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Hidden sources like saline flushes make a significant contribution to the fluid intake of very low birth weight infants during the first postnatal week

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Abstract

Aim: We examined actual fluid intake, and routes of administration, in very low birth weight (VLBW) infants during the first week of life in a neonatal intensive care unit.

Methods: This retrospective cohort study comprised 953 infants born at less than 32 weeks and 1500g and treated at Helsinki University Children's Hospital from 2005-2013. All parenterally and enterally administered fluids, and their sources, were obtained from our patient information system. Infants were divided into three groups according to their gestational age: 23-26, 27-29 and 30-31 weeks.

Results: Fluid intake exceeded European guidelines during the first three days. On days 1-7, total fluid intake was highest in the most premature group ($p < 0.001$) and the median total fluid intake in this group peaked at 177 ml/kg/d (IQR 154-209) on day three. Intravascular flushes provided a considerable source of fluids, with the median intake in the most preterm group peaking at 26.4 ml/kg/d, which represented 15.6% of total fluid intake.

Conclusion: During the first three days of life, our VLBW infants had a higher total fluid intake than the European guidelines. A considerable percentage came from hidden sources, such as saline flushes, which should be taken into account when prescribing fluids.

Key Notes

- This study examined fluid intake in 953 very low birth weight infants during the first week of life in a tertiary neonatal intensive care unit.
- Fluid intake exceeded European guidelines during the first three days of life and hidden sources made a significant contribution.
- Total fluid intake was highest in the most premature group, born at 23-26 weeks, with intravascular flushes peaking at 15.6% of total fluids.

Keywords: European guidelines, Fluid therapy, Intravascular flushes, Prematurity, Very low birth weight

INTRODUCTION

Appropriate fluid intake during the first weeks of life is essential for sustaining vital functions and optimising the growth of very low birth weight (VLBW) infants (1–3). Physiologic contraction of extracellular fluid with negative fluid and sodium balances occurs during the first days of life and is associated with early postnatal weight loss (4–6). The European guidelines on paediatric parenteral nutrition suggest that a weight loss of 7-10% is adequate in VLBW infants (7). Enteral feeds start as early as possible, but most VLBW infants need parenteral nutrition during the first days of life (8). Early parenteral nutrition can lead to high fluid intake with inadequate contraction of extracellular fluid, which can increase the risk of complications, such as patent ductus arteriosus, necrotising enterocolitis and bronchopulmonary dysplasia (9–13).

Data are scarce on the actual fluid intake of VLBW infants in the first days of life. The landmark studies in this field were conducted over three decades ago (10,12,14,15), well before the introduction of current clinical nutritional practices, such as the early initiation of parenteral protein and lipids. Many previous studies on fluid management in VLBW infants have been based on fluid regimes and prescribed intakes. Actual intakes may differ markedly from prescriptions due to changes in the infant's condition (16). However, with the use of data on actual intakes derived from an electronic patient information system, the accuracy of the data can be improved.

Against this background, the aims of our study were to use detailed data collected in an electronic patient information system to answer three research questions. Firstly, we wanted to know how administered fluid volumes developed during the first days of life in VLBW infants. Secondly, we were keen to examine how fluid intake differed in infants with a different gestational age (GA). Thirdly, we wanted to identify the main sources of fluid intake.

PATIENTS AND METHODS

This study was part of the Big Data - Tiny Infants research project. The study cohort consisted of 953 VLBW infants admitted to the neonatal intensive care unit (NICU) of the Helsinki University Children's Hospital between 2005 and 2013 (Figure 1). The inclusion criteria were: birth weight below 1500g, gestational age below 32 weeks, admission to the NICU during the first 24 hours of life, no gastrointestinal or other major malformations or chromosomal abnormalities and spending at least one full 24-hour period in the NICU.

The infants were studied during the first seven postnatal days. All parenteral and enteral fluids given to each infant were acquired retrospectively from the NICU's electronic patient information system, Centricity Critical Care Clinisoft (GE Healthcare, Chicago, Illinois, US). The database contained detailed, timestamped records of all fluids and medications given and their routes of administration, which allowed us to carry out separate analyses of different sources of fluid intake. The daily fluid intake for each infant was calculated over 24-hour periods, with each period starting at 14.00 hours, the point determined by the NICU's clinical practice. The time period from birth until the first 14.00 hours was regarded as day zero. Only full 24-hour periods in the NICU were included in the analyses, which means that the first and last days of NICU admission were excluded for each infant. Daily weight measurements were obtained to assess weight changes during the first postnatal week. For consistency, fluid intakes were adjusted by dividing the volume by birth weight and fluid intake is given throughout as ml/kg birth weight/day.

