Original Research Article

Fluid restriction in term neonates with moderate to severe perinatal asphyxia: A randomised controlled trial

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Abstract

Introduction: Management of newborns who suffer perinatal asphyxia is primarily based on supportive management, of which fluid and electrolyte management plays a very important role. We studied the role of restriction of fluids in the first 72 h in term neonates suffering from moderate to severe perinatal asphyxia. **Methods:** Term newborns with moderate to severe perinatal asphyxia were randomised to receive full or restricted fluids (25 newborns each) during the first 72 h of life. The primary outcome measures were mortality and neurological status at discharge. **Results:** Mortality among the full (FF) and restricted fluid (RF) groups was not significantly different, 4 in the FF group and 3 in the RF group with a relative risk (RR) of 1.52 [confidence interval (CI) 0.38-6.04]. The neurological status at discharge was also comparable in both the groups with RR (CI) 0.61 (0.22-1.7). **Conclusion:** Routine restriction of fluids in term neonates with moderate to severe perinatal asphyxia does not have any advantage.

Keywords: Cerebral edema, Fluid restriction, Perinatal asphyxia, SIADH

Introduction

India is still tackling with the problem of high neonatal mortality rate (NMR), the present NMR being 28 per 1000 live births [1]. Despite advances in perinatal care, one of the common causes of neonatal mortality continues to be perinatal asphyxia. [2,3]. Newborns who suffer perinatal asphyxia constitute a major proportion of newborns who need intensive care management immediately after birth [4]. Such neonates not only have high risk of mortality but even if they survive they have poor neurodevelopmental outcomes on long term follow up.

Perinatal asphyxia causes serious damage to the neonatal brain and the mechanism of damage is still not completely understood. A search for a definitive treatment to reduce the mortality and poor neurological outcome in these babies has not been very promising. Most of the management modalities that have been tried in asphyxiated neonates have failed to significantly improve survival or neurological outcome. Supportive management remains the mainstay of treatment offered in such babies. One of the components of supportive care is judicious fluid administration to avoid both fluid overload and inadequate blood volume. The major consequence of fluid overload is considered to be cerebral edema, which apparently contributes to neurological damage [5]. Fluid restriction has almost universally been used to avoid cerebral edema. But there is no clear evidence to support the benefits of fluid restriction. Fluid restriction in neonates is mostly based on experiences from older children adults [6].

However, as the body fluid composition of newborns is unique and is different from that at any other age and the fact that there is simultaneous CNS and renal insult the fluid management becomes complex. There are no RCTs in neonates to refute or support the use of fluid restrictions in perinatal asphyxia [7,8]. We, therefore conducted this study to look for the effect of fluid restrictions in the first 72 h of life in term neonates (≥37weeks) suffering from moderate to severe perinatal

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asphyxia on the immediate mortality (before discharge), electrolyte imbalance, seizure activity and renal functions.

Methods

Place of study: Neonatal intensive care unit of a tertiary care teaching hospital.

Type of study: This was a randomised control trial done over a period of 12m from July 2014 to June 2015.

The study was approved by the Institutional ethical committee. A written informed consent was taken from either of the parents. The inclusion criteria were: i) Newborns born at term (≥ 37 weeks of gestation), ii) presented within 6 h of birth and iii) moderate to severe birth asphyxia (Apgar score at 5 min ≤6) [9].

The exclusion criteria were: i) Newborns presenting with bleeding or shock and ii) newborns with gross congenital malformations.

Sampling methods: The newborns fulfilling all the inclusion criteria were randomised, using block randomization with blocks of 4. Random numbers were generated using a randomization website (www.randomiser.org). The babies were randomised into two groups; full fluid (FF) group and the restricted fluid (RF) group. The allocation was concealed in sequentially numbered opaque envelopes (SNOSE).

The primary outcome measures were i) mortality among the study population and ii) neurological status of the newborns at discharge. The secondary outcome measures were, i) need for a second anticonvulsant and ii) electrolyte imbalance at 24 h of life.

