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ORIGINAL ARTICLE

Evaluation of the safety and efficacy of metoprolol infusion for children and adolescents with hypertensive crises: a retrospective case series

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Abstract
Background Acute severe hypertension occurs infrequently in pediatric patients and, consequently, data on the efficacy and safety of most antihypertensive agents, as well as the adverse events associated with these agents, are very limited in this population. In this case series, we evaluated the use of metoprolol infusion in children with hypertensive emergencies.
Methods The study population comprised children younger than 18 years who had been admitted to the pediatric intensive care unit at King Abdullah University Hospital with blood pressure above the 99th percentile for age, height, and sex and who were symptomatic at the time of presentation. Metoprolol was given as an infusion at a dose of 1–5 mcg/kg/min. The rate of decrease in blood pressure, side effects from the medication, and outcome were assessed.
Results Thirteen patients ranging in age from 2 months to 16 years were included in this study. The initial mean blood pressure was 23–75 mmHg above the 99th percentile for age, height, and sex. Metoprolol was initiated at a dose of 0.5 mcg/kg/min and titrated according to the target blood pressure to a maximum of 5 mcg/kg/min. Mean blood pressure fell by an average of 12.3, 20.4, and 27.1% at 1, 8, and 24 h, respectively, which is consistent with findings on the use of other intravenous medications reported in published studies. The heart rate did not decrease below the normal range for age. There were no significant side effects of the metoprolol infusion. All patients were discharged home with no neurological sequelae secondary to their hypertension.
Conclusion An infusion of metoprolol for a hypertensive emergency is a safe and effective treatment for pediatric patients.

Keywords Hypertension · Hypertensive crises · Metoprolol · Intravenous infusion

The original version of this article was revised to correct the presentation of the figures.

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Introduction

The definition of hypertension in children and adolescents has remained unchanged over the years; it is defined by blood pressure (BP) percentiles that exceed the 95th percentile for age, sex, and height [1]. Although the prevalence of primary hypertension is increasing in children, the etiology is most likely to be secondary in children. Acute severe hypertension occurs infrequently in the pediatric population, and these patients usually have secondary hypertension [2]. A hypertensive crisis is defined as an acute severe elevation in BP. Depending on the degree of increase in BP and the presence of acute end-organ damage, a hypertensive crisis can be further classified as a hypertensive emergency or hypertensive urgency [3]. A hypertensive urgency is known to be as acute severe elevation in BP without the presence of end-organ damage, while in the presence of acute end-organ damage the sudden severe elevation of BP is referred to as a hypertensive emergency.

Hypertensive encephalopathy is a hypertensive emergency characterized by a sudden increase in BP which results in malfunction of cerebral autoregulation, leading to disruption of the blood–brain barrier and, consequently, an imbalance in oxygen delivery, microhemorrhages, and brain edema [4]. Such changes cause posterior reversible encephalopathy syndrome (PRES) and signs of increased intracranial pressure, including headache, focal neurological deficit, and seizures. Proper management of this potentially life-threatening condition and prevention of its complications depend on prompt

detection and treatment [5]. Just as a sudden increase in BP affects cerebral autoregulation, so does a rapid drop in BP; children cannot adapt to a rapid fall in BP, which may lead to cerebral ischemia. Both situations can cause permanent neurological deficit [6]. According to the "Fourth report on the diagnosis, evaluation, and treatment of high BP in children and adolescents," the aim of antihypertensive medications is to decrease BP to less than the 95th percentile, or to less than the 90th percentile in those with comorbid conditions [1]. This target BP should be achieved between 24 and 48 h of presentation; the mean BP should not be decreased to lower than 25% of the initial value in the first hour [1].

Management of severe hypertension should be initiated by using intravenous antihypertensive drugs [1]. Many drugs have been used efficiently for treating this condition, but some of them lead to a rapid decrease in BP [3]. Patients receiving this treatment usually develop hypotensive complications, which can lead to irreversible neurological damage. In addition, many of the drugs used for hypertensive children still lack pediatric labeling, with most data having been obtained from adult studies [7]. In the pediatric population, data on the efficacy, safety, and adverse events for most antihypertensive agents are very limited or are extrapolated from adult clinical trials or deduced from personal experience [7]. However, in a recent Cochrane review, the authors were unable to determine which drug or drug class is the most effective [8]. The intravenous antihypertensive medications used to treat hypertensive emergencies in children include hydralazine, nicardipine, labetalol, esmolol, and sodium nitroprusside [9–14].

