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Research Article

Short Term Effect of Norepinephrine on Circulatory Parameters, Acidosis and Kidney Function and Survival in Neonates with Severe Hypotension' and Shock

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Abstract

Norepinephrine is an endogenous catecholamine that increases systemic vascular resistance (SVR) via the activation of α1 receptors. Cardiac output is increased by activation of cardiac β1 receptors to improve contractility, and α1 mediated venoconstriction to help increase venous return and preload. In view of its predominant α1 activity, Norepinephrine is the preferred vasopressor for the treatment of septic shock in children and adults which is characterised by a low SVR. The clinical literature on norepinephrine use in neonates is predominantly involving refractory shock and demonstrates increased BP, improved oxygenation, and decreased serum lactate within hours of initiation. Our study showed positive effect on urine output and blood pressure, but also a significant rise in lactate levels following the administration of Norepinephrine which could be attributed to the extremely sick nature of these babies.

Keywords: *Norepinephrine; Acidosis; Kidney Function; Neonates; Hypotension; Shock*

Introduction

Norepinephrine is an endogenous catecholamine that increases systemic vascular resistance (SVR) via the activation of α1 receptors. Cardiac output is increased by activation of cardiac β1 receptors to improve contractility, and α1 mediated venoconstriction to help increase venous return and preload. In view of its predominant α1 activity, Norepinephrine is the preferred vasopressor for the treatment of septic shock in children and adults which is characterised by a low SVR. However, owing to the marked variation in the management of hypotension in extreme preterm and preterm babies, there is a comparable lack of experience with norepinephrine in neonates compared to older children and adults. Preterm infants with late-onset sepsis commonly present with similar pathophysiology of high cardiac output and low SVR, but the pathophysiology in preterm infants with cardiovascular compromise immediately after birth is less uniform. Preterm infants with a cardiovascular compromise during the transitional period can have variable cardiac output, SVR, and variable pulmonary vascular resistance depending on the severity of pulmonary hypertension. The ideal treatment and supportive medications for preterm infants with cardiovascular compromise remain difficult to determine and might change with the progression of time and underlying disease progression.

Methods

A total of 47 neonates who were admitted to our NICU with severe hypotension and shock were selected for the study to determine the effect of norepinephrine on circulatory parameters, acidosis, kidney function, and survival. Demographics such as gestational age and birth weight were recorded along with baseline parameters such as sodium, potassium, creatinine, BUN, WBC count, PLT count, and CRP before starting the Norepinephrine. Blood culture results were documented as well. To evaluate the changes in the circulatory parameters, acidosis, and kidney function, certain parameters such as the heart rate, SBP, DBP, MBP, Fio2, pH, bicarb, BE, lactate, and body weight were measured before and after administering the norepinephrine injections to the neonates. All the recorded data were statistically analysed to determine the impact of norepinephrine administration on the blood markers and circulatory functions. Two tailed or paired student T test was used to compare the mean differences between the values collected before and after norepinephrine administration. The values are given in table 1 along with mean differences, t value and P-value. The P value was calculated at a confidence interval of 95% with a 0.05 alpha level. P-value less than 0.05 is considered statistically significant.

Variable	N	Before μ1	SD	After μ2	SD	Mean difference μ2-μ1	95% CI for mean difference	T value	p value
Urine output	47	2.063	1.761	2.885	2.023	0.822	[0.166, 1.477]	2.52	0.015*
HR	47	165.28	29.85	170.96	23.37	5.68	[-1.1, 12.47]	1.69	0.09
SBP	47	47.17	13.47	57.57	16.37	10.1	[5.78, 15.03]	4.53	0.001*
DBP	47	27.79	12.24	38.47	14.49	10.68	[6.22, 15.14]	4.82	0.001*
MBP	47	34.15	11.83	45.66	15.54	11.51	[6.96, 16.06]	5.09	0.001*
Fio2	47	57.57	29.97	62.38	32.01	4.81	[-3.56, 13.18]	1.16	0.253

Table 1: *Comparison of circulatory parameters before and after Norepinephrine in the study participants.*
**p < 0.05 - statistically significant.*

