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Editorial

In this issue we have an interesting mix of articles on topics such as newborn hypothermia, septic shock and pediatric cardiopulmonary resuscitation. In 2010, the American Heart Association (AHA)permitted the use of a single dose of vasopressin to replace 1st or 2nd dose of epinephrine in pulseless arrest in adults as it had been found to be safe, acceptable and clinically useful in this age group. However, no such recommendation could be made for the use of this drug in pediatric cardiac arrest owing to a paucity of literature on this topic. The research paper on use of combination of vasopressin and epinephrine vs. use of epinephrine alone would definitely add to the scarce literature available on this topic and provide the platform for future adequately powered trials or observational studies on this topic so that a recommendation could be made on the use of this drug by the time the next Advanced Pediatric Life Support (APLS) guidelines are published.

Thermal care of newborn represents the basic care provided to the neonate. Hypothermia is regarded as one of the major causes of neonatal death in developing world. The article on hypothermia is an excellent attempt at reviewing the basic mechanisms of thermoregulation and treatment of any grade of hypothermia, particularly severe hypothermia, as a neonatal emergencyin the developed world.

Having reviewed the first line agents for pediatric septic shock in a previous issue of this journal, it was time to review the evidence for newborns as to which of the two agents i.e. dopamine or dobutamine would be appropriate for managing the hypotensive neonate as the physiologic states and response to disease states vary between these two populations. We hope the clinical query would provide answers to this very important clinical query in neonatal septic shock. Toeing on similar lines we have an interesting commentary on why children often present in late stages of septic shock in our country (or in similar resource limited settings) and often in decompensated state when death is inevitable, with a brief discussion of the surviving sepsis campaign guidelines (2008)in pediatric septic shock.

Finally a clinical image of bilateral basal ganglia lesions in a school going child is well illustrated and would certainly add to the literature on bilateral basal ganglia lesions in children.

JhumaSankar (Executive editor)
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For ***Indian Journal of Emergency Pediatrics***

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Outcome of Children Receiving Epinephrine plus Vasopressin vs. Epinephrine alone during In-hospital Cardiac Arrest

Jhuma Sankar, MD; Archana Singh, MD; Aditi Jain, MD; Suresh CP, MD

Abstract

Objective: Our objective was to compare the effects of combination of vasopressin and epinephrine with epinephrine alone on rates of return of spontaneous circulation (ROSC) and mortality in children with in-hospital cardiopulmonary arrest (CPA).

Methods: This was a retrospective chart review of children with cardiac arrest admitted to the Pediatric intensive care unit (ICU) of a tertiary care hospital in North India between May and July 2012. The study period was divided into two intervals- period 1 where only epinephrine was used and period 2 where a single dose of vasopressin was used at a dose of 0.8u/kg in addition to epinephrine. Children were resuscitated as per the 2010 AHA guidelines for cardiopulmonary resuscitation (CPR) during both time periods. Data regarding baseline characteristics, clinical course and predetermined clinical outcomeswere recorded in a pre-structured proforma. Data was entered into Microsoft excel and analyzed using *Stata* 11.

Results: A total of 28 case records of children with CPA were retrieved during the study period. Of these only 6 (21%) children survived to hospital discharge while the remaining children (n= 22, 19%) succumbed to their illnesses. A total of 14 children each were enrolled during the two time periods. The most common reasons for ICU admission as well as mortality were severe sepsis and septic shock seen in almost all (n=14) the children in period 1 and 85% (n=12) of the children in period 2. Compared to period 1 children from period 2 were sicker at admission with higher mortality risk scores(p=0.03) higher incidence of tachyarrhythmia and of refractory shock.

Almost 50% (n=7) of the children receiving vasopressin as the second drug had ROSCimmediately after the arrest in comparison to 43% (n=6) of children receiving epinephrine alone. At 24 hours however, only 5(35%) and 4 (28.6%) of these children from period 2 and period 1 respectively were found to be surviving. Ultimately only 2 children (14%) from period 2 and 4 children (28.6) from period 1 survived to hospital discharge. The differences between the two time periods with respect to all of these primary outcomes were statistically insignificant (p>0.05).

Conclusion: Use of vasopressin as an add-on drug during CPR did not seem to affect the clinical outcomes of children with in-hospital cardiac arrest in comparison to the standard practice of using epinephrine alone.

Key words: CPR; Cardiopulmonary resuscitation; Vasopressin; Epinephrine, In-hospital cardiac arrest.

Introduction

Cardiac arrest both in-hospital and out-of-hospital is a significant cause of mortality and morbidity in the pediatric age group. Nearly 40% of cardiac arrests are in-hospital arrest of which only 27% are reported to survive (1, 2). The management of children with cardiac arrest irrespective of the setting is as per the recommendations of the American Heart Association (AHA) guidelines for cardiopulmonary resuscitation and emergency Cardiovascular Care (3). The first step in the management of cardiac arrest after a patient does not respond to basic life support, is to identify the type of rhythm. Shockable rhythms, i.e. ventricular tachycardia/ fibrillation (VT/VF) should be given immediate defibrillation. However, asystole or

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pulseless electrical activity (PEA) as the initial rhythm or persisting VT/VF after 2 shocks require prompt administration of epinephrine (3).

Epinephrine has formed the backbone of these recommendations for many decades, based mainly on the success of this drug in animal models(4-6).Till date, no prospective clinical trial hasclearly demonstrated its efficacy in improving outcomes of cardiac arrest in humans. Thus a search for other potential drugs had become essential. One such drug is vasopressin, high levels of which have been found in successfully resuscitated adults(7,8). It had therefore become the centre of many studiesover the years to determine its efficacy in cardiac arrest.The evidence generated from years of research in adults has resulted in vasopressin being given a class IIb recommendation in adult cardiac life support guidelines. The ACLS guidelines 2010 permits use of a single dose of vasopressin to replace 1st or 2nd dose of epinephrine in pulseless arrest with an 'indeterminate' level of recommendation (9). With regard to Pediatric Advanced cardiac Life Support however, there is no recommendation for or against its use (class indeterminate) in the guidelines owing to a scarcity of literature on the use of this drug.

In pediatric asphyxiated animal models the combination of vasopressin and epinephrine was superior (10) to epinephrine or equal to it (11). In children, vasopressin was first reported to be beneficial in a retrospective case series in 2002 (12) wherein beneficial effects of vasopressin (0.4units/kg/dose) was found in patients with prolonged cardiac arrest not responding to conventional CPR.A recent prospective feasibility pilot study (13) examined the use of vasopressin in in-hospital cardiac arrests in children and found that patients given vasopressin were found to have increased 24 hour survival, though there was no difference in ROSC, survival to hospital discharge, or favorable neurological outcome.

Given this background we decided to compare the effects of vasopressin after the initial 3 doses of epinephrine vs. epinephrine alone on rates of return of spontaneous circulation and mortality.

Materials and Methods

Design and setting

This was a retrospective chart review of children with cardiac arrest admitted to the Pediatric intensive care unit (ICU) of a tertiary care hospital in North India between May and July 2012. The study period was divided into two intervals- period 1 where only epinephrine was used (May and 1st 2 weeks of June) and period 2 where vasopressin was used in addition to epinephrine (last 2 weeks of June andJuly).

Subjects and data collection

The case records of all children d"17 years of age admitted to the PICU during the study periodswho had cardiopulmonary arrest (CPA) requiringchest compressions and/or defibrillation,and had received all three doses of epinephrine were retrieved. Patients were excluded if first-dose epinephrine was given via the endotracheal tube or parents refused to give verbal consent and previous enrollment. After the advent of the 2010 PALS guidelines which does not give any specific recommendation for or against the use of vasopressin in pediatric cardiac arrest, we had attempted to make it a protocol of administering vasopressin in case of failure of return of spontaneous circulationafter the initial three doses of epinephrine. This was done during the period as mentioned above (June –July). Before administering vasopressin to any child we would obtain informed verbal consent from one of the parents of each child while the third dose of epinephrine was being administered. Vasopressin is readily available in our hospital formulary and is routinely being used as a second line agent in septic shock at starting dosage of 0.01u/kg/hr. We observed beneficial effect of this drug in the initial 2-3 patients in whom it was administered in case of arrest and therefore we decided to continue using the drug subsequently (June- July) as mentioned above.

However, before incorporating it into our PICU protocols we decided to evaluate the effects of this combination therapy in comparison to use of epinephrine only on important clinical outcomes such as sustained return of spontaneous circulation and survival.

Objectives and outcome measures

Our primary objectives were to compare the effect of use of combination therapy of epinephrine and vasopressin (period 2) with use of epinephrine only (period 1) in children with in-ICU cardiac arrest on *a)* proportion of children with return of spontaneous circulation (ROSC) immediately after the arrest and *b)* sustained ROSC at 1 hour and 24 hours after arrest. Return of spontaneous circulation is defined as return of heart beat/ palpable carotid pulsations (ROSC) immediately post arrest (15). Sustained return of spontaneous circulation at 1 hour is defined as ROSC sustained at 1 hour after ROSC. Sustained ROSC at 24 hours is defined as ROSC sustained at 24 hours after ROSC. If a child suffered more than one cardiac arrests during his/her hospital stay only the data of the first cardiac arrest was used for the purpose of the study and the same drug regimen was followed throughout his/her hospital stay.

