

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

4

5 *Original Study Protocol and Statistical Analysis Plan*

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31 **BACKGROUND**

32 *Fluid therapy in children: historical background and feared complications*

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

45
46 *Previous randomized controlled clinical studies*

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

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

69
70

71 ***Problems with implementation of fluid therapy***

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

80

81 **AIM OF THE STUDY**

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

87

88 **COURSE OF THE STUDY**

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

94

95 *i. Randomization*

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

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

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

107 *ii. Blinding*

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

111 *iii. Endpoints*

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

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

117 *iv. Measures to prevent adverse effects*

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

129

130 **STUDY POPULATION**

131

132 *i. Inclusion criteria:*

- 133 • Age \geq 6 months and $<$ 12 years
- 134 • Need of hospital treatment and IV rehydration in any pediatric ward

135 *ii. Exclusion criteria:*

- 136 • Na $<$ 130 or $>$ 150
- 137 • K $<$ 3
- 138 • Need of 10% glucose solution as initial fluid
- 139 • Diabetes
- 140 • Diabetes insipidus
- 141 • Ketoacidosis
- 142 • Kidney disease requiring dialysis
- 143 • Severe liver disease
- 144 • Metabolic disease that requires rehydration according to protocol
- 145 • Leukemia or other malignancy that requires rehydration according to protocol

146 *iii. Sample size*

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

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157

158 **FOLLOW-UP AND LABORATORY SAMPLES**

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

181

182 **FLUID PRODUCTS AND THEIR ADMINISTRATION**

183 Plasmalyte Glucos 50 mg/mL contains sodium 140 mmol/l, potassium 5 mmol/L, chloride 98
184 mmol/L, magnesium 1.5 mmol/L, acetate 27 mmol/L and gluconate 23 mmol/L. Plasmalyte Glucos
185 50 mg/mL has a pH of about 7.4 (6.5–8.0). The semi-physiological fluid is made with 5% glucose
186 with the addition of sodium chloride 80 mmol/L and potassium chloride 20 mmol/L. The amount of
187 fluid and the infusion rate are calculated based on the child's weight using the Formula of Holliday-
188 Segar (fluid requirement 100 mL/kg <10 kg, 1,000 mL + 50 mL/kg > 10 kg, > 20 kg 1,500 ml + 20
189 mL/kg > 20 kg). Potential correction of dehydration is calculated based on estimated weight loss.
190 Based on assessment by the physician on call, fluid replacement with 20 mg/kg Ringer solution
191 may be given before the onset of study fluid administration for the study patients.

192

193 **STATISTICAL ANALYSIS PLAN**

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

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

204

205 The occurrence of any clinically significant electrolyte disorder in children receiving isotonic fluid
206 therapy was estimated to be at least 13% based on a previous study reporting the need of adding
207 potassium in plasma-like fluid in children (17). We considered the difference between groups to be
208 clinically significant if the occurrence of electrolyte disorder would be 7% lower in children
209 receiving moderately hypotonic fluid. We set alpha error at 5% and beta error at 20%, i.e. power of
210 80%, which resulted in 275 children/group. To make sure that the final analysis included the
211 required number of children with measured primary outcome, we decided to recruit 300
212 children/group.

213

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

229

230 **STUDY ORGANIZATION, FUNDING AND SCHEDULE**

231 The study is an independent investigator-driven study. Saara Lehtiranta, MD, is a pediatric resident.
232 In addition to her day job, she does research on fluid therapy in children at the Department of
233 Children and Adolescents of Oulu University Hospital under the guidance of Docent Terhi
234 Tapiainen, Ass. Professor of Pediatrics, Oulu University Hospital. All members of the study team
235 are employed in the units indicated on the title page. Funding is applied from various foundations to
236 enable personal full-time research months (Saara Lehtiranta, MD). The study commenced in spring
237 2016 and is expected to last 1.5–2 years.

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240 **ETHICAL CONSIDERATIONS AND STUDY REGISTRATION**

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

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

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

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

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267

268 **CLINICAL SIGNIFICANCE OF THE STUDY**

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

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369 intravenous fluid therapy of sick children, has given rise to debate in recent years. A healthy body is
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371 secretion of antidiuretic hormone (ADH) may cause accumulation of fluid in the body, which
372 results in hyponatremia (Kataja 2015, Wang et al. 2014). Potential and even life-threatening
373 complications of severe hyponatremia include seizures and hyponatremic encephalopathy (Moritz
374 & Ayus 2010, Sarnaik et al. 1991).