Metoprolol, a selective β1-receptor blocker, is safely used in the oral form in adults with heart failure [15, 16], and it has been used safely as an infusion in adults with hypertensive emergencies. In addition, the use of extended-release metoprolol has been shown to be safe and effective in treating children with established hypertension [17]. However, to our knowledge, the efficacy and safety of metoprolol as an intravenous infusion in pediatric patients with hypertensive crises has not been investigated.

Pediatricians in Third World countries should be able to make decisions to compensate for the unavailability of drugs. On the basis of the cost and market availability, at our institution we have opted to use metoprolol.

In the present study, we reviewed pediatric patients admitted to our hospital with hypertensive emergencies who received metoprolol infusion to decrease their BP.

Materials and methods

Study design

This was a retrospective chart review of patients from King Abdullah University Hospital/ Jordan University of Science and Technology. Pediatric patients between the age of 2 months and 18 years who were admitted to the pediatric intensive care unit (PICU) due to a hypertensive emergency and who had received metoprolol infusion between September 2008 and December 2015 were identified using electronic health records (EHRs). This study was approved by the institutional research board committee approval number 3/96/2016.

Patients and treatment

Patients were eligible if they presented with a sudden increase in BP above the 99th percentile for their age, height, and sex and had any evidence of target organ abnormalities, such as severe headache, seizures, intracranial hemorrhage, PRES, a focal neurological deficit, congestive cardiac failure, papilledema, retinal hemorrhages, and acute vision loss.

Assessment

Blood pressure and heart rate were measured upon presentation to the PICU, and each patient was examined for the presence of any neurological deficit. Each patient with evidence of severe target organ abnormality presenting as seizures or altered level of consciousness underwent a head computed tomography scan (CT scan) or a magnetic resonance imaging (MRI) examination. Metoprolol was started as an intravenous infusion at a dose of 0.5 mcg/kg/min; the dose was increased every 30 min until the target BP was achieved or the heart rate decreased. The maximum dose used was 5 mcg/kg/min. Continuous cardiac and BP monitoring was started for all patients admitted to the PICU. We recorded the BP and heart rate at the time of admission and again at 1, 8, and 24 after the initiation of the metoprolol infusion. Patients were evaluated before discharge to the pediatric ward for any neurological sequelae.

Data collected were represented by mean ± standard deviation (SD) using Microsoft Excel (Microsoft Corp., Redmond, WA).

Results

Of the patients identified from the EHR database, 13 met the inclusion criteria and their data analyzed (Table 1). All 13 patients were symptomatic upon presentation (hypertensive emergency). Four of these patients who presented with seizures were put on the ventilator as their level of consciousness was impaired, they were agitated and their respiration was compromised. Despite receiving sedation they were still hypertensive with BP readings of above the 99th percentile. None of the patients showed evidence of heart failure.

Of the 13 patients who were known to be hypertensive eight received at least one antihypertensive medication, which

Table 1 Characteristics of the study population

Variable	Values [range (mean ± SD)]
Age (years)	0.16–16 (7.85 ± 4.8)
Sex	8 males
	5 female
Initial diagnosis	Chronic kidney disease (9 patients)
	No renal impairment (4 patients)
Presenting symptoms	Headache (7 patients)
	Seizures (5 patients)
	Irritability (1 patient)
Heart rate (beats/min)	75–150 (111.5 ± 29.6)
Initial BP (mmHg)	
Systolic BP	120–200 (168.5 ± 23.57); mz = −0.0016
Diastolic BP	85–130 (110 ± 18.5); mz = −1.45
Increase in systolic BP above the 99th percentile	23–75 (41 ±15.6)
No. of patients undergoing brain imaging	5 patients (4 MRI scans and 4 CT scans)[a]

SD, standard deviation; BP, blood pressure; MRI, magnetic resonance imaging; CT, computed tomography mz, mean *z* score.

[a] Two patients with intracranial bleeding; three patients with posterior reversible encephalopathy syndrome

was adjusted during their stay in the PICU; these were mostly angiotensin-converting enzyme inhibitors (enalapril or captopril) and calcium channel blockers (amlodipine). Two of our patients were discharged on carvedilol in addition to the abovementioned drugs. The other five patients were started on oral antihypertensives once their BP stabilized; the cause of hypertension was determined, and their condition was conducive to the administration of oral medications.

