RESEARCH PAPER

Urine Specific Gravity Measurement for Fluid Balance in Neonates on Intravenous Fluids in a Neonatal Intensive Care Unit: *An Open Label Randomized Controlled Trial*

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Background: Urine specific gravity reflects hydration status and correlates well with urine osmolality.

Objective: To compare intravenous fluid therapy guided with and without inclusion of urine specific gravity to the standard parameters for maintaining postnatal weight loss within permissible limits in neonates admitted to the intensive care unit.

Methods: An open-label randomized controlled trial was conducted, including neonates requiring intravenous fluids for ≥72 hours, randomized into the study (urine specific gravity guided fluids) and control arms. The outcomes of the study were to determine proportion of neonates with weight loss within permissible limits, mean percentage weight loss and number of days to reach maximum weight loss.

Results: 80 preterm and term neonates (40 in each arm) were enrolled. A comparable proportion of neonates had weight loss within permissible limits in study arm and in control arms [39 (97.5%) vs 36 (90%); *P*=0.165]. The (mean (SD) percentage weight loss was significantly less in the study arm compared to control arm [All neonates: 7.2(2.6) vs 9.3(3.5); *P*=0.004); preterm neonates: 7.7 (2.8) vs 11 (3.9); *P*=0.008)]. Preterm neonates in the study arm attained nadir weight significantly earlier than in the controls (*P*=0.03) and attained complete enteral feeding earlier. Urine specific gravity showed a moderate negative correlation with the percentage weight loss.

Conclusion: Using urine specific gravity to regulate intravenous fluids in neonates resulted in a significant reduction in postnatal weight loss, especially in preterm neonates.

Keywords: *Postnatal weight loss, Urine refractometry, Weight loss*.

Trial Registration: CTRI/2019/04/018661

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Neonates on intravenous fluid therapy require daily adjustments in their fluid volume and electrolyte intake in view of their changing total body water. While in term neonates, birth weight may reduce by 10%, postnatal weight loss of 10-15% is acceptable in preterm neonates [1,2]. This postnatal weight loss is primarily due to contraction of the extracellular fluid (ECF) compartment, and a higher ECF volume in preterm neonates accounts for their greater weight loss [3,4]. In preterm neonates, overzealous intravenous fluids increases the risk for symptomatic patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) and hyponatremia, while fluid restriction places them at risk for dehydration and hypernatremia [5-9]. Neonatal kidneys have limited ability to excrete a water load and effectively dilute urine [10]. Despite daily adjustments of intravenous fluid based on change in body weight, clinical status, serum biochemistry, blood gas, urine output and urine specific gravity [11,12], a significant proportion of neonates experience postnatal weight changes outside the permissible limits [13].

In neonates, urine specific gravity has a linear correlation with urine osmolality, which mirrors the serum osmolality and reflects their hydration status, thereby being a potentially useful adjunct in regulating fluid management [14-18]. In euvolemic state with normal urine output of 1-3 mL/kg/hour, the urine specific gravity lies between 1.002-1.010 [4,12,17,19]. Despite the direct correlation and ease of measurement, urine specific gravity estimation is not routinely used for maintaining fluid balance in neonates [20], due to lack of data regarding its utility. We aimed to compare daily intravenous fluid adjustment with and without including urine specific gravity estimation to the standard parameters for maintaining postnatal weight loss within permissible limits in neonates admitted in neonatal intensive care unit (NICU).

METHODS

This open-label randomized controlled trial was conducted in the NICU of a tertiary care hospital between May, 2019 and October, 2020. The trial was approved by the institutional ethics committee and registered with the Clinical Trials Registry of India. Written informed consent was obtained from parents prior to randomization. All neonates in NICU requiring intravenous fluids for ≥72 h were included. Exclusion criteria included neonates with perinatal asphyxia, shock, congenital malformations, complex congenital heart diseases, antenatally diagnosed hydronephrosis, and when weighing the neonate was not possible due to the clinical condition. Enrolled neonates were randomly assigned within 3 hour of birth to either the study arm (urine specific gravity guided fluids) or the control arm (standard care). Randomization was done by computer-generated, permuted blocks stratified by gestational age (<37 weeks, preterm; ≥37 weeks, term) and serially numbered opaque sealed envelopes were used for allocation concealment. The investigators were not masked as they assessed the urine specific gravity to make daily fluid adjustments.