After an initial rapid assessment and emergency management, the babies were allocated to their respective groups. The babies in the full fluid group were started with the standard fluid protocol i.e. 60ml/kg/d at admission with an increment of 15 ml/kg/d till 72 h of life.

The newborns in the restricted fluid group were given two third of the total fluid requirement from admission till 72 h of age. After 72 h of life all the neonates of both groups were administered fluids according to a similar protocol i.e. normal maintenance fluids with daily increments without any restrictions upto a maximum of 150 ml/kg/d. Apart from the volume of fluids in the first 72 h, all the management remained similar in both groups.

Fluids given in the first 48 h of age was plain dextrose @ 4-6 mg/kg/min by a syringe infusion pump. Electrolytes were added after 48 h with sodium (Na^+) @2-3 meq/kg/d and potassium (K^+) @2meq/kg/d. Neonates in both the groups were managed according to standard protocols. All the babies were nursed under a servo controlled radiant warmer and weighed daily in the morning (pre feed in case the baby was on feeds) on a digital weighing machine with a sensitivity of 10g. Urine output was measured in all the babies by a urine collection bag or catheterisation for first 72 hours. Blood sugar was measured at admission and thereafter as required. Calcium gluconate (10%) was given to all newborns @ 4 ml/kg/d for 72 h and further if needed.

Serum Na^+, K^+, calcium (Ca^{++}), urea, creatinine, Urinary Na^+ and specific gravity (s.g.) were measured at 24 h of age and then repeated accordingly. Other investigations like hematocrit, serum bilirubin, cerebrospinal fluid analysis, sepsis screen, blood culture, chest X ray were done as and when required.

Regular vital monitoring like temperature, respiratory rate, heart rate, capillary refill time (CRT), SpO2 were monitored closely. Hypoxic ischaemic encephalopathy (HIE) staging was done according to the Levene classification and classified as mild/ moderate/ severe [10]. Convulsions were managed according to standard protocols. Intra venous phenobarbitone was given @ 20 mg/kg (after ruling out other treatable causes like hypocalcemia, hypoglycaemia) followed by a maintenance of 5 mg/kg/d in 2 divided doses. If needed a repeat loading dose of phenobarbitone was given @ 10 mg/kgupto a maximum of 40 mg/kg. Phenytoin was used as a 2nd anticonvulsant if required. Feeding was started as soon as possible, when the baby was hemodynamically stable and free from convulsions for 24 h. The babies were discharged when, i) vitals were stable without any support, ii) they were convulsion free for 72 h and iii) accepting paladai/ breast feeds.

Babies going into shock i.e. CRT>3 sec and HR> 160/min and cold extremities (in absence of hypothermia) were given a fluid bolus of 20 ml/kg over 10 min and started on full fluids if the baby was in the restricted fluid group. Shock was further managed as per protocol. Babies having oliguria (urine output (U.O.) < 1 ml/kg/h were given a bolus of 20 ml/kg of normal saline over 20 min. If the U.O. output improved to >1 ml/kg/h over next 4 h the baby was shifted to full fluids (if in restricted fluid group) and labelled as pre renal acute kidney injury (AKI). If the U.O. did not improve they were labelled as renal AKI and fluids administered accordingly[11].

At the time of discharge a detailed neurological examination of the babies was done and the neurologic status of the baby categorised as normal or abnormal.

The examination included assessment of the sensorium, tone, presence of seizures and neonatal reflexes.

If the neurologically examination was abnormal then the baby was discharged on oral phenobarbitone.

Statistical analysis: The analysis was done using the Epi info 7 software. An intention to treat analysis was followed. The continuous variables were expressed as mean ± standard deviation and as numbers and percentages for categorical variables. Student's *t* test and chi square/fisher exact test was used to determine significance for numerical and categorical values respectively. A p value of < 0.05 was considered as significant.