Results

The mean gestational age of the study population was 27.65 weeks. The mean age in days of the study population when starting the norepinephrine infusion was 20.98 days. The average neonatal sequential organ failure score [2] was 10.255 ± 3.698 before starting the norepinephrine infusion. Of the scores, the minimum score was 3 and the maximum was 15. The mean weight of the neonates was 1138 grams ± 877 grams. Among the 47 neonates, 10 were diagnosed with necrotizing enterocolitis, 18 were diagnosed with sepsis and the remaining 19 were diagnosed with other conditions. 23 neonates had a positive culture report of bacteria in the blood and the remaining 24 were negative reports.

Biochemical parameters

The initial biochemical analysis prior to the administration of norepinephrine included electrolyte levels such as sodium and potassium are provided in table 2. The average sodium levels were 139.74 mEq/L and the average potassium levels were 5.149 mEq/L. Along with the electrolyte levels, markers like creatinine, urea WBC and CRP were also recorded for the neonates.

The creatinine and BUN levels are indicators of kidney function, assessing which is one of the prime objectives of this study. The mean serum creatinine levels of the 47 study participants were 98.6 μmol/L. The mean blood urea nitrogen (BUN) levels in the study participants were 10.251 mg/dl. Of the neonates, 34 (72%) had acute kidney injury. The mean initial dose of the norepinephrine administered

Variable	N	Mean	SE Mean	SD	Minimum	Maximum
GA [weeks]	47	27.685	0.882	6.047	22	41
Weight [gms]	47	1138	128	877	450	3860
Age at starting [days]	47	20.98	4.02	27.55	0	125
nSOFA [Neonatal Sequential Organ Failure Score]	47	10.255	0.539	3.698	3	15
Noerpi/initial dose	47	0.677	0.0625	0.4287	0.01	1
Norepi/maximum dose	47	0.967	0.0237	0.1623	0.05	1
Sodium	47	139.74	1.37	9.39	123	163
Potassium	47	5.149	0.241	1.654	2.6	9.2
Creatinine	47	98.6	7.22	49.47	15	245
Blood Urea Nitrogen	47	10.251	0.748	5.13	0.8	21
Platelet count	47	67295	12440	85285	23	364000
White blood cell count	47	19.55	2.16	14.82	2.1	59.1
C-Reactive Protein	47	56.7	11.1	76	0.3	328

Table 2: *Demographic characteristics, serum electrolytes and blood parameters before starting the norepinephrine infusion.*

was 0.677 mg/kg/min and the average maximum dose administered was 0.967 mg/kg/min. The mean platelet count was 67,295 cells/mm^3, and the mean white blood cell count is 19.55 per microliter.

Before administering norepinephrine 89% were on dobutamine, 87% were on epinephrine, and 83% were on hydrocortisone. 96% of the study population were administered with normal saline before starting the norepinephrine regimen. In all the participants, norepinephrine was administered with dopamine.

Upon analysis, we found that the urine output, SBP, DBP, MBP, Lactate, and body weight increased significantly with P-values less than 0.05.

Circulatory functions pre and post norepinephrine infusion

The circulatory parameters before and after starting norepinephrine are analysed and tabulated in table 1. After starting the norepinephrine infusion, the mean blood pressure (MBP) rose from 34.15 ± 11.83 to 45.66 ± 15.54 mmHg, which is an average increase of 11 mmHg. Upon comparison, the rise in the mean blood pressure was statistically significant with a p value of 0.001 (Figure 1).

