INTRAVENOUS FLUID THERAPY IN CHILDREN – A RANDOMIZED AND CONTROLLED CLINICAL STUDY OF THE EFFECTS OF FLUID THERAPY ON ELECTROLYTE LEVELS

Original Study Protocol and Statistical Analysis Plan

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BACKGROUND

Fluid therapy in children: historical background and feared complications

For more than 50 years, the daily fluid requirement in children has been calculated with the formula developed by Malcolm Holliday and William Segar, which is based on energy expenditure in relation to weight in healthy children. The amounts of electrolytes added to the fluid are determined based on the amount of electrolytes in breast milk and cow's milk. When calculated with the Holliday-Segar formula, intravenous fluids are inevitably hypotonic, i.e. with a lower concentration of sodium compared to plasma (Kataja 2015). The safety of hypotonic fluids, particularly in intravenous fluid therapy of sick children, has given rise to debate in recent years. A healthy body is able to eliminate any excess water due to IV therapy via kidneys, but in sick children, activated secretion of antidiuretic hormone (ADH) may cause accumulation of fluid in the body, which results in hyponatremia (Kataja 2015, Wang et al. 2014). Potential and even life-threatening complications of severe hyponatremia include seizures and hyponatremic encephalopathy (Moritz & Ayus 2010, Sarnaik et al. 1991).

Previous randomized controlled clinical studies

In recent years, several randomized and controlled studies have been conducted comparing isotonic (having the same sodium concentration as plasma) and hypotonic solutions in maintenance fluid therapy in children (Pemde et al. 2015, Shamim et al. 2014, Choong et al. 2011, Rey et al. 2011, Saba et al. 2011, Kannan et al. 2010, Yung & Keeley 2009). Based on the studies, isotonic solutions cause less hyponatremia than hypotonic solutions. In addition, the results show that isotonic solutions are safe in maintenance fluid therapy in children. However, the generalizability of the results in question to normal pediatric patient populations is complicated by the fact that the studies have mostly included pediatric patients in intensive care as well as post-operative patients. Furthermore, the comparator used in most studies was 0.18% saline, which has a sodium concentration of only 31 mmol/L (Pemde et al. 2015, Shamim et al. 2014, Kannan et al. 2010, Yung & Keeley 2009).

Evidence of the superiority of isotonic fluids in general pediatric patients with common upper and lower respiratory infections and acute gastroenteritis is scarce, as pointed out by Foster et al. (2014) in their recent systematic review and meta-analysis. Friedman et al. (2015) compared isotonic and hypotonic solution in a sample of 110 general pediatric patients; based on the results, there was no statistically significant difference between the groups in hyponatremia or in any other endpoints. The study of Neville et al. (2006) included 102 children with acute gastroenteritis. The results showed that compared to hypotonic fluid, isotonic fluid therapy caused statistically significantly less hyponatremia, but on clinical evaluation, the differences in sodium levels following the fluid therapy were quite small. A similar finding in favor of isotonic fluid was also made by McNab et al. (2015) in a large randomized study with 676 pediatric patients. However, less than half of the patients in their study were general pediatric patients.

Problems with implementation of fluid therapy

Isotonic fluid therapy is usually implemented with so-called readymade solutions. Isotonic ready-made solutions contain almost the same amount of sodium and potassium as human plasma. In traditional maintenance fluid therapy in children calculated with the Holliday-Segar formula, on average 20 mmol/L potassium is added to fluids. The addition of potassium is considered particularly important in the case of acute gastroenteritis because there may be a substantial loss of potassium if the infection persists for several days. There is thus a potential risk of hypokalemia when using isotonic solutions that contain low levels of potassium in IV fluid therapy. In the study of McNab et al. (2015), extra potassium was added to the fluids for 13% of the patients.

AIM OF THE STUDY

The aim of the randomized clinical study is to compare two alternative intravenous fluid products in the fluid therapy of acutely sick children. The first IV fluid is a readymade isotonic solution, Plasmalyte Glucos 50 mg/mL, which contains sodium 140 mmol/L, potassium 5 mmol/L, and chloride 98 mmol/L. The second is a 5% glucose solution which is a semi-physiological fluid in terms of sodium, containing sodium chloride 80 mmol/L and potassium chloride 20 mmol/L.