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376 *Previous randomized controlled clinical studies*

377 *Addition Aug 2019: Full updated literature review is presented as a separate summary table.* In
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380 therapy in children (Pemde et al. 2015, Shamim et al. 2014, Choong et al. 2011, Rey et al. 2011,
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407 particularly important in the case of acute gastroenteritis because there may be a substantial loss of
408 potassium if the infection persists for several days. There is thus a potential risk of hypokalemia
409 when using isotonic solutions that contain low levels of potassium in IV fluid therapy. In the study
410 of McNab et al. (2015), extra potassium was added to the fluids for 13% of the patients.

411

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

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

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

431

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434 the fluid therapy of acutely sick children. The first IV fluid is a readymade isotonic solution,
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444 signed consent forms are stored in the upper cabinet in the doctor's office in the ER.

445

- 446 v. *Randomization*
- 447 The patients who have or whose parents have given a written consent to participate in
- 448 the study are randomized into two groups. The following treatments are compared:
- 449 • Isotonic fluid (readymade solution Plasmalyte Glucos 50 mg/mL, with Na 140
- 450 mmol/L, K 5 mmol/L and Cl 98 mmol/L)
- 451 • Semi-physiological fluid (G5%, to which NaCl 80 mmol/L and KCl 20 mmol/L is
- 452 added)
- 453 The current standard of care is based on a local model which has not been scientifically
- 454 evaluated and is associated with a significant possibility for calculation errors, as shown
- 455 by a survey we conducted among the physicians in our clinic. The current standard of
- 456 care is thus not comparable in this study as its safety has not been established and it is
- 457 not evidence-based.
- 458 vi. *Blinding*
- 459 This is an open label study because the endpoints can be objectively measured. Thanks
- 460 to the open label design, the treating physician is also aware of the electrolyte
- 461 concentrations of the fluids and can make adjustments to them if necessary.
- 462 vii. *Endpoints*
- 463 • Primary: hypokalemia < 3.5
- 464 • Secondary: hyponatremia (< 132), hypernatremia (> 148), weight gain, change of
- 465 maintenance fluid, added sodium and potassium, duration of fluid therapy during
- 466 hospital treatment within 7 days of admittance, admittance to intensive care, duration
- 467 of hospital treatment
- 468 • *Addition 4 Feb 2019: Secondary: effect of fluid therapy on ADH secretion*
- 469 *(copeptin), readmittance to ER and/or ward following discharge, deaths over a*
- 470 *period of 30 days*
- 471 viii. *Measures to prevent adverse effects*
- 472 Before the onset of fluid therapy, blood electrolytes are measured from venous blood
- 473 samples taken in connection with cannula insertion from all patients taking part in the
- 474 study. In all patients, electrolytes are analyzed from venous blood samples taken in the
- 475 morning while in hospital. Based on the assessment of the physician on call, electrolytes
- 476 can be measured in the evening as well, especially if the patient has repeated fluid loss
- 477 during the treatment, or if the time between the onset of fluid therapy and the blood
- 478 sampling the next morning is long. Any other additional blood samples required can be
- 479 taken as capillary samples. The treating physician has the right to withdraw
- 480 administration of study fluid and treat the patient with the fluids he/she considers best.
- 481 The treating physician may also increase or decrease the amount of electrolytes in the
- 482 fluid.
- 483 ix. *Addition 4 Feb 2019: Determination of copeptin in the assessment of fluid retention due*
- 484 *to excess sodium input. Copeptin is measured in a random sample of study patients who*
- 485 *receive IV fluid therapy. All plasma samples are frozen during the study and the random*
- 486 *sample will be retrieved from the frozen samples.*
- 487

488 **STUDY POPULATION**

489

490 *iv. Inclusion criteria:*

- 491 • Age \geq 6 months and $<$ 12 years
- 492 • Need of hospital treatment and IV rehydration in any pediatric ward

493 *v. Exclusion criteria:*

- 494 • Na $<$ 130 or $>$ 150
- 495 • K $<$ 3
- 496 • Need of 10% glucose solution as initial fluid
- 497 • Diabetes
- 498 • Diabetes insipidus
- 499 • Ketoacidosis
- 500 • Kidney disease requiring dialysis
- 501 • Severe liver disease
- 502 • Metabolic disease that requires rehydration according to protocol
- 503 • Leukemia or other malignancy that requires rehydration according to protocol

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

505 *vi. Sample size*

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

516

517

518 **FOLLOW-UP AND LABORATORY SAMPLES**

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

- 531 • Pathogens are investigated according to current practice in all patients with infections. In
532 patients with acute gastroenteritis, the presence of adeno, rota and noro viruses in the feces
533 is investigated. Patients with respiratory infections are investigated for the presence of
534 influenza and RSV virus; if necessary, a more extensive viral analysis of a nasopharyngeal
535 sample is undertaken.
- 536 • The following are recorded in the medical record: fever, oral fluid therapy, IV fluid therapy,
537 vomiting, diarrhea and weight (every morning and at discharge). At the end of the treatment
538 period, the recordings of oral and IV fluids are scanned into the medical record.
- 539 • Data on patients entering the study is collected regularly (weekly) by investigators from
540 medical records and entered into SPSS.