The data consisted of 747,204 fluid recordings. Before the analyses, all data were screened for possible outliers and these were removed. We removed six single recordings (0.0008%) due to disproportionately large registered administered doses. There were 28, 24-hour periods with missing data due to software updates to the electronic patient information system and 423 recordings (0.06%) were removed as a result of this. When we excluded the first and last days in the NICU, 16,643 recordings (2.2%) were removed.

In our unit, nutritional practices follow the European guidelines on parenteral and enteral nutrition (7,17,18). Parenteral nutrition is started for all VLBW infants after birth as soon as an intravenous line is available. Enteral feeds are initiated on the first day of life, with 1-2 ml of mother's milk or donor human milk every three hours, and gradually increased by 10-20 ml/kg/d according to tolerance. In our study, according to our NICU's clinical practice, the water content of breast milk and formula was estimated to be 80%. Preparations administered intravenously were considered to consist entirely of fluid. To study the different sources of total fluid intake, we divided the fluids into parenteral and enteral nutrition, volume expanders, flushes and others. Ringer's solution, fresh frozen plasma, 4-5% albumin solution and sterile water were defined as volume expanders. Saline solutions of 0.225%, 0.45% and 0.9% and 5% glucose solution used for flushing medication or arterial and venous lines were defined as flushes. Drugs and vitamins, sodium bicarbonate solutions, 20% albumin solutions, electrolyte preparations and glucose solutions not administered as part of parenteral nutrition and sterile water used for flushing the nasogastric tube were defined as others.

Data on the clinical characteristics, such as GA and diagnoses, were obtained from the Finnish Medical Birth Register, a nationwide register administered by The National Institute of Health and Welfare, Finland. The Medical Birth Register contains data on all live births with a birth weight of at least 500g and with a GA of at least $22^{+0/7}$ weeks in Finland. Data on infants with a birth weight of less than 1501g or a GA of less than $32^{+0/7}$ weeks are collected in a separate file from birth until they are discharged from the hospital, reach a GA of $42^{+0/7}$ weeks or die, whichever occurs first. Due to missing register data, equivalent information on 17 infants was acquired manually from the medical records. GA was determined from the first day of the last menstrual period and in 86% of the cases it was confirmed by ultrasonography at $11^{+0/7}$ to $13^{+6/7}$ weeks of gestation. A birth weight Z-score of less than -2 standard deviations on the Finnish growth charts was considered small for gestational age (19).

Statistical analyses were conducted using R3.4.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria). Descriptive data are presented as medians and interquartile ranges (IQR) or numbers and percentages within categories, where appropriate. The chi-square test and Fisher's exact test were used for categorical data and the Kruskal-Wallis test was used for skewed continuous data. Fluid intakes and weight changes were not normally distributed and this means that the data are presented as medians and interquartile ranges. For the analysis of skewed fluid intake data, the non-parametric Kruskal-Wallis test and Mann-Whitney U test, with Bonferroni correction to correct for the multiple comparisons, were applied. To test the statistical association between total fluid intake and postnatal weight change, Pearson's correlation was applied. In box plots, whiskers are shown according to the style of Tukey. A p value of < 0.05 was considered statistically significant.

The study protocol was approved by the Ethics Committee of the Helsinki University Hospital and by The National Institute of Health and Welfare, Finland. All data were anonymised. Due to its retrospective nature, the study did not alter the treatment of the infants and this means that parental consent was not required.

RESULTS

A total of 1,227 VLBW infants were admitted to the NICU of the Helsinki University Children's Hospital between 2005 and 2013. Based on the exclusion criteria presented in Figure 1, 274 infants were excluded and the final study cohort was 953 infants. The infants were divided into three groups according to the gestational age at birth: 23-26 weeks (n = 277), 27-29 weeks (n = 433) and 30-31 weeks (n = 243). The clinical characteristics of the study groups are summarised in Table 1.

Towards the end of the seven-day study period, the group sizes decreased because of transfers to other hospitals or mortality. On day seven, 91% of infants born at 23-26 weeks, 85% born at 27-29 weeks and 49% born at 30-31 weeks were still in the NICU. There were 28 deaths during the study period: 22 infants born at 23-26 weeks and six born at 27-29 weeks.

The total fluid intake (ml/kg/d) was significantly higher in the most premature group than in the other groups ($p < 0.001$) (Figure 2A). The median total fluid intake in infants born at 23-26 weeks peaked at 177 ml/kg/d (IQR 154-209) on day three, whereas it was highest on day six in those born at 27-29 weeks (147, IQR 134-160 ml/kg/d) and 30-31 weeks (148, IQR 135-158 ml/kg/d), respectively (Figure 2A). The median total fluid intake of the most premature group significantly exceeded the intakes of the other two groups especially during the first four days, whereas no differences existed between the two older groups (Figure 2A).

The main proportion of fluid intake was derived from nutrition, with parenteral nutrition accounting for the largest single source in all the groups (Figure 3).