COURSE OF THE STUDY

The study is a prospective, randomized and controlled clinical treatment trial. Patients are recruited to the study by pediatric residents and specialists working in the pediatric ER. The doctors who recruit patients to the study tell about the study to the children and patients. They also hand out an information and consent document and a form with basic information for them to complete. The signed consent forms are stored in the upper cabinet in the doctor's office in the ER.

i. *Randomization*

The patients who have or whose parents have given a written consent to participate in the study are randomized into two groups. The following treatments are compared:

- Isotonic fluid (readymade solution Plasmalyte Glucos 50 mg/mL, with Na 140 mmol/L, K 5 mmol/L and Cl 98 mmol/L)
- Semi-physiological fluid (G5%, to which NaCl 80 mmol/L and KCl 20 mmol/L is added)

The current standard of care is based on a local model which has not been scientifically evaluated and is associated with a significant possibility for calculation errors, as shown by a survey we conducted among the physicians in our clinic. The current standard of care is thus not comparable in this study as its safety has not been established and it is not evidence-based.

ii. *Blinding*

This is an open label study because the endpoints can be objectively measured. Thanks to the open label design, the treating physician is also aware of the electrolyte concentrations of the fluids and can make adjustments to them if necessary.

iii. *Endpoints*

- Primary: hypokalemia < 3.5
- Secondary: hyponatremia (< 132), hypernatremia (> 148), weight gain, change of maintenance fluid, added sodium and potassium, duration of fluid therapy during

hospital treatment within 7 days of admittance, admittance to intensive care, duration of hospital treatment

iv. Measures to prevent adverse effects

Before the onset of fluid therapy, blood electrolytes are measured from venous blood samples taken in connection with cannula insertion from all patients taking part in the study. In all patients, electrolytes are analyzed from venous blood samples taken in the morning while in hospital. Based on the assessment of the physician on call, electrolytes can be measured in the evening as well, especially if the patient has repeated fluid loss during the treatment, or if the time between the onset of fluid therapy and the blood sampling the next morning is long. Any other additional blood samples required can be taken as capillary samples. The treating physician has the right to withdraw administration of study fluid and treat the patient with the fluids he/she considers best. The treating physician may also increase or decrease the amount of electrolytes in the fluid.

STUDY POPULATION

i. Inclusion criteria:

- Age ≥ 6 months and < 12 years
- Need of hospital treatment and IV rehydration in any pediatric ward

ii. Exclusion criteria:

- Na < 130 or > 150
- K < 3
- Need of 10% glucose solution as initial fluid
- Diabetes
- Diabetes insipidus
- Ketoacidosis
- Kidney disease requiring dialysis
- Severe liver disease
- Metabolic disease that requires rehydration according to protocol
- Leukemia or other malignancy that requires rehydration according to protocol

iii. Sample size

Based on previous studies, we estimate that the prevalence of hypokalemia is about 13% in patients who receive isotonic maintenance fluids that do not contain, or contain only small amounts of potassium. In our study, a reduction in prevalence to 6% in the group where maintenance fluid therapy is given using semi-physiological fluid that contains potassium is considered clinically significant. We set alpha at 5% and power at 80%, which means that we need 275 children/group. To make sure that the final analysis includes the required number of children, we chose 305 children/group (a total of 610 children) as sample size.

FOLLOW-UP AND LABORATORY SAMPLES

- Before the onset of fluid therapy, sodium and potassium are measured from a venous blood sample taken in connection with cannula insertion from all patients taking part in the study. During fluid therapy, sodium and potassium are determined from a venous blood sample taken in the morning. The time of onset of study fluid administration differs between the study patients, which is why the venous blood samples are also taken at different times in the morning. However, in a randomized study design this is not a problem; the groups are still comparable. Based on the assessment of the physician on call, electrolytes can be measured in the evening as well, especially if the patient has repeated fluid loss during the treatment, or if the time between the onset of fluid therapy and the blood sampling the next morning is long.
- The study patients are weighed before the onset of fluid therapy, in the morning following the onset of fluid therapy, and after the fluid therapy has ended.
- Pathogens are investigated according to current practice in all patients with infections. In patients with acute gastroenteritis, the presence of adeno, rota and noro viruses in the feces is investigated. Patients with respiratory infections are investigated for the presence of influenza and RSV virus; if necessary, a more extensive viral analysis of a nasopharyngeal sample is undertaken.
- The following are recorded in the medical record: fever, oral fluid therapy, IV fluid therapy, vomiting, diarrhea and weight (every morning and at discharge). At the end of the treatment period, the recordings of oral and IV fluids are scanned into the medical record.
- Data on patients entering the study is collected regularly (weekly) by investigators from medical records and entered into SPSS.