The secondary objectives were to compare the effects of these two treatments on proportion of children requiring prolonged CPR, duration of CPR, duration of sustained ROSC in those who died, survival to hospital discharge and neurologic outcomes as measured by change in pediatric cerebral performance category (PCPC) scores (14) from baseline. Proportion of children requiring prolonged CPR is defined as 'no of patients requiring prolonged CPR (>20 minutes) to achieve sustained ROSC' (15). Duration of CPR is defined as the interval between the beginning of CPR and the return of spontaneous circulation.Twenty four hour survival is defined as number of patients surviving at 24 hours and survival to hospital discharge is defined as discharge from the hospital either to home or to another facility in a stable condition.

Survival to hospital dischargewas defined as neurologic outcome as per the PCPC scale the components of which are *1)* normal age-appropriateneurodevelopmental function, *2)* milddisability, *3)* moderate disability, *4)* severe disability,*5)* coma or vegetative state, and *6)*brain death. The method of scoring the PCPC scale is provided in panel 1. Favorable neurologic outcome at hospital dischargewas defined as a PCPC of 1–3 or PCPCunchanged from hospital admission.We also recorded the adverseevents following AVP administration such as proportion of children developing thrombocytopenia (platelet count <100000) after resuscitation, proportion with increased liver transaminases, hyponatremia, acute kidney injury (AKI), allergic reaction, hypertension (immediately after the dose), and/or theneed for dialysis (13).

Study methods

Children with CPA were resuscitated according to the 2010 AHA-PALS guidelines (3). Accordingly,as soon as a child was found to be in CPA chest compressions were initiated followed by support for breathing if the patient was not on a ventilator or if the patient was already on a ventilator both chest compressions and ventilations were delivered simultaneously. Subsequently cardiac rhythm evaluation was done and defibrillation performed if indicated. Adrenaline was administered as the first vasopressor in all cases at a dose of 0.01mg/kg intravenously. In cases of asystole or ventricular tachycardia/ fibrillation not responding to CPR including the initial 3 doses of ADR and/or shock vasopressin was given as the second vasopressor at a dose of 0.8 U/kg(13) during period 2 as previously mentioned. If furtherdoses of medication were required, epinephrinewas administered as per the pediatricadvanced life support guidelines until theend of the event. Only patients with in-ICU arrests were included and not those presenting in cardiac arrest to the ICU or those developing arrest in the ward after being shifted out. Although we cannot be assertive about the quality of CPR performed by the physicians and nurses we are certain that good

Panel 1. Pediatric Cerebral Performance Category score

Score 1. Normal - Normal; at age-appropriate level; school-age child attending regular school classroom

Score 2. Mild disability - Conscious, alert, and able to interact at age-appropriate level; school-age child attending regular school classroom, but grade perhaps not appropriate for age; possibility of mild neurologic deficit

Score 3. Moderate disability - Conscious; sufficient cerebral function for age-appropriate independent activities of daily life; schoolage child attending special education classroom and/or learning deficit present

Score 4. Severe disability - Conscious; dependent on others for daily support because of impaired brain function

Score 5. Coma or vegetative state- Any degree of coma without the presence of all brain death criteria; unaware, even if awake in appearance, without interaction with environment; cerebral unresponsiveness and no evidence of cortex function (not aroused by verbal stimuli); possibility of some reflexive response, spontaneous eye-opening, and sleep-wake cycles

Score 6. Brain death Apnea- areflexia, and/or electroencephalographic silence

quality CPR was delivered by all our team members at any point of time. In a previous study from our institute (16) we observed that there was a decline in resuscitation knowledge and skills with time among the nursing staff posted in the ICU and therefore we had made it a unit policy to update/retrain the nurses and residents at 3 monthly intervals and evaluate them appropriately every 3 months using laederal skill meter for ensuring delivery of good quality CPR (which included appropriate rate and depth of ventilation, adequate rate and depth of chest compressions and minimal interruptions in between CPR) to the sick children at all times.Therefore we presumed that the quality of CPR performed to be optimal during the study period. We collected data regarding baseline characteristics such as age, gender, admission diagnosis, cause of cardiac arrest, admission pediatric index of mortality (PIM) scores, pediatric logistic organ dysfunction score (PELOD), clinical course including need for mechanical ventilation, need for inotropes, need for blood products and dialysis. We also collected information regarding the outcome variables such as return of spontaneous circulation, sustained return of spontaneous circulation and critical outcome such as death or discharge from the hospital and PCPC scores at discharge in case of survival to hospital discharge.

Statistical analysis

Data were analyzed using Stata 11.2 (StataCorp, College Station, TX). Categorical data are presented as number (%) while continuous variables are presented as mean (SD), if normally distributed and median (interquartile range), if skewed. Statistical analysis was performed using Student's t-test, Wilcoxon rank sum test and Chi-square test for continuous and categorical variables respectively. A p-value of 0.05 was considered significant.

Results

A total of 112 children were admitted during the 3 months. Of these 28 children had suffered one or more episodes of cardiac arrest and 22 succumbed (19%). Only 6 (21%) children survived to hospital discharge. Of the 28 children 14 children each were enrolled from the two time periods.The baseline characteristics of the studied children during the two time periods are described in table 1. When we compared the baseline characteristics of the two groups we found that females were in majority during both periods. The most common reason for ICU admission was sepsis/ severe sepsis (n=14 vs. n=12, p=0.24) during both periods with the focus of infection being the lung commonly(n= 8, 57%) in period 1 as compared to period 2

(n=4, 29%). Children receiving epinephrine plus vasopressin had higher PIM and PELOD scores in comparison to children receiving epinephrine only, the difference being statistically significant for PIM scores only (p=0.03). The common causes of death in those admitted were refractory shock and hypoxemia during both periods and raised ICP in addition in period 1.

The predominant arrest rhythm in both groups was asystole with only 1 child in period 1 (VF) and 3 children in period 2 (2 had VF and 1 had VT) having tachyarrhythmia's. The average number of doses of epinephrine required was almost similar at both time pointswith the maximum number of doses in period 1 being as high as 9 in few cases. The average duration between cardiac arrest and termination of resuscitation efforts was 20 minutes at both time points in those dying.

Primary outcomes

Almost 50% (n= 7) of the children receiving vasopressin as the second drug had return of spontaneous circulation immediately after the arrest. In comparison nearly 43% (n=6) of children receiving epinephrine only had ROSC. However, 1 hour after revival 43% (n=6) of children fromboth time periods continued to have spontaneous circulation, the difference between the two groups being statistically insignificant (p=0.7). At 24 hours the proportion of children with sustained

Table 1: Baseline characteristics of children from the two time periods

Variables	Period 1 (Epinephrine alone) N=14	Period 2 (Epinephrine + Vasopressin) N=14	P value
Median age (years)	8 (1, 14)	3 (0.2, 11)	0.02
Female gender	8 (57)	9 (64)	1
Diagnostic subgroups (admission)			0.4
Sepsis/severe sepsis	14 (100)	12 (85)	
○ CNS infection	2 (14)	0	
○ GIinfection	2 (14)	0	
○ Respiratory infection	8 (57)	4 (29)	
○ Urosepsis	0	2 (14)	
○ Skin and soft tissue	2 (14)	2 (14)	
○ Without focus	0	4 (28)	
Poisoning	0	0	
Liver failure	0	0	
Congestive heart failure	0	2 (14)	
Any underlying chronic illness			0.2
CKD	1 (7)	0	
CHD	0	2 (14)	
PIM score	-2.2 (-1.6)	-2.9 (2)	**0.03**
PELOD score	10.7 (5.2)	15.5 (6.3)	0.3
Cause of arrest			0.05
Refractory shock	6 (42)	11 (78)	
Refractory hypoxemia	4 (28)	2 (14)	
Raised ICP	4 (28)	0	
Refractory CHF	0	1 (7)	
Resuscitation details			
Tachyarrhythmia	1 (7)	3 (21)	0.73
Asystole	13(92)	11 (78)	-
Epinephrine no. of doses	2.5 (1, 7)	3 (3,5)	0.43
Duration between CA and death (min)	30 (20, 30)	30 (22, 85)	0.29
Hospital course			
Need for mechanical ventilation	14 (100)	14 (100)	undefined
Need for inotropes before arrest	8 (57)	12 (85)	0.12
Median duration -inotropes before arrest (hrs)	8 (5, 48)	20 (8, 38)	0.38
Median duration of ICU stay (days)	1.3 (0.4, 2.5)	3.5 (0.5, 12)	0.38