Parenteral fluid intake was higher in the infants born at 23-26 weeks than in the other two groups ($p < 0.001$) (Figure 2B).

Enteral fluid intake was highest in those born at 30-31 weeks ($p < 0.001$) (Figure 2C). There was a statistically significant difference between those born at 23-26 and 27-29 weeks in enteral fluid intake on days 4-7 ($p < 0.001$), with the most premature group having the lowest intake. The median proportion of enteral intake in this group remained below 20% of total intake during the entire study period.

During the first two days of life, fluid from volume expanders accounted for a significant proportion of total fluid intake, especially in the infants born at 23-26 weeks, where the median proportion of volume expanders reached 14.2% (21.9 ml/kg/d) on day one (Figure 3). Flushes were a considerable source of fluid intake in all study groups. The highest median intake of flushes was 26.4 ml/kg/d, which was 15.6% of total intake, in the most premature group on day two.

In the entire cohort, daily weight measurements were available for an average of 96% of the infants being treated in the NICU each day. Even though missing weight data were most frequent in the most premature infants, an average of 92% of these infants had their weight recorded on each day. In these infants, the median postnatal weight loss from birth weight reached a maximum of -2.0% (IQR -6.8 to 4.0%) on day three (Figure 4). The respective values were -2.7% (IQR -6.2 to 1.3%) on day two for infants born at 27-29 weeks and -2.8% (IQR -6.1 to 0.8%) on day three for infants born at 30-31 weeks. The percentages for daily weight changes were similar in all groups on days 1-6. On day seven, the weight change was significantly more positive in the least premature group than in the 27-29 week group ($p < 0.05$).

The change in body weight on a given day was considered to reflect the fluid management of the previous day. Therefore, we adopted Pearson's correlation to examine the association between fluid intake on days 1-7 and percentage weight changes from birth weight on days 2-8. A weak linear positive covariance was detected, with a Pearson's correlation coefficient of 0.28 in the most premature group ($p < 0.001$), 0.32 in the 27-29 week group ($p < 0.001$), and 0.32 in the 30-31 week group ($p < 0.001$).

DISCUSSION

Our study found that the actual fluid intake in VLBW infants was high during the first three days of life, especially among the most premature infants. In all the age groups, the enteral fluid intake increased steadily during the first week of life, but a major proportion of fluids was administered parenterally over the entire study period. A clinically important finding was that fluid intake from flushes accounted for a considerable proportion of fluid intake, especially among the most premature infants. It should be noted that the European guidelines do not recommend leaving out the volumes of flushes from fluid volume calculations, even though this may often happen in clinical practice.

Optimal fluid intake in VLBW infants has been the subject of debate in the last few decades. According to the 2005 European guidelines, parenteral fluid intake in VLBW infants should be started at 80-90 ml/kg/d and gradually increased to 160-180 ml/kg/d during the first postnatal week (17). New European guidelines on paediatric parenteral nutrition were published in 2018 and these contained minor changes to the fluid intake recommendations. The new guidelines recommend that fluid intake in preterm neonates with a birth weight of less than 1000g should start at 80-100 ml/kg/d and at 70-90 ml/kg/d in those with birth weights between 1000 and 1500g. In both groups, the fluid intake should be gradually increased with increments of 20-30 ml/kg/d up to 160-180 ml/kg/d by day five (7). In our study, the actual fluid intake in VLBW infants was higher than the European guidelines (7,17) during the first three days of life. In the most premature group, with a GA of 23-26 weeks, the median total fluid intake had already exceeded 150 ml/kg/d on day one. The total fluid intake in the more mature groups remained closer to the guidelines. The high fluid intake in the most premature group was expected, due to cardiorespiratory instability with increased need of volume expansion and medications in these infants.

Current guidelines on the fluid management of VLBW infants are largely based on studies conducted more than two decades ago. Extrapolating the results of these prospective trials of varying fluid intake to today’s clinical practices is challenging, since nutritional practices have changed markedly. Yet the physiology remains similar. In 1979, Bell et al carried out a randomised trial of 170 low birth weight infants and found that high-volume fluid intake was associated with increased risks of patent ductus arteriosus and necrotising enterocolitis (10,12). The total fluid intake over the entire study period of 30 days was as mean of 169 ± 20 ml/kg/d in the high-volume group, compared to 122 ± 14 ml/kg/day in the low-volume group. The fluid intake in the high-volume group paralleled the total fluid intake of the most premature infants in our study, but the study periods differed markedly in duration.

