

The Tolerability and Efficacy of Oral Isotonic Solution versus Plain Water in Dengue Patients: A Randomized Clinical Trial

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Abstract

Background: Plasma leakage plays an important role in dengue infection, and this condition can lead to hemoconcentration, hypovolemia, and shock. Fluid replacement is the main treatment for dengue. There is a lack of evidence to support certain oral fluid therapy as a treatment for dengue patients. **Objectives:** The objective of this study is to evaluate tolerability and efficacy of oral isotonic solution (OIS) compared to plain water as a fluid replacement in dengue patients. **Materials and Methods:** A randomized, clinical trial with single-blinded groups was conducted to compare tolerability and efficacy of OIS and plain water in dengue patients. We evaluated gastrointestinal disturbances (nausea, vomiting, and bloating), body temperature, mean arterial pressure (MAP), fluid balance, hematocrit, Na⁺, and K⁺ levels. Data were analyzed with SPSS 20.0, and figures were made with GraphPad Prism version 5.01. **Results:** Twenty four subjects were included and divided equally into two groups. Our results showed that there are no significant differences but indicate several noteworthy trends. The intervention group (OIS) experienced less nausea, less vomiting, had positive fluid balance and higher MAP, and became afebrile faster compared to the control group (plain water). **Conclusion:** Although not statistically significant, this study shows the trend that OIS is well-tolerated and effective for dengue patients compared to plain water.

Keywords: Dengue, oral fluid therapy, oral isotonic solution, plain water, randomized clinical trial

INTRODUCTION

Dengue infection manifestations vary from dengue fever (DF) to dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS), and death. The severity of the disease is mainly dependent on the amount of plasma leakage, which is shown through hemoconcentration, decreased level of albumin, and/or accumulation of fluid in the pleura, pericardial, and peritoneal cavities.^[1-4]

The main treatment of dengue infection is fluid replacement therapy. The 2009 World Health Organization (WHO) guidelines classify dengue patients into Group A, B, and C according to disease severity and management approach. The guidelines state that not all dengue patients need hospitalization and oral fluid administration has a place, especially for patients in group A and a portion of group B.^[3,5]

The lack of evidence to support the oral fluid administration in addition to gastrointestinal disturbances lead to overtreatment of patients with mild dengue that can be treated with oral

fluid therapy. Previous study concluded that oral fluid intakes during the 24 h before being seen by a physician was statistically associated with decreased risk for hospitalization.^[6] The majority of those patients ingested plain water (70%). Interestingly, the 2011 WHO guidelines do not recommend plain water as an oral fluid therapy.^[7] To the best of our knowledge, there is no clinical trial that evaluates oral isotonic solution (OIS) with plain water as an oral fluid therapy for dengue. Our study is performed to investigate the tolerability and efficacy of OIS compared to plain water in managing dengue patients.

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MATERIALS AND METHODS

Sampling and subjects

This study is a randomized, clinical trial with single-blinded, parallel groups which was conducted in Jakarta, Indonesia from June to September 2014. This study is a pilot study, and the minimum amount of sample needed is 12 subjects per treatment arm.^[8]

The inclusion criteria are dengue patients with no warning signs, age >18 years, having fever <48 h, able to tolerate an adequate volume of oral fluids, positive dengue NS 1 antigen test and confirmed by polymerase chain reaction (PCR), and agreed to participate in the study. The exclusion criteria were subject develop severe dengue (DSS), pregnant/lactating, having menstrual cycle during the study period, hematologic disease, chronic disease, immune disorder, and malignancy. Eligible subjects were included from patients that visited a community health center (“Puskesmas”) in Jakarta and subsequently were admitted and monitored at Cipto Mangunkusumo Hospital.

Intervention protocol

Participants were randomized using a block random allocation scheme with