CNS, central nervous system; GI, gastrointestinal; CKD, chronic kidney disease; CHD, congenital heart disease; PIM score, Pediatric index of mortality score; PELOD score, Pediatric logistic organ dysfunction score; ICP, intracranial pressure; CHF, congestive heart failure; ICU, intensive care unit

Table 2: Primary and secondary outcomes of the study population

Variables	Period 2 (Epinephrine + Vasopressin) N=14	Period 1 (Epinephrine alone) N=14	Adjusted OR (95% CI)	P value
Primary outcomes				
ROSC	7 (50)	6 (42.8)	1.16 (0.52, 2.5)	0.7
Sustained ROSC at 1 hour	6 (42.8)	6 (42.8)	1 (0.42, 2.3)	1.0
Sustained ROSC at 24 hours	5 (35.7)	4 (28.6)	1.25 (0.42, 3.7)	1.0
Secondary outcomes				
Need for prolonged CPR	7 (50)	7 (50)	1 (0.47, 2.1)	1.00
Duration of CPR	20 (12, 30)	20 (6, 30)	-	0.94
Survival to hospital discharge	2 (14.3)	4 (28.6)	0.5 (0.1, 2.3)	0.64
Duration of sustained ROSC (hrs.) – in those who died	30 (30, 40)	30 (20, 76)	-	0.91
Change in PCPC scores	-1.25 (0.95)	-1.5 (0.7)	0.25 (-1.9, 2.4)	0.76

spontaneous circulation declined further at both time points (table 2).

Secondary outcomes

When we compared the secondary outcomes between the two time periods we found that the proportion of children requiring prolonged CPR (>20 minutes) or being discharged from the hospital was comparable between the groups (table 2) although the numbers were higher in the epinephrine only group. The median duration of resuscitation did not differ between the groups and was 20 minutes on an average in both (table 2). However the duration of ROSC was insignificantly prolonged in children receiving vasopressin in addition to epinephrine in comparison to those receiving epinephrine only (table 2). There was no significant difference with regard to other secondary outcomes, such as,change in PCPC scores from baseline to discharge among those surviving to hospital discharge between both groups (Table 2).

Discussion

In this retrospective study of 22 children with in-hospital cardiac arrest we observednosurvival benefit with vasopressin as an add-on drug in cardiopulmonary resuscitation in comparison to the standard practice of using epinephrine alone. However, there was an insignificant trend towards increased proportion of children with ROSC and sustained ROSC at 24 hours (24 hour survival) in those receiving vasopressinin addition to epinephrine when compared to use of epinephrine alone. Unfortunately, this did not translate into survival benefit or benefit in terms of improved neurological outcome in such patients. Our study findings are therefore in accordance with few of the previously reported studieswhich showed neutral results meaning, results not favoring one drug over the other (17-19). However,as discussed earlier, there was an insignificant trend towards improved ROSC and 24 hour survival in our study similar to many of the prior studies in the adult population (20-23). The small numbers evaluated in our study probably resulted in this lack of significant effect seen in our study population.

In addition, there could have been several other explanations as to why our study population responded poorly to use of vasopressin epinephrine combination in comparison to epinephrine alone. Important among these could be *a)* higher PIM scores in children admitted during period 2 which could have made this group more vulnerable *b)* greater proportion of childrenwith refractory septic shock in the same group c*)* increased proportion of children with VF/VT in this

group and finally *d)* only a single dose of vasopressin was administered after the 3rd dose of epinephrine which could have been a suboptimal dosage or inappropriate timing for the drug to show any favorable response.

We observed that children with VF/VT as the initial rhythm did not respond favorably to vasopressin in our study population similar to previous studies in adults. These findings are in contrast to the expected physiologic effects of this drug observed in animal models with ventricular fibrillation. When compared with epinephrine under laboratory conditions in animals with ventricular fibrillation, it was found to have several benefits. It improved coronary systolic and diastolic perfusion pressures, generated higher left ventricular myocardial flow, and produced a higher coronary venous pH (24- 26). This effect on coronary perfusion pressure occurred after every dose of vasopressin as compared to a one time effect with only the first dose of epinephrine. Not only did it improve cardiac perfusion but also improved cerebral blood flow. Furthermore, the effects of vasopressin on vital organs lasted longer than epinephrine and it was also more effective in resuscitating swine models with prolonged cardiac arrest without causing any significant neurological deficit (24-26). From the above discussion it is clear that vasopressin is beneficial in animal models with ventricular fibrillation. However, in human beings why the reverse phenomenon is observed with vasopressin is not clear. A probable assumption could be that in cases of prolonged asystolewith out of hospital or in-hospital cardiac arrest, a state of epinephrine resistance from down-regulation of catecholamine receptors may occur which makes these patients less responsive to epinephrine. As vasopressin acts via different receptors it may have a favorable response in this population.

Vasopressin is known to act Via V1 receptors in vascular smooth muscle cells and cause peripheral vasoconstriction unlike other vasopressors which act predominantly by their action on alpha or beta receptors (23, 24, 26). Therefore, in cases of refractory septic shock where there is receptor down regulation, vasopressin should have had beneficial effect in such cases as compared to epinephrine as most patients would already be on epinephrine at the time of arrest. However we observed that patients with refractory septic shock did not respond favorably to vasopressin. It is well known that refractory septic shock has a mortality rate of almost 50% (28) despite best efforts due to factors such as organ dysfunction, coagulopathy and acidosis. Such patients are unlikely to respond to a single large dose of vasopressin in cardiac arrest as they may succumb to complications of the disease as such- like bleeding, acidosis and associated myocardial dysfunction which would make them unresponsive to any kind of resuscitative efforts.

We also observed that prolonged duration of cardiac arrest did not respond favorably to the administration of vasopressin in our study population contrary to what has been reported in adults (21, 27). This could probablybe attributed to *1)*differences in the cause of arrest which is most often respiratory in origin in children (29) in contrast to adults where it is of cardiac origin and *2)*differences in the physiologic response to disease states between these two patient populations.

The strength of our study is that the findings of our study would certainly add to the scant literature on vasopressin in pediatric cardiac arrest as there are large knowledge gaps in this subject with only few observational studies and a recent feasibility pilot trial as discussed earlier. The major limitations of our study are the inadequate sample size and retrospective nature. A large randomized controlled trial with an adequate sample size may provide definitive answers to the hypothesis generated from our study. The other limitation is that we used vasopressin only after 3rd dose of epinephrine and did not evaluate the effect of vasopressin replacing the second or third dose of epinephrine. Also, we had not evaluated the effect of this combination in children with out of hospital cardiac arrest which accounts for a significant

proportion of cardiac arrests in the community.

In conclusion, use of vasopressin did not seem to affect the clinical outcomes of children with in-hospital cardiac arrest in comparison to epinephrine alone. However, our study findings need further validation through adequately powered clinical trials in both in-hospital and out of hospital cardiac arrest settings, before anyrecommendations could be made about the use of this drug in pediatric CPR.

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Cold Injury in Newborns: Still an Emergency

Kamaldeep Arora, Rashmi Ranjan Das, M. Jeevasankar

Abstract

Thermal care of newborn represents the basic care provided to the neonate. In the developed world, thermal protection of the neonate has resulted in improved survival of the newborns, but this issue still needs to be addressed in developing world. Hypothermia in neonates is an important contributor to neonatal morbidity and mortality; with premature and low birth weight (<1500 gm) infants at greatest risk of hypothermic injury.Hypothermia is regarded as one of the major causes of neonatal death in developing world. It does not require a special equipment to keep the neonate warm but requires knowledge of importance of thermal care and methods to keep the neonate warm. In this review we would be discussing, why newborns are at risk of hypothermia,basic mechanisms of thermoregulation and treatment of any grade of hypothermia, particularly severe hypothermia, as a neonatal emergency. The small but important interventions to protect newborn from hypothermia would not only reduce the individual mortality but also reduce the global burden of neonatal mortality.

Keywords: Hypothermia; Low birth weight; Neonate; Prematurity; Thermal care; Thermoregulation.

