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A randomized controlled trial of the impact of dopamine on outcome of asphyxiated neonates

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Abstract*: Background:* Vasoactive drugs such as low dosage dopamine are often used in the intensive care of asphyxiated term neonates but there is insufficient evidence to support the practice.
Aims: To evaluate the impact of low dose dopamine on the clinical course and outcome of newborns with severe perinatal asphyxia and to determine factors that predict survival.
Methods: This was a randomized controlled trial. Term asphyxiated newborns were alternately recruited into 'dopamine' and 'no-dopamine' sub groups. Asphyxia was defined as Apgar score ≤3 at one minute or ≤5 at five minutes, and/or clinical evidence of hypoxic ischemic encephalopathy (HIE). The intervention comprised dopamine infusion at 3.0mcg/kg/minute. Primary outcome was death or survival till discharge while secondary measures were apnoea, oliguria, seizures and other clinical morbidities. The Student t-test was used to compare outcomes between the subgroups.
Results: A total of fifty five asphyxiated infants took part in the study: 27 in the intervention group while 28 were in the control group. The subgroups were similar in mean gestational age, Apgar scores, age at admission and modes of delivery ($p>0.05$). HIE occurred in over a half of the subjects. The frequency of apnoea, oxygen requirement, duration of anticonvulsant treatment and urine outputs were similar between the subgroups($p > 0.05$).The mean durations of admission (days) were 5.13±3.0 and 5.3±3.0 for the intervention and non-intervention subgroupsrespectively ($t=0.183$, $p=0.856$). Likewise,survival rates were similar ($x^2 = 1.261$, $p = 0.948$). Selected perinatal events-did not influence outcome ($p>0.05$).
Conclusion: Low-dosedopamine has no impact on the short term outcome of asphyxiated infants.

Key words: hypoxic ischemic encephalopathy, clinical course, outcome, dopamine

Introduction

Perinatal asphyxia manifests with adverse systemic effects in newborn infants. The nervous, cardiovascular and renal systems are often affected.[1] Several interventions have been attempted to minimize organ damage in asphyxiated neonates. These include cardiovascular support using ionotropes, reduction of reperfusion injuries and neuroprotection.[2,3]Available evidence suggest that prophylactic barbiturate has no significant impact on the outcome of perinatal asphyxia but the neuro protective effects of cooling therapies have been clearly proven in recent years.[4]In a meta-analysis of 11 randomized controlled trials, Jacobs *et al*[5] found that therapeutic hypothermia is beneficial in term and late preterm asphyxiated newborns, reducing their mortality without increasing neuro developmental deficits.

In contrast, the use of inotropic agents such as dopamine in asphyxiated infants is widespread among clinicians but the only available clinical trial on the impact of dopamine on mortality and neurocognitive development of asphyxiated term infants found no benefit compared to placebo. The study is however, limited by the small number of subjects- only seven neonates were recruited into each cohort.[6]Treatment of asphyxiated infants with dopamine is often done based on the theoretical reasoning that it can prevent hypotension and hence enhance tissue perfusion.[2]Dopaminehas been shown to significantly improve splanchnic blood flow but it does not improve splanchnic oxygen consumption.[7]When infused at a low dose (<5 µg/kg per minute), dopamine dilates the afferent and efferent renalarterioles. The net effect is a relatively large increase in renal blood flow without significant increase in creatinine clearance.[8]Hence, theutility of low dose dopaminein clinical practice remains doubtful. Hunt *et al*[9] in a recent systematic review

concluded that there was insufficient data to make commentson the benefits of dopamine infusion in perinatal asphyxia.
Considering the forgoing and diverse opinions on the usefulness of low–dose dopamine, we evaluated the impact of this intervention on the clinical course and outcome of infants with severe perinatal asphyxia. Also, we determined factors that predict survival in the cohort.

Methods

Study Setting and Participants

The study was carried out at the level II Neonatal Intensive Care Units (NICUs) of two Mother and Child Hospitals (MCHs) in Ondo State, which are public facilities providing specialized free healthcare services to people in the State and communities in neighboring states. The two hospitals were the busiest in the State with over 10,000 deliveries per year at MCH Akure.[10]
The study population was all asphyxiated term normal birth weight inborn infants admitted into the NICUs from October 2014 to March 2015. Asphyxia was defined as Apgar score ≤3 at one minute or ≤ 5 at five minutes, and/ or clinical evidence of hypoxic ischemic encephalopathy (HIE) in the neonate.[11,12]

Ethical considerations

Ethical clearance was obtained from the Research and Ethics Committee of the MCH, Akure. Informed consent was obtained from parents of the participants, having explained to them the purpose of the study, the safety profile of low dosage dopamine and that participation was entirely voluntary. No participant was deprived of any necessary medication throughout the study; bedside labeling of infant's study group was not done to avoid observer bias and inadvertent influence of NICU staff.
The minimum sample size was determined using the formula for detection of a difference between two proportions proposed by Bonita *et al*.[13]A total of 55neonates were recruited consecutively from the MCHs during the study period: 27of them into the intervention (dopamine) group and28 into the control (no-dopamine) group.