Later studies reporting fluid intakes in preterm infants have primarily focused on parenteral nutrition. A Dutch study examined the impact on fluid balance of new national guidelines recommending a restricted fluid intake and early initiation of total parenteral nutrition (TPN) during the first three days of life in 143 infants with a GA of less than 28 weeks (20). Two groups were retrospectively compared before and after the introduction of the new guidelines in 2005. The fluid recommendation for infants with a birth weight of less than 1000g was identical to the lower limit of the new European guidelines (7) during the first three days of life. For infants with a birth weight of 1000-1500g it was more restricted, at 60-100 ml/kg/d. In both cohorts, the actual fluid intakes were higher than recommended: the mean extra fluid intake was up to 6.4 and 12.6 ml/kg/d in the before and after TPN groups, respectively. The study did not describe the sources of fluid intake. In the TPN group assessed after the new recommendations, the mean postnatal weight loss was modest compared with the TPN group assessed before they were introduced (-0.8% (SD 8.0) vs -6.0% (SD 7.7)). The postnatal weight loss in the after group was in line with our results. During the first postnatal days, extracellular fluid contracts due to insensible water loss and natriuresis. The goal of fluid management during this period is to allow the contraction of extracellular fluid and thus postnatal weight loss (21).

We found that fluid intake from hidden sources, such as the saline and 5% glucose solution used to flush medication or arterial and venous lines, accounted for a substantial proportion of fluid intake, especially among the most premature infants. The fluid volume of a flush solution remains similar, regardless of the infant's body weight. This means that the volume per kilogram body weight is higher in the smallest infants. The standard volumes of flushes are often adapted to the small dead space of the catheters used. In 1986, Noble-Jamieson et al studied the hidden sources of fluid intake in ill newborn infants. They defined hidden sources as fluids for flushing arterial catheters, bronchial lavage and drug administration. They found that extremely low birth weight infants gained up to 12.3 ml/kg/d of extra fluid, most of which came from the saline used to flush the intravenous lines when administering drugs (22). In our study, the highest daily median intake from flushes in the most premature group was more than double the volumes reported by Noble-Jamieson et al. It is possible that these hidden sources are not always considered when assessing daily fluid intake. Also, when we examined just the fluids administered as part of parenteral nutrition on the first day of life, we found that the median volume administered accounted for approximately 75% of the recommended fluid intake in the European guidelines. To minimise the fluid intake from hidden sources, the volumes of flushes should be kept as low as possible.

The maximal postnatal weight loss of 2.0-2.8% from birth weight on days two to three in our cohort was less than expected from previous studies. We detected a weak positive correlation between postnatal weight loss and total fluid intake. In 1986, Gill et al reported a mean postnatal weight loss of 14% at a mean of six days in 184 VLBW infants (23). In 2017, Späth et al presented a postnatal weight change of -10 ± 7% (range -31% to +13%) in a cohort of 592 extremely low birth weight infants, with a nadir at a postnatal age of four days. They found that the average daily fluid intake on days 0-3 after birth correlated positively with the percentage weight change from birth to day four of life (24). It has been proposed that, in addition to the contraction of extracellular fluid, up to half of the initial postnatal weight loss in low birth weight infants might represent failure to accrete or actual loss of lean mass and, or, fat (25). These days, due to the softer treatment conditions with less metabolic disturbances, it could also be possible that a higher proportion of protein can be metabolised, which in turn might reduce the postnatal weight loss.

Strengths and limitations

The strength of our study was the large, detailed data on the actual fluid intakes of 953 VLBW infants collected in the era of current neonatological practices. Furthermore, our cohort included a considerable number of extremely preterm infants born before 28 weeks of gestation. Many previous studies have applied fluid prescriptions or fluid regimes. Our data were derived from an electronic patient information system, which allowed us to examine how much fluid the infants actually received and the routes of administration. This improved the accuracy of the data. Feeding intolerance and metabolic disturbances are commonly encountered in VLBW infants and they may hinder the administration of prescribed fluids. Therefore, it is crucial to study the actual intakes. An electronic patient information system enables the on-line follow up of fluid management and enables us to adjust the infusion rates when needed.

We conducted our study as a retrospective chart review, which causes some limitations. There were missing data because not all the infants stayed in the NICU for the full seven days. This may have caused a possible selection bias, as the healthiest infants were transferred to lower-level units before the end of the study. Another limitation is that we only included full 24-hour periods and the first hours of life were not always included.

CONCLUSION

During the first three days of life, the total fluid intake in our cohort of VLBW infants exceeded the European guidelines. A considerable proportion of fluid intake in the first days of life came from hidden sources. These hidden sources should be taken into account when prescribing fluids for VLBW infants and efforts should be made to reduce the volume of flushes used for these vulnerable patients. It is important to emphasise that all fluid volumes should be included in the fluid calculations.

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ABBREVIATIONS

VLBW:	very low birth weight
GA:	gestational age
NICU:	neonatal intensive care unit
SD:	standard deviation
IQR:	interquartile range

TPN: total parenteral nutrition

CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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Figure legends

Figure 1.
Flow chart of the patients.