Introduction

Thermal care represents one of the fundamental aspects of neonatal care.The incidence of neonatal hypothermia has decreased in the developed world but it is still very high in the developing world.It is estimated that annually, about 17 million neonates develop hypothermia in the developing world.[1]The incidence of neonatal hypothermia in developing countries is still at large with incidence as high as 67.6% in Nigeria, and 43% in India among normal weight neonates.[2,3]In Nepal the condition is even worse, with 85% neonates hypothermic within 2 hours of birth even in institutional setting.[4]In study in Uganda hypothermia was detected in 8 out 10 newborns in immediate postpartum period.[5]

Hypothermia in neonates is an important contributor to neonatal morbidity and mortality.[6]In astudy by mathur et al, fatality rate was 39.3% in mildly hypothermic infants, 51.6% in moderatelyhypothermic babies and 80% in severely hypothermic babies.These figures are even higher in newborns who are low birth weight and suffer asphyxia or have neonatal depression.[7]Hypothermia also carries a high neonatal morbidity due to increased risk of respiratory distress, metabolic acidosis, jaundice and hypoglycemia.[8]

As per the WHO definition hypothermia in newborn is defined as temperature below 36.5°C and is further categorized into cold stress (36-36.4°C), moderate hypothermia (32-36°C) and severe hypothermia (<32°C). A newborn placed naked in an environment of 23°C at birth suffers the same cold as does a naked adult at 0°C.[9]Care providers and mothers need to be aware of the importance of temperature maintenance of the newborn.Lack of knowledge among mothers and care providers of simple methods to maintain the "WARM CHAIN" has been

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found to be the most common factor contributing to hypothermia.[10]World health organization (WHO) developed ten step practice guidelines, described as **"WARM CHAIN"** which emphasized in keeping the newborn warm from immediately after birth to first few days of life.[9]

Appropriate policies, comprising simple practices such as establishing a warm delivery room, immediate drying at birth, skin-to-skin contact, early breastfeeding, delay in bathing the newborn, appropriate clothing, warm resuscitation, warm transportation, and training/awareness, are essential to prevent hypothermia.[9]

Mechanism of thermoregulation in neonates

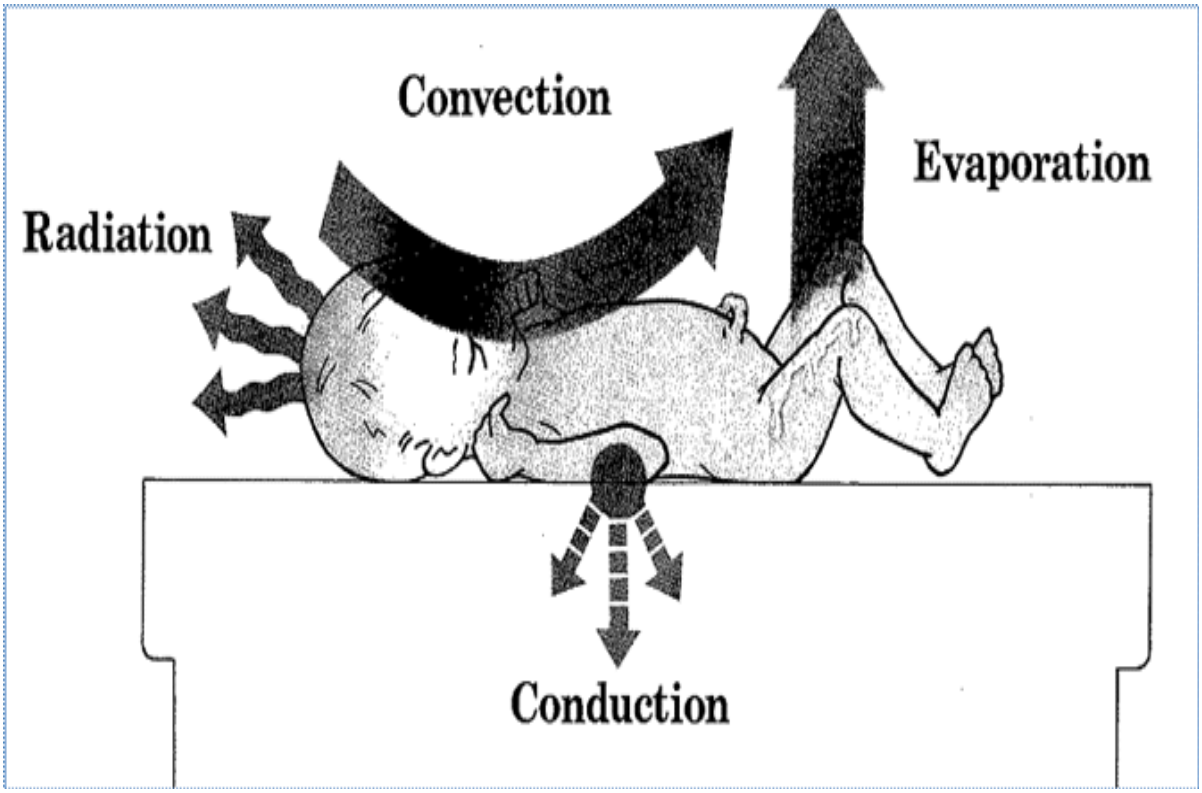
The basic aim of thermoregulation in neonates is to maintain the neonate's body temperature in thermo-neutral rangealso known as 'neutral thermal environment'.It is defined as the temperature range in which the basal metabolic rate of the neonate is at a minimum, oxygen utilization is least,yet theneonate maintains its temperature well.[11] For each baby, this range of temperature varies depending on gestational age and day of life.

Let's discuss in brief the mechanism by which the neonate loses and gains heat from environment and the ways by which he maintains his thermo neutral rangeof temperature.

Heat loses

New born loses heat to the environment immediately after birth as the milieu from where the newborn comes (amniotic fluid) is warm with temperature of nearly 38°C. The newborn loses heat by four different ways i.e evaporation, conduction, convection, radiation (Figure 1).[9]Newborn loses heat by evaporation particularly soon after birth (due to evaporation of amniotic fluid from skin surface), conduction (by coming in contact with cold objects-cloth,hands, tray), convection (by air currents in which cold air replaces warm air around baby-open

Figure 1: Four different ways a newborn can lose heat. Adapted from WHO[9] thermal protection in newborn(See text)



windows, fans) and radiation (to colder solid objects in vicinity like walls).

Heat Gain

The process of heat gain is by conduction, convection and radiation in addition to non-shiveringthermogenesis. Non-shivering thermogenesis is typical of newborn and occurs predominantly in the brown adipose fat.Brown fat is localized around the adrenal glands, kidneys, nape of neck, inter scapular region and axillary region.It is rich in mitochondria and is major source of heat production.[12]Blood flowing through the brown fat becomes warm and through circulation transfers heat to other parts of the body. Brown fat is richly supplied by parasympathetic, non epinephrine mediated nerve endings. When neonate's temperature decreases, the thermoreceptors get stimulated and activate the temperature regulating area in hypothalamus.[13]This results in norepinephrine release and this triggers nonshivering thermogenesis, and leads to lipolysis of brown adipose tissue, and this maintains the neonate's temperature.

Why neonates are different from adults in regulating thermal control?

Neonates, in contrast to adults, are at increased risk of hypothermia and are far more sensitive to changes in the external environment. Neonates are handicapped in many ways including a higher body surface areatobodymass ratio (which implies more radiant heat and more insensible water loss), large head in proportion to the body,higher metabolic rate, limited stores of metabolic substrates like glycogen andlittle subcutaneous fat.[14] In addition, neonates have inability to reduce the surface area by assuming flexed posture and limited and immature thermoregulatory behaviors, including inability to mount a shivering response and decreased heat production due to less brown fat. In preterm neonates all these factors are aggravated and cause more pronounced hypothermia as compared to term counterparts.

Assessment of neonatal hypothermia

Assessment of neonate's temperature is done by using the clinical thermometer which reads till 35°C but if the temperature reads low, a low reading thermometer (30-40°C) will be required to record the temperature below 35°C**.** The site of measurement of hypothermia is notspecified in WHO classification.[9]The site of measurement can be rectal or axillary, but for ease of measurement, safety and hygiene the axillary temperature measurement is the preferred method.The other method which can be used in peripheral/community setting to detect hypothermia and can be assessedwith reasonable precision is by human touch.[1] The basis of this method is that abdominal temperature is representative of the core temperature and the feet temperature is representative of peripheral temperature as abdominal vasculature does not vasoconstrict. The warm and pink feet of the baby indicate that the baby is in thermal comfort. But when feet are cold and abdomen is warm it indicates that the baby is in cold stress. In hypothermia both feet and abdomen are cold to touch. The reliability of this method can be enhanced by training the mothers and care providers.This method has been proven to be useful in many studies.[15–17]

Clinical features of severe hypothermia

Clinical features of hypothermia vary from mild hypothermia to severe hypothermia. It can range from lethargy, poor feeding, and unresponsiveness to apnea, metabolic acidosis, coagulopathy, neurological dysfunction and asystole/death. In addition severe hypothermia leads to impaired growth,increased risk of infections, sclerema, pulmonary haemorrhage, hypoglycemia. [18]

Management of hypothermia

Prevention of hypothermia

Thermal protection of newborn is a series of steps taken to ensure that the newborn does not become cold or overheated during birth or during the first few days of life. World health organization (WHO)declared neonatal

hypothermia as emergency and developed a series of ten step practice guidelines called "WARM CHAIN" (table 1), which was aimed to maintain the neonate's temperature from immediately after birth to first few days of life.[9]

Prevention of hypothermia

In the delivery room

The delivery room should be warm (>25°C), the newborn should be immediately dries and wrapped in a warm dry towel with head

Table 1: Ten steps of "WARM CHAIN" in maintaining newborns temperature

The warm Chain	
1	Warm delivery room
2	Immediate drying
3	Skin to skin contact
4	Breast feeding
5	Bathing and weighing postponed
6	Appropriate clothing/bedding
7	Mother and baby together
8	Warm Transportation
9	Warm resuscitation
10	Training and awareness raising

Adapted from WHO 1997 thermal care of newborn guidelines

adequately covered. After ensuring all these, place the baby in skin-to-skin contact with the mother and initiate early breastfeeding.