The usual standard of care for preterm and term neonates, including extreme preterm neonates using radiant warmers, cling film application, respiratory humidifiers, infusion pumps for intravenous fluid administration, early and exclusive use of breast milk and parenteral nutrition, was followed. Fluid volume was commenced with 60 mL/kg/day for term neonates, and 70 mL/kg/day, 65 mL/kg/day, and 60 mL/kg/day for preterm neonates with birth weight ≤1000 g, 1001 to 1500 g, and >1500 g, respectively [12,15]. A cumulative weight loss of up to 10% for term neonates was acceptable while for preterm neonates this was 15%, 12-15%, and 12% at birth weight ≤1000 g, 1001 to 1500 g, and >1500 g, respectively [4,6,21]. In the study arm daily fluid requirement was adjusted according to absolute and percentage weight change over the previous 24 hours, cumulative percentage weight change from the birth weight, and clinical parameters including hepatomegaly, edema, tachycardia and urine specific gravity.

Urine specific gravity was tested using a handheld prism-based refractometer and total daily fluid intake reduced by 5-10 mL/kg/day for urine specific gravity <1.006; increased by 5 mL/kg/day for urine specific gravity between 1.006 - 1.008 and increased by 8-10 mL/kg/day if the urine specific gravity was >1.008. Urine specific gravity by refractometry and urine osmolality show a linear positive correlation, with urine specific gravity of 1.006 and 1.008 indicating a urine osmolality of 275 mOsm/kg and 315 mOsm/kg, respectively [17].

In the control arm, total daily fluid intake was guided by all the standard parameters as in the study arm except urine specific gravity, with a daily increment of 10 mL/kg/day or continuation on the same total fluid volume. The maximum permissible daily fluid volume of IV fluids inclusive of drugs and milk feeds was 140 and 150 mL/kg/day for preterm and term neonates, respectively. The mean weight of the study population each day subtracted from the mean weight of the next day divided by the mean weight of that day was used to derive the rate of percentage decline in weight. Neonates with gestation ≤32 week or older neonates unlikely to receive enteral feeds for 3-5 days in both groups received parenteral nutrition from first day of life. Intravenous fluids were discontinued when target enteral intake of 80 mL/kg/day in term neonates and 110, 100 and 90 mL/kg/day in preterm neonates weighing ≤1000 g, 1001 g to 1500 g and >1500 g, respectively was achieved.

The primary outcome was to determine the percentage weight loss and number of days to reach the maximum weight loss in both the groups. The secondary outcomes of the study were the number of days to regain the birth weight, number of days for discontinuation of intravenous fluids (and to reach full feeds), correlation between urine specific gravity and weight loss, and adverse events related to fluid therapy.

Sample size was estimated based on a pilot study conducted earlier at our NICU enrolling 10 neonates each in the study and control arms over two months. The proportion of neonates showing weight change outside permissible limits was 50% in the control arm. Incorporating urine specific gravity in the decision-making algorithm reduced this to 20%. Keeping the relative risk at 0.4, α-error as 0.05 and β-error as 0.2, a sample of 40 neonates in each arm was required.

Statistical analysis: An intention to treat analysis was done. Differences in continuous variables were estimated using the student *t*-test or Mann-Whitney *U* test, and categorical variables using the chi-square test or Fischer exact test. Time to achieve was plotted using Kaplan-Meir curves and compared using the log-rank (Mantel-Cox) test. Spearman correlation coefficient was used to see relation between urine specific gravity and percentage weight loss. A *P* value <0.05 was considered as statistically significant. All the statistical analyses were performed using GraphPad Prism version 9 for Windows (GraphPad Software).