Study design

This was an interventional study using a randomized controlled trial design. Participants were coded and recruited into alternate study groups (dopamine vs. no-dopamine) consecutively; there was no bedside labeling of participants' study groups.

Intervention

Dopamine infusion at 3.0mcg/kg/minute was administered to the asphyxiated infants in the interventional group for 48 hours, alongside routine maintenance intravenous fluids and other relevant medications. Incompatible drugs such as sodium bicarbonate were not mixed with dopamine to avoid deactivation. Participants in the control group received maintenance intravenous fluids and other relevant medications except dopamine. This did not preclude the use of adrenaline during resuscitation of any of the participants, when necessary, as per standard guidelines.[15]

Data Collection

Data on each asphyxiated infant was extracted using a structured questionnaire comprising biodata, clinical features at presentation, clinical course and outcome. Primary outcome was death or survival till discharge while secondary measures were apnea, oliguria, seizures and other clinical morbidities. Hypotension was diagnosed based on absent peripheral pulses and prolonged capillary refill time>3secs and was managed according to unit protocols. Clinical evaluation of the participants was done at admission into NICU and repeated12 hourly thereafter by the researchers/ attending paediatricians. The clinical notes of the infants were reviewed to ascertain the frequency of evolving morbidities as well as their outcome. Participants that were discharged/ referred were considered to have a good outcome while death or leaving against medical outcome (LAMA) was described as a poor outcome.

Data Analysis

The data were analyzed using SPSS version 20.0 statistical software for Windows (IBM, Armonk, N.Y., United States). Fisher's Exact test or Chi-square was used to compare categorized data (*gender, modes of delivery, outcome and presence of maternal systemic illness*) between the intervention and control groups. The Student t -test determined any significant difference between the mean gestational ages, Apgar scores and durations of therapies/ admission of the cohorts. Binary analysis was done to identify factors associated with good outcome among the asphyxiated infants. The level of significance of each test was set at $p<0.05$.

Results

Baseline characteristics of the participants

A total of fifty five asphyxiated inborn infants took part in the study: 27 in the intervention group while 28 in the control group. The overall male: female ratio was 1.8:1; the gender distribution was similar in both groups ($p>0.05$). Mean gestational age (weeks) at delivery, Apgar scores and age at admission (hours) were similar in both groups ($p > 0.05$). Likewise, mode of delivery was similar between the groups ($x^2=1.344$, $p=0.81$), with caesarian section (40%) being the commonest route. In addition, the pattern of maternal systemic illnesses was comparable in both groups ($p > 0.05$; Table 1).

Clinical features and diagnoses

There were several multi-systemic manifestations of asphyxia among the participants at admission. The commonest symptoms were cyanosis (40.0%), respiratory distress (34.0%), convulsion (18.0%) and hypotonia (18.0%). The frequency of cardiovascular, nervous and respiratory system involvement was similar in both subgroups at admission (p > 0.05;Table 2). Hypoxic is chaemic encephalopathy (HIE) occurred in over a half of the participants: *mild (8.0%), moderate (18.0%) and severe (26.0%)*. Co-morbid disorders such as sepsis (54.0%) and meconium aspiration syndrome (6.0%) had similar incidence in both groups (p>0.05; Table 2).

Table 1: Baseline characteristics of the asphyxiated infants

Characteristics	Study groups Dopamine	No-Dopamine	Tests (x^2,t)	p-value
Gender				
Male	16(59.3)	19(67.9)	0.439[a]	0.508
Female	11(40.7)	9(32.1)		
Gestational age (wks.)				
Mean ±SD	38.67±3.21	37.2±4.15	0.520[b]	0.622
Age at admission (hrs.)				
Mean ±SD	0.83±0.55	0.74±0.38	0.649[b]	0.519
Apgar Score				
1 minute	2.46±0.95	2.29±0.90	0.700[b]	0.486
5 minutes	5.05±1.53	5.00±1.51	0.100[b]	0.920
10 minutes	6.14±2.67	4.88±1.46	1.162[b]	0.266
Mode of Delivery				
Breech	4(15.4)	4(14.8)	1.029[c]	0.862
Emergency CS	11(42.3)	20(37.0)		
Forceps	1(3.8)	3(11.1)		
SVD	10(38.5)	10(37.0)		
Maternal Illness				
Eclampsia	4(28.6)	3(27.3)	0.273[a]	0.697
APH	2(14.3)	3(27.3)	0.142[a]	1.000
Malaria	5(35.7)	0(0.0)	6.019[a]	1.000
Others	6(42.9)	6(54.5)	0.025[a]	0.874

aChi -square-test; bStudent t-test; CS = caesarian section, SVD = spontaneous vertex delivery, APH= antepartum haemorrhage