Immediate postnatal care

The neonate should be maximum time in skin to skin contact with mother; breast feeding should be encouraged exclusively and frequently. Neonate should be dressedwith extra clothing and his head covered. A baby who is born LBW (less than 2500 g) often needs special care in a hospital. If there are no signs of distress or extreme prematurity, a mother can provide warm environment by "Kangarooing" the baby at home or hospital.

Management of hypothermia

Management of hypothermia is always regarded as an emergency as unrecognized and untreated hypothermia would lead to devastating consequences as mentioned above. At health centrethe diagnosis of hypothermia should be confirmed by recording axillary/rectal body temperature. A hypothermic baby should be rewarmed as quickly as possible to maintain the integrity of vital organs of the body. The method selected will depend on the severity of hypothermia and availability of equipment**.** Methods used can be using any of the following**:** Skin-to-skin contact,warm room or bed, a heater, a radiant warmer or an incubator. Regular monitoring is the key for maintaining the temperature. Monitor axillary temperature every ½ hour till it reaches 36.5°C, then hourly for next 4 hours, 2 hourly for 12 hours thereafter and 3 hourly as a routine. Sepsis should always be kept in mind, if hypothermia persists despite above measures.

The management would depend on the degree of hypothermia as described below:

Cold stress (36°C to 36.4°C)

Ensure that the baby is covered adequately; remove cold clothes andreplace with warm clothes. Use a room heater to warm the room. Measures should be taken to reduce further heat loss. Skin-to-skin contact with mother and breastfeeding should be initiated as soon as possible.

Moderate hypothermia (>32°C to < 36°C)

Moderate hypothermia at home is treated rapidly by keeping the baby in warm room in skin-to-skin contact with mother or care provider. Cover the baby on the mother's chest with her clothes and an additional warmed blanket. In hospital settings warmer/incubator should be used. Temperature monitoring should continue every 15-30 minutestill neonate is euthermic.

Severe hypothermia (<32°C)

This degree of hypothermia poses a real threat to the life of the newborn. Rewarming should begin as early as possible and can be

achieved by three methods: passive external, active external and active internal rewarming.[19,20]

Passive external rewarming measures included drying the baby, covering the head with warm cloth like hat and wrapping the baby in warmed blankets. Active external rewarming measures include the use of air heated incubator or manually operated radiant warmer or thermostatically controlled heated mattress set at 37-38°C and packing warmed saline bags against the body. Internal rewarming measures included administration of warm intra-venous fluids and warm, humidified ventilator gases.

Passive external cooling increases the body temperature rise at rate of 0.5-2°C/hour. The combined measures from all three techniques results in a rapid initial rise in core temperature of approximately 5- 8°C/h over 2 hours.[20]Once baby's temperature reaches 34°C, the rewarming process should be slowed down (0.5°C/hr) for the danger of hyperthermia.Vitals (heart rate, blood pressure, temperature)should be monitored regularlyalong with blood glucose. Blood sugar monitoring is very important in these neonates as they are prone to hypoglycemia,intravenous line should be established and dextrose should be started as these infants are lethargic and not able to take feeds. If no equipment is available as in home conditions or during transport to health facility, neonates should be kept in skin to skin contact with the mother and mother neonate dyad properly covered. All neonates with severe hypothermia should be given Inj. Vitamin K 1 mg for term and 0.5 mg forpreterm as there is risk of coagulopathy with severe hypothermia. These neonates are at risk of hypoxia due to increased energy demand and poor circulation and should be provided supplemental oxygen.

Rapid cooling versus slow cooling

Although the controversy of rapid versus slow rewarming in neonatal hypothermia is debated, the available literature points towards beneficial effects of rapid rewarming over hours rather than slow rewarming over days.Till date, there are no randomisedstudies on rapid versus slow rewarming in accidental neonatal hypothermia. A retrospective study from Israel in late 80's on rewarming 56 hypothermic infants reportedbetter outcomes (death) with rapid rewarming (no deaths versus 3 deaths in rapid versus slow rewarming, respectively).[8]There are many proposedphysiological consequences of rapid rewarming as these neonates should be monitored closely because of the risk of apnea, rewarming shock and the after-drop phenomenon.[21] Possible causes of rewarming shock include vasodilatation and lowered peripheral vascular resistance which occurs during the process of rewarming, especially rapid rewarming. The intravascular volume depletion can add on to this and cause significant hypotension. The other problem with rapid rewarming is the 'after-drop phenomenon'..This condition refers to deterioration following early rewarming of the peripheries. The blood in the peripheries is under anaerobic metabolism and leads to accumulation of lactic acid. This lactic acid rich blood when returns to the central parts leads to metabolic acidosis and the cooler blood results in decrease in core temperature.[22]The active external rewarming should be applied to thetrunk rather than the extremities because an "afterdrop" incore temperature may occur when blood supply to the coldperiphery is re-circulated to the core.[19]

Conclusion

In conclusion, neonates are handicapped in their thermal protection and need support from the mother/care provider to maintain their temperature. Knowledge of importance of temperature maintenance and simple, low cost methods such as warming of the delivery room, immediate drying, keeping in skin to skin contact with mother, immediate and frequent exclusive breastfeeding, appropriate clothing; can prevent this devastating neonatal emergency. This holds true especially for low resource settings. In severely hypothermic infants, rapid external rewarming is effective

and safe with no evidenced no complications. Increased knowledge among mothers and care providers including the hospital staff can significantly decrease the current incidence and case fatality of hypothermia.

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Bilateral Thalamic Lesions in a Pre-schooler with Parvovirus Infection

Nidhi Narsaria MD, Smriti Sangwan MD, Archana Singh MD

Abstract

The T2 weighted MRI image of a school going child with parvovirus B-19 infection is described here. Parvovirus B19 infection is associated with a variety of neurologic manifestations of which encephalopathy and/or encephalitis are most commonly reported. However, bilateral basal ganglia lesions due to parvovirus B-19 infection have never been previously reported. We chose to report this image to highlight this uncommon association of human parvovirus B-19 infection in man.

Key words: Basal ganglia; Parvovirus B19; B19; Virchow- Robin spaces; Bilateral basal ganglia lesions.

Image details

Bilateral basal ganglia lesions are an uncommon entity with a limited differential diagnosis that includes infection, metabolic disturbances, vascular lesions and neoplasia (1). We report here the case of a pre-schooler who presented to the emergency with features of viral meningoencephalitis and was found to have lesions in the basal ganglia bilaterally suggestive of prominent Virchow-Robin spaces.

A 4 year old female child presented to the emergency with history of a viral prodrome followed by loose stools and vomiting of 10 days duration. At admission, she was comatose, hypotensive and had features of raised intracranial tension. She was managed symptomatically with measures to maintain her cerebral perfusion pressure. Her cerebrospinal fluid was suggestive of aseptic meningitis with lymphocytic predominance and T2 weighted magnetic resonance imaging scan revealed bilateral cerebrospinal fluid hyper-intensities in the basal ganglia suggestive of prominent Virchow-Robin spaces. The cause for bilateral basal ganglia involvement was presumed to be due to parvovirus B19 infection as the real-time polymerase chain reaction was positive for parvovirus B19 antigen in serum. The child survived the acute illness but had sequelae in the form of extrapyramidal movements. Parvovirus B19 infection is associated with a variety of neurologic manifestations of which encephalopathy and/or encephalitis are most commonly reported (2). The outcome of CNS disease is often poor and neurologic sequelae may occur in as many as ¼th of the cases (3).

Small Virchow- robin spaces are a normal occurrence in all age groups. However, these may be enlarged due to perivascular cuffing by mononuclear cells in various infective and inflammatory conditions of CNS (4). We chose to report this image to highlight this uncommon manifestation of human parvovirus B19 infection in man.