Figure 2.
The daily total (2A), parenteral (2B) and enteral (2C) fluid intake in VLBW infants during the first week of life in three gestational age groups. In Figure 2A, the asterisk (*) presents a statistically significant difference between infants born at 23-26 and 27-29 weeks, and infants born at 23-26 and 30-31 weeks of GA ($p<0.001$, pairwise Mann-Whitney U test with Bonferroni correction). In Figure 2B, there were * statistically significant differences between all the groups ($p<0.001$, pairwise Mann-Whitney U test with Bonferroni correction). In Figure 2C, there were *statistically significant differences between the infants born at 23-26 weeks of GA and 30-31 weeks of GA and those born at 27-29 weeks and 30-31 weeks ($p<0.001$, pairwise Mann-Whitney U test with Bonferroni correction).

Figure 3.
Sources of fluid supply during the first week of life in the three gestational age groups. The others category consists of drugs and vitamins, sodium bicarbonate solutions, 20% albumin solutions, electrolyte preparations, such as calcium and sodium chloride concentrates, and glucose solutions not administered as part of parenteral nutrition and sterile water used for flushing the nasogastric tube. Flushes consist of saline solutions and 5% glucose solution used for flushing medications and venous and arterial lines.

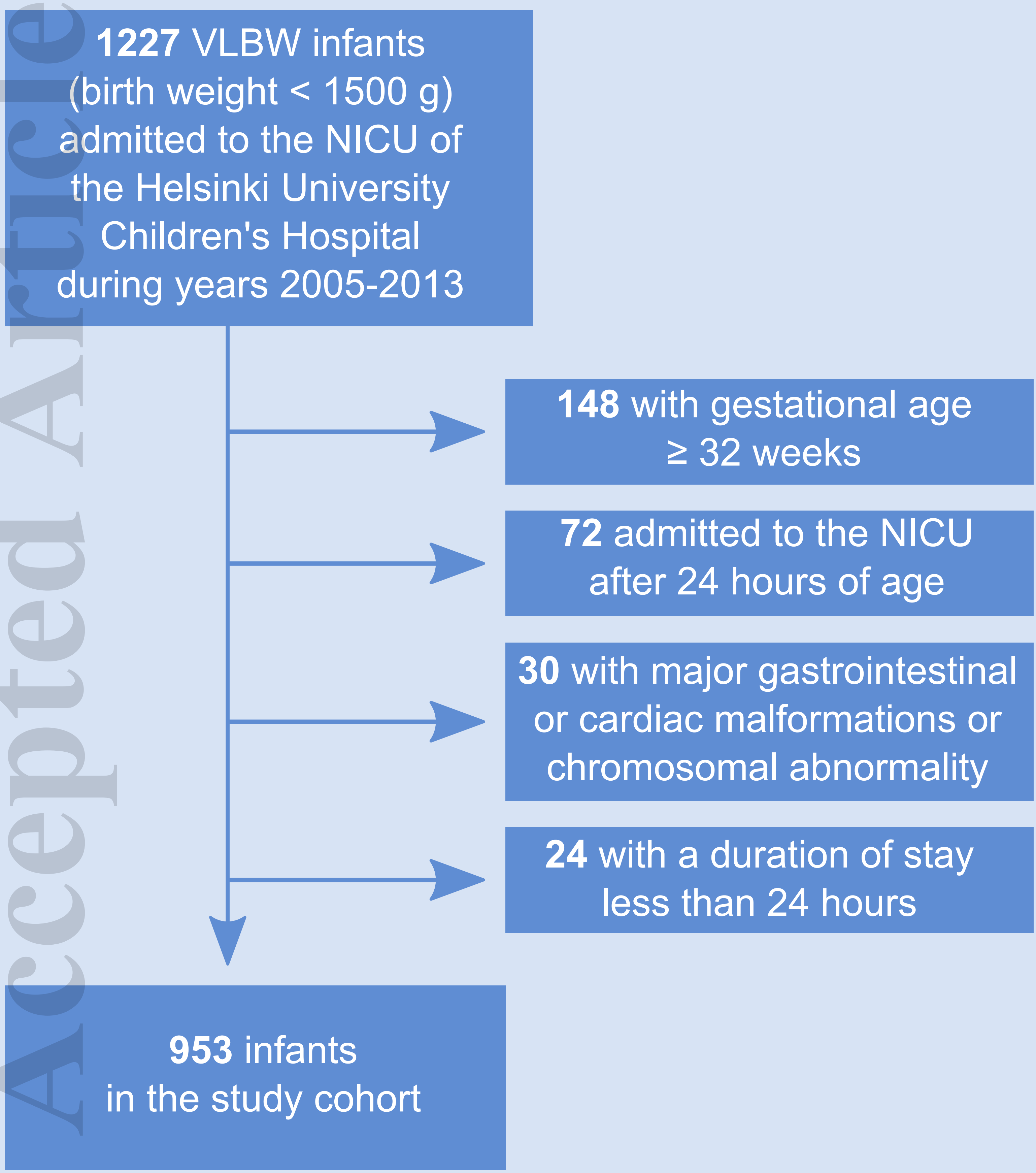
Figure 4.
Daily weight change from birth weight during the first week of life in three gestational age groups. *There was a statistically significant difference between the groups born at 27-29 and 30-31 weeks of GA ($p<0.05$, pairwise Mann-Whitney U test with Bonferroni correction).