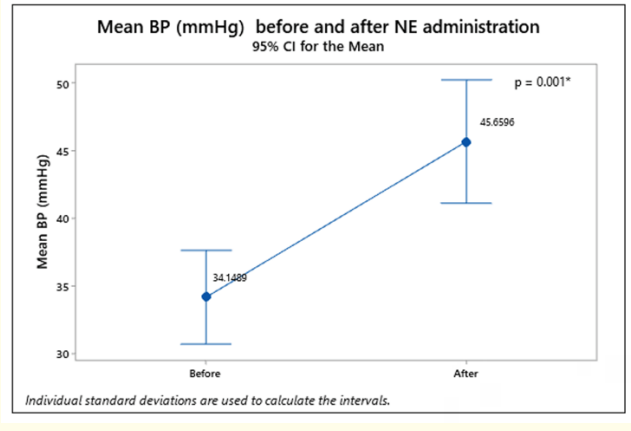

Figure 1

The diastolic BP increased from 27.79 ± 12.24 to 38.47 ± 14.49 mmHg and the systolic BP increased from 47.17 ± 13.47 to 57.57 ± 16.37 mmHg (Figure 2 and 3). The increase in both systolic and diastolic BP were statistically significant with a P-value of 0.001.

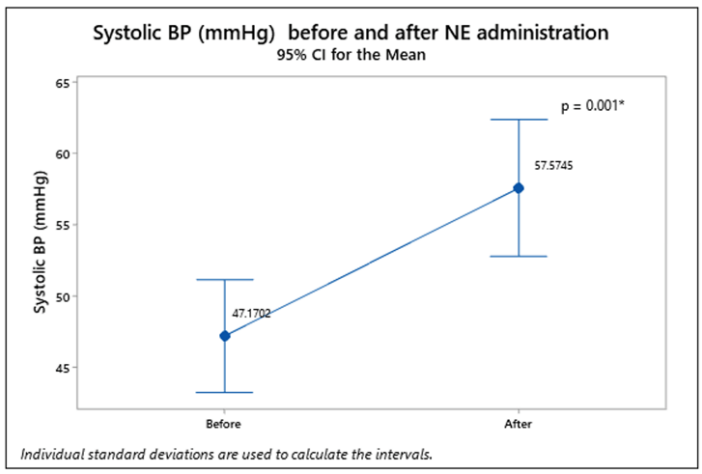

Figure 2

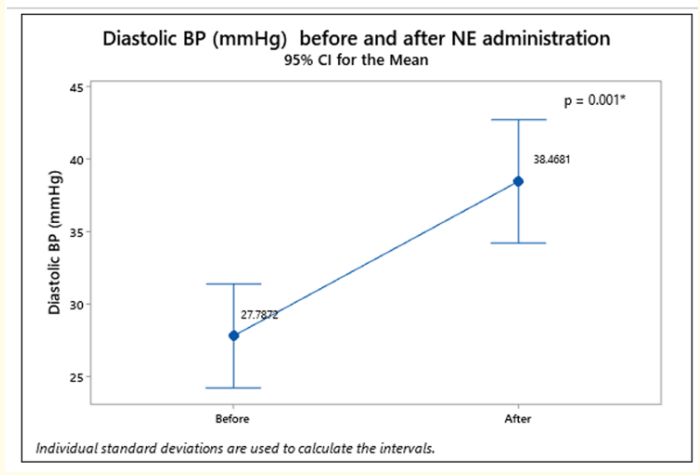

Figure 3

The heart rate of the neonates increased from 165.28 ± 29.85 to 170.96 ± 23.37 beats, however, the increase was not statistically significant (Figure 4).

The FiO_2 increased from 57.57 ± 29.97 to 62.38 ± 32.01 percentage and the difference was statistically not significant (p = 0.253) (Figure 5).