In nine patients the primary cause of hypertension was chronic kidney disease. Five of these patients had end stage renal disease (ESRD) with a glomerular filtration rate (GFR) of <15 ml/min/1.73 m^2, of whom four were already on dialysis (2 on hemodialysis and 2 on peritoneal dialysis), and the fifth was started on hemodialysis as soon as his condition stabilized. One patient showed evidence of fluid overload and was started on dialysis once her condition allowed, with subsequent modifications to her dialysis prescription as needed. The BP of this patient dropped during dialysis and 1 h thereafter; metoprolol had been withheld 15 min prior to and during dialysis. Her BP readings necessitated the re-institution of metoprolol, following which her BP stabilized. There was no evidence of fluid overload in any of the other patients and no change in the dialysis prescription was made.

Of the four other patients with chronic kidney diseases, the primary renal disease was focal segmental glomerulosclerosis in two patients. One other patient had a decreased GFR (57 ml/min/1.73 m^2) at the time of admission, and one had renal artery stenosis secondary to a vascular malformation (Moyamoya disease). This latter patient was found to have an atrophied kidney and aneurysms involving the renal artery in the other kidney. Reflux nephropathy with scarring was the cause of hypertension in one patient.

The remaining four patients had no renal impairment and had a normal GFR. One patient had renal artery stenosis, one patient had lymphoma with renal involvement, one patient had inferior vena cava syndrome, and one patient (the youngest in this group) had an extensive thrombus in his inferior vena cava secondary to umbilical catheterization performed previously in the neonatal intensive care unit (Table 1).

All patients were started on metoprolol immediately upon arrival to the PICU. The starting dose was 0.5 mcg/kg/min, and this was tapered according to each patient's BP to a maximum dose of 5 mcg/kg/min. The average dose range of the metoprolol infusion needed to stabilize BP was 3–5 mcg/kg/min (Fig. 1).

The average decrease in the mean systolic BP and heart rate in addition to the average stay in the pediatric ICU are shown

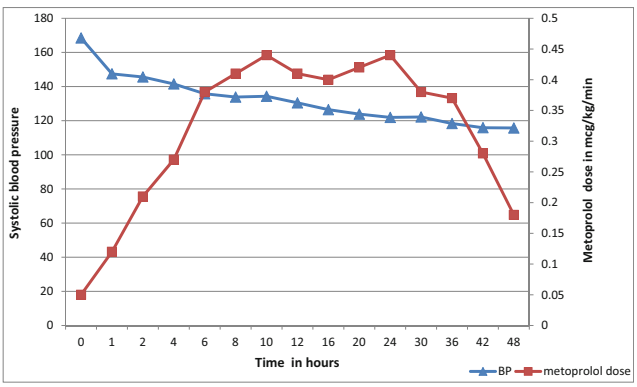

Fig. 1 The relation between systolic blood pressure and metoprolol dose. The average blood pressure and the average metoprolol dose used over time are shown

in Table 2. The trend in BP drop is shown in Fig. 2. All patients were discharged to the ward with a BP of less than the 90th percentile for their age and height. Twelve patients had no neurological sequelae.

One patient presented with stroke and had a high BP; he was admitted to the PICU for treatment of hypertension. He had an underlying vascular malformation in the brain, which also involved other organs (Moyamoya disease), with one atrophied kidney secondary to renal artery stenosis and aneurysms involving both renal arteries. The treatment to decrease BP was effective, but his neurological status remained unchanged before and after treatment. His neurological manifestations and sequelae were attributed to the underlying disease and not to hypertension or clinical management.

Discussion

The Joint National Committee on Detection, Evaluation, and Treatment of Hypertension has defined hypertensive crisis in adults as an acute increase in BP of more than 180/120 mmHg [18]. A hypertensive crisis is not clearly defined in children, and the level of the maximum BP in the pediatric population is a purely statistical concept. It is further sub-classified based on the presence of acute target organ damage, including the brain (i.e., seizures, focal neurological deficit, intracranial hemorrhage, and PRES) as well as cardiac and eye abnormalities (e.g., retinal hemorrhage and loss of vision) into a hypertensive emergency or hypertensive urgency in the absence of target organ abnormalities [3].

BP should be decreased slowly to prevent irreversible neurological damage. To achieve this, the intravenous form of medications should be used, preferably as an infusion as the dose can be titrated to achieve the target BP level leading to a steady decrease in BP [19]. Many antihypertensive drugs have been used [20, 21], most of which have been proven to be effective and are still used but with caution.