FLUID PRODUCTS AND THEIR ADMINISTRATION

Plasmalyte Glucos 50 mg/mL contains sodium 140 mmol/l, potassium 5 mmol/L, chloride 98 mmol/L, magnesium 1.5 mmol/L, acetate 27 mmol/L and gluconate 23 mmol/L. Plasmalyte Glucos 50 mg/mL has a pH of about 7.4 (6.5–8.0). The semi-physiological fluid is made with 5% glucose with the addition of sodium chloride 80 mmol/L and potassium chloride 20 mmol/L. The amount of fluid and the infusion rate are calculated based on the child's weight using the Formula of Holliday-Segar (fluid requirement 100 mL/kg <10 kg, 1,000 mL + 50 mL/kg > 10 kg, > 20 kg 1,500 ml + 20 mL/kg > 20 kg). Potential correction of dehydration is calculated based on estimated weight loss. Based on assessment by the physician on call, fluid replacement with 20 mg/kg Ringer solution may be given before the onset of study fluid administration for the study patients.

STATISTICAL ANALYSIS PLAN

The primary outcome is defined as the proportion of children with any clinically significant electrolyte disorder defined as hypokalemia < 3.5 mmol/L, hyponatremia < 132 mmol/L, or hypernatremia > 148 mmol/L within 7 days of randomization. **The main secondary outcome** is fluid retention measured by weight change (g) during hospitalization: weight (g) at discharge - weight (g) on admission. **Other secondary outcomes** are the duration of intravenous fluid therapy (hours), proportion of children requiring any change of fluid therapy, proportion of children admitted to intensive care after admission, duration of hospitalization, proportion of children with

mild hyponatremia defined as plasma sodium 132-135 mmol/L, and severe hypokalemia < 3.0 mmol/L. All secondary outcomes were reported within 7 days after randomization except the number of deaths within 30 days of randomization.

The occurrence of any clinically significant electrolyte disorder in children receiving isotonic fluid therapy was estimated to be at least 13% based on a previous study reporting the need of adding potassium in plasma-like fluid in children (17). We considered the difference between groups to be clinically significant if the occurrence of electrolyte disorder would be 7% lower in children receiving moderately hypotonic fluid. We set alpha error at 5% and beta error at 20%, i.e. power of 80%, which resulted in 275 children/group. To make sure that the final analysis included the required number of children with measured primary outcome, we decided to recruit 300 children/group.

All analyses were performed in intention-to-treat population. Only primary and secondary outcomes that were prespecified in the protocol and statistical analysis plan before study completion will be compared. As all study participants were hospitalized, missing data were rare. Differences between proportions will be compared with standard normal deviate test (SND test) and 95% CI of the difference will be given to readers. Risk ratios (RR) will be calculated for the outcomes. We will calculate the number needed to treat to avoid one patient developing a clinically significant electrolyte disorder (NNT) in children receiving semi isotonic fluid therapy presented as number needed to harm (NNH) if isotonic fluid therapy increased the risk. Continuous variables will be compared with t test and 95% CI of the difference will be given to readers. For primary and secondary outcomes, we will calculate95% confidence intervals (CIs) of the differences. The widths of CI intervals of prespecified secondary outcomes will not be adjusted for multiplicity and therefore will not be interpreted as definite treatment effects. All analyses will be performed using IBM Statistics for Windows version 25 (Armonk, NY: IBM Corp.) and StatsDirect statistical software version 3 (StatsDirect Ltd, England). Figures were drawn using OriginPro 2018 software (OriginLab Corporation, Northampton, MA, USA).

STUDY ORGANIZATION, FUNDING AND SCHEDULE

The study is an independent investigator-driven study. Saara Lehtiranta, MD, is a pediatric resident. In addition to her day job, she does research on fluid therapy in children at the Department of Children and Adolescents of Oulu University Hospital under the guidance of Docent Terhi Tapiainen, Ass. Professor of Pediatrics, Oulu University Hospital. All members of the study team are employed in the units indicated on the title page. Funding is applied from various foundations to enable personal full-time research months (Saara Lehtiranta, MD). The study commenced in spring 2016 and is expected to last 1.5–2 years.

ETHICAL CONSIDERATIONS AND STUDY REGISTRATION

For decades, hypotonic solutions calculated with the Holliday-Segar formula have been used in fluid therapy in children, and in many pediatric units they are still the current standard of care. However, fluid calculation is a cumbersome process that is prone to errors. In addition, cases of

hyponatremia caused by hypotonic fluids have been described in the literature. In recent years, there have been several randomized controlled studies on the use of isotonic fluids in pediatric patients. Based on the findings, the use of isotonic solutions has been considered safe in the maintenance fluid therapy in children, particularly IC and surgical patients. Based on this evidence, some pediatric units have already switched to using isotonic fluids in maintenance fluid therapy in all pediatric patients. Semi-physiological fluids have been commonly used in maintenance fluid therapy in children, and their use has not been associated with severe or clinically significant hyponatremia in previous studies.