Results

We enrolled a total of 50 newborns, 25 each in the FF group and the RF group. Final analysis of 45 neonates was done as 4newborn in the FF group and 1 in RF group were discharged on request before the study could be completed [Fig.1]. The newborns enrolled were comparable in sex distribution and birth weight.

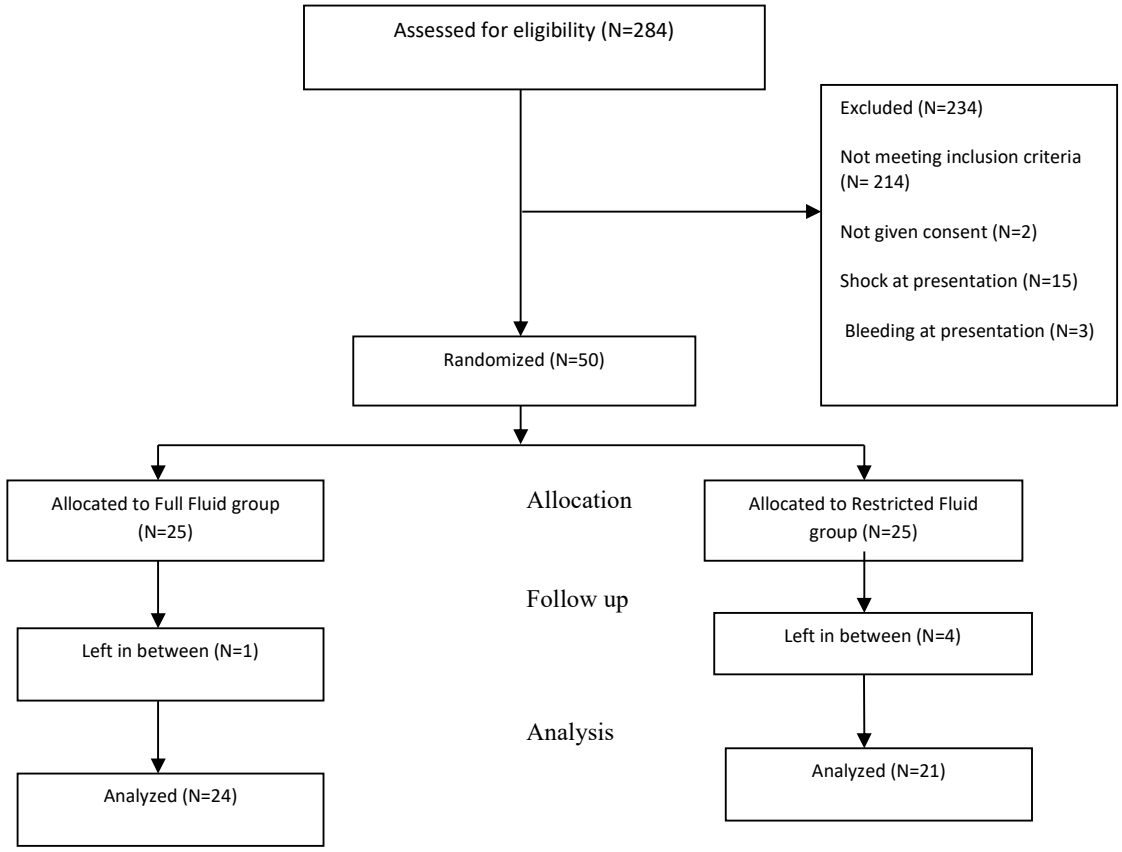

Fig-1: Flowchart for randomization and follow up

Mortality among the two groups was also not significantly different, 4 in the FF group and 3 in the RF group with a relative risk (RR) of 1.52 [confidence interval (CI) 0.38-6.04].

The neurological status at discharge was also comparable in both the groups with RR (CI) 0.61 (0.22-1.7). In each group 7 neonates went into shock, those in the RF group were shifted to full fluids. Three babies in the FF group and 6 babies from the RF group had oliguria.

