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Original Research Article

Evaluation of the Efficacy and Safety of Intravenous Labetalol in Pediatric Patients Suffering from an Acute Hypertensive Crisis

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Abstract

Objective: The purpose of this study was to evaluate the effectiveness and safety of intravenous (IV) labetalol in the treatment of hypertensive crises in children.

Methods: A analysis of the medical records of 56 children who were consecutively hospitalized to a pediatric intensive care unit (PICU) with hypertensive crises during the years of July 2009 and 2019.

Results: The percentage of children who reached the primary endpoint (target 95th percentile in more than 12 to 48 hours) was significantly higher in the group that received labetalol as first-line or add-on treatment (n = 23) than it was in the group that did not (62.5% vs. 30.3%, p = 0.03). This difference was statistically significant.

In the labetalol group, a significantly larger number of patients experienced neurological recovery (56.2% versus 18.7%, p = 0.02) In both therapy groups, the percentage of children who experienced hypotension during the first 12 hours was comparable (13% vs. 15%, p = 0.82) The differences in clinical practice over two time periods of five years each (2009–2013 and 2014–2019) demonstrated a statistically significant increase in the use of labetalol in the most recent cohort (53% for 2014–2019 vs. 25% for 2009–2013, p = 0.03).

Conclusion: When compared to intravenous (IV) nitroprusside or nitroglycerine, labetalol was found to be more effective in achieving the primary endpoint in children up to 12 years of age who were experiencing hypertensive crisis. This was the case regardless of whether the drug was administered on its own or in combination with another medication. Labetalol was shown to be safe and was connected to a faster neurological recovery.

Keywords: labetalol; pediatric; hypertensive crises

Introduction

A hypertensive crisis is a life-threatening medical emergency in children, however it is rather uncommon. Early detection and controlled decrease in blood pressure are both crucial components for preventing irreparable damage to target organs, particularly those of the nervous and visual systems [1]. When trying to induce a gradual reduction in blood pressure, intravenous infusions of antihypertensives are recommended over bolus drug administration [2,3]. The vast bulk of the information used to choose drugs is derived from case series involving adults or very

small numbers of youngsters. In third-world nations, sodium nitroprusside is the first-line treatment for hypertensive emergencies that is most frequently utilized. Concerns have been raised, however, about the drug's propensity to produce cyanide poisoning with extended usage and its relative incompatibility with the treatment of children who have renal or hepatic disorders. The fact that labetalol can be administered by infusion makes it a potentially useful alternate treatment option. Once more, the vast bulk of the knowledge about the use of labetalol in acute hypertensive crises originates from adult literature. The data that we have about its effectiveness in children are almost entirely restricted to a few case series [3–6]. Because of this lack of agreement, the selection of first-line medicines to treat children experiencing hypertensive crises is a contentious issue. In addition, the American Association of Pediatrics notes that there is a dearth of robust management guidelines that are based on evidence [7]. In light of the information presented above, the case records of children who had acute hypertensive crises and were treated in the research PICU between July 2009 and 2019 were investigated. The purpose of the present study was to investigate the effectiveness and safety of intravenous (IV) continuous infusion of labetalol as a first-line agent or an add-on medicine in the therapy of the acute hypertensive crisis in comparison to intravenous (IV) nitroprusside/nitroglycerine.

Materials and the Methods

After receiving approval from the Institute Ethics Committee, we were able to access the patient electronic database in order to retrieve the case records of children with acute hypertensive crises who were admitted to a level III pediatric intensive care unit (PICU) of a tertiary care teaching and referral hospital between July 2009 and 2019. These children were older than one month and younger than 12 years of age. An acute hypertensive crisis was defined as a sudden and severe increase in blood pressure (BP), and it was categorized as either hypertensive urgency (without end-organ damage) or hypertensive emergency (with end-organ damage, including hypertensive encephalopathy, cardiac failure, and renal dysfunction) [8]. At the beginning of the study, the systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) of every kid who participated in the research was lower than the 95th percentile for their age, gender, and height. Children with systemic hypertension that was not presenting in a state of crisis, pulmonary hypertension, and hypertension that was owing to elevated intracranial pressure or coarctation of the aorta were not included in this study.