The use of standardized fluids, i.e. isotonic readymade fluids and predetermined semi-physiological fluid as study products is well-motivated from the viewpoint of patient safety: the less the on-call physician needs to focus on calculating the amount of electrolytes to be added to fluids, the smaller the risk of miscalculation. However, there are still only few studies comparing different maintenance fluids, and in selected patient populations only. Above all, well-executed, randomized and controlled studies on maintenance fluid therapy in children with common infections are needed before deciding what kind of fluid therapy requiring less calculation should be adopted more widely.

Compared with current treatment, the use of the readymade fluids in the study is not expected to cause any risks, such as electrolyte impairment, longer treatment time or other complications. The study is an open label study, so the doctors treating the study patients are aware of the fluid solutions used and their electrolyte contents. The blood electrolyte levels of the study patients are monitored in accordance with the study protocol as well as whenever necessary, so that any disturbances in electrolyte levels can be addressed rapidly.

CLINICAL SIGNIFICANCE OF THE STUDY

The study provides new information about the selection and safety of IV fluids for children with common pediatric diseases, such as acute upper and lower respiratory infections and gastroenteritis. A switch to readymade solutions would also facilitate the work of on-call physicians, reduce the risk of calculation errors, and allow physicians more time to focus on patient care instead of fluid calculation.

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<u>Final</u> Study Protocol and Statistical Analysis Plan

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BACKGROUND

Fluid therapy in children: historical background and feared complications

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Previous randomized controlled clinical studies

Addition Aug 2019: Full updated literature review is presented as a separate summary table. In recent years, several randomized and controlled studies have been conducted comparing isotonic (having the same sodium concentration as plasma) and hypotonic solutions in maintenance fluid therapy in children (Pemde et al. 2015, Shamim et al. 2014, Choong et al. 2011, Rey et al. 2011, Saba et al. 2011, Kannan et al. 2010, Yung & Keeley 2009). Based on the studies, isotonic solutions cause less hyponatremia than hypotonic solutions. In addition, the results show that isotonic solutions are safe in maintenance fluid therapy in children. However, the generalizability of the results in question to normal pediatric patient populations is complicated by the fact that the studies have mostly included pediatric patients in intensive care as well as post-operative patients. Furthermore, the comparator used in most studies was 0.18% saline, which has a sodium concentration of only 31 mmol/L (Pemde et al. 2015, Shamim et al. 2014, Kannan et al. 2010, Yung & Keeley 2009).

Evidence of the superiority of isotonic fluids in general pediatric patients with common upper and lower respiratory infections and acute gastroenteritis is scarce, as pointed out by Foster et al. (2014) in their recent systematic review and meta-analysis. Friedman et al. (2015) compared isotonic and hypotonic solution in a sample of 110 general pediatric patients; based on the results, there was no statistically significant difference between the groups in hyponatremia or in any other endpoints. The study of Neville et al. (2006) included 102 children with acute gastroenteritis. The results showed that compared to hypotonic fluid, isotonic fluid therapy caused statistically significantly less hyponatremia, but on clinical evaluation, the differences in sodium levels following the fluid therapy were quite small. A similar finding in favor of isotonic fluid was also made by McNab et al. (2015) in a large randomized study with 676 pediatric patients. However, less than half of the patients in their study were general pediatric patients.

Problems with implementation of fluid therapy

Isotonic fluid therapy is usually implemented with so-called readymade solutions. Isotonic ready-made solutions contain almost the same amount of sodium and potassium as human plasma. In traditional maintenance fluid therapy in children calculated with the Holliday-Segar formula, on average 20 mmol/L potassium is added to fluids. The addition of potassium is considered particularly important in the case of acute gastroenteritis because there may be a substantial loss of potassium if the infection persists for several days. There is thus a potential risk of hypokalemia when using isotonic solutions that contain low levels of potassium in IV fluid therapy. In the study of McNab et al. (2015), extra potassium was added to the fluids for 13% of the patients.

Addition 4 Feb 2019: Measurement of copeptin and its use in fluid therapy

The optimal implementation of fluid therapy in acutely sick children is not known because fluid therapy is influenced by the degree of dehydration, renal function, and hormones that regulate fluid balance. In recent years, increasing attention has been focused on the risk of severe hypernatremia in sick patients who may have abnormally high secretion of antidiuretic hormone (ADH) in acute illness. According to this view, the use of isotonic, i.e. high-sodium fluid therapy would be safe as it prevents the severe hyponatremia associated with high secretion of ADH. However, based on a study in healthy adults, isotonic fluid therapy may lead to fluid retention and decreased diuresis (Van Regenmortel et al. 2017). In addition, animal studies have revealed that increased ADH level may mediate renal damage if dehydration is corrected with fluids that contain fructose (Garcia-Arroyo et al. 2017).

