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Effects of combined vasopressin-noradrenaline in pediatric patients with refractory septic shock

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Keypoints

The catecholamines refractory septic shock is a disease with high mortality, these drugs are the first line when the shock does not respond to management with fluids. By comparisons between using noradrenaline alone vs. combined vasopressin-noradrenaline, it described the use of vasopressin with noradrenaline improves and supports MAP in patients who do not respond to norepinephrine as the only vasopressor.

Abstract

Background

The evidence of use vasopressin is limited in the pediatric population and therefore this study seeks to evaluate its effect on mean arterial pressure, hospital stay, mortality and tissue perfusion in children with refractory septic shock in the referral Pediatric Intensive Care Unit.

Materials and methods

Observational, retrospective cohort study in children from 1 month to 18 years old with refractory septic shock. 129 infants are included, of which 70 received noradrenaline alone, and 59 received vasopressin-noradrenaline. As measures of association, relative risks, with their respective 95% confidence intervals, were estimated.

Results

The initial mean arterial pressure in both groups showed a significant increase, which was sustained for the following three hours ($p<0.005$). Mortality in the PRISM III low-risk group was lower with noradrenaline alone ($p<0.005$), but equal in both groups with moderate risk according to this scale ($p=0.42$). There were no statistically significant a difference in PICU stay ($p=0.79$) or total hospital stay ($p=0.96$), but there was improved liver ($p=0.004$) and kidney ($p<0.005$) function in the vasopressin-noradrenaline group.

Conclusion

Combined vasopressin-noradrenaline improves mean arterial pressure when the goals have not been reached with a single vasopressor in children with refractory septic shock. Prospective studies are needed to corroborate these findings.

Keywords: shock, septic, noradrenaline, vasopressin, catecholamines, mortality.

Introduction

Shock is a frequent, life-threatening problem, and is considered the most common cause of death in intensive care units, reaching levels cited in the literature of 40-60% (1,2). Aggressive fluid treatment is the initial sup-

port in the resuscitation of hemodynamically unstable children. Catecholamines are the most commonly used vasoactive agents for maintaining blood pressure and perfusion of vital organs (3,4). However, diminished sensitivity of the vascular bed and the myocardium to catecholamines has been demonstrated in shock, which can lead to refractory states (5-7). Vasopressin is an attractive agent for managing shock, since it acts by inactivating the mechanisms responsible for the pathologic vasodilation and the resistance to catecholamine activity (8-10). According to the case reports and studies carried out so far, vasopressin may be used as rescue therapy in pediatric patients with septic shock (11-14). However, a large part of this recommendation is based on adult studies, and therefore more studies in the pediatric population are needed to clarify its role in children in shock. For this reason, this study was performed in a university referral hospital, seeking to evaluate the effect of combined vasopressin-noradrenaline on MAP, its tendency as well as its repercussion on mortality and hospital stay.

Materials and methods

This was retrospective, observational cohort studies, involving patients from one month to 18 years old, who were admitted to the pediatric intensive care unit of the Fundación Cardioinfantil, Bogotá, Colombia, between June 2008 and December 2013. Children were included who had crystalloid-refractory septic shock and who required the use of noradrenaline singly, or combined with vasopressin, as determined by the attending physician, according to the response to this intervention. Patients were excluded if they had another type of shock, congenital cardiopathies, brain death, diabetes insipidus, severe head trauma, or terminal liver failure, or if they were referred to another institution to finish treatment extra-institutionally, (regardless of the reason for this referral), and, therefore, their outcome is unknown.

Sample size and power were estimated to compare paired means, using the G-Power program version 3.1 for Windows. The estimate was made taking into account a difference n means of 5, a correlation coefficient between groups of 0.5, a 20% beta error, a 5% alpha error and a 95% level of confidence. The estimated sample size for each group was 55 patients.

A tool for data collection was designed on the Microsoft Excel® program, based on Visual Basic programming, on which the data obtained from the medical charts was compiled.

The SPSS program was used for data analysis, and a descriptive analysis of the data was performed, showing central tendency and variability measurements for continuous variables through averages and standard deviation, or medians and interquartile ranges; for categorical variables, proportions or frequency tables were reported for each of the analysis groups. In addition, the baseline characteristics were described according to the vasopressor used (noradrenaline, or vasopressin-noradrenaline), and comparison between means was performed according to the time in hours of the MAP assessment, using ANOVA for repeated measurements. Relative risks with 95% confidence intervals were estimated as the indicator for association of the qualitative variables. Differences in averages were used for quantitative variables.