Data were obtained on the following: vitals at baseline (heart rate and respiratory rate); blood pressure at baseline (SBP, DBP, and mean BP (MBP)) using both automatic and manual techniques; Glasgow Coma Scale (GCS); and Pediatric Risk of Mortality (PRISM) score. All of the symptoms that were present at presentation as well as the etiological history were recorded in a predesigned proforma. This included the prior medical history, treatment information, family history, sleep difficulties, and previous urinary tract infections. A complete blood count, serum creatinine, blood urea nitrogen, serum electrolytes, blood glucose, urinalysis, urine culture, fundus examination, end-organ work-up (chest radiography, echocardiography, and neuroimaging), and specific etiological work-up for renal (antinuclear antibodies, complement levels, renal ultrasound, voiding cystourethrogram, renal scan, and renal biopsy) and endocrine (plasma cortisol, The blood pressure reading taken at the beginning of the study was followed by readings taken every hour for the first six hours, then every six to twelve hours, then every twelve to twenty-four hours, and finally every twenty-four to forty-eight hours. An automated oscillometric instrument was used to test the patient's blood pressure. The intra-arterial blood pressure of this group was not monitored in

any way. During this time span, there were also fluctuations in the blood pressure that were documented. Notations were made regarding the pharmacological agent(s) (single or multiple) that were utilized for the treatment of hypertensive crises, as well as any transitions that took place, such as switching to an oral antihypertensive. End-organ involvement of adverse effects linked to neurological (classified as GCS 12 and/or seizure and/or focused deficit), renal, ocular, and cardiac conditions, as well as problems connected to the medication itself, were all noted. Both the patient's outcome (survival or death) and the ultimate diagnosis were taken into account and reported.

The primary endpoint was defined as meeting the goal blood pressure within 12 to 48 hours of admission. This target blood pressure was the 95th percentile for age and gender according to the BP percentile tables based on the fourth report [9].

The need for end-organ supportive care, bouts of hypotension, duration of stay, end-organ involvement at discharge, and death were the secondary outcomes that were measured. Graph Pad Prism version 5 was used to do the statistical analysis on the collected data.

It was determined whether or not the quantitative variables were normal. The summary statistics for categorical variables are presented as frequencies and proportions, the summary statistics for normally distributed continuous variables are presented as means and standard deviations, and the summary statistics for nonparametric continuously variable are presented as median and interquartile range.

For qualitative data, we used the Chi square test or the Fisher exact test; for normally distributed continuous data, we used the students' t-test and the analysis of variance (ANOVA) test; and for nonparametric continuous data, we used the Mann–Whitney U test and the Wilcoxon signed rank test. All of these tests were used to perform intergroup comparisons. The Pearson and Spearman correlation analyses, which are appropriate for parametric and nonparametric data, were utilized, respectively, in order to investigate the relationships that exist between a number of quantitative variables. Every test of significance was conducted with two branches, and a p value of 0.05 was regarded to be statistically significant.

Results

The Pediatric Intensive Care Unit (PICU) took in 8,300 new patients during the course of the research period.

Table 1: Comparison of primary and secondary endpoints in labetalol and non-labetalol groups

	Labetolol Group	Non Labetolol group	P-value
Primary endpoint 95th percentile BP attained > 12 to ≤ 48h	15	11	0.02
Secondary end points			
Mechanical ventilation	3	10	0.06
RRT	0	4	0.33
Raised ICP	0	5	0.35
Duration of PICU stay in survivors (h) (median, IQR)	55.22	72.33	0.43
Neurological involvement	8	16	0.44
Renal involvement	12	15	0.45
Cardiac involvement	11	19	0.39
Hypotension	5	7	0.76
Hyperkalemia	0	3	0.45
Mortality	3	7	0.55

Only one percent of hospitalizations to the pediatric intensive care unit were due to acute hypertensive crises. The bulk of the patients in critical condition had hypertensive emergencies whereas the remaining patients had urgent situations. In 30 of these children, renal etiology was the primary reason why they had high blood pressure. Pheochromocytoma was identified in 7% of instances, while the etiologies were untested in the remaining 93% of cases.