Plasma copeptin is a glycopeptide cleaved from the ADH precursor which is secreted into the circulation in equimolar amounts with ADH (Koistinen 2012). As determination of ADH is slow and unreliable, determination of the more stable copeptin enables reliable evaluation of ADH concentration. Measurement of copeptin has thus been investigated in recent years, particularly as a predictive factor for cardiovascular disease and metabolic syndrome, but also in severely ill patients. Studies have shown that a high copeptin level on admission predicts mortality in adult intensive care patients (Krychtiuk et al. 2017). Copeptin is a promising new tool that could potentially be used in the evaluation of prognosis and fluid therapy in acutely sick children.

AIM OF THE STUDY

The aim of the randomized clinical study is to compare two alternative intravenous fluid products in the fluid therapy of acutely sick children. The first IV fluid is a readymade isotonic solution, Plasmalyte Glucos 50 mg/mL, which contains sodium 140 mmol/L, potassium 5 mmol/L, and chloride 98 mmol/L. The second is a 5% glucose solution which is a semi-physiological fluid in terms of sodium, containing sodium chloride 80 mmol/L and potassium chloride 20 mmol/L.

COURSE OF THE STUDY

The study is a prospective, randomized and controlled clinical treatment trial. Patients are recruited to the study by pediatric residents and specialists working in the pediatric ER. The doctors who recruit patients to the study tell about the study to the children and patients. They also hand out an information and consent document and a form with basic information for them to complete. The signed consent forms are stored in the upper cabinet in the doctor’s office in the ER.

v. *Randomization*

The patients who have or whose parents have given a written consent to participate in the study are randomized into two groups. The following treatments are compared:

- Isotonic fluid (readymade solution Plasmalyte Glucos 50 mg/mL, with Na 140 mmol/L, K 5 mmol/L and Cl 98 mmol/L)
- Semi-physiological fluid (G5%, to which NaCl 80 mmol/L and KCl 20 mmol/L is added)

The current standard of care is based on a local model which has not been scientifically evaluated and is associated with a significant possibility for calculation errors, as shown by a survey we conducted among the physicians in our clinic. The current standard of care is thus not comparable in this study as its safety has not been established and it is not evidence-based.

vi. *Blinding*

This is an open label study because the endpoints can be objectively measured. Thanks to the open label design, the treating physician is also aware of the electrolyte concentrations of the fluids and can make adjustments to them if necessary.

vii. *Endpoints*

- Primary: hypokalemia < 3.5
- Secondary: hyponatremia (< 132), hypernatremia (> 148), weight gain, change of maintenance fluid, added sodium and potassium, duration of fluid therapy during hospital treatment within 7 days of admittance, admittance to intensive care, duration of hospital treatment
- *Addition 4 Feb 2019: Secondary: effect of fluid therapy on ADH secretion (copeptin), readmittance to ER and/or ward following discharge, deaths over a period of 30 days*

viii. *Measures to prevent adverse effects*

Before the onset of fluid therapy, blood electrolytes are measured from venous blood samples taken in connection with cannula insertion from all patients taking part in the study. In all patients, electrolytes are analyzed from venous blood samples taken in the morning while in hospital. Based on the assessment of the physician on call, electrolytes can be measured in the evening as well, especially if the patient has repeated fluid loss during the treatment, or if the time between the onset of fluid therapy and the blood sampling the next morning is long. Any other additional blood samples required can be taken as capillary samples. The treating physician has the right to withdraw administration of study fluid and treat the patient with the fluids he/she considers best. The treating physician may also increase or decrease the amount of electrolytes in the fluid.

ix. *Addition 4 Feb 2019: Determination of copeptin in the assessment of fluid retention due to excess sodium input. Copeptin is measured in a random sample of study patients who receive IV fluid therapy. All plasma samples are frozen during the study and the random sample will be retrieved from the frozen samples.*

STUDY POPULATION

iv. *Inclusion criteria:*

- Age ≥ 6 months and < 12 years
- Need of hospital treatment and IV rehydration in any pediatric ward

v. *Exclusion criteria:*

- Na < 130 or > 150
- K < 3
- Need of 10% glucose solution as initial fluid
- Diabetes
- Diabetes insipidus
- Ketoacidosis
- Kidney disease requiring dialysis
- Severe liver disease
- Metabolic disease that requires rehydration according to protocol
- Leukemia or other malignancy that requires rehydration according to protocol