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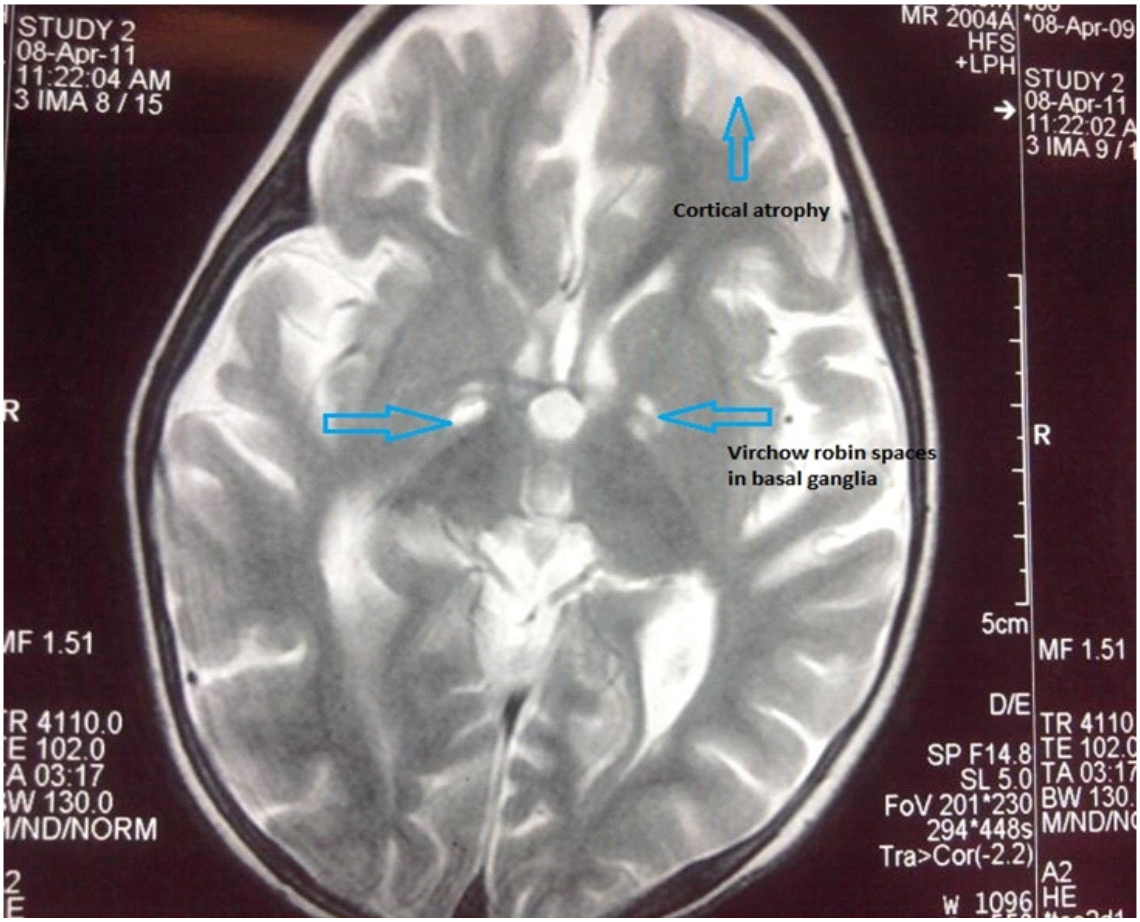
Image 1: T2-weighted MRI image of the child showing small signal intensity bilaterally in the basal ganglia suggestive of prominent Virchow-Robin spaces and mild cortical atrophy



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Management of Neonatal Emergencies: Current Evidence from Chrane / Other Systematic Reviews

Kamaldeep Arora, Rashmi Ranjan Das, M. Jeeva Sankar

Abstract

Hypotension in neonates, particularly preterm, is a matter of debate in all its aspects (definition, monitoring and treatment).The neonate is uniquely at risk of hypotension and low systemic blood flow states due to failure or delay in the normal transition of circulatory processes.While managing the hypotensive neonate, it is not clear whether the issue to be addressed is low blood pressure or low flow states. With the development of newer technologies to assess this issue; the subject becomes more challenging and interesting.Most of the neonatal units use a stepwise approach for managing hypotension in neonates. Although the understanding of cellular mechanisms of action of inotropes is well founded, there is little information on their clinically relevant long-term benefits in the neonatal patient population. Also data regarding their safety and efficacy are lacking. The current clinical query tries to answer the issue of use of dopamine versus dobutamine as first line inotrope of choice in this group of neonates. This would hopefully help the clinician to apply the evidence based practice for management of hypotension in preterm neonate and would provide insight for future well designed studies.

Keywords: Hypotension; Preterm; Dopamine; Dobutamine.

Clinical question

You are a resident in neonatal intensive care, taking care of a 34 week neonate at 14 hours of life diagnosed as a case of severe birth asphyxia with shock. The neonate has low blood pressure as measured by the oscillometric method and you plan to give normal saline,fluid bolus (10ml/kg). The administration of fluid bolus increased the blood pressure but it was still below the 5th centile. You repeat the bolus (10ml/kg), which leads to no improvement in blood pressure. You plan to start inotropes fearing the chances of heart failure on giving more fluid boluses. You ask the staff on duty to prepare dopamine as it would help to raise the blood pressure, but your colleague warns you that dobutamine would be better in cases of shock caused by birth asphyxia. You get confused as the blood pressure will drop further on administration of dobutamine. So youplan to start dopamine in emergency and in the meantime read the evidencefortreatment of shock in preterm neonates, in order to review the treatment.

You are now confronted with the following questions:

1. What is the first line drug treatment for the newborn with shock associated with birth asphyxia?
2. Is there any evidence for dopamine versus dobutamine for such a situation?
3. Does evidence suggest decrease in blood pressure with dobutamine?

You plan to review the treatment and inform your colleague after reading the available literature.

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Table 1: Drugs used in treatment of hypotension[5]

Name	Category	Mode of action	Dose
Dopamine	Inotrope/ Vasopressor	α and β adrenergic effects	2-20µg/kg/min
Dobutamine	Inotrope	α adrenergic effects	5-20µg/kg/min
Adrenaline	Inotrope/ Vasopressor	α and β adrenergic effects	0.05-2.5µg/kg/min
Noradrenaline	Vasopressor	α and (some) β adrenergic effects	0.05-2.5µg/kg/min
Hydrocortisone	Steroid	Multiple	2.5 mg/kg 6 hourly

Background

hedefinition of hypotension in the preterm infant has been a contentious issue.[1]Besides, there are wide differences in the practice of monitoring, timing of intervention, measurement of outcomes and treatment strategies for hypotension. With its varied pathophysiology added to the inherent immaturity of the preterm infant; these issues assume greater significance. The main goal of achieving the normal tissue oxygenation requires maintenance of systemic blood flow and normal blood oxygen levels.[2,3] Reduction in either of these physiological parameters may result in organ damage.To maintain these parameters the clinician uses the volume expansion (filling the pump), inotropes (tightening the pump), and hydrocortisone (compensating for an immature pump). The accurate treatment of hypotensive and low cardiac output states in the preterm infant requires a proper understanding of the actions of various drugs on the immature cardiovascular system.Despite our limited understanding of the pathophysiology of hypotension and the benefits of therapeutic intervention in the preterm infant, a significant number of preterm newborns receive cardiovascular support. [4]None of the current treatments for hypotension, including the use of inotropic agents (Table 1), have been well studied in the preterm population, and data regarding safety and efficacy are lacking. The injudicious use of inotropes in preterm neonates may be hazardous rather than supportive. In this clinical query, we have tried to review the evidence behind use of dopamine versus dobutamine as a first line drug of choice in preterm neonates with shock.

Evidence

With the updated current evidence, there are two cochrane reviews[6,7]and another single systematic review[8]addressing the issue of dopamine versus dobutamine as first line drug treatment of shock in neonates:

Cochrane review:[6,7]

(a) Thereview by *Subhedar et al* (2003),[6,7]comparing the effectiveness and safety of dopamine versus dobutamine in the treatment of systemic hypotension in preterm infants. It included five studies that enrolled a total of 209 hypotensive preterm neonates.There was no evidence of a significant difference between dopamine and dobutamine in terms of neonatal mortality (3 trials, 103 patients; RR 1.17 95% CI 0.47, 2.92), no difference in incidence of periventricular leukomalacia (3 trials, 103 patients, RR 0.43 95% CI 0.12, 1.52), or severe intraventricular haemorrhage (2 trials, 83 patients; 0.73 95% CI 0.15, 3.50). Dopamine was more successful than dobutamine in treating systemic hypotension, with fewer infants having treatment failure (4 trials, 189 patients; RR 0.41 95% CI 0.25, 0.65; NNT = 4.4, 95% CI 2.9 to 7.7). Treatment with dobutamine was associated with a significantly greater increase in left ventricular output in the single study reporting that outcome. There was no evidence of a significant difference between the two agents with respect to the incidence of tachycardia (RR 0.74 95% CI 0.26, 2.08).

(b) The other cochrane review by *Osborn et al*[4]updated in year 2007 included one study (n=43). The study compared the dopamine versus dobutaminegroup enrolled patients who had low superior vena cava (SVC) flow. They reported the short term as well as the

long term neurological outcomes of the surviving neonates. No significant difference was reported in mortality to discharge, intraventricular haemorrhage (IVH) grade 3 or 4 IVH or NEC. At three years follow up (n=13), there was no significant difference in cerebral palsy(RR 0.16 95% CI 0.01, 2.64), deafness, developmental quotient > 2 SD below norm or combined disability. But the surviving infants treated with dobutamine had a significantly higher development quotient (RR35.0, 95% CI:17.68, 52.32). There was no significant difference in death ordisability at follow up (RR 0.95, 95% CI: 0.66, 1.38).