RESULTS

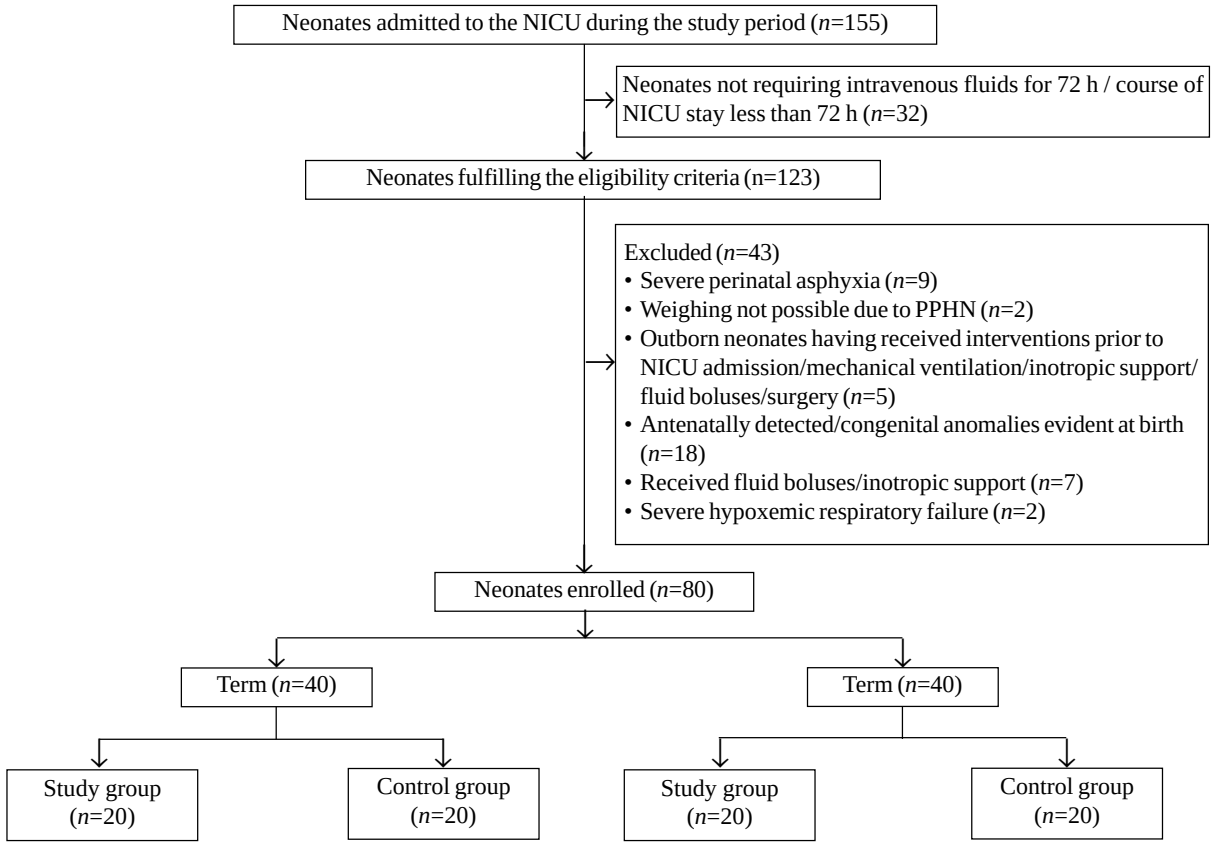
Of the 155 neonates admitted in the NICU during the study period, 123 were eligible and 80 were enrolled and

randomly allocated to either the study or the control arm (**Fig. 1**). Baseline characteristics were similar between the two groups (**Table I**).

There was no significant difference in the proportion of neonates with weight loss within permissible limits between the study arm (*n*=39, (97.5%) and control arm (*n*=36 (90%) (*P*=0.165). One preterm in the study arm (weight loss: 21.57%) and four term neonates in the control arm (weight loss: 10.6%, 11.9%, 12.25% and 13.88%) lost weight beyond permissible limits. The mean (SD) percentage weight loss was significantly lower in the study group than in the control population [7.2 (2.6)% vs 9.3 (3.5)% *P*=0.004] (**Fig. 2a**). This difference was comparable in term neonates [6.7 (2.5)% vs 7.9 (2.4)%; *P*=0.15], but not in the preterm population [7.7 (2.8)% vs 11 (3.9)%; *P*=0.008], respectively for study arm and control arm. This significant difference in the preterm population was also reflected in the mean (SD) absolute weight loss between the study arm and control arm [122 (40) g vs 172 (54) g; *P*=0.002] (**Fig. 2b**). The rate of percentage decline in weight was similar between the study and control arms (*P*=0.15), and between the term neonates (*P*=0.07) and preterm neonates (*P*= 0.46) (**Web Fig. 1**). The day of life by which maximum weight loss occurred was comparable for the study and control arm of the complete study cohort (*P*=0.11) and term neonates (*P*=0.71). However, among the preterm neonates, the study group attained the lowest weight significantly earlier than the control group (*P*=0.03). (**Table II**). There was no significant difference in the number of days to regain birth weight or number of days for discontinuation of intravenous fluids (**Web Fig. 2**).