Within the first twenty-four hours of treatment, twenty-three children were given an infusion of labetalol either as a first-line, add-on, or transitional treatment from prior IV antihypertensive infusions (sodium nitroprusside, nitroglycerine). In 10 patients, labetalol was the only antihypertensive that was used initially; in 20 patients, labetalol was added to nitroglycerine or nitroprusside because the initial treatment did not adequately control the patient's blood pressure (BP), the patient had renal dysfunction, or the patient experienced side effects. On the other hand, 35 children did not get labetalol infusions for the regulation of their blood pressure (non-labetalol group). They may have also been given infusions of nitroglycerine or sodium nitroprusside. Both groups had equivalent baseline characteristics, including demographics, median systolic and diastolic blood pressures, mean arterial pressure (MAP), PRISM score, GCS score, and other presenting concerns. The study groups also had similar mean arterial pressures. There was no statistically significant difference between the two groups in terms of neurologic involvement at presentation renal involvement at presentation or cardiac involvement at presentation.

The percentage of children who reached the primary end point was substantially greater in the group that received labetalol (62%) compared to the group that did not receive labetalol. A subgroup comparison was carried out between the children who were given only labetalol (n = 7) and those who were given no labetalol at all (n = 33) in order to gain a deeper understanding of the effectiveness of labetalol. In the most recent investigation, 16 individuals who had been given labetalol in conjunction with nitroglycerine or nitroprusside were disregarded in order to eliminate the possibility of a conflicting effect caused by the other medication. It was discovered that labetalol had not lost any of its effectiveness; the main endpoint was still much greater in the labetalol group. Even if the time period for achieving the primary end objective was shortened from 72–120 h to 24–48 h, the superior performance of labetalol was not diminished in any way.

At the time of the presentation, there was neurological involvement in sixteen children across both the labetalol and non-labetalol groups. There was one patient in the labetalol group who had a GCS of 8, while there were three individuals in the non-labetalol group who had this score. It was necessary to use mechanical breathing in both groups, as well as renal replacement therapy (RRT), and treatment of elevated intracranial pressure (ICP). The percentage of children who experienced bouts of hypotension in the 12 hours following an infusion was comparable in both treatment groups; however, this was not statistically significant. There was no discernible difference in the levels of hyperkalemia between the two groups. The length of time that survivors spent in the pediatric intensive care unit was comparable across the groups who received labetalol and those that did not. In comparison to the non-labetalol group, the proportion of children with neurological recovery at discharge was substantially greater in the labetalol group. In the group that received labetalol, one kid passed away, whereas in the group that did not get labetalol, three children passed away.

For the purpose of analyzing any differences in practice that may have occurred between the two time periods, two distinct five-year epochs (2009–2013 and 2014–2019) were arbitrarily selected as

different time periods. The usage of labetalol was substantially higher among the more recent cohort (53 percent for 2014–2019 against 25 percent for 2009–2013, p = 0.03). Over the course of the two epochs, it was determined that there was not a statistically significant difference between the primary and secondary endpoints.

Discussion

According to the findings of the current research, a noticeably greater proportion of patients who were given labetalol infusion either on its own or as an adjunctive medication attained the primary aim. The necessity of organ supportive care, in addition to the detrimental consequences of hypotension and hyperkalemia, were equivalent in both of the groups. The percentage of patients in the labetalol group who had neurological recovery before being discharged was much greater. Between the two groups, there was no discernible difference in either the length of time spent in the PICU or the fatality rate.

