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ORIGINAL ARTICLE

Hydrocortisone for the treatment of refractory hypotension: a randomised controlled trial☆,☆☆

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KEYWORDS
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Abstract
Introduction: Systemic hypotension is a common sign in critically sick infants. Several studies have suggested that the use of short series of corticosteroids increases arterial blood pressure and reduces the inotropic support needs in preterm neonates with hypotension. There are a small number of reports on the use of hydrocortisone (HC) for the treatment of refractory hypotension in infants.
Material and methods: To assess the effectiveness of hydrocortisone in the reduction of inotropic support in infants with refractory hypotension. Population: infants who required dopamine ≥ 14 μg/kg/min and/or epinephrine.
Design prospective, controlled, randomised, double-blind trial with placebo.
Intervention: HC: 2.5 mg/kg every 12 hours, for 48 hours intravenously (intervention group [IG]); placebo: isotonic saline 1.25 ml/kg/doses intravenously (placebo group [PG]) every 12 hours, for 48 hours. Randomisation was performed in blocks with blind assignment.
Results: A total of 50 infants with refractory systemic hypotension were prospectively recruited. Patient characteristics were similar in both groups. Requirements for inotropic support at 48 hrs were achieved in 60% of the IG versus 24% of the PG *(P*=.009, RR: 2.5, 95% CI, 1.16-5.38). A significant association was observed between the administration of HC in infants treated with epinephrine and the presence of hyperglycaemia *(P* =.008).
Conclusion: In patients with refractory hypotension hydrocortisone administration reduced the need for inotropic support. Further studies with a greater number of patients are needed to confirm the effectiveness of HC as a therapeutic tool in these infants.

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PALABRAS CLAVE
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Dopamina;
Epinefrina; Esteroides

Hidrocortisona para el tratamiento de hipotensión refractaria: ensayo clínico controlado y aleatorizado

Resumen
Introducción: La hipotensión arterial es un signo frecuente en recién nacidos críticamente enfermos. Varios estudios clínicos señalan que series cortas de corticoides aumentan la PA y disminuyen el requerimiento de inotrópicos en prematuros con hipotensión. Existe escaso número de estudios de empleo de hidrocortisona para el tratamiento de la hipotensión refractaria en recién nacidos (RNT). El objetivo de este estudio es evaluar la eficacia de la hidrocortisona (HC) para la reducción del soporte inotrópico en RNT con hipotensión arterial refractaria.
Material y métodos: Se incluyó a todos los RNT con requerimientos de dopamina ≥ 14 μg/k/min y/o epinefrina. Diseño: prospectivo, controlado, aleatorizado, doble ciego con placebo.
Intervención: HC: 2,5 mg/kg c/12 h, por 48 h por vía intravenosa (IV) (grupo intervención [GI]); placebo: solución fisiológica 1,25 ml/kg/dosis IV (grupo placebo [GP]). Se efectuó aleatorización en bloques con asignación oculta.
Resultados: Ingresaron al estudio 50 RNT con hipotensión refractaria. No se observaron diferencias significativas entre los 2 grupos. La reducción del soporte inotrópico a las 48h en el GI se alcanzó en el 60% de los pacientes vs. el 24% en el GP (p = 0,009, RR = 2,5, IC del 95%, 1,16 a 5,38). Se observó una asociación significativa entre la administración de HC en RNT tratados con epinefrina y la presencia de hiperglucemia (p = 0,008).
Conclusión: La administración de HC en pacientes con hipotensión refractaria redujo la necesidad de soporte inotrópico. Estos datos contribuyen a continuar investigando acerca del papel de los esteroides en el soporte hemodinámico de pacientes críticos.