Addition 4 Oct 2016: Previous IV fluid therapy is not an exclusion criterion.

vi. *Sample size*

Based on previous studies, we estimate that the prevalence of hypokalemia is about 13% in patients who receive isotonic maintenance fluids that do not contain, or contain only small amounts of potassium. In our study, a reduction in prevalence to 6% in the group where maintenance fluid therapy is given using semi-physiological fluid that contains potassium is considered clinically significant. We set alpha at 5% and power at 80%, which means that we need 275 children/group. To make sure that the final analysis includes the required number of children, we chose 305 children/group (a total of 610 children) as sample size. *Addition 3/2018: We decided to increase the sample size so that a total of 660 subjects are recruited to the study to ensure the sufficient number of patients to compensate the number of drop-outs.*

FOLLOW-UP AND LABORATORY SAMPLES

- Before the onset of fluid therapy, sodium and potassium are measured from a venous blood sample taken in connection with cannula insertion from all patients taking part in the study. During fluid therapy, sodium and potassium are determined from a venous blood sample taken in the morning. The time of onset of study fluid administration differs between the study patients, which is why the venous blood samples are also taken at different times in the morning. However, in a randomized study design this is not a problem; the groups are still comparable. Based on the assessment of the physician on call, electrolytes can be measured in the evening as well, especially if the patient has repeated fluid loss during the treatment, or if the time between the onset of fluid therapy and the blood sampling the next morning is long.
- The study patients are weighed before the onset of fluid therapy, in the morning following the onset of fluid therapy, and after the fluid therapy has ended.

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- The following are recorded in the medical record: fever, oral fluid therapy, IV fluid therapy, vomiting, diarrhea and weight (every morning and at discharge). At the end of the treatment period, the recordings of oral and IV fluids are scanned into the medical record.
- Data on patients entering the study is collected regularly (weekly) by investigators from medical records and entered into SPSS.

FLUID PRODUCTS AND THEIR ADMINISTRATION

Plasmalyte Glucos 50 mg/mL contains sodium 140 mmol/l, potassium 5 mmol/L, chloride 98 mmol/L, magnesium 1.5 mmol/L, acetate 27 mmol/L and gluconate 23 mmol/L. Plasmalyte Glucos 50 mg/mL has a pH of about 7.4 (6.5–8.0). The semi-physiological fluid is made with 5% glucose with the addition of sodium chloride 80 mmol/L and potassium chloride 20 mmol/L. The amount of fluid and the infusion rate are calculated based on the child's weight using the Formula of Holliday-Segar (fluid requirement 100 mL/kg <10 kg, 1,000 mL + 50 mL/kg > 10 kg, > 20 kg 1,500 ml + 20 mL/kg > 20 kg). Potential correction of dehydration is calculated based on estimated weight loss. Based on assessment by the physician on call, fluid replacement with 20 mg/kg Ringer solution may be given before the onset of study fluid administration for the study patients. *Addition 4 Oct 2016: Other cristalloids such as physiological saline or Plasmalyte may also be used for fluid replacement.*

STATISTICAL ANALYSIS PLAN

The primary outcome is defined as the proportion of children with any clinically significant electrolyte disorder defined as hypokalemia < 3.5 mmol/L, hyponatremia < 132 mmol/L, or hypernatremia > 148 mmol/L within 7 days of randomization. **The main secondary outcome** is fluid retention measured by weight change (g) during hospitalization: weight (g) at discharge - weight (g) on admission. **Other secondary outcomes** are the duration of intravenous fluid therapy (hours), proportion of children requiring any change of fluid therapy, proportion of children admitted to intensive care after admission, duration of hospitalization, proportion of children with mild hyponatremia defined as plasma sodium 132-135 mmol/L, and severe hypokalemia < 3.0 mmol/L. All secondary outcomes were reported within 7 days after randomization except the number of deaths within 30 days of randomization.

*Addition 4 Feb 2019: **Post hoc analysis.** Comparison of copeptin values (as a precursor of ADH) with a t-test in a random sample of 10% of participants at 6-24 hours, using the frozen plasma samples obtained during the study,*

*Addition 15 Nov 2019: **Post hoc analysis** regarding the time to the electrolyte disorder in hours (after noticing 7-fold risk in electrolyte disorders between groups analysis) is added for the analysis plan.*

*Addition 15 Nov 2019. **Post hoc analysis** regarding the proportion of children with low pH value <7.35, low base excess <-2.5 and low bicarbonate <21 on day 1 is added after pediatric*

anesthesiologist department at Oulu Univ Hospital gave comments for the manuscript since acidosis and alkalosis may have an impact on the electrolyte balance.