The urine specific gravity showed a moderate negative correlation with the percentage weight loss for the entire study population (r= -0.23; 95% CI= -0.38, -0.06; *P*=0.006; *n*=143 pairs), and for the term neonates (r= -0.31; 95% CI= -0.52, -0.06; *P*=0.01; *n*=66 pairs). However, the percentage weight loss did not correlate with urine specific gravity among the preterm neonates (r= -0.17; 95% CI= -0.38, 0.07; *P*=0.15; *n*=77 pairs) (**Fig. 3a-c**). One preterm neonate in the control group was diagnosed with a hs-PDA.

The median (IQR) percentage weight loss was not significantly different in neonates whose mothers had received antenatal steroids compared to those whose



PPHN: primary pulmonary hypertension of newborn; NICU: neonatal intensive care unit.

Fig. 1 Flow diagram of study.

Table I Baseline Characteristics of the Enrolled Neonates (*N* = 80)

Variable	*Study group*	*Control group*	*Preterm neonates, n=40*		*Term neonates, n=40*	
	n=40	*n=40*	*Study, n=20*	*Control, n=20*	*Study, n=20*	*Control, n=20*
Maternal age (y)[a]	27 (4)	26 (3.6)	28 (4)	27 (4.0)	27 (3.9)	26 (3.2)
Primigravida	22 (55)	15 (37.5)	11 (55)	4 (20)	11 (55)	11 (55)
Gestational age (wk)[a]	35 (3.3)	35 (3.1)	32 (1.8)	33 (1.9)	38 (1.0)	38 (1.1)
Antenatal steroid course						
Completed	16 (40)	16 (40)	16 (80)	16 (80)	-	-
Not completed	4 (10)	4 (10)	4 (20)	4 (20)	-	-
Mode of delivery						
Cesarean section	28 (70)	28 (70)	17 (85)	15 (75)	11 (55)	13 (65)
Intravenous fluid units given to mother before delivery[a]	4.2 (0.65)	3.9 (0.76)	3.9 (0.64)	3.8 (0.62)	4.5 (0.51)	4.1 (0.89)
Maternal illnesses						
Pre-eclampsia	9 (22.5)	10 (25)	7 (35)	4 (20)	2 (10)	6 (30)
GDM	7 (17.5)	9 (22.5)	3 (15)	1 (5)	4 (20)	8 (40)
Hypothyroidism	12 (30)	8 (20)	5 (25)	3 (15)	7 (35)	5 (25)
APH	1 (2.5)	3 (7.5)	1 (5)	2 (10)	0	1 (5)
Seizure disorder	2 (5)	1 (2.5)	2 (10)	1 (5)	0	0
Others	2 (5)	8 (20)	0	7 (35) [b]	2 (10) [c]	1 (5) [d]
Antenatally detected abnormalities						
Oligohydramnios	5 (12.5)	4 (10)	4 (20)	2 (10)	1 (5)	2 (10)
FGR	3 (7.5)	2 (5)	3 (15)	2 (10)	0	0
A/REDF	1 (2.5)	1 (2.5)	1 (5)	1 (5)	0	0
Birthweight (g)[a]	2254 (768)	2111 (634)	1603 (271)	1663 (354)	2685 (495)	2560 (526)
Indication for intravenous fluids						
Extreme preterm	5 (12.5)	3 (7.5)	5 (25)	3 (15)	-	-
Respiratory illness[e]	25 (62.5)	27 (67.5)	11 (55)	14 (70)	14 (70)	13 (65)
Depression at birth	3 (7.5)	3 (7.5)	-	-	3 (15)	3 (15)
IUGR	3 (7.5)	2 (5)	3 (15)	2 (10)	-	-
A/REDF	1 (2.5)	1 (2.5)	1 (5)	1 (5)	-	-
EONS	2 (5)	3 (7.5)	-	-	2 (10)	3 (15)
Rh-HDN	1 (2.5)	1 (2.5)	-	-	1 (5)	1 (5)

Data are shown as no. (%), or [a]mean (SD). [b]Intrahepatic cholestasis (n=1), rheumatic heart disease (n=1), bad obstetric history (n=3), systemic lupus erythematosus (n=1), chronic hepatitis-C virus infection (n=1); [c]systemic lupus erythematosus (n=1), primary hypertension (n=1); [d]ventricular septal defect with bicuspid aortic valve (n=1); [e]preterm respiratory distress syndrome (n=16), transient tachypnea of newborn (n=25), meconium aspiration syndrome (mild-moderate) (n=11). APH-antepartum hemorrhage; A/REDF- absent/ reversed end diastolic flow on umbilical artery Doppler; EONS-early onset neonatal sepsis; FGR-fetal growth restriction; GDM gestational diabetes mellitus; IUGR: intrauterine growth restriction; LSCS-lower segment caesarian section; NVD-normal vaginal delivery; Rh-HDN- rhesus hemolytic disease of the newborn.

mothers had not received antenatal steroids.