Introduction

Arterial hypotension is a common sign in critically ill newborns admitted to neonatal intensive care units (NICUs). It is estimated that approximately half the patients admitted to a NICU receivwe some treatment to raise their arterial blood pressure (ABP) in order to maintain blood flow to vital organs, such as the central nervous system, myocardium and kidneys.[1,2] The current treatments for hypotension are volume expanders and inotropes (dopamine, dobutamine, epinephrine, norepinephrine).[3,4] Most infants with arterial hypotension respond to conventional treatment; however, there is a group of extremely ill infants (severe asphyxia, prolonged and complex surgery, septic shock, pulmonary hypertension) who show serious haemodynamic instability with hypotension that is refractory to conventional treatment.[5] Hypotension is termed refractory if it persists despite maximum medical treatment (high doses of inotropes and expanders). It has been postulated that this phenomenon is due to a gradual desensitisation of cardiovascular system receptors to catecholamines (down-regulation), involving lysosomal destruction of these receptors. This down-regulation would occur after the receptors had been exposed for several hours to high doses of endogenous or exogenous catecholamines.[6,7] On the other hand, various clinical situations have been reported of absolute or relative adrenal insufficiency that could contribute to resistance to vasoactive drug effects. However, not all children with low cortisol levels will present with refractory hypotension, and conversely, children with normal cortisol levels can develop clinically severe haemodynamic instability.[5]

The possibility of using corticosteroids to treat refractory hypotension has been investigated in adults,[8] in paediatric patients[9,10] and in premature infants.[11-13] Corticosteroids regulate the expression of adrenergic receptors and of some second messenger system components (genomic effects), they stimulate binding of cell-surface receptors to catecholamines, decrease catecholamine metabolism and increase intracellular calcium availability.[3,14,15] The Hospital Juan P. Garrahan is a public tertiary paediatric hospital, without a maternity unit. Infants admitted to neonatal intensive care are all transferred there as a result of some condition that could not be resolved in the original maternity unit. A high percentage of the infants admitted to intensive care are critically ill, with haemodynamic instability. If these symptoms do not resolve with conventional treatment, a short course of hydrocortisone (HC) is often administered; however, the effectiveness of this treatment has yet to be demonstrated.

The aim of this study is to establish whether administration of HC, compared with placebo, reduces the need for inotropic support in full term infants (FTIs) with arterial hypotension that is refractory to treatment. Our secondary endpoint is to assess the effect of HC on haemodynamic parameters, mortality and the appearance of short-term adverse effects associated with HC administration.

Material and methods

- Population: 50 FTIs with refractory hypotension were prospectively recruited. Inclusion criteria were

gestational age ≥ 37 weeks; systemic hypotension despite treatment with volume expanders (10-20 ml/kg isotonic saline solution) and dopamine ≥ 14 μg/kg/min for at least 2 hours. Patients that met the eligibility criteria were consecutively enrolled after the informed consent had been signed by a parent or the main caregiver.

- The following were considered exclusion criteria: patients with major malformations or lethal chromosomal abnormalities, congenital adrenal hyperplasia, hypovolaemic or haemorrhagic shock, congenital heart defect with left ventricular outflow tract obstruction, or those who had received postnatal corticosteroids.
- Design: a prospective, double-blind, randomised placebo-controlled trial, performed in the Neonatal Intensive Care Unit of the Hospital de Pediatría Prof. Dr. J. P. Garrahan, Buenos Aires, Argentina.
- Randomisation: We used a single randomisation method in blocks of four, generated using a random-number table. The sequence was hidden using opaque envelopes in the hospital pharmacy and was not accessible to the other investigators.
- Implementation: two pharmacists (MT, ML) were responsible for defining assignment and preparing the product (placebo or HC). They were the only ones who knew the contents of each syringe; the syringes were left prepared, numbered and ready to be used in the NICU. To ensure trial blinding, the two products (HC and placebo) were the same colour, odourless, diluted to the same administration volume and equivalent to a dose of 2.5 mg/kg of HC. Each patient received a two-day course of treatment with HC sodium succinate, 2.5 mg/kg per dose intravenously every 12 hours, or isotonic saline solution as a placebo.
- Assessment of therapeutic effect: the intervention was considered effective if inotropic support could be reduced 48 hours after entering the trial, defined as a reduction in the dopamine dose to 50% of the initial value and/or discontinuation of epinephrine treatment.
- Elimination criteria: glycaemia greater than 300 mg % despite reducing the glucose infusion rate to 4 mg/kg/min or gastrointestinal haemorrhage (haematemesis or melaena). In these cases, administration of the treatment was suspended; the data were incorporated into the final intention-to-treat analysis.
- Treatment of hypotension: hypotension was defined as a mean ABP below the 5th percentile for corresponding age in hours/days and weight.[16] According to the treatment protocol in our Unit, the treatment sequence in full term infants with systemic hypotension is to start with one to two boluses of saline solution at 10 ml/kg/dose for expansion; if the two volume expansions are not sufficient, dopamine is added at 5-10 μg/kg/min and gradually increased until the desired ABP is reached. The use of dobutamine is restricted to patients with contractility disorders. If the expected effect is not achieved with these inotropes, epinephrine at 0.1 μg/kg/min is administered. Blood products, such as red blood cells or fresh plasma or platelets, are not used unless the patient has anaemia, coagulation disorders or thrombocytopaenia.
- For the purposes of the trial, refractory hypotension was defined as ABP below normal values after 2 hours of treatment (two volume expansions and dopamine ≥ 14 μg/kg/min and/or initiation of epinephrine).
- Mortality: the mortality analysis was performed within 15 days of admitting each patient to the protocol.