Results

Patients were included who were admitted to the Pediatric Intensive Care Unit of the Fundación Cardioinfantil between January 2008 and December 2013, for a total sample of 2,190 patients, of which 290 patients had an admitting diagnosis of septic shock due to other etiologies, and 129 had fluid-refractory shock and fulfilled the inclusion criteria. Of these, 70 received noradrenaline, and 59 did not respond to high doses of this medication (1 mcgr/k/min), and therefore were labeled refractory to catecholamines, requiring the addition of vasopressin. 161 patients were excluded who had other types of shock, congenital cardiopathies, diagnosed brain death, diabetes insipidus, severe head trauma, terminal liver failure, or were referred to another institution to finish treatment extra-institutionally, (regardless of the reason

for this referral), and therefore the outcome is unknown (1).

Of the 129 patients included in the study, the average age (in months) was 49.36 (SD +/- 58.950) with a mean of 24. The minimum value was 1 and the maximum was 204. Girls were an average of 62 (SD +/- 66) months old, and boys an average of 37 (SD +/- 48) months and the comparison between these two (girls and boys) showed a statistically significant difference (p=0.0017). The male sex predominated, 51.2%, 95.3% of patients were of urban origin and 64.3% of patients were undernourished. The predominant etiology of the septic shock was respiratory (65%), followed by gastrointestinal (24%). 71.3% of cases required conventional mechanical ventilation (Table 1).

Variable	Vasopressin + noradrenaline n=59	Noradrenaline n=70	p Value
Age in months (average-SD)	49 (59)	50 (60)	0.124
Sex			
Female (%)	23,3	25,5	0.423
Male (%)	22,5	28,7	
Origin			
Urban (%)	45,0	50,4	0.875
Rural (%)	0,8	3,9	
Nutritional status			
Normal (%)	15,3	20,4	0.451
Undernourished (%)	32,7	31,6	
Monitoring			
Invasive (%)	44,2	41,9	0.123
Non-invasive (%)	1,6	7,0	
Both (%)	0	5,3	

Table 1. Demographic variables of all the included patients

The patients in both groups were classified according to the severity of their disease, and the risk of dying from it, using the PRISM III scale, as is routinely done when patients are admitted to the Pediatric Intensive Care Unit. In the noradrenaline group, we found a greater proportion of patients considered low risk for mortality according to this scale, and a greater proportion of patients in the vasopressin-noradrenaline group with moderate and severe risk (p=0.000) (Table 2).

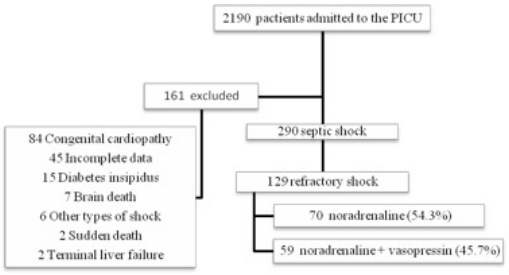

Figure 1. Flow chart of children included in the study.
PICU: Pediatric intensive care unit

Effects on mortality

Death occurred in 34.1% of cases. A greater mortality was found in the vasopressin-noradrenaline group, with a RR of 4.70 (95% CI 1.984, 11.152), adjusted for the confounding variables. However, the patients in this group had a lower PRISM III scale on admission than the noradrenaline alone group (Table 2). A sub-group analysis of mortality according to the PRISM III scale classification showed that in the low risk group there was a greater mortality among those who received vasopressin-noradrenaline compared to patients who received noradrenaline alone (p<0.005; RR: 3.75 95% CI: 1.16-12.12). However, when moderate risk patients according to the PRISM III scale were analyzed, no statistically significant differences in mortality were found between the two groups (p=0.42 RR:0.88 95% CI: 0.60-1.30). The high-risk group cannot be compared, because there were no cases of mortality in the patients who received only noradrenaline (Table 2).

A multivariate analysis of the characteristics or interventions which were statistically significant in the bivariate, showed that the variables which maintained an independent statistical association with the risk of death were: female sex (p<0.001; RR 1.89 95% CI 1.12-

3.195), the use of noradrenaline doses greater than 1 mcg/k/min (p<0.005; RR 2.64 95% CI 1.75-3.98) and the need for inotropes (p<0.005; RR 3.8 95% CI 1.34-10.71).