In the current research, one percent of admissions to the pediatric intensive care unit were due to a hypertensive crisis. In a retrospective research conducted in Taiwan, a comparable frequency was observed (55 children between the years 2000 and 2007, accounting for 0.021% of the total number of visits to emergency departments) [10]. On the other hand, the Taiwan study and the present study are not comparable in a few of ways. The majority of the children in the cohort presented with hypertensive crises, which brings us to our first point: the cohort was part of the PICU. As was seen in this study (renal etiology, 61%), the majority of cases of hypertension in children are secondary. This conclusion is corroborated by previous studies that have been published in the medical literature [11–13]. Due to the absence of randomized controlled studies addressing this topic, there is a dearth of data about the management of the acute hypertensive crisis in children. Most data are drawn from adult literature. Infusion drugs (nitroprusside, labetalol) led to improved management of blood pressure compared to bolus medications (hydralazine, diazoxide), according to the findings of a research carried out by Deal *et al*. [3]. When dealing with a hypertensive crises in a child, sodium nitroprusside is the infusion that is administered the majority of the time [2]. On the other hand, it is common knowledge that people who have renal failure are at increased risk for thiocyanate poisoning. Nicardipine and esmolol, both of which are suggested for usage by the guidelines provided by the American Academy of Pediatrics, are not easily accessible for use in the research environment. Because of the adverse effects associated with its use, nitroglycerine is no longer widely used. Because of these limitations, the consumption of labetalol has grown over the course of the past several years, a tendency that was also detected in the current investigation in the more recent eras (2014–2019).

When compared to IV nitroprusside or nitroglycerine, it was discovered that labetalol, whether administered on its own or in combination with another medication, was more effective in reaching the primary objective. The investigations on the effectiveness and safety of labetalol in pediatric patients only involve a relatively small number of case series. Thomas *et al*. examined a reduction of 20% in SBP in children 24 months old who were experiencing hypertensive crises. They discovered that labetalol was successful in achieving this objective within 8 hours [5]. Those who were given either nicardipine or labetalol were put through a series of tests to determine which drug caused a greater drop in their systolic blood pressure and diastolic blood pressure during the first few hours of the infusion [6].

The majority of guidelines suggest that the intended endpoint should be the accomplishment of a blood pressure that is within the 95th percentile for age at 24–48 hours. This threshold, on the other hand, is based more on widespread agreement than

on substantial evidence [1,7,9,14]. The authors, on the other hand, decided that the primary endpoint would be reaching the 95th percentile of blood pressure for age and gender at > 12 to 48 hours. Since this significance was maintained even in the shorter time interval of 24–48 hours, it is highly improbable that the longer time interval chosen played a role in the larger proportion of patients in the labetalol group who achieved primary endpoints in the current trial.

In addition, the results of the current research showed that the endpoint was reached in the labetalol group without a significant increase in the incidence of hypotension in the first 12 hours or hyperkalemia. This was one of the findings of the study. Labetalol does not pose a significant risk to users. Bradycardia, hypotension, hyperkalemia, weakness, and drug eruption were not shown to be major side effects of either nicardipine or labetalol in a research that was conducted by Lee *et al*. [6]. In a similar vein, Bunchman *et al*. [4] did not identify any notable side effects associated with the administration of labetalol intravenously. Patients who had suffered an ischemia or traumatic brain damage were found to have significantly lower blood pressure after receiving IV labetalol, as stated in a study conducted by Thomas and colleagues [5].

The requirement for ventilation, the necessity for RRT, the management of increased ICP, the length of stay, and the death rate were all comparable across the two groups. There was no significant difference in the length of stay in critical care units and death between those taking labetalol, nicardipine, or nitroprusside [5], which is in agreement with the findings of Thomas *et al*.

The findings of the current study demonstrated that although the neurological involvement at presentation was comparable between the two groups, a considerably larger proportion of children in the labetalol group showed neurological recovery. This was the conclusion drawn from the data of the study. There is a difference in recovery between the two groups, but the causes for this variation are not evident. Both groups had similar baseline GCS, elevated ICP, and episodic hypotension.

The present study is an important contribution to the scant body of information available in children about the effectiveness and safety of labetalol in the treatment of hypertensive crises. On the other hand, it is subject to the limitations that are typical of retrospective research. In addition, participants in the labetalol group were taking various antihypertensive drugs in an effort to get their blood pressure under control. The correct method for determining the most effective strategy for the management of hypertensive crises in children is to conduct randomized control trials comparing the various drugs.

Conclusion

When compared to intravenous (IV) nitroprusside or nitroglycerine, labetalol, whether administered on its own or as an add-on drug, proved to be more effective in achieving the primary endpoint and promoting neurological recovery. In both the labetalol and non-labetalol groups, the likelihood of developing hypotension and hyperkalemia was comparable. The current research demonstrates that labetalol is both safe and effective in the management of hypertensive emergencies in children up to the age of 12 years old.

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