The trial had an open design in that the neonatologist in charge of the patient, despite being blind to group assignment, could administer corticosteroids outside protocol if considered necessary in his/her clinical judgement. Such treatment was recorded in every case as a co-intervention.

We collected data for the following study variables: gestational age, birth weight, weight at admission to the protocol, reason for hospital admission of each patient. The systolic, diastolic and mean ABP were recorded (by invasive or noninvasive methods) immediately before the intervention and at 2, 6, 12, 24 and 48 hrs. In addition, we recorded the following parameters: heart rate, urine output, intravenous fluid volume input, dose and type of inotropes used, glycaemia values and other therapeutic co-interventions in the same time intervals. The appearance of digestive haemorrhage, signs of infection and/or confirmed sepsis and overall evolution were systematically recorded up to 15 days after inclusion of the patient in the protocol. The trial was approved by the Hospital Institutional Review Board and Ethics Committee (registration no.: 729/04) and by the regulatory body in Argentina, ANMAT, in March 2005, in the independent researcher category (Prov. no.1674. File no.1-0047-0000-01284-02-5).

- Statistical analysis: We have expressed the descriptive statistics as the mean or median, « standard deviation or interquartile range and percentage. Student's *t* test or the Mann-Whitney U test was used for continuous variables and the chi-squared test for categorical variables. In addition, Kaplan-Meier curves were plotted to estimate the effect of the intervention on the reduction in vasopressor use during trial follow up; the comparative analysis was performed using the Log-Rank test. The results are expressed as relative risk, number needed to treat and 95% confidence interval (CI). We used the statistical software package STATA 9.0 for Windows (Statacorp, Texas, USA). A significance level of 5% was established for all the comparisons. The results for all the patients included in the trial were analysed by intention to treat.

To calculate the sample size, prior data from the unit were used, showing a baseline favourable response rate of 10%. We calculated that 21 patients needed to be recruited in each arm to show a significant difference in the effect (estimated as an increase in response from 10% to 60% after corticosteroid treatment), with a power of 90% (β error = 0.10) and an α error of 0.05 (two-sided).

Results

Of a total of 51 infants who met the eligibility criteria, 50 were included in the protocol. Just one patient was excluded owing to lack of consent from the family. 25 patients were

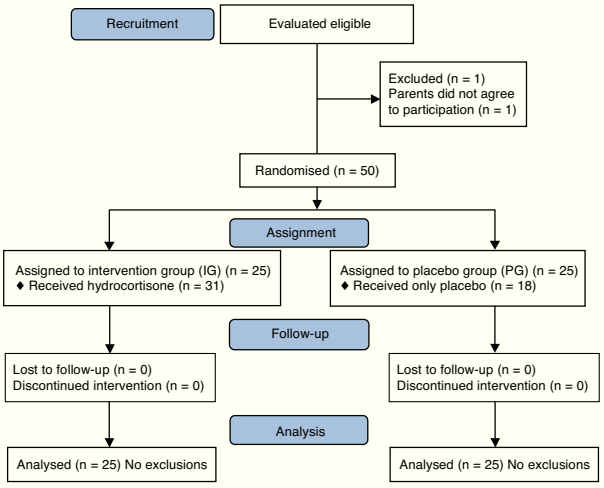

Figure 1 Flow diagram.