The intravenous vasodilator hydralazine has been approved by the U.S. Food and Drug Administration for use in the pediatric population. Hydralazine is the most widely used drug in children with acutely elevated BP. It has a rapid onset of action (5–20 min), an effect lasting up to 6 h, and is effective in lowering BP with minimal adverse effects. However, little data are currently available on its safety and efficacy in the pediatric population. In the study of Flynn et al. on the effect of hydralazine in hypertensive pediatric inpatients, almost one-third of the patients were reported to have an excessive drop in BP, with a reduction exceeding 25% mean arterial pressure [9]. Another study by Ostrye et al. reported similar results [22].

Nifedipine, a calcium channel blocker, is an oral antihypertensive with a rapid onset of action (1–5 min) that lowers BP through vasodilation. The main concern with this drug is the uncontrolled hypotension that might be followed by a paradoxical rise in BP. There is limited published literature regarding its use in the pediatric patient population. The use of immediate-acting nifedipine in the setting of hypertensive crises is currently avoided in the adult population for the abovementioned reason which results in an increased risk of stroke, myocardial infarction, and even death [10]. Another concern with its use in pediatric population is that it comes in oral form, necessitating that the capsule be dissolved before being given to the child, with a high margin of error in dosing.

Sodium nitroprusside, a short-acting intravenous vasodilator, has been utilized for a long time, with only limited data still available on its safety and efficacy. Although this limited body of evidence supports its efficacy in reducing BP, this drug should be used with caution, especially in children whose hypertensive crises are commonly secondary to renal disease, because of the accumulation of the toxic metabolites (cyanide and thiocyanate). [14, 23–25].

Nicardipine belongs to the calcium channel blocker group and can be delivered in intravenous form. Many studies have reported its effectiveness in lowering severely elevated BP due to different etiologies in children in different age groups. It has been reported to have minimal side effects and acts within minutes, but it should be used with caution in patients with heart failure due to its negative inotropic effect. This drug is preferably given through a central line as thrombophlebitis has been reported with use through peripheral intravenous access [11, 12].

Table 2 Clinical findings

Variable	Range and median	Average + SD
Duration of stay in the PICU	2–12 days	5.3 days
Percentage systolic BP reduction after 1 h	7–18% (12%)	12.3 ± 2.9%
Percentage systolic BP reduction after 8 h	11–33% (20%)	20.4 ± 4.8%
Percentage systolic BP reduction after 24 h	15–44% (27%)	27.1 ± 6.5%
Percentage heart rate reduction after 24 h	0–28%	16.4%
Dose of metoprolol used to stabilize BP	3–5 mcg/kg/min	4.2 mcg/kg/min
Duration of metoprolol infusion	1–5.5 days	3.2 days

PICU, pediatric intensive care unit

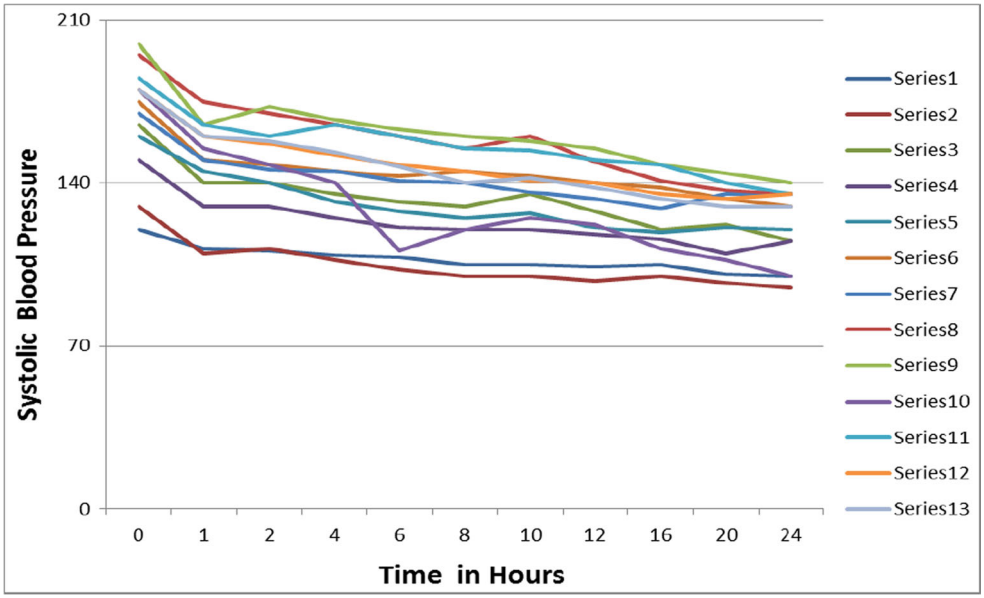

Fig. 2 Drop in blood pressure (BP) in all 13 subjects over the first 24 h of metoprolol infusion

Labetalol is both an α1- and β-adrenergic blocking agent with a rapid onset of action when administered in the intravenous form (2–5 min); it can be given either as boluses or preferably in the infusion form in the setting of a hypertensive crisis. In their study of hypertensive crisis in infants and small children, Thomas et al. reported a reduction in mean systolic BP of at least 20% in less than 8 h with continuous labetalol infusion; they also reported a satisfactory adverse effect profile [13]. Yet only a limited studies have been carried out on its effectiveness and side effects in the pediatric age group, leading to some concern when used in children younger than 2 years of age [13].