Other systematic review

The review by *Higgins et al*[8] in the year 2011 includedseven trials, comparing the effect of dopamine versus dobutamine;(a)Dopamine administration was associated with a significantly greater overall therapy efficacy than dobutamine in terms of increase in blood pressure in hypotensive preterm infants (n=251; RR 0.26; 95% CI 0.20 to 0.32). (b) Secondly, dopamine was associated with a trend towards a lower incidence of short term adverse neurological outcome than dobutamine (three studies; n=118; r = -0.13; 95% CI -0.31 to 0.059), however, this comparison did not reach statistical significance($P_{one\text{-}tailed}$= 0.10).

To summarize, using dopamine versus dobutamine for hypotensive preterm neonates

- *Dopamine administration is associated with significant increasesin blood pressure in the hypotensive preterm infants as compared to dobutamine*
- *Possibly reduces short term adverse neurological outcome than dobutamine, reassuring that dopamine has good safety profile.*
- *Long term neuro-developmentaloutcome is possibly better in patients treated with dobutamine if they had low SVC flow(n=13).*

Discussion

The available evidence seems to favor either of the inotropes depending upon the clinical situation and the cause of hypotension in the hypotensive preterm neonate. The above mentioned studies enrolled infants with low blood pressure (B.P) as defined by their gestation in weeks, though there is no consensus on definition of hypotension in preterm infants. So treating the numerical values (B.P) has always been an issue and as stated above the SVC flow may be better indicator of organ perfusion rather than the systemic blood pressure. In the single study[3]using SVC flow as a marker; dobutamine had a better long term developmental quotient, although C.P rates were similar. So, it depends upon which parameter we are using to assess the hypotension, pressure or flow.

There are concerns while making general statements regarding this issue in regards of the available studies. They need to be addressed before a definite recommendation regarding dopamine or dobutamine is made.The concerns include:

Methodological issues

The trials included in cochrane review are not blinded (except one)[9] in regards to intervention. Though the Cochrane review did not find any significant heterogeneity between the results from trials using different randomizationmethods, the possibility of biascannot be completely ruled out. Similarly, lack of blinding - though unlikely to affect a 'hard' outcome like mortality - could result in different level of care in the two groups thus affecting the observed results.

Lack of proper and adequate long-term follow-up data

Thisis the major problem in accepting the results of the systematic reviews as such. The follow-up data available comes from a single study[3], is incomplete with a small sample size

(n=13), and points toward better developmental quotient in dobutamine treated infants, although the cerebral palsy rates were same. Given that the particular study was not powered enough to detect a small difference in the incidence of long-term outcomes, one has to be really cautious in interpreting this data.

Ethical considerations

The studies have looked at either dopamine or dobutaminefor hypotension in preterm infants. Some studies would have used the epinephrine or corticosteroids as a back up for dopamine or would have combined the two after failing to achieve the desired pressure level. Using strict criteria for the using of either drug may not be feasible as the neonates with shock are at a risk of organ damage and this may not be ethical feasible to use a single drug.

Generalization of results

Since the studies have been done in preterm population with varied reasons for shock. The reasons can vary from septic shock to shock due to persistent pulmonary hypertension or asphyxia (myocardial depression).The result may not apply to all preterm neonates where the causes of shock may be different. So extrapolating the results in all neonates with shock should be done with caution.

Proposed Recommendations (Table 2)[2,7–11]

Based on above discussion we could formulate that the patho-physiological factors which predominate in the first 24 hours are mainly related to vasoconstriction as seen by low SVC flow, normal or low BP and poor myocardial contractility. Those which affect subsequently are predominately vasodilatation associated with low BP, normal SVC flow and myocardial function. Since the babies on the first day are more likely to have low SVC flow and poor myocardial contractility, dobutamine would be the first choice of inotropes.Dopamine and epinephrine may be added as second and third line medications to titrate to blood pressure.

Summary

Systematic research on the effectiveness of inotropic agents points toward the superiority of dopamine at improving blood pressure in these neonates. [2,9,15–17]However, some studies in preterm infants using dopamine at doses >5 µg/kg per min suggest that dopamine exerts its effects byincreasing systemic vascular resistance, which could be counterproductive for the myocardium.[17,18]In fact, dobutamine[2,6,17]have had a better effect on

Table 2: Proposed treatment options for dopamine versus dobutamine in treatment of preterm shock

Interventions	Evidence	Recommendations
Dopamine / Dobutamine in treatment of neonatal shock[2,7–11]	Five RCTs[2,6,12–14] comparing dopamine with dobutamine with metaanalysis: Dobutamine is less effective than dopamine in increasing BP, But in 30-84% of babies, dobutamine is more effective in maintaining cardiac output. Dobutamine is also more effective than dopamine in maintaining SVC flow (68% Vs 45%) 40% of babies with low flows failed to maintain SVC flows despite use of both inotropes.	*In states of myocardial dysfunction, PPHN and low flow states, dobutamine may be a better choice.* *In states of normal SVC flow with hypotension, dopamine would be the choice.*

cardiac performance, probably because of a predominant â-effect. Aside from information about the short-term effects of these drugs on the cardiovascular system in preterm infants, little data are available on the systematic evaluation of the effects of catecholamines on neonatal morbidity and mortality, [6,19]and long term neurodevelopmental effect[3], so it is difficult to document specific recommendations for treatment strategies. Currently, many infants receive potentially toxic therapies based solely on simplistic criteria, such as a mean blood pressure less than the gestational age in weeks, in the absence of any evidence that such an approach is beneficial. Good clinical practice requires a careful assessment of the risks and benefits of an intervention before starting it. Also, on the another hand, it is important, on those promoting a more interventionist approach to perform the requisite randomized controlled trials to prove that clinical outcomes are improved.

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Delays in Resuscitation of the Septic Child in Indian Settings: A Clinician's Perspective

Jhuma Sankar, Suresh C.P.

Abstract

Severe sepsis and septic shock are the leading causes of death in children admitted to any intensive care unit of a developing country. The most important reason for unfavorable outcomes in these children is the severity of illness at presentation which makes these children refractory to any goal directed measures undertaken thereafter. Apart from the agent and host related factors, environmental factors such as delay in seeking timely and appropriate healthcare and use of inappropriate modes of transport may be equally responsible in adding to the disease severity in these children. In this article we shall briefly review the importance of early recognition and treatment and the probable reasons for delay in our set up.

Key word: Sepsis; Septic shock; Transport; Resuscitation; Golden hours; Early goal directed therapy.

Introduction

Severe sepsis and septic shock are *'the'* most important causes of mortality in emergency and intensive care units of most resource limited countries. While the mortality rates reported with septic shock from developed countries is 50%, it is 40-67% in children form developing countries (1,2). Despite the best resuscitative efforts in the first 6 hours (*ongoing study*) a major proportion of these children die every year. The most important reason for unfavorable outcomes in these children is increased severity at presentation due to delay in seeking timely and appropriate healthcare. The importance of early recognition and treatment and the probable reasons for delay in our set up are briefly discussed here.

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Early goal directed therapy in septic shock

A cascade of clinical, hemodynamic and metabolic changes occur in septic shock, which if not identified early and managed appropriately could result in irreversible multi-organ damage. The first hours following the diagnosis of severe sepsis and septic shock are known as the "golden hours" as it is during this period that aggressive hemodynamic resuscitation has been shown to be associated with higher survival rates and improved organ dysfunctions (3, 4). The lack of rapid restoration of adequate microcirculation triggers a cascade of inflammation and disseminated micro thrombosis for which, no effective treatment is available at present. Inadequate early resuscitation results in multiple organ system failure and in death days to weeks after the initial presentation (5). This has been confirmed by a recent meta-analysis that suggested that aggressive resuscitation efforts that begin early (before the onset of organ failure) may prove more beneficial than resuscitation carried out after the establishment of organ failure (6). After the "golden hours", aggressive hemodynamic resuscitation is no longer effective in restoring organ function or in decreasing mortality (6). Goal directed resuscitation in these golden hours has been the target of several adult and

few pediatric studies including an ongoing trial in our ICU (3,7, 8, 9).

Early goal-directed therapy (EGDT) is a research innovation that has been shown to reduce mortality in adults with severe sepsis and septic shock (3). EGDT is simply a protocol derived from components that have long been recommended as standard care for the septic patient. EGDT involves adjustments of cardiac preload, after load, and contractility to balance oxygen delivery with oxygen demand which in turn is important for early hemodynamic optimization. The protocol is initiated as soon as sepsis induced hypo-perfusion is identified and it targets specific end points of resuscitation derived from hemodynamic monitoring (central venous pressure [CVP], mean arterial pressure [MAP], and central venous oxygen saturation [$Scvo_2$] (3, 10). Current consensus recommendations now advocate EGDT as best practice for the first 6 hour resuscitation in severe sepsis in adults. The EGDT protocol has been modified and advocated for pediatric septic shock in the "surviving sepsis campaign guidelines" (SSSG) with similar resuscitation end points like $Scvo_2$ >70 %, decreased lactate, urine output of > 1ml/kg/hr, CRT<2 sec, normal mental status and normal pulses with no difference between peripheral and central pulses (11). A detailed review of the SSCG 2008 is available in an earlier issue of this journal (volume 3, number 2) (12).