DISCUSSION

The trial found the mean percentage postnatal weight loss to be significantly lesser in neonates when their intravenous fluids were adjusted using standard parameters as well as urine specific gravity, compared to those without adjustment made for urine specific gravity. Further analysis showed that this significant difference was only observed in the preterm sub group. Preterm neonates in the study arm showed lesser mean absolute weight loss and also attained the lowest weight significantly earlier than the control arm. These findings indicate a beneficial effect of incorporating daily bedside urine specific gravity for regulating intravenous fluids in neonates. [11,22-24].

Even though the average duration of intravenous fluid administration was comparable between the study and control arms, preterm neonates in the study arm transitioned earlier from parenteral to full enteral nutrition than neonates in the control arm.

Previous studies have evaluated correlation between urine specific gravity by refractometry and urine osmolality and found a linear correlation between the two, but not

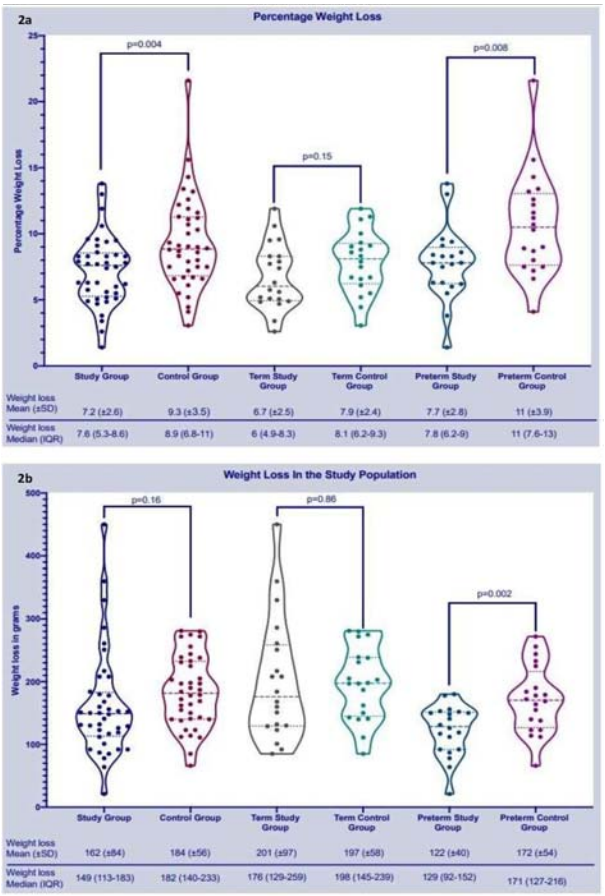


Fig. 2 Violin plots comparing *a*) percentage weight loss and *b*) absolute weight loss (g) between the study and control arms, and between the term neonate subgroups and preterm subgroups.