Table 2: Clinical features and diagnoses of the asphyxiated infants

Clinical Features/ Diagnosis	Study groups Dopamine	No-dopamine	Test (x^2)*	p-value
Clinical Features				
Convulsion	2(15.4)	7(38.9)	2.922	0.142
Hypertonia	2(15.4)	2(11.1)	0.007	1.000
Hypotonia	2(15.4)	7(38.9)	2.922	0.142
Coma	3(23.1)	1(5.6)	1.270	0.340
Respiratory distress	7(53.8)	10(55.6)	0.480	0.559
Cyanosis	7(53.8)	13(72.2)	2.257	0.159
Apnea	0(0.0)	3(16.7)	2.946	0.236
Bleeding	3(23.1)	1(5.6)	1.270	0.340
Cephalohaematoma	5(38.5)	3(16.7)	0.802	0.456
Pallor	3(23.1)	3(16.7)	0.011	1.000
Shock	0(0.0)	2(11.1)	1.923	0.491
Diagnosis				
Severe Perinatal Asphyxia/HIE	27(100.0)	28(100.0)	-----	------
Sepsis/ DIC	11(45.8)	16(61.5)	1.239	0.266
Meconium Aspiration Syndrome	3(12.5)	0(0.0)	3.457	0.103
Others	4(16.7)	0(0.0)	4.473	0.051

HIE= hypoxic ischaemic encephalopathy;DIC= disseminated intravascular coagulopathy; others include neonatal jaundice and skull fracture.*Fishers Exact for expected frequency <5.

Clinical course and outcome

Table 3 shows the clinical course and outcome of the dopamine and no-dopaminesubgroups. The frequency of apnoea, oxygen requirement, duration of anticonvulsant treatment and urine outputs were similar between the cohorts (p > 0.05). Also, oral feeding was tolerated after a similar length of stay (days) on admission (2.9±1.0 vs. 3.0±0.8; t= 0.336, p = 0.739). Mean hematocrits (*39.5±6.9 vs. 43.5±7.3*) and mean random blood glucose levels(*5.4±2.6 vs.6.8±3.8 mMol/L*)were similar on admission (*p>0.05*).Mean durations of admission (days) were5.1±3.0 and 5.3±3.0 in the treatment and non-treatment subgroups respectively (t=0.183, p=0.86).The survival outcomes of both subgroups were also similar ($x^2 = 1.261$, $p = 0.948$).

Table 3: Clinical course and outcome of the asphyxiated infants

Clinical course/ outcome	Study groups Dopamine	No-Dopamine	Test (t,x^2)*	p-value
Clinical course				
Episodes of apnea	2.50±1.29	3.00±1.41	0.547[a]	0.601
Duration of oxygen therapy (*days*)	2.00±1.34	1.60±0.995	0.946[a]	0.352
Duration of anticonvulsant use (*days*)	3.50±2.20	2.75±1.96	0.798[a]	0.435
Day of life oral feeding tolerated	2.90±1.04	3.00±0.78	0.336[a]	0.739
Oliguria *(urine< 1ml/kg/hour*)	3 (11.1)	0 (0.0)	3.291	0.111
Duration on admission (*days*)	5.13±2.98	5.28±2.95	0.183[a]	0.856
Outcome				
Discharge	17(73.1)	16(66.7)	1.261[b]	0.948
Died	4(15.4)	4(16.7)		
LAMA	3(11.1)	3(12.5)		
Referred	0(0.0)	1(4.2)		

[a]Student t-test,[b]Chi -square-test; LAMA = leaving against medical advice;*Fishers Exact test for expected frequency <5

Factors influencing survival

Bivariate analysis for possible factors associated with outcome of the asphyxiated infants is shown on Table 4. Participants' gender did not influence survival (x^2 = 2.00, p = 0.156). Also, perinatal events (mode of delivery, Apgar score), clinical course and therapies were not significantly associated with outcome in this study (p > 0.05).