Table 1 Clinical characteristics of the study groups

	GA 23-26 weeks (n=277)	GA 27-29 weeks (n=433)	GA 30-31 weeks (n=243)	p-value
Male, n(%)	139 (50.2)	234 (54.0)	107 (44.0)	0.044*
Birth weight (grams), median (min-max)	760 (375-1200)	1110 (400-1495)	1285 (650-1495)	<0.001**
Small for gestational age, n(%)	31 (11.2)	64 (14.8)	91 (37.4)	<0.001*
Multiple births, n(%)	67 (24.2)	117 (27.0)	86 (35.4)	0.013*
Cesarean section, n(%)	151 (54.5)	305 (70.4)	180 (74.1)	<0.001***
Inborn, n(%)	268 (96.8)	420 (97.0)	243 (100.0)	0.0086***
Antenatal corticosteroid given, n(%)	260 (93.9)	410 (94.7)	237 (97.5)	NS(0.26)***
Surfactant given, n(%)	276 (99.6)	355 (82.0)	98 (40.3)	<0.001***
Duration of mechanical ventilation (days), median (IQR)	19.0 (7.0-39.0)	3.0 (0.9-7.0)	2.0 (0.4-3.3)	<0.001**
Central venous catheter, n(%)	252 (91.0)	269 (62.1)	58 (23.9)	<0.001***
Died before age 28 days, n(%)	43 (15.5)	8 (1.8)	2 (0.8)	<0.001*
Bronchopulmonary dysplasia, n(%)	113 (40.8)	89 (20.6)	16 (6.6)	<0.001*
Patent ductus arteriosus, n(%)	182 (65.7)	181 (41.8)	44 (18.1)	<0.001*
Necrotising enterocolitis, n(%)	24 (8.7)	20 (4.6)	1 (0.4)	<0.001*
Intraventricular haemorrhage (grade III-IV), n(%)	58 (20.9)	29 (6.7)	4 (1.6)	<0.001*
Culture-positive sepsis, n(%)	138 (49.8)	115 (26.6)	34 (14.0)	<0.001*

NS = not significant

Statistical tests: *Chi-square test, **Kruskal-Wallis test, ***Fisher's exact test