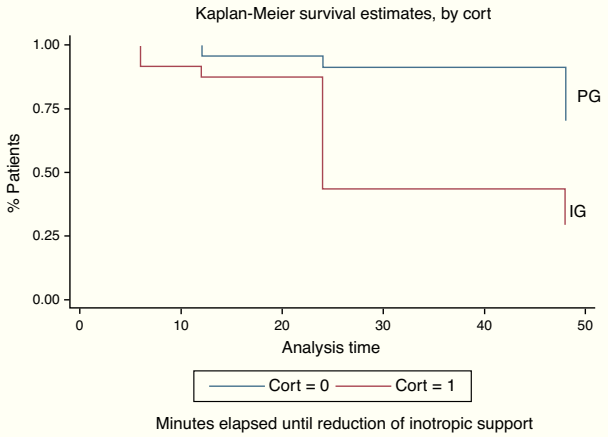

Figure 2 Comparison of Kaplan-Meier curves between the IG (cort = 1) and the PG (cort = 0).
IG: intervention group; PG: placebo group. gr2

randomised to the intervention group (IG) and 25 to the placebo group (PG); 31 infants received HC and 19 placebo, since it was an open trial in which the treating physician could prescribe corticosteroids if considered necessary. The 6 patients who received corticosteroids belonged to the placebo group. Figure 1 shows a flow diagram of the trial subjects at every stage, following CONSORT Group recommentations.[17] The IG and PG groups were similar at the beginning of the study (Table 1). The main reasons for hospitalisation were pulmonary hypertension (n = 23), congenital heart defects (n = 18) and surgical treatment (n = 9). Of the infants with pulmonary hypertension, 11 had congenital diaphragmatic hernia, 4 had meconium aspiration syndrome, 4 primary pulmonary hypertension, 3 pneumonia and 1 had cystic adenomatoid malformation. The reason for indicating HC was refractory hypotension due to septic shock in 34% of cases. Reduction of inotropic support during the follow-up period took place in 21 of the 50 patients admitted to the trial; 15 patients (60%) belonged to the IG and 6 patients (24%) to the PG. This difference was statistically significant, p = 0.009; RR 2.5 (95% CI, 1.16-5.38). According to this difference, the number needed to treat is 2.77. In addition, we investigated whether the decrease in inotropic support differed over the course of the trial, and for this purpose we measured the time (hrs) in which each patient reached the event of interest (reduction of inotropic support). Figure 2 shows differences in the two survival curves in favour of the treated group, in which the expected response occurred significantly earlier (Log-Rank test 0.02). No statistically significant differences were found in the other haemodynamic variables examined: heart rate, ABP or urine output at 2, 6, 12, 24 and 48 hrs after intervention. Figure 3 shows the ABP values for both groups at 0, 12, 24 and 48 hr timepoints. 84% of the patients (42/50) required the use of additional volume expansion during the trial; the frequent expansion requirement (> 2)

Table 1 Characteristics of the populations treated with hydrocortisone or with placebo at the beginning of the trial.