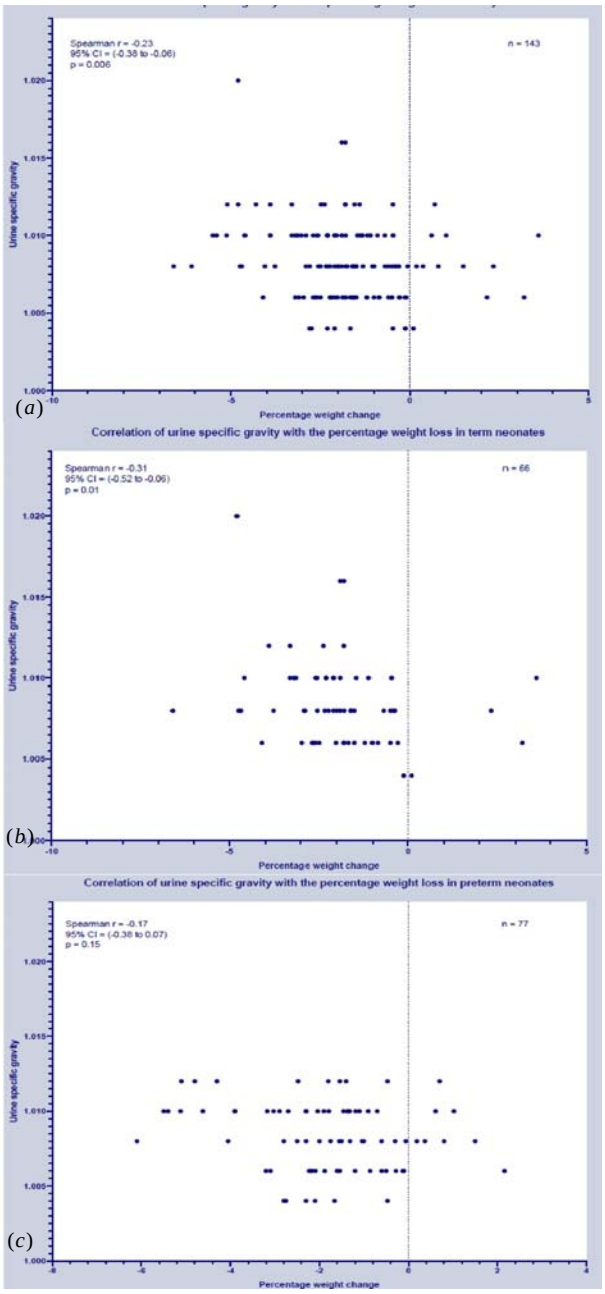


Fig. 3 Correlation between urine specific gravity and percentage weight loss *a*) in the entire study population, *b*) in term neonates, and *c*) preterm neonates.

with urine specific gravity done by dipstick evaluation [14,16,17,27]. Since serum osmolality governs urine osmolality, which in turn gets reflected as urine specific gravity, estimation of urine specific gravity indicates the hydration status. Our study did not demonstrate a strong correlation between urine specific gravity and daily weight change, as shown by the previous studies, probably due to inclusion of preterm neonates with immature renal concentrating abilities. We did not find any significant adverse events.

Relying on refractometry and not dipstick estimation of urine specific gravity, inclusion of preterm neonates, and assiduous care for reducing insensible water losses are the strengths of this study. The small sample size, non-availability of humidified incubators for the preterm neonates, and inability to directly estimate urine osmolality using an osmometer are the major limitations of this study.

To conclude, urine specific gravity measurement by refractometer is a bedside, non-invasive method, which may be helpful in modifying the estimated fluid intake in neonates and in optimizing weight loss during early neonatal period. It results in a lower mean absolute weight loss and an earlier attainment of nadir weight. Studies with larger sample size, including neonates with underlying hypoxia, shock and congenital cardiac anomalies are required along with measurement of osmolality of enteral intake.

WHAT IS ALREADY KNOWN?

- Urine specific gravity has a linear correlation with urine osmolality and in turn with serum osmolality, thereby reflecting the hydration state.

WHAT THIS STUDY ADDS?

- Including urine specific gravity estimation by refractometry to the daily intravenous fluid calculation of neonates in intensive care unit leads to decreased postnatal weight loss, especially among preterm neonates.

Table II Outcome Parameters of Neonates in the Study and Control Groups (*N*=80)

Outcomes	*Study group, n=40*	*Control group, n=40*	*Preterm neonates, n=40*		*Term neonates, n=40*		*P*
			Study, n=20	*Control, n=20*	*Study. n=20*	*Control, n=20*	
Weight loss (%)[ab]	7.2 (2.6)	9.3 (3.5)	7.7 (2.8)	11 (3.9)	6.7 (2.5)	7.9 (2.4)	0.15
Absolute weight loss (g)[b]	162 (84)	184 (56)	122 (40)	172 (54)	201 (97)	197 (58)	0.86
Time to regain birth weight (d)	11 (3.6)	12 (4.5)	14 (3.5)	15 (4.9)	9 (1.8)	9.5 (1.6)	0.36
Duration of IV fluids (d)	4.9 (1.5)	5.4 (2.7)	5.4 (1.9)	6.7 (3.4)	4.5 (0.8)	4.2 (0.4)	0.15
Serum sodium, day-7 (mEq/L)	134.5 (5.6)	138 (4.4)	-	-	-	-	-
Serum creatinine, day-7 (mg/dL)	0.5 (0.1)	0.5 (0.2)	-	-	-	-	-
Urine specific gravity	1.008 (0.0027)	-	1.0082 (0.0022)	-	1.0083 (0.0027)	-	-

All data expressed as mean (SD). [a]P<0.01 for comparison between the study and control group as a whole; [b]P<0.001 for comparison between study and control groups among preterm neonates.