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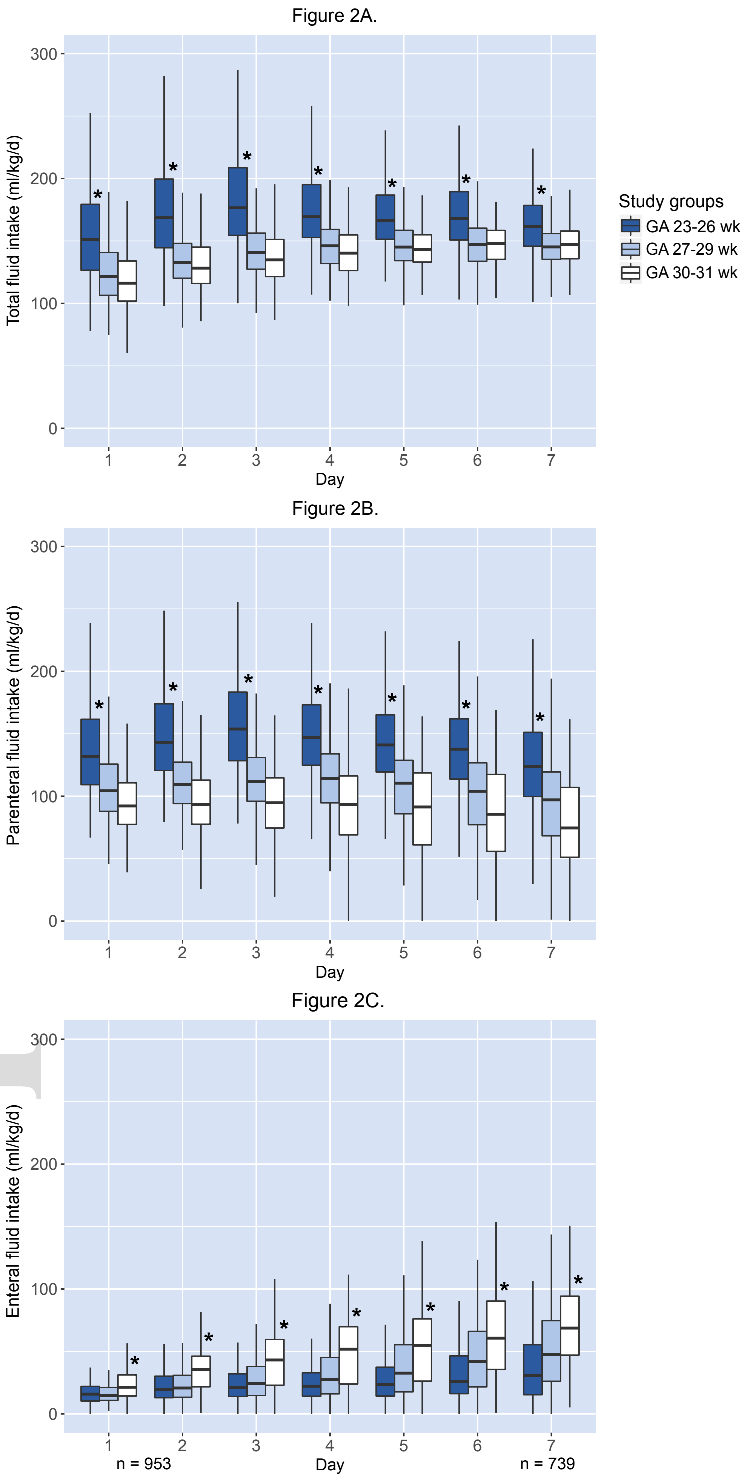
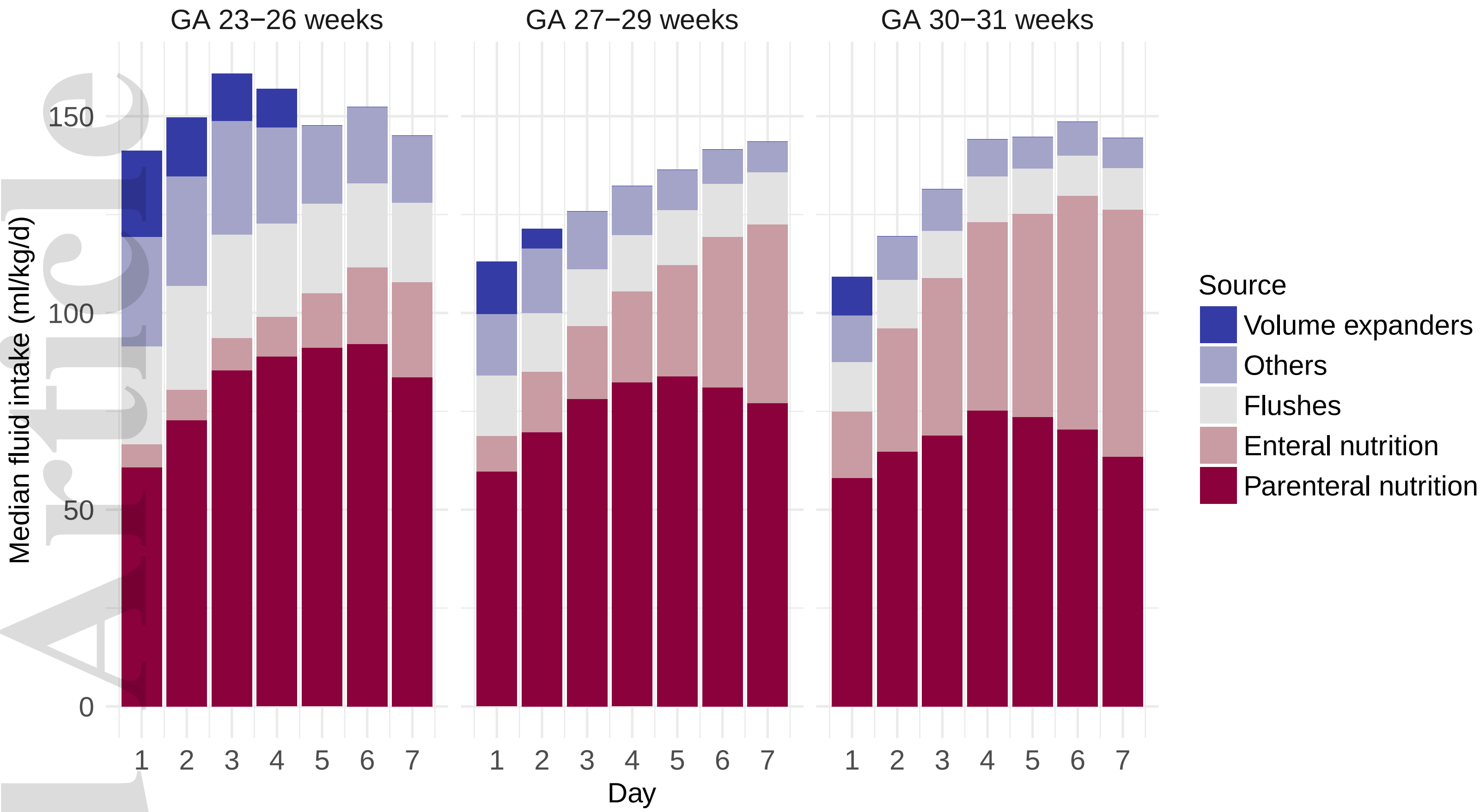