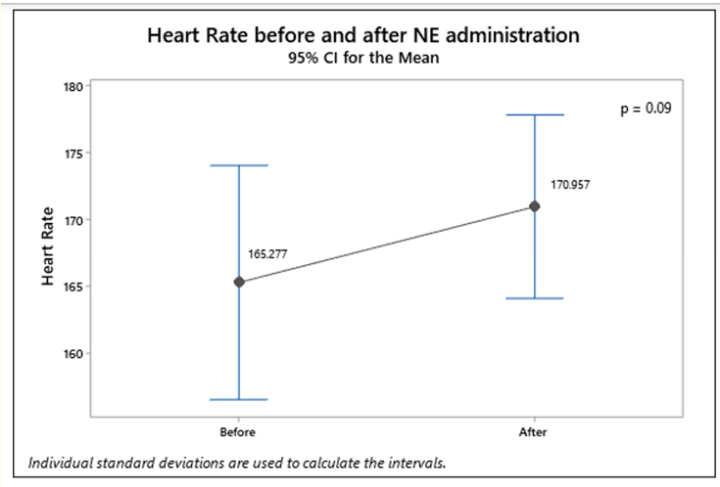

Figure 4

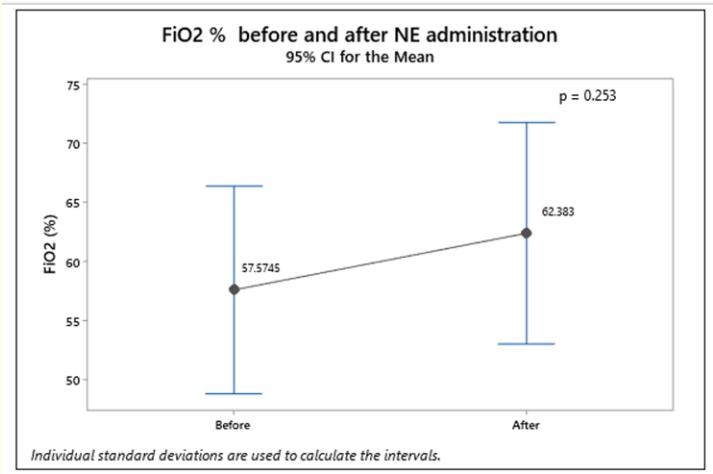

Figure 5

Urine output variation pre and post norepinephrine infusion

The urine output (Figure 6) increased by an average of 0.822 ml/kg from 2.063 ± 1.761 to 2.885 ± 2.023 ml/kg. The increase in the urine output was statistically significant with a P-value of 0.015.

Blood acid-base levels variation pre and post norepinephrine infusion

The blood pH values dropped from 7.1881 ± 0.1712 to 7.173 ± 0.1786, p=0.64, the reduction in pH was not statistically significant. The bicarbonate levels increased from 18.74 ± 7.48 to 19.29 ± 7.35, the increase was not statistically significant (p = 0.50). The serum lactate

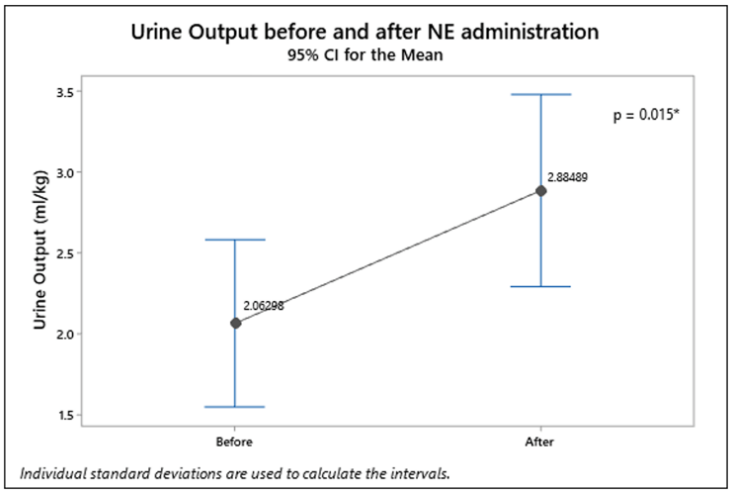

Figure 6

levels increased significantly from 6.279 ± 5.255 to 7.572 ± 6.261 with a P-value 0.01. The body post norepinephrine also increased significantly by 0.1169 Kgs from 1.568 ± 1.213 to 1.685 ± 1.286 Kgs. The comparison results are tabulated in table 3.