Ethics clearance: IEC, Armed Forces Medical College, Pune; No. IEC/067/2018, dated Oct 22, 2018.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
Contributors: VVT, RJ: conceptualized the study, collected the data, performed the statistical analysis, and drafted the manuscript; VVT: managed the cases; DT: Extracting information from study proforma and contributed to drafting the manuscript; AD: reviewed the manuscript for important intellectual content. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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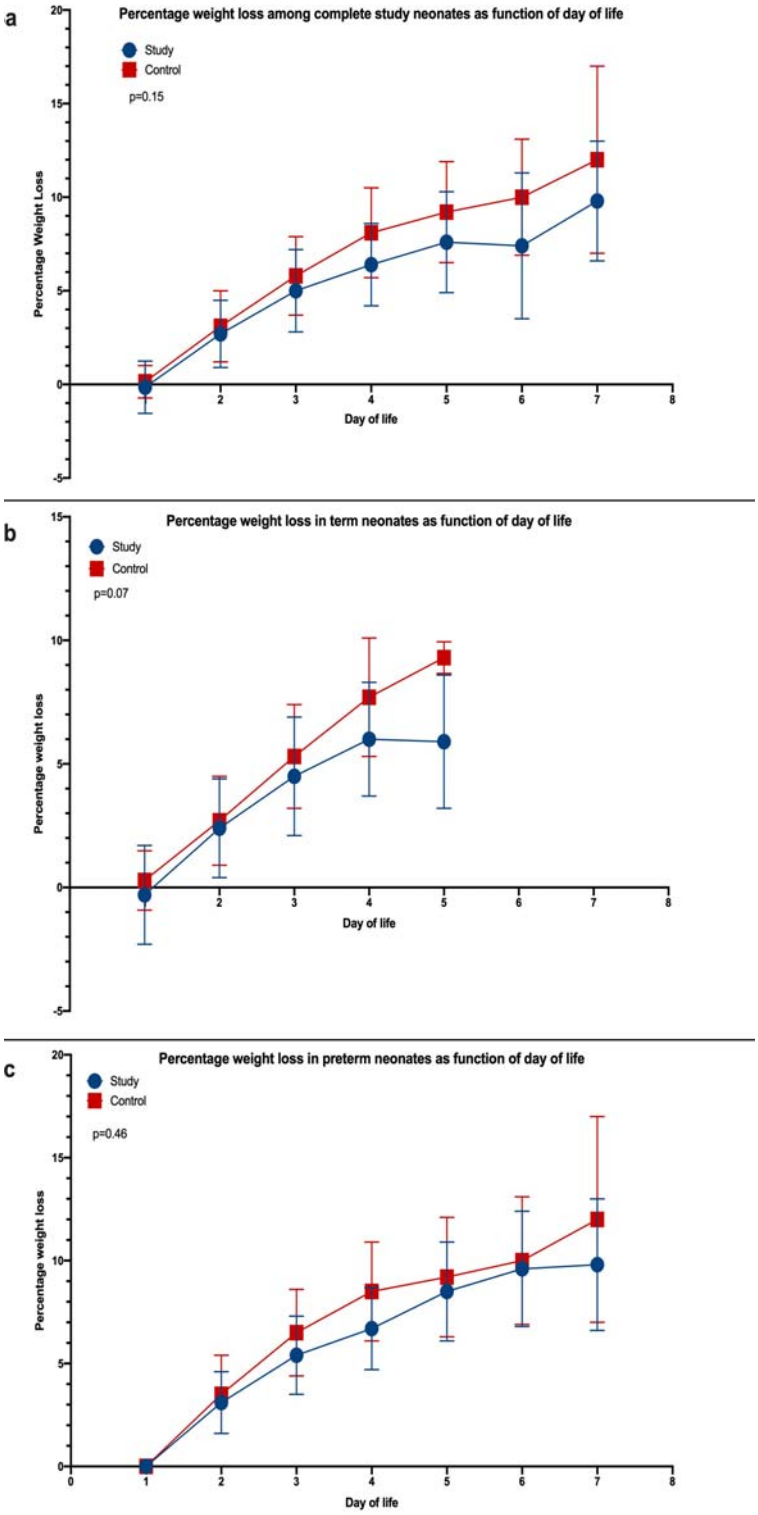
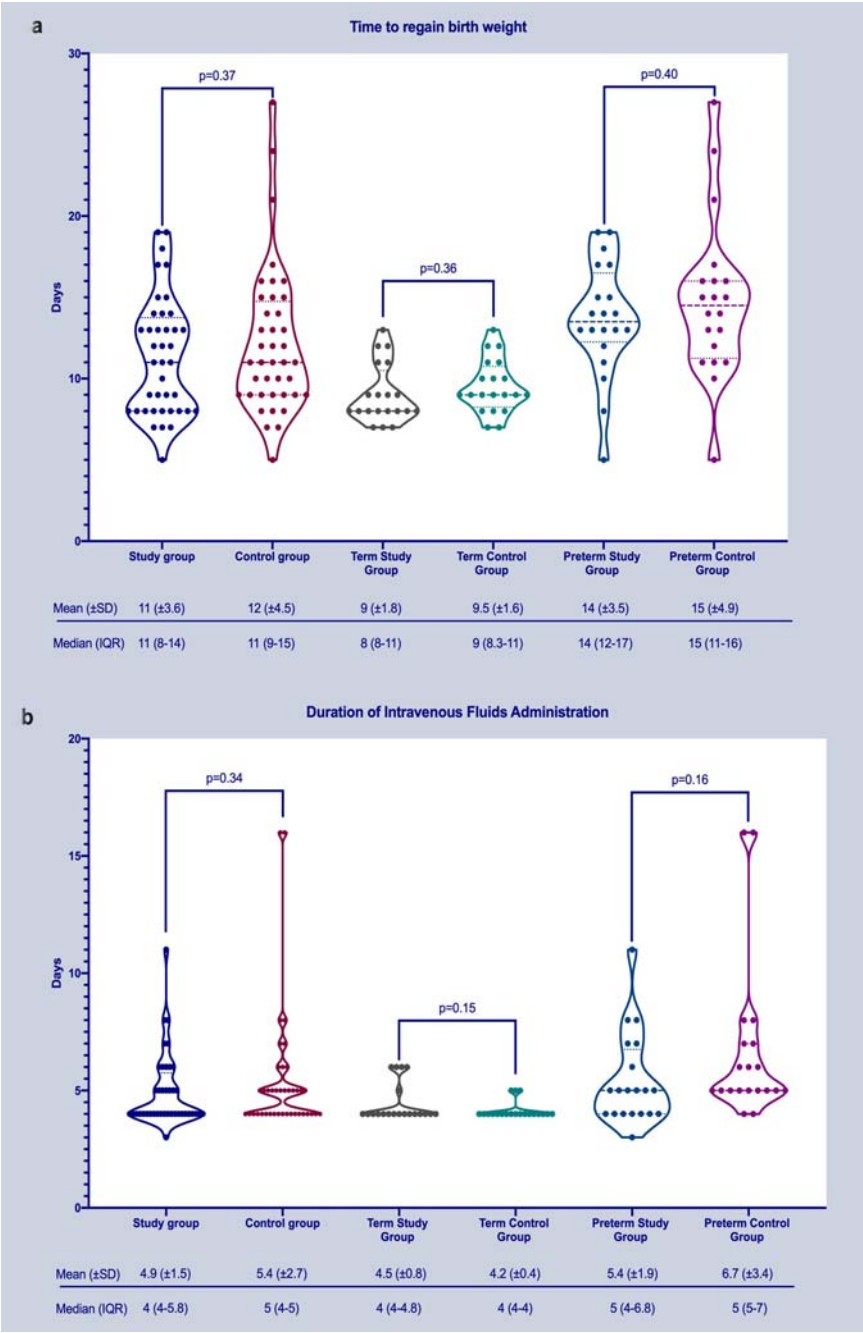


Web Fig. 1 Comparable rate of percentage weight loss as a function of postnatal age (%) (a) between the study and control arms, (b) between term neonates subgroup, and (c) in preterm subgroup.



Web Fig. 2 Violin plot showing (a) no significant difference in time to regain birth weight, and (b) no significant difference in duration of intravenous fluids, between the study and control arms.