Figure 2A.
Total fluid intake (ml/kg/d)
300
200
100
0
1
2
3
4
5
6
7
Day
Study groups
GA 23-26 wk
GA 27-29 wk
GA 30-31 wk
Figure 2B.
Parenteral fluid intake (ml/kg/d)
Day
Figure 2C.
Enteral fluid intake (ml/kg/d)
n = 953
Day
n = 739



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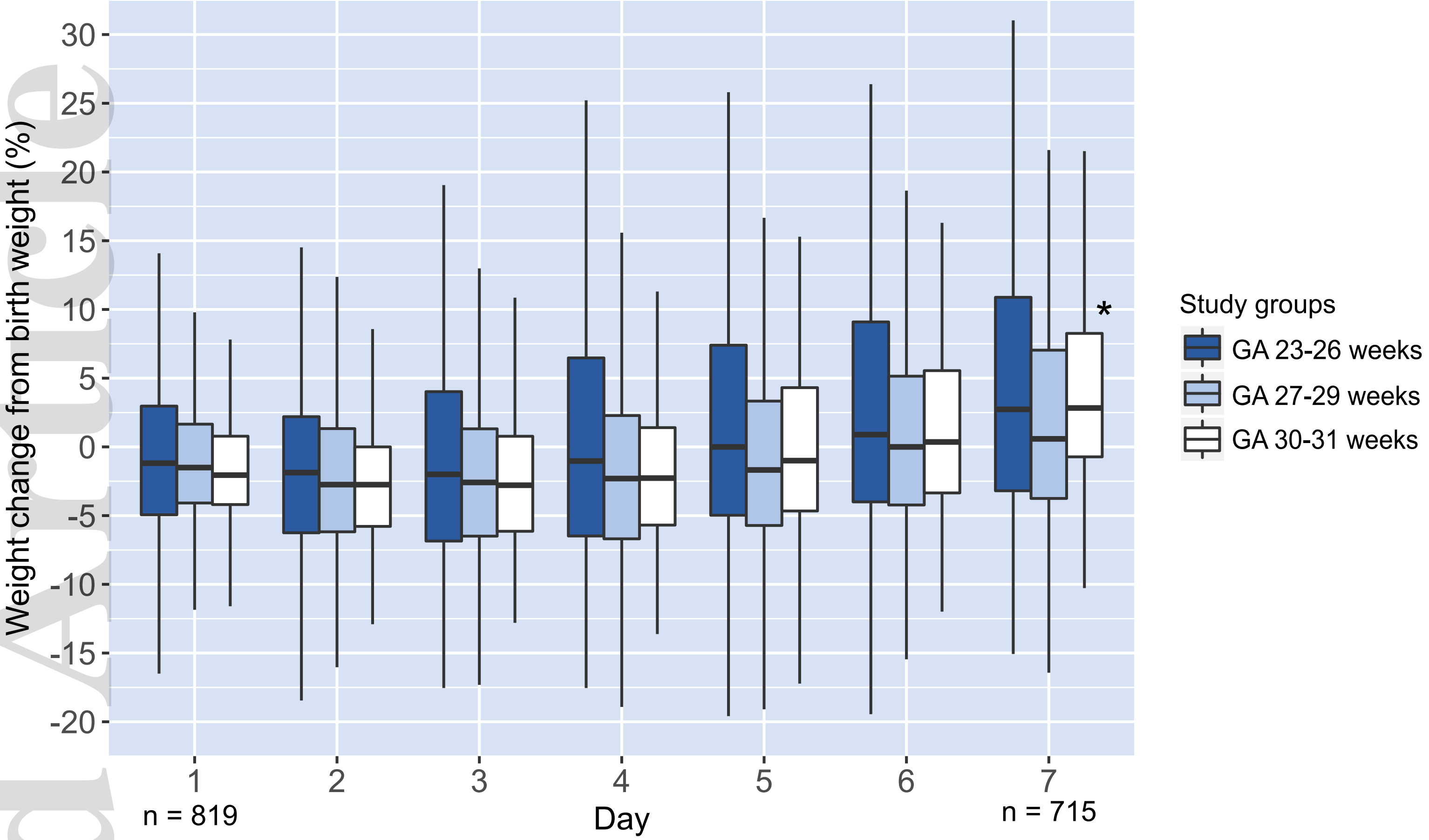

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