Variable	N	Before μ1	SD	After μ2	SD	Mean difference μ2-μ1	95% CI for mean difference	T value	P value
pH	47	7.1881	0.1712	7.173	0.1786	-0.151	[-0.0629, 0.0327]	-0.64	0.528
Bicarb	47	18.74	7.48	19.29	7.35	0.553	[-1.083, 2.19]	0.68	0.5
BE	47	-8.96	8.38	-9.05	9.17	-0.091	[-1.808, 1.625]	-0.11	0.915
Lactate	47	6.279	5.255	7.572	6.261	1.294	[-0.325, 2.263]	2.69	0.01*
Weight [kg]	47	1.568	1.213	1.685	1.286	0.1169	[-0.0706, 0.1633]	5.08	0.001*

***Table 3**: Comparison of blood acid base parameters before and after norepinephrine infusion in the study participants.*
**p < 0.05- statistically significant.*

After administering norepinephrine, the following events such as tachycardia, hypertension, CLD, ROP, NEC and death occurred in 34%, 2%, 38%, 38%, 49% and 77% of the population respectively. Extravasation and ischemic events were not identified in any of the study participants. The descriptive results of events post norepinephrine infusion are tabulated in table 4.

Discussion

Norepinephrine is an endogenous sympathomimetic amine that acts on the vascular and myocardial α-1 receptors with a mild to moderate β-1 adrenoreceptor agonism. As the effect on β-2 adrenoreceptors is minimal, norepinephrine has combined inotropic and peripheral vasoconstrictive effects. The clinical literature on norepinephrine use in neonates is predominantly involving refractory shock and demonstrates increased BP, improved oxygenation, and decreased serum lactate within hours of initiation [11]. However, our study showed a significant rise in lactate levels following the administration of Norepinephrine [p 0.01] as was shown in another study where

Categorical Variables	N-Sample Size	No		Yes	
AKI Y/N	47	13	28%	34	72%
Tachycardia Y/N	47	31	66%	16	34%
Hypertension Y/N	47	46	98%	1	2%
Weaning other inotropes within 48 hours Y/N	47	32	68%	15	32%
CLD	47	29	62%	18	38%
ROP	47	29	62%	18	38%
Death	47	11	23%	36	77%
NEC	47	24	51%	23	49%
Extravasation Y/N	47	47	100%	0	0%
Ischemic events Y/N	47	47	100%	0	0%

Table 4: *Descriptive analysis of observed events in the study participants.*

Norepinephrine was associated with higher lactate and glucose levels than dopamine in low birth weight infants [15]. This could be attributed to the extremely sick nature of these babies as shown by the need for multiple inotropes or increase SVR. Two retrospective studies of norepinephrine use in preterm neonates (n = 48, < 32 weeks and n = 30, < 34 weeks) demonstrated improvements in BP and oxygenation parameters within 3 - 8h, with a variable effect on urine output. Of note, two-thirds of the patients had sepsis with the majority receiving norepinephrine as an adjunctive therapy [14] which is in our study too. In these studies, tachycardia was very common, and mortality was high (30 and 46%, respectively) [14]. This was comparable to our study which showed similar effects on both urine output [p 0.015] and heart rate [though in our study the effect on heart rate was statistically insignificant]. Another study showed Norepinephrine was effective in improving blood pressure in the majority of preterm infants at a median dose of 0.5 mcg/kg/min, including those refractory to first-line inotropes [10]. After blood pressure normalised, it remained normal until Norepinephrine was ceased suggesting a sustained effect of Norepinephrine on the cardiovascular system [10]. Although not all significant, additional parameters of oxygenation and perfusion improved suggesting that Norepinephrine may improve organ perfusion [10], however our study showed an opposite increase in Fio_2 following use of Norepinephrine. In our study we did use higher doses of Norepinephrine ranging between 0.6 to 0.99 mcg/kg/min. Derleth., *et al*. reported improvement in blood pressure in 29 babies with a gestational age ranging from 22 to 38 weeks following the use of Norepinephrine in addition to dopamine [9]. Tourneux., *et al*. showed in a cohort of 22 newborns > 35 weeks' gestation with septic shock refractory to volume expansion and other inotropes that Norepinephrine could increase blood pressure and urine output and reduce lactate. They used a norepinephrine dose ranging from 0.2 to 2.0 mcg/kg/ min, and only four infants died [8]. The similar effect is shown in our study in terms of increasing blood pressure and urine output [p < 0.05] [1-7,16-45].

Conclusion

Norepinephrine is effective in raising blood pressure and urine output in hypotensive neonates, without causing major short-term side effects.

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