Table 4: Bivariate analysis of possible factors influencing outcome of the infants

Factors	Outcome Bad	Good	Test (c^2)*	p-value
Gender				
Male	25(69.4)	7(50.0)	1.654	0.198
Female	11(30.6)	7(50.0)		
Mode of Delivery				
EMCS	12(34.3)	6(42.9)	0.316	0.574
Others	23(65.7)	8(57.1)		
Apgar score (5min)				
1-3	4(14.3)	3(25.0)	0.668	0.410
>3	24(85.7)	9(75.0)		
Episode of Apnea				
1-2	0(0.0)	3(62.5)	1.406	0.444
>2	1(100.0)	5(37.5)		
Convulsion				
Yes	5(13.9)	3(21.4)	0.426	0.514
No	31(86.1)	11(78.6)		
Dopamine infusion				
Yes	19(52.8)	7(50.0)	0.031	1.000
No	17(47.2)	7(50.0)		
Days on Oxygen				
1-2 days	11(64.7)	10(90.9)	2.446	0.191
>2days	6(35.3)	1(9.1)		
Oral feeding				
≤3days	23(71.9)	3(50.0)	1.119	0.357
>3days	9(28.1)	3(50.0)		

*Fishers Exact test for expected frequency <5

Discussion

The current study found no difference between the clinical course of asphyxiated infants in the experimental group and the controls, consistent with a prior report by DiSessa*et al*[6] in 1981 that dopamine infusion did not influence the clinical course of asphyxiated infants. There is paucity of data on the utility of dopamine infusion compared to 'no inotrope' in asphyxiated term and preterm neonates. Osborn *et al*[16] found in a systematic review that there was no significant difference in the incidence of renal impairment, pulmonary haemorrhage and neurologic complications among hypotensive preterm infants treated with dopamine when compared to controls that received other inotropes. This shows that low dose dopamine may not prevent organ injuries in critically ill infants.[2,17]

Dose–dependent response to dopamine infusion has been described. Its neurotransmission effect is dopaminergic at the low dosage used in the current study; beta-adrenergic at an intermediate dosage (5-15µg/kg/minute) and alpha-adrenergic at a high dosage.[18] Hence,high dose dopamine should be administered with caution to avoid adverse systemic effects such as tachycardia and increased myocardial oxygen consumption.[18] The cardiovascular effect of dopamine is not superior to other ionotropes and does not significantly influence neonatal survival.[6,16]Although cardiovascular complications including hypotension can occur in nearly one half of asphyxiated infants especially in those with HIE stage III,[19] clinical evidence of cardiovascular compromise was rare among our participants.

Low dose dopamine infusion has a predominant renovascular effect, shown by an improved renal blood flow without associated improved creatinine clearance.[17]The few cases of oliguric acute kidney injury (AKI) requiring a fluid challenge/furosemide in this trial occurred in the intervention group. This study did not find any improvement in urine output attributable to low dose dopamine. Nonetheless, neonatal AKI is often non-oliguric and serial creatinine measurement is required for its diagnosis.[20] Serum creatinine level is highly variable in newborns and it is a late marker of neonatal AKI.[21] Determination of participants' serum creatinine level was not included in the current trial.

The overall outcome was similar in both subgroups consistent with the earlier findings by DiSessa *et al*[6]that dopamine infusion did not significantly improve the long term outcome of asphyxiated infants, despite its transient cardiovascular effects. This corresponds with the essentially similar clinical course of participants in both the intervention and control groups throughout the current study. Early neonatal deaths of asphyxiated infants occur less in developed settings due to the use of advanced respiratory supports,[9] as well as therapeutic hypothermia.[5] Only short term outcome was assessed in the current study. Long term neurodevelopmental outcome are often similar among asphyxia survivors, as reported by Hunt *etal*[9] and Osborn *et al*.[16] Hence, the usefulness of low dose dopamine in the management of severely asphyxiated infants remains unproven.

Electroencephalograph (EEG) is the "gold standard" for predicting outcome of perinatal asphyxia.[22] It is non-invasive, detecting subclinical seizure and has early predictive value if normal. Other prognostic tools include acid-base balance, Apgar score and temporal neurologic manifestations but these may not strongly predict long-term outcome.[22] In a retrospective study in Osogbo southwestern Nigeria, Adebami *et al*[14] found that more babies with respiratory distress, apnoea, feed intolerance, oliguria, bleeding, seizures and coma died than those without multi-systemic complications. Also, Kuti *et al*[23] associated seizures with neonatal mortality. None of these clinical variables significantly predict adverse outcome in this trial, perhaps due to its relatively smaller sample size.

The strength of the current study includes its experimental design and the baseline clinical-demographic similarity of the participants.

Conclusion

The current study confirms that a low dose dopamine infusion does not influence the short term outcome of asphyxiated infants. A longitudinal study of the impact of moderate dosage dopamine on the long-term outcome of asphyxiated infants is desirable.

Authors' Contribution
This work was carried out in collaboration among the authors. Author MTA and BD designed the study; MTA wrote the protocol, and wrote the first draft of the manuscript. Author ROO participated in the literature searches, data collection and critical review of the manuscript. All authors approved the final manuscript.
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