	Hydrocortisone (25)	Placebo (25)	p
Age in days[a]	7 (2-20)	6 (3-19)	0.80
Weight (g), mean ± SD	2,936 ± 680	3,184 ± 805	0.24
Male sex, n (%)	11 (44%)	12 (48%)	0.77
GA (wks), mean ± SD	38 ± 1.4	38 ± 1.8	0.67
Dopamine dose (μg/kg/min)[a]	18 (14-20)	17 (9-18)	0.39
Epinephrine dose (μg/kg/min)[a]	0.5 (0,5-0,7)	1 (0,3-1)	0.80
Urine output (ml/kg/h)[a]	2.55 (1,3-3,6)	2.6 (1-3)	0.65
Infusion volume (ml/kg)[a]	60 (40-70)	60 (60-80)	0.33
Mean blood pressure (mmHg)[a]	46 (38-58)	46 (39-50)	0.63
Heart rate (beats per min)[a]	168 (150-180)	153 (143-167)	0.08

SD: standard deviation; GA: gestational age.
[a]Results are expressed as median (interquartile range).

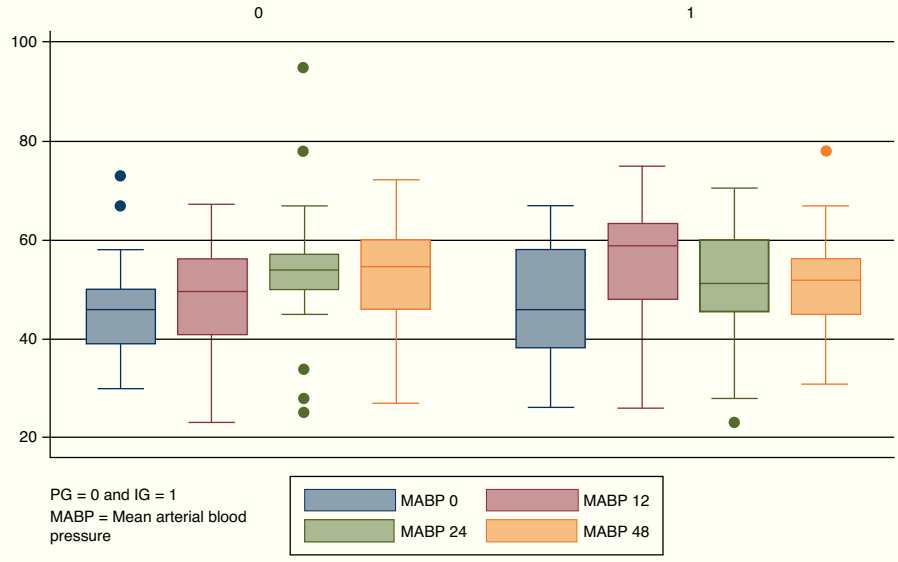

Figure 3 Blood pressure after 0, 12, 24 and 48 hrs in the two groups.

was more common in the placebo group (32%) than in the intervention group (24%), although this difference was not statistically significant. Table 2 presents the adverse effects in the two groups; there were no significant differences in the presence of complications attributed to HC treatment. Hyperglycaemia was more frequent in patients who received epinephrine (14/28, 50%); by contrast, only one patient had hyperglycaemia among those who did not receive epinephrine. This difference was significant and proved the association between hyperglycaemia and the use of epinephrine (p = 0,008). No differences were observed between the groups for the other adverse effects (Table 2). 10 of the 50 patients died (20%); 3 belonged to the IG (12%) and 7 to the PG (28%) (p = 0.15, RR 0.42, 95% CI, 0.12-1.42); although the difference in this outcome in our sample does seem significant, the trial was not designed to establish the effect on mortality and therefore it does not have sufficient statistical power to enable us to deduce whether the use of corticosteroids may be related to a reduction in mortality in this group of children whose lives are at high risk on account of their initial condition.