The incidence of shock and oliguria was not significantly different between the two groups [Table I]. Urine output improved after a fluid bolus in 1 newborn in the FF group and 3 babies in RF group.

Table-I: Outcome parameters (categorical) in the two groups.

Characteristics	Full Fluid Group (n=21) [N (%)]	Restricted Fluid Group (n=24) p [N (%)]	VALUE RR (CI)
Expired [N (%)]	4 (19%)	3 (12.5%)	0.42 1.52 (0.38-6.04)
Abnormal neurological status at discharge	4/17 (23.5%)	7/21 (33.3%)	0.33* 0.61(0.22-1.7)
2nd anticonvulsant	6 (28.5%)	12 (50%)	0.08 0.5 (0.21-1.17)
Shock	7 (33.3%)	7 (29.1%)	0.76 1.14 (0.47-2.7)
Weight gain on D2	10 (47.6%)	7 (29.1%)	0.78 1.07 (0.62-1.87)
#Hyponatremia	3(15%)	9(39.1%)	0.07*0.38 (0.12-1.22)
#↑Urinary sodium	3(15%)	6(26%)	0.79*0.57 (0.16-2.0)
#Oliguria	3(15%)	6(26%)	0.3* 0.57 (016-2.0)

*Fisher exact test; RR relative risk; CI confidence interval

#N is 20 in FF and 23 in RF as one baby died in each group before the sample could be sent

The electrolyte values at 24 h were similar in both groups [Table II]. The urine specific gravity was significantly higher in the RF group with a p value of 0.02. Weight gain along with hyponatremia (suggestive of SIADH) was seen in 5 babies (4 from RR group and 1 from FF group) with a RR (CI) of 1.14 (0.93-1.39). Only 2 out of these 5 newborns showed a simultaneous increase in urinary sodium.

Table-II: Laboratory parameters in the two groups

Characteristics	Full Fluid Group (n=20)* (Mean ± SD)	Restricted Fluid Group (n=23)* (Mean ± SD)	p VALUE
Serum Na+ (meq/L)	135.6 ± 5.6	133 ±14.5	0.5
Serum K+ (meq/L)	4.7 ± 0.9	4.7 ± 0.7	0.8
Serum Ca2+ (mg/dL)	6.02 ± 3.0	5.96 ± 2.6	0.95
Blood urea (mg/dL)	51.7 ± 29.1	51.9 ± 32	0.9
Serum Creatinine (mg/dL)	1.06 ± 0.4	0.99 ± 0.5	0.6
Urinary Sodium (meq/L)#	192.4 ± 179	186.6 ± 127	0.9
Urine specific gravity[1]	1.011 ± 0.006	1.014 ± 0.007	0.02
Urine output (ml/kg/h)	2.1 ± 1	1.7 ± 1	0.2

*N is 20 in FF and 23 in RF as one baby died in each group before the sample could be sent

normal range 40-220 meq/L/d; 1 normal range 1.005-1.012; SD standard deviation

Discussion

We did not find any significant difference in the outcomes of babies with moderate to severe perinatal asphyxia who received full fluids or restricted fluids.Asphyxiated neonates are prone to fluid overload and cerebral edema due to i) SIADH which is manifested as hyponatremia, hypo-osmolarity along with low urine output and inappropriately concentrated urine ii) acute tubular necrosis (ATN) due to redistribution of blood to brain, heart and adrenal glands (diving reflex) [12]. After perinatal asphyxia, during the first phase of early cell death, which occurs within minutes, there is exhaustion of cellular energy stores. Immediate intervention may give an opportunity to minimize brain damage and restore oxygen supply and blood circulation. A second phase of damage starts after several hours which includes mechanisms like free radical injury, intracellular calcium entry and apoptosis [13,14]. Management in the intensive care unit largely addresses this second phase and interventions are aimed at blocking these brain damaging processes. Aim of all interventions is to minimize mortality and brain damage and simultaneously cause minimal side effects. Early management of perinatal asphyxia is extremely crucial to minimize the harm to the neonatal brain. There has been a constant search for newer modalities which would reduce the neurological damage. These neuroprotective strategies include NMDA antagonists, free radical scavengers, anti inflammatory and anti oxidative drugs [15,-17]. But all these are still only at experimental or research stage and have not been included in the standard management as yet. The most promising strategy that has emerged out of all these is

