases in which we applied esmolol treatment were in septic shock. We saw that the drug was started most often due to sinus tachycardia, which is a result of sympathetic system activation in the septic shock cases. In recent studies on adult cases, the effects of esmolol infusion on heart rate control and clinical outcomes in septic shock patients with tachycardia and hyperdynamic hemodynamic profile have been examined and it has been reported that it can reduce heart rate and increase survival rate. It has also been reported that there is no increase in the adverse effect of esmolol infusion on average arterial pressure[8,9].

In our cases, the median value of blood pressures was within the normal range. Monitoring patients under inotropic treatment and the doses of esmolol infusion may explain this situation. Since our study was a retrospective research, it was not classified as an adverse event, but the reasons for discontinuing the drug could be examined from this perspective. We had cases that developed bradycardia, hypotension and atrial flutter. Hypotension may have developed due to the progression of the shock syndrome in the patient. The case with bradycardia had diastolic dysfunction and pulmonary hypertension along with valve insufficiencies in the echocardiography evaluation. Due to his hypertensive values, esmolol infusion was started and he was not currently receiving inotropic treatment. In the other case where the reason for discontinuation was identified as atrial flutter, we think that we cannot provide definite information about the specific side effect of esmolol infusion in this critical patient due to the multiple medications being taken.

In our study, it was seen that there was no difference in esmolol dose (mcg/kg/min), infusion time, and heart peak values depending on the use of inotropes. At least 1 inotrope was used in 78% of cases. We think that the very small number of patients in our study who did not receive inotropes may affect this result. No difference was also detected when the use of different inotropes was categorized. Dynamic titration of inotropic doses according to the clinic and vital signs of the patient may have affected these values. In a study of cardiac surgery cases, it was shown that esmolol infusion was associated with a decrease in inotropic score in the postoperative period[10]. In our study, the relationship between esmolol infusion and inotropic score was not examined because this should have been prospectively recorded but our study was retrospective. The ejection fractions determined by echocardiography in patients who started inotropes were found to be significantly low. This is an expected situation that can be explained by the need for inotropes in these patients.

It was observed that cases where exitus occurred while receiving esmolol infusion were lost due to acute multiple organ failure related to the underlying illness. This was not due to a complication related to esmolol. Additionally, the low maximum doses of esmolol in these patients suggests that there was not sufficient hemodynamic stability for titration to higher doses of esmolol. Efforts to correct hemodynamic findings in septic shock may not always have a positive outcome. In a randomized controlled study of 1122 adult patients, it

was reported that esmolol did not reduce the need for vasopressors or improve the return of shock in patients with septic shock[11].

We saw that in most of the patients (81.1%), a cardiology consultation was requested and an echocardiographic evaluation was performed. We strongly recommend a cardiology evaluation for the detection of primary heart pathologies and secondary cardiac involvement in critically ill children and intensive care patients. Before starting esmolol infusion, the ejection fraction, contractile functions, and valve functions of the heart can be evaluated. The compensatory mechanisms that occur to ensure sufficient blood circulation in the body should be considered[12]. We recommend closely monitoring blood gas lactate levels and capillary filling times to see the adequacy of tissue circulation in patients receiving esmolol. In addition, in our cases, we saw that electrocardiogram evaluation with cardiac enzyme levels normal in cases where echocardiography was not seen prior to esmolol infusion. These cases were all evaluated as sinus tachycardia.

We frequently detected the reason for discontinuation of infusions in patients using esmolol as normotension and normocardia. It can be said that sympathetic system activation was controlled in these cases. Titration and effectiveness of inotropes may also have contributed to this process. In terms of case numbers, we only analyzed the reasons for discontinuation separately in noradrenaline and adrenaline infusions. The number of patients receiving other inotropic treatments was not sufficient for analysis. In critically ill children, sedation and analgesia play an important role in the success of treatment in intensive care. Inadequate sedation/analgesia should definitely be considered as one of the causes of tachycardia[13]. We have identified that sedation/analgesia has been initiated in all of our cases. In our clinic, we frequently use benzodiazepines and opioid derivative agents. The sedoanalgesic agents used are dynamically titrated according to patient need, so we could not access them from retrospectively recorded notes.

Study Limitation

Limitations of our study include being retrospective, having a small number of patients, being unable to determine the presence of different interventional procedures during tachycardic episodes, and being unable to evaluate the detailed trends of heart rate in detail.

CONCLUSION

In summary, the use of esmolol through intravenous infusion in PICUs requires careful consideration and monitoring of the patient's hemodynamic and clinical parameters. Our experience has shown that esmolol can effectively regulate heart rate at low dosages. Further research, in the form of prospective, randomized controlled studies, is necessary to evaluate the effects of esmolol in combination with various inotropic agents, sedative medications, and inotropic scores in critically ill pediatric patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Health Sciences University of Turkey Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital (protocol no: 813, date: 09.02.2023).

Informed Consent: Written informed consent was obtained from the parents of all participating subjects.

Author Contributions

Surgical and Medical Practices: P.H., Concept G.A., Design: G.A., P.H., U.K., Data Collection or Processing: A.G., Ö.S.S., Analysis or Interpretation: G.A., F.S., G.C., Literature Search: G.A., Ö.S.S., P.H., Writing: G.A., G.C., H.A.

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