Mortality risk	n= 129	Mortality	p value
Low			
Noradrenaline (%)	60 (71,4%)	4 (6,7%)	p<0,005
Noradrenaline + Vasopressin (%)	24 (28,6%)	6 (25%)	
Moderate			
Noradrenaline (%)	10 (24,4%)	8 (80%)	p=0,42
Noradrenaline + Vasopressin (%)	31 (75,6%)	22 (71%)	
High			
Noradrenaline (%)	0 (0%)	0 (0%)	p=not estimatable
Noradrenaline + Vasopressin (%)	4 (100%)	4 (100%)	

Table 2. Distribution of the sample and mortality according to PRISM III assessment

Effects on hepatic and renal function

Evaluation of terminal tissue perfusion in solid organs such as the liver and kidney showed that liver function had a greater alteration in the noradrenaline alone group, compared to the vasopressin-noradrenaline group. The relative risk of liver function alteration in the noradrenaline alone group versus vasopressin-noradrenaline was RR 1.61, 95% CI 1.13 -2.30 (p=0.004). These same results were found when renal function was assessed. There was less alteration of renal function in the group that received vasopressin. The estimated relative risk of having renal function alteration if noradrenaline alone was received was 2.12 95% CI 1.41-3.073 (p=0.000) when compared with combined vasopressin-noradrenaline (Table 3).

Effects on cardiovascular function

There was a greater tendency to require the use of inodilators in the vasopressin-noradrenaline group compared with the noradrenaline alone group, although it was not significant. (RR: 1.33 95% CI 1.09, 1.63 p=0.152) (Table 3).

Effects on respiratory function

The main cause of septic shock was pulmonary infection (65%), with an association found between a greater level of plateau pressure and a greater severity on the PRISM III scale in the group that received vasopressin-noradrenaline (RR 1.99 95% CI 1.19, 3.34). No statistically significant differences in mean airway pressure and proportions of partial pressure arterial oxygen/fraction of inspired oxygen (PaO2/FiO2) presentations were found (p=0.175). (Table 3)

Effects on hospital stay

Total hospital stay in days was on average 32.86 (SD+/-27.16, IQR 129). Time spent in the intensive care unit was 18.7 (SD+/-15.14 days, IQR 89). No significant differences in hospital stay (p=0.960) or intensive care unit stay (p=0.791) were found between the two groups, in spite of the fact that the vasopressin-noradrenaline group had a lower PRISM III scale severity on admission (p=0.168).

Effects on mean arterial pressure

In both analyzed groups there was a statistically significant improvement in MAP, regardless of the age group in which the medication was used, which was maintained over time. In the noradrenaline group, the mean arterial pressure showed a significant increase one, two, and three hours after initiating it (p<0.005), compared to baseline. No differences were found between the measurements at two (p=0.145) and three hours (p=0.798) (Figure 2).

Meanwhile, the group of patients who received vasopressin-noradrenaline showed a significant increase in

Variable	Vasopressin + noradrenaline n=59	Noradrenaline n=79	p Value
Hypotension			
Yes (%)	44,2	47,3	0.055
No (%)	1,6	13,2	0.000
Liver function			
Normal (%)	26	41,1	
Altered (%)	18,7	19,7	0.006
Kidney function			
Normal (%)	29,5	35,4	
Altered (%)	16,3	4,7	0.175
Cardiovascular function			
Normal (%)	6,3	2,6	
Altered (%)	38,6	29,1	
Respiratory function (PaFiO2)			
>300	0,8	7,1	
200 - 300	18,7	48,1	0.013
100 - 200	25,2	6,2	
< 100	11,0	37,3	0000
Urinary output			
Normal (%)	31,0	17,5	
Altered (%)	14,0		
Coagulopathy			
No (%)	15,9		
Yes (%)	29,4		

Table 3. Comparison between groups, clinical characteristics

mean arterial pressure (p<0.005) from the moment it was started. Comparison at two (p=0.853) and three (p=0.758) hours after adding vasopressin showed no significant differences, because MAP was maintained during this time. There were no significant differences in initial mean arterial pressure between the two groups (p=0.519).

Neither were there significant differences in mean arterial pressure at one hour (p=0.944), two hours (p=0.714) or three hours (p=0.482) when the effect of the two groups was compared, but it was shown that MAP was sustained over time regardless of the medication used (Figure 2).