Discussion

The use of corticosteroids for managing haemodynamic support in infants has been proposed in many studies. Although the results are not conclusive, some authors recommend using them in patients with hypotension that is refractory to treatment with volume expanders and vasopressors.[18] There is a larger number of studies on the neonatal period for preterm newborns[19-23] than for FTI (5, 15). In a recent blind, randomised, controlled trial, Ng et al. assessed the effectiveness of a stress dose of HC (1 mg/kg every 8 hrs for 5 days) versus placebo for rescue treatment in very low birth weight preterm infants with refractory hypotension and adrenal insufficiency. The results showed that inotropic support could be discontinued in 79% of patients treated with HC versus 33% of patients in the placebo group within 72 hrs of initiating treatment.[19]

In paediatric patients with hypotension caused by infection or recovering from cardiovascular surgery, various studies have been conducted showing improved haemodynamic status after steroid administration.[23-25] In the clinical guidelines developed by the American College of Critical Care Medicine for neonates and children with septic shock, the committee maintains "equipoise" on the question of adjunctive treatment with corticosteroids for paediatric sepsis, except for adrenal or hypothalamic-pituitary-adrenal axis insufficiency. These guidelines propose adding HC to the treatment of newborn infants at risk of adrenal insufficiency, defined as a peak value of cortisol following adrenocorticotropic hormone stimulation < 18 μg/dl or a basal cortisol value < 18 μg/dl after appropriate expansion and epinephrine.[10]

As regards published experience with FTI, Baker et al. reported a retrospective study of 117 infants with refractory hypotension (61 patients with birth weight > 2,500 g) treated with a standardised HC protocol. Even though the study population was heterogeneous, administration of HC

Table 2 Incidence of adverse effects in the two groups.

	Corticosteroids	Placebo	p
Hyperglycaemia	9 (36%)	6 (24%)	0.35
Arterial hypertension	2 (8%)	0	0.14
Mild GI haemorrhage	3 (12%)	2 (8%)	0.63
Sepsis	0	2 (8%)	0.14

was uniformly associated with a rise in ABP, a reduction in the dose of inotropes and an increase in diuresis. These results were independent of gestational age, birth weight and basal cortisol value prior to treatment initiation.[26]

In 1999, Tantivit et al. reported their experience with dexamethasone administration in 7 FTI with refractory hypotension. All the infants showed a decrease in the requirement for inotropes and the need for expanders and an increase in diuresis. [27]

In an observational and prospective study, Noori et al.assessed whether HC administration was associated with haemodynamic changes in infants receiving high doses of dopamine. The results showed that after 48 hrs of treatment with HC, the dopamine dose had been reduced by 72% and ABP and systolic volume had increased by 31% and 33% respectively.[28]

Kamath et al. assessed the presence of adrenal insufficiency in 34 FTI with congenital diaphragmatic hernia. They observed that 67% of the patients had low plasmatic cortisol levels (< 15 μg/dl) and that this situation was associated with more severe forms of this condition. In this report, 100% of patients with low cortisol levels and 69% of patients with high cortisol received corticosteroids as part of their treatment.[29]

Studies on FTI are generally retrospective or involve small numbers of patients. Our study, despite being prospective, controlled, and involving a larger number of patients, has some limitations. The population under study comprises a group of children transferred from maternity units because of serious illnesses, and the transfer may have a negative impact on the primary condition. [30] Overall mortality in the NICU is around 5%; however, these patients are in the critically-ill group, which would explain their high mortality. In our study, the outcome was measured using the neonatologist's clinical judgement, which in turn takes into account the ABP value associated with the evaluation of the patient's perfusion status (diuresis, capillary refill, temperature of extremities) for making decisions on inotrope management. Finally, our study did not document adrenal insufficiency through plasma cortisol dosage to establish the role of adrenal insufficiency in this population.

Finally, although no significant difference has been observed in the appearance of adverse events in this study in the short term, the long-term impact of this intervention has not yet been evaluated, especially in relation to the neurological development, but all these patients are still being followed up. This study shows that HC treatment decreased requirements for inotropes in the study population. On the basis of this information, we consider it reasonable to use low doses of HC in FTI with persistent hypotension despite high doses of vasopressors. The optimum daily dose, duration of treatment and the need for routine measurement of plasma cortisol values are aspects that still need to be determined. Although the use of corticosteroids cannot yet be recommended in health care practice for managing hypotension in these patients, their administration may be considered in refractory cases, provided that the clinician considers each case carefully and the NICU implements a standardised protocol that enables the results to be evaluated in the short and long term.

Conflicts of interest

The authors have no conflicts of interest to declare.

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