The occurrence of any clinically significant electrolyte disorder in children receiving isotonic fluid therapy was estimated to be at least 13% based on a previous study reporting the need of adding potassium in plasma-like fluid in children (17). We considered the difference between groups to be clinically significant if the occurrence of electrolyte disorder would be 7% lower in children receiving moderately hypotonic fluid. We set alpha error at 5% and beta error at 20%, i.e. power of 80%, which resulted in 275 children/group. To make sure that the final analysis included the required number of children with measured primary outcome, we decided to recruit 300 children/group.

All analyses were performed in intention-to-treat population. Only primary and secondary outcomes that were prespecified in the protocol and statistical analysis plan before study completion will be compared. As all study participants were hospitalized, missing data were rare. Differences between proportions will be compared with standard normal deviate test (SND test) and 95% CI of the difference will be given to readers. Risk ratios (RR) will be calculated for the outcomes. We will calculate the number needed to treat to avoid one patient developing a clinically significant electrolyte disorder (NNT) in children receiving semi isotonic fluid therapy presented as number needed to harm (NNH) if isotonic fluid therapy increased the risk. Continuous variables will be compared with t test and 95% CI of the difference will be given to readers. For primary and secondary outcomes, we will calculate95% confidence intervals (CIs) of the differences. The widths of CI intervals of prespecified secondary outcomes will not be adjusted for multiplicity and therefore will not be interpreted as definite treatment effects. All analyses will be performed using IBM Statistics for Windows version 25 (Armonk, NY: IBM Corp.) and StatsDirect statistical software version 3 (StatsDirect Ltd, England). Figures were drawn using OriginPro 2018 software (OriginLab Corporation, Northampton, MA, USA).

STUDY ORGANIZATION, FUNDING AND SCHEDULE

The study is an independent investigator-driven study. Saara Lehtiranta, MD, is a pediatric resident. In addition to her day job, she does research on fluid therapy in children at the Department of Children and Adolescents of Oulu University Hospital under the guidance of Docent Terhi Tapiainen, Ass. Professor of Pediatrics, Oulu University Hospital. All members of the study team are employed in the units indicated on the title page. Funding is applied from various foundations to enable personal full-time research months (Saara Lehtiranta, MD). The study commenced in spring 2016 and is expected to last 1.5–2 years.

ETHICAL CONSIDERATIONS AND STUDY REGISTRATION

For decades, hypotonic solutions calculated with the Holliday-Segar formula have been used in fluid therapy in children, and in many pediatric units they are still the current standard of care. However, fluid calculation is a cumbersome process that is prone to errors. In addition, cases of hyponatremia caused by hypotonic fluids have been described in the literature. In recent years, there

have been several randomized controlled studies on the use of isotonic fluids in pediatric patients. Based on the findings, the use of isotonic solutions has been considered safe in the maintenance fluid therapy in children, particularly IC and surgical patients. Based on this evidence, some pediatric units have already switched to using isotonic fluids in maintenance fluid therapy in all pediatric patients. Semi-physiological fluids have been commonly used in maintenance fluid therapy in children, and their use has not been associated with severe or clinically significant hyponatremia in previous studies.

The use of standardized fluids, i.e. isotonic readymade fluids and predetermined semi-physiological fluid as study products is well-motivated from the viewpoint of patient safety: the less the on-call physician needs to focus on calculating the amount of electrolytes to be added to fluids, the smaller the risk of miscalculation. However, there are still only few studies comparing different maintenance fluids, and in selected patient populations only. Above all, well-executed, randomized and controlled studies on maintenance fluid therapy in children with common infections are needed before deciding what kind of fluid therapy requiring less calculation should be adopted more widely.

Compared with current treatment, the use of the readymade fluids in the study is not expected to cause any risks, such as electrolyte impairment, longer treatment time or other complications. The study is an open label study, so the doctors treating the study patients are aware of the fluid solutions used and their electrolyte contents. The blood electrolyte levels of the study patients are monitored in accordance with the study protocol as well as whenever necessary, so that any disturbances in electrolyte levels can be addressed rapidly.