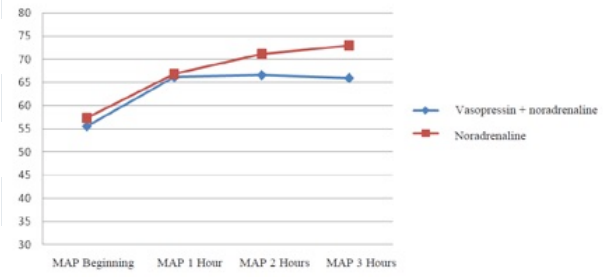

Figure 2. Comparison of mean arterial pressure

MAP: mean arterial pressure

Vasopressor doses used

The most frequently used noradrenaline dose used was less than 0.5 mcg/kg/minute when it was used as the only vasoactive (n= 40.3%); patients who had more than 1 mcg/kg/min of noradrenaline (n=38.0%) had vasopressin added on due to the lack of therapeutic response and because they did not achieve MAP goals. However, 61.3% required low vasopressin doses between 0.1 and 2 mcg/kg/min.

Discussion

Sepsis is one of the main causes of morbidity and mortality in pediatrics, and one of the main reasons for admission to the Intensive Care Unit (15). The criteria for sepsis in adults have been described since the 80´s, but only until 2004, in the International Consensus, were these definitions adapted to the pediatric population according to the age ranges and physiological variables of this population, which allowed the development of management guidelines for severe sepsis and septic shock, as well as the unification of criteria for carrying out research in the pediatric context. Catecholamines have been the vasopressors of choice used in vasodilated septic shock with decreased systemic resistance, in order to optimize mean arterial pressure and therefore the tissue perfusion pressure of vital organs (16). Unfortunately, many patients do not respond to catecholamines, and animal studies have documented that low vasopressin

levels may be found in refractory septic shock (17). This hormone, at doses above its endocrine physiological effects, has a potent vasopressor effect by stimulating the V1 receptors located in the endothelium (18-20). Based on these principles, vasopressin is used widely in cardio-brain-pulmonary resuscitation in adults, and as a potent vasopressor in patients with catecholamine-refractory vasodilatory septic shock (21-23).

One of the most important research studies on this subject has been the VASST study by Russell et al. (17), where, in 778 adult patients with vasodilatory septic shock, vasopressin was used in one group, and noradrenaline in the other, as the vasopressor of choice. Upon analysis of the primary objective, no statistically significant difference was found in terms of mortality at 28 days (p=0.26) or 90 days (p=0.11). Neither were significant side effects found in either of the two groups (p=1.00), nor a longer hospital stay in the ICU. Unfortunately, both medications were not used simultaneously, nor was an evident improvement in systemic vascular resistance, by optimization of the mean arterial pressure, reported (16). Our study evaluated the systemic vascular resistance response as evidenced by an improved MAP in pediatric patients with fluid-refractory septic shock, and in whom noradrenaline alone or combined vasopressin-noradrenaline was used in order to achieve a mean arterial pressure which would guarantee good tissue perfusion pressure. A statistically significant increase in MAP was found, which persists up to three hours after starting the medication, both in the noradrenaline alone group ($p< .005$), as well as in the vasopressin-noradrenaline group ($p< 0.005$).

Usual practice in pediatric intensive care is to add another vasopressor when noradrenaline alone is not improving MAP and the patient continues to be hypotensive, especially if high doses are being administered; in this regard, we found that adding vasopressin to noradrenaline initially improved MAP and also sustained it for the following three hours ($p< 0.005$) (24-26). The average dose of noradrenaline at which it was decided to add vasopressin in most of the patients in the present study (67.7%) was high (greater than 1 mcgr/k/min). There are no studies in children where combined vasopressin-noradrenaline was used in refractory shock with these noradrenaline doses. It is important to emphasize that all the patients with doses of noradrenaline greater than 0.5 mcgr/k/min received supplementary steroids to treat functional suprarenal failure, in accordance with our management guidelines. This confirms the hypothesis that the etiology of refractory vasodilated shock in children involves non-adrenergic phenomena, which necessitates the consideration of the use of other vasopressors with different mechanisms of action. In fact, most of the patients responded to low initial doses of vasopressin when the decision was made to combine it (61.3%) with noradrenaline.