In the first study on EGDT by Rivers et al (8) of 263 adult patients, EGDT was associated with a 16% absolute risk reduction for in-hospital mortality, which to date is the largest mortality benefit demonstrated in septic shock. Following this the outcome benefit has been replicated in 19 before-and-after adult studies of 1,677 pre-implementation and 2,361 post-implementation adult patients and a randomized pediatric trial in the last decade (12). In the pediatric study by Oliviera et al (13) there was an 82% reduction in mortality risk in the intervention group. In the ongoing study in our ICU wherein more than half the calculated sample size has been recruited we have also found a trend towards decreased mortality rates in the group in which intermittent monitoring of $Scvo_2$ is done as part of EGDT protocol (mortality 34% vs. 57% in the $Scvo_2$ vs. no $Scvo_2$ group respectively). Although the mortality rates due to septic shock have declined in our unit with the implementation of the EGDT protocol the overall mortality rate of the study population is still 45% which is much higher in comparison to figures from the developed countries. When we tried to analyze the factors associated with unfavorable outcome in the study patients we found the time to hospitalization and the duration of illness to be two of the important factors associated with poor outcomes in these patients (*unpublished data*).

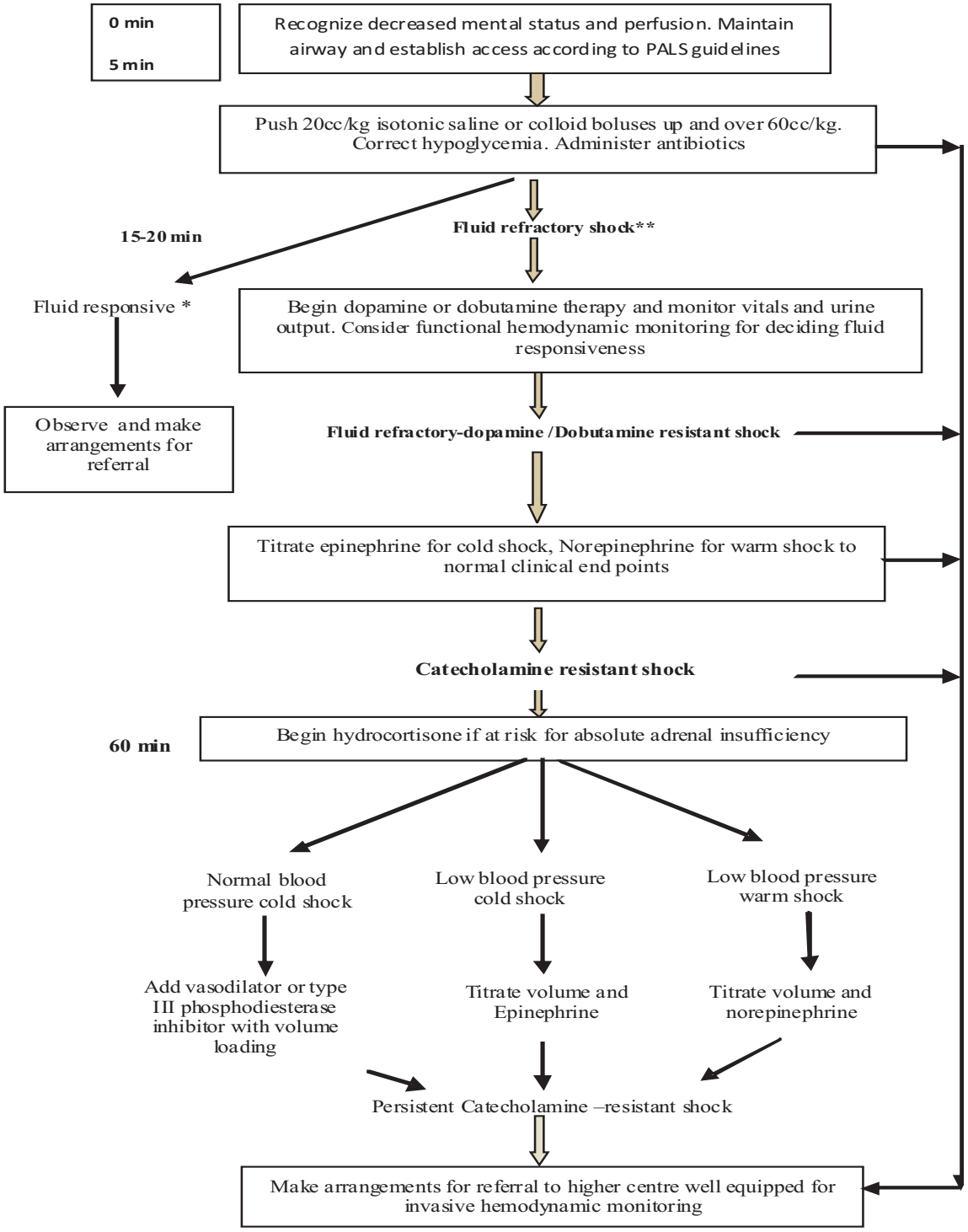
Reasons for delay in resuscitation of the septic child

The major reasons for loss of 'golden hours' in our country may be due to the three major delays: delay in recognition of shock, delay in transport of the affected child and delay in initiating appropriate treatment. The result is that the patient often reaches the tertiary care center in the late stages of septic shock wherein end organ failure has already started to set in (13).

Delay in recognition could be due to lack of knowledge and awareness in the treating pediatricians and physicians of the markers of tissue perfusion. In most circumstances clinical assessment at primary contact is based on appearance and activity of the child and measurement of blood pressure only. If the blood pressure is normal which is often the case, the physicians are in no hurry to resuscitate the child thereby defeating the purpose of early goal directed therapy.

Septic shock can be identified by clinical variables, hemodynamic variables, oxygen use variables, or cellular variables. The clinical diagnosis of early septic shock is possible with presence of the following in a setting of suspected infection: hypothermia or hyperthermia along with clinical signs of decreased perfusion, including decreased

mental status, prolonged capillary refill time of > 2 seconds or flash capillary refill, diminished or bounding peripheral pulses, mottled cool extremities, or decreased urine output of < 1ml/kg/hr. Blood pressure, a hemodynamic variable, drops only in late shock and should not be relied on to make the diagnosis; however, its presence in a child with clinical suspicion of infection is confirmatory (5, 14). The shock may further be classified as cold shock which is characterized by decreased perfusion including decreased mental status, decreased urine output,



capillary refill > 2 sec, diminished peripheral pulses and mottled cool extremities and warm shock characterized by decreased perfusion including decreased mental status, decreased urine output, and flash capillary refill and bounding peripheral pulses (5, 14). It is important to create awareness about utility of these clinical parameters among pediatricians so that septic shock is suspected early and the patient is either managed appropriately or provided initial care and transported to appropriate centers.

The second and major cause of unavoidable delay is due to poor availability of transport facilities from rural areas and outskirts to the tertiary care centers. Patients often reach the appropriate centers by train, auto rickshaw, taxi, buses or other locally available transport facilities without any monitoring. This leads to further deterioration of the hemodynamic status. Therefore, the role of the pediatrician (who suspects septic shock in a child and decides to send him to a higher center) includes initial aggressive management (figure 1) with arrangement of proper transport with facilities for monitoring during transport by reasonably trained person. Transport is often the key element in deciding the outcomes as it is often observed that even relatively stable patients may deteriorate while being moved for investigations, procedures etc.

The third and important cause of avoidable delay is delay in initiating treatment which may be due to delay in recognition, non-availability of life saving drugs or lack of expertise in resuscitating a child with septic shock in the peripheral health centers. To overcome these problems there is need for development of human resources by organizing short term training courses, workshops and other educational activities by experts; for pediatricians, intensive care nurses and other staff.

A modified protocol of the SSCG guidelines to guide the community physicians in management of septic shock is depicted in figure 1.

Conclusion

In conclusion we would like to quote the famous poet of all time 'Robert Frost' who once said "Miles to go before I sleep' in the context of reducing mortality rates due to septic shock in our country. A consolidated effort at all levels of health care targeting this group of children who can be salvaged with timely help needs to be taken from our side so as to reduce the *pathos* caused by this disease in our country. There is also a need to generate evidence for better management of children with septic shock in our country. There is need to do operational research especially with regard to addressing our local problems of missed diagnosis, reasons for delayed reporting, problems of transportation, etc.

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