Metoprolol belongs to the β-blocker class of drugs. It has been safely used in adults [26] and has also been used in the oral form in children [17]. It is generally a safe medication with minimal side effects; the main concern when using this drug is bradycardia [27]. Other side effects include dizziness and constipation, but these are not sufficiently significant to warrant ceasing its use.

Clinicians have been reluctant to initiate beta-blocker treatment in patients with obstructive airway disease due to the concern that the pulmonary disease may be exacerbated. Metoprolol is a cardio-selective beta blocking agent which is at least 20-fold more potent at blocking β-1 than β-2 receptors. When used in therapeutic doses it has negligible bronchoconstrictive effect. Early clinical trials suggest an increased risk of bronchospasm in patients with chronic obstructive airway disease (COPD) given higher doses of intravenous metoprolol [28]. Other studies suggest changes in the forced expiratory volume, first second, and peak expiratory flow with no clinically apparent respiratory effects, and even if bronchospasm does occur it can usually be reversed with inhaled bronchodilators [29]. The evidence from subsequent clinical trials and meta-analysis suggests that cardioselective β-blockers do not increase the risk of bronchospasm: in fact, they improve patients' outcome and therefore should not be withheld in patients with reactive airway disease or COPD [30].

In one case report, intravenous boluses of metoprolol were used in a 12-year-old female patient with spastic cerebral palsy and global developmental delay. She presented with hypertensive emergency secondary to post-infectious glomerulonephritis. Intravenous metoprolol resulted in a safe decrease in heart rate and BP [31].

In our retrospective case studies, metoprolol infusion at a dose of 3–5 mcg/kg/min was used safely. The dose was tapered slowly starting at 0.5 mcg/kg/min, and it was increased every 30 min to reach the desired effect (Fig. 1). The BP decreased slowly within the safe range set by the guidelines [1]. A significant decrease in BP was achieved in the first 8 h of treatment. These results are similar to the decrease in BP reported in patients receiving labetalol, nicardipine, and sodium nitroprusside infusions. The time to achieve a 20% decrease in the mean systolic BP is comparable among the four agents.

There were no significant side effects in our 13 patients associated with metoprolol infusion. Bradycardia did not occur. However, there was a mild decrease in the heart rate of up to 28% at most; but it did not decrease lower than 68 beats/min, and the heart rate did not decrease below the normal range for age. None of our patients showed evidence of heart failure at presentation, so we cannot guarantee its safety in such patients. Also, none of our patients had asthma, and none developed bronchospasm. Patients were weaned off the infusion at around 5 days after treatment initiation, and they were discharged safely to the ward; no patient had any neurological sequelae related to their hypertension management. In patients with neurological findings at the time of admission, the

metoprolol infusion was found to be a safe treatment, and there were no residual findings upon examination at the time of hospital discharge.

In terms of cost, comparison of the maximum dose needed per hour revealed that sodium nitroprusside cost the least, followed by metoprolol and finally labetalol, making metoprolol a more appropriate option considering the higher cost of labetalol and the toxicity of sodium nitroprusside. The cost of these three medications was calculated according to our local market price.

Our study had a number of limitations, including its retrospective study design and small number of patients. An additional limitation is that the use of metoprolol infusion may not be licensed in some countries for the treatment of hypertension in children.

Conclusions

The children included in our study ranged from 2 months to 16 years in age. To our knowledge no prior studies have demonstrated the use of this drug in the infusion form in this age group. In our study group metoprolol was effective in lowering BP safely regardless of the etiology of hypertension. However, given our limited data it was difficult to compare the dose and the duration needed to reach the desired BP according to the etiology.

Our data show that the clinical effectiveness and safety of metoprolol infusion for the management of hypertensive crises are comparable to those of other antihypertensive drugs used in the pediatric population. Further studies with a larger number of patients are needed to confirm this conclusion. Until then, in the situation where metoprolol may be the only drug available, it would appear to be safe to use in children presenting with hypertensive crises.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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