induced hypothermia whether total body cooling or selective head cooling and has become a part of standard care for neonates with perinatal asphyxia in many centres [18,19]. But the facility is not available in most of the establishments providing care to newborns because of costs involvement as well as the lack of trained staff and infrastructure. Therefore, the mainstay of management of neonates who suffer from perinatal asphyxia remains supportive. An important unresolved issue in the supportive care is the amount of fluid to be administered in the initial period of 48-72 h after birth. As cerebral edema is anticipated, treatment modalities include measures to minimise edema. Modalities to counter the cerebral edema which have been tried are corticosteroids, hyperventilation and osmotic agents (mannitol and glycerol) but none showed promising benefits and are no longer used [20]. Ramesh et al recommended two third fluid restriction in presence of hyponatremia till the serum sodium returns to normal [21].

Various modalities such as allopurinol, calcium channel blockers, corticosteroids, fluid restriction, head or whole body cooling, hyperbaric oxygen, hyper-ventilation, magnesium sulphate, mannitol, opiate antagonists were studied in a systematic review by Mc Guire W. [8]. They were not able to find any systematic review or RCT to study the benefits and harms of fluid restriction in term or near term babies with perinatal asphyxia. In a Cochrane review conducted to determine the effect of fluid restriction on short term (mortality within first 28 d, grade of HIE, electrolyte abnormalities, renal functions and seizure activity) and long term outcomes (death during first year of life, CT/MRI changes or severe neurodevelop-mental disability at 12 m of age) in term infants following perinatal asphyxia, the authors found no (RCTs or quasi randomized) fulfilling their selection criteria [7]. Excessive fluid restriction may lead to hypotension and dehydration resulting in decreased cerebral perfusion and in turn aggravating brain damage. This may also predispose the baby to renal compromise and can lead to pre renal AKI which may progress to renal AKI. Girish et al studied AKI in perinatal asphyxia and found 64% neonates to suffer from acute kidney injury [22]. Out of these 78.12% had pre renal AKI and remaining 21.88% had intrinsic AKI.

In our study 3 neonates in FF group and 6 neonates in RF group had oliguria i.e. 9 out of 45 (20%). Although the incidence of oliguria was higher in RF group but it was not significantly different. In the study by Girish et al 63.6% of the babies with AKI responded to fluid boluses suggesting that optimising/expansion of intravascular compartment can prevent AKI in many newborns with asphyxia as well as prevent pre renal AKI to progress to renal AKI.Nouri et al in their study of renal failure in term babies with birth asphyxia found an incidence of 17.2% [23]. They found renal failure to be related to the severity of neurological damage. The limitation of our study is that we did not follow up the infants to look for the long term neurologicaloutcome. Myocardial contractility is impaired after hypoxic ischaemic insult leading to a decrease in cardiac output, hypotension and further compromising the cerebral perfusion. Therefore, maintaining normovolemia is extremely crucial to maintain adequate perfusion to brain. Moreover, it is now increasingly felt that cerebral edema may be marker of the brain damage rather than being a cause of it. Therefore, targeting cerebral edema may not be an important part of the neuroprotective strategy [5,10].

Conclusion

Routine restriction of fluids may not have any advantage in term newborns with moderate to severe perinatal asphyxia. More randomised controlled trials are needed to make a definite conclusion regarding the standard fluid therapy in newborns with perinatal asphyxia.

What this study adds to existing knowledge? Restriction of fluids in term babies with perinatal asphyxia may not improve outcome in terms of mortality or neurological status at the time of discharge.

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