Choong et al.´s work (27) evaluated the effect of vasopressin in 79 children with vasodilated shock, using vasopressin or placebo, and its repercussion on the hemodynamic state. The average dose of noradrenaline was 0.1 mcgr/k/min, and there was no significant improvement in MAP with the addition of vasopressin ($p=0.18$). This may be explained by the fact that they used a dose of noradrenaline 10 times less than that used in the patients in our study. Accordingly, the children did not strictly have refractory shock, but rather just vasodilated shock, which might improve with higher doses of any catecholamine. The use of vasopressin in children with refractory shock combined with high-dose noradrenaline has only been described in this study, with a significant and sustained improvement in MAP. This suggests that the response of this group of patients could be due to different mechanisms of action related to the effects of vasopressin, and could be an interesting research line for future prospective studies in children who do not respond to high doses of noradrenaline.

Likewise, in this study we found that patients with fluid-refractory septic shock had a global mortality of 34.1%, and those who received vasopressin-noradrenaline, in general, had a greater mortality compared with nora-

drenaline alone (RR 4,7 95% CI 1.9-11.15). However, these findings should be interpreted with caution, because in order to be analyzed, the severity of the disease should be standardized, using the most accepted scale for this purpose, which is the PRISM III. When the results were analyzed taking into account the severity of the disease, we found that in patients at low risk of dying on admission (PRISM III Scale less than 20), the group with noradrenaline alone had a lower mortality (6%) compared to the vasopressin-noradrenaline group. ($p<0.005$).

The study of mortality in the moderate risk group (PRISM III from 20 to 30) showed no statistically significant differences between the two ($p=0.42$). Russell et al.´s study (16) had similar mortality findings, as was mentioned earlier, when the totality of patients was stratified by severity. Likewise, Choong et al. (27) found no statistically significant differences ($p=0.24$) between vasopressin and placebo in mortality.

Analysis of the high risk for mortality sub-group was not possible, because we did not have enough patients (only four in the vasopressin-noradrenaline group), and, in addition, no patient in the noradrenaline-alone group had a high risk of mortality severity scale on admission (PRISM III >30).

An important finding in our study is that the multivariate analysis showed that the use of high doses of noradrenaline (>1mcg/k/min) together with the use of other inotropes was associated with greater mortality ($p<0.005$). This is very important, because we should design prospective studies to compare an earlier introduction of vasopressin in patients with fluid- and catecholamine-refractory hypotensive shock, and thereby evaluate if the use of a potent vasopressor medication due to non-adrenergic effects (vasopressin) may have an impact on improving MAP, mortality, PICU stay, and on optimizing the perfusion of end organs such as the liver and kidney, which are very sensitive to hypoxia due to hypoperfusion. Also, when the involvement of other organs, such as the liver and kidney, was evaluated in this study, we found that the vasopressin-noradrenaline group had a progressive improvement in biochemical tests, compared with the group in which noradrenaline alone was used $p<0.005$). This could be explained by tissue perfusion optimization phenomena as MAP improves with the addition of vasopressin to the noradrenaline, but animal model studies should be taken into consideration, which have shown that the use of vasopressin improves renal function and reduces liver apoptosis, which usually presents in shock and tissue hypoperfusion (12,28). These liver and renal function findings in the current study have not been seen in other series.

These study´s limitations arise from its retrospective nature. One limitation is the little control of the researcher over the data capture protocol and treatment schemes used. In addition, few patients with a high severity PRISM III scale were found. These patients may have greater mortality to begin with, and the impact of the vasopressin-noradrenaline combination in them could not be evaluated objectively, since no patient receiving noradrenaline alone had this disease severity, as described earlier.

Conclusion

The use of noradrenaline alone and combined vasopressin-noradrenaline is associated with an increase in mean arterial pressure from its initiation, regardless of the severity stratification of the disease on admission. The use of vasopressin with noradrenaline improves MAP from its initiation in patients who are hypotensive in spite of the use of moderate to high doses of noradrenaline. The use of one strategy or the other did not affect hospital stay, but the vasopressin-noradrenaline combination had lower alteration of renal and liver function. However, it was seen that children who receive noradrenaline at doses greater than 1 mcgr/k/min, with or without vasopressin, have a 2.6 times greater risk of mortality than those who receive a lower dose. Prospective studies are needed to evaluate the impact of combining vasopressin and noradrenaline in pediatric patients with fluid-

refractory septic shock, in terms of mortality, improved MAP, and hospital stay.

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