Additions in 2016:

1) *Ethical Committee of Oulu University Hospital reviewed the study protocol prior to study in 2016, with a decision number EETTMK 48/2016*
2) *Finnish Medical Agency (FIMEA) reviewed and accepted the study protocol prior to the study in 2016, with a EUDRA-CT number 2016-002046.*
3) *Study was registered using ClinicalTrials.gov prior to the recruitment period, with number NCT02926989*

CLINICAL SIGNIFICANCE OF THE STUDY

The study provides new information about the selection and safety of IV fluids for children with common pediatric diseases, such as acute upper and lower respiratory infections and gastroenteritis. A switch to readymade solutions would also facilitate the work of on-call physicians, reduce the risk of calculation errors, and allow physicians more time to focus on patient care instead of fluid calculation.

Addition 4 Feb 2019: Determination of copeptin and possible changes in copeptin levels during fluid therapy provide valuable additional information about the physiological effects of the clinical study. Copeptin levels could potentially be utilized in determining the clinical status of children in the ER setting and in choosing optimal fluid therapy.

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AMENDMENTS

Additions in Sep 2016:
Ethical Committee of Oulu University Hospital reviewed the study protocol prior to study in 2016, with a decision number EETTMK 48/2016
Finnish Medical Agency (FIMEA) reviewed and accepted the study protocol prior to the study in 2016, with a EUDRA-CT number 2016-002046.
Study was registered using ClinicalTrials.gov prior to the recruitment period, with number NCT02926989

Addition 4 Oct 2016: Previous IV fluid therapy is not an exclusion criterion

Addition 4 Oct 2016: Other cristalloids such as physiological saline or Plasmalyte may also be used for fluid replacement at ER before fluid therapy

Addition March 2018: We decided to increase the sample size so that a total of 660 subjects are recruited to the study to ensure the sufficient number of patients to compensate the number of drop-outs.

Addition 4 Feb 2019: Measurement of copeptin and its use in fluid therapy
The optimal implementation of fluid therapy in acutely sick children is not known because fluid therapy is influenced by the degree of dehydration, renal function, and hormones that regulate fluid balance. In recent years, increasing attention has been focused on the risk of severe hypernatremia in sick patients who may have abnormally high secretion of antidiuretic hormone (ADH) in acute illness. According to this view, the use of isotonic, i.e. high-sodium fluid therapy would be safe as it prevents the severe hyponatremia associated with high secretion of ADH. However, based on a study in healthy adults, isotonic fluid therapy may lead to fluid retention and decreased diuresis (Van Regenmortel et al. 2017). In addition, animal studies have revealed that increased ADH level may mediate renal damage if dehydration is corrected with fluids that contain fructose (Garcia-Arroyo et al. 2017).

Plasma copeptin is a glycopeptide cleaved from the ADH precursor which is secreted into the circulation in equimolar amounts with ADH (Koistinen 2012). As determination of ADH is slow and unreliable, determination of the more stable copeptin enables reliable evaluation of ADH concentration. Measurement of copeptin has thus been investigated in recent years, particularly as a predictive factor for cardiovascular disease and metabolic syndrome, but also in severely ill patients. Studies have shown that a high copeptin level on admission predicts mortality in adult intensive care patients (Krychtiuk et al. 2017). Copeptin is a promising new tool that could potentially be used in the evaluation of prognosis and fluid therapy in acutely sick children.

Addition 4 Feb 2019: Secondary: effect of fluid therapy on ADH secretion (copeptin), readmittance to ER and/or ward following discharge, deaths over a period of 30 days

Addition 4 Feb 2019: Determination of copeptin in the assessment of fluid retention due to excess sodium input. Copeptin is measured in a random sample of study patients who receive IV fluid therapy. All plasma samples are frozen during the study and the random sample will be retrieved from the frozen samples.

Addition 4 Feb 2019: Determination of copeptin and possible changes in copeptin levels during fluid therapy provide valuable additional information about the physiological effects of the clinical study. Copeptin levels could potentially be utilized in determining the clinical status of children in the ER setting and in choosing optimal fluid therapy.

Addition 4 Feb 2019: ***Post hoc analysis.*** *Comparison of copeptin values (as a precursor of ADH) with a t-test in a random sample of 10% of participants at 6-24 hours, using the frozen plasma samples obtained during the study,*

Addition Aug 2019: **Full updated literature review with a summary table** is *created.*

Addition 15 Nov 2019: ***Post hoc analysis*** *regarding the time to the electrolyte disorder in hours (after noticing 7-fold risk in electrolyte disorders between groups analysis) is added for the analysis plan.*

Addition 15 Nov 2019. ***Post hoc analysis*** *regarding the proportion of children with low pH value <7.35, low base excess <-2.5 and low bicarbonate <21 on day 1 is added after pediatric anesthesiologist department at Oulu Univ Hospital gave comments for the manuscript since acidosis and alkalosis may have an impact on the electrolyte balance.*