541

542 **FLUID PRODUCTS AND THEIR ADMINISTRATION**

543 Plasmalyte Glucos 50 mg/mL contains sodium 140 mmol/l, potassium 5 mmol/L, chloride 98
544 mmol/L, magnesium 1.5 mmol/L, acetate 27 mmol/L and gluconate 23 mmol/L. Plasmalyte Glucos
545 50 mg/mL has a pH of about 7.4 (6.5–8.0). The semi-physiological fluid is made with 5% glucose
546 with the addition of sodium chloride 80 mmol/L and potassium chloride 20 mmol/L. The amount of
547 fluid and the infusion rate are calculated based on the child's weight using the Formula of Holliday-
548 Segar (fluid requirement 100 mL/kg <10 kg, 1,000 mL + 50 mL/kg > 10 kg, > 20 kg 1,500 ml + 20
549 mL/kg > 20 kg). Potential correction of dehydration is calculated based on estimated weight loss.
550 Based on assessment by the physician on call, fluid replacement with 20 mg/kg Ringer solution
551 may be given before the onset of study fluid administration for the study patients. *Addition 4 Oct*
552 *2016: Other crystalloids such as physiological saline or Plasmalyte may also be used for fluid*
553 *replacement.*

554

555 **STATISTICAL ANALYSIS PLAN**

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

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

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

572 *Addition 15 Nov 2019. Post hoc analysis regarding the proportion of children with low pH value*
573 *<7.35, low base excess <-2.5 and low bicarbonate <21 on day 1 is added after pediatric*

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

576

577 The occurrence of any clinically significant electrolyte disorder in children receiving isotonic fluid
578 therapy was estimated to be at least 13% based on a previous study reporting the need of adding
579 potassium in plasma-like fluid in children (17). We considered the difference between groups to be
580 clinically significant if the occurrence of electrolyte disorder would be 7% lower in children
581 receiving moderately hypotonic fluid. We set alpha error at 5% and beta error at 20%, i.e. power of
582 80%, which resulted in 275 children/group. To make sure that the final analysis included the
583 required number of children with measured primary outcome, we decided to recruit 300
584 children/group.

585

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

601

602 **STUDY ORGANIZATION, FUNDING AND SCHEDULE**

603 The study is an independent investigator-driven study. Saara Lehtiranta, MD, is a pediatric resident.
604 In addition to her day job, she does research on fluid therapy in children at the Department of
605 Children and Adolescents of Oulu University Hospital under the guidance of Docent Terhi
606 Tapiainen, Ass. Professor of Pediatrics, Oulu University Hospital. All members of the study team
607 are employed in the units indicated on the title page. Funding is applied from various foundations to
608 enable personal full-time research months (Saara Lehtiranta, MD). The study commenced in spring
609 2016 and is expected to last 1.5–2 years.

610

611

612 **ETHICAL CONSIDERATIONS AND STUDY REGISTRATION**

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

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

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

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

638

639 *Additions in 2016:*

- 640 1) *Ethical Committee of Oulu University Hospital reviewed the study protocol prior to study in*
641 *2016, with a decision number EETTMK 48/2016*
- 642 2) *Finnish Medical Agency (FIMEA) reviewed and accepted the study protocol prior to the*
643 *study in 2016, with a EUDRA-CT number 2016-002046.*
- 644 3) *Study was registered using ClinicalTrials.gov prior to the recruitment period, with number*
645 *NCT02926989*

646

647

648 **CLINICAL SIGNIFICANCE OF THE STUDY**

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

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

658

659

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715

716 **AMENDMENTS**

717

718 *Additions in Sep 2016:*

719 *Ethical Committee of Oulu University Hospital reviewed the study protocol prior to study in 2016,*
720 *with a decision number EETTMK 48/2016*

721 *Finnish Medical Agency (FIMEA) reviewed and accepted the study protocol prior to the study in*
722 *2016, with a EUDRA-CT number 2016-002046.*

723 *Study was registered using ClinicalTrials.gov prior to the recruitment period, with number*
724 *NCT02926989*

725

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

727

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

730

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

734

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

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

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

754

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

757

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

762

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

767

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

771

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

773

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

777

778 *Addition 15 Nov 2019. **Post hoc analysis** regarding the proportion of children with low pH value*
779 *<7.35, low base excess <-2.5 and low bicarbonate <21 on day 1 is added after pediatric*
780 *anesthesiologist department at Oulu Univ Hospital gave comments for the manuscript since*
781 *acidosis and alkalosis may have an impact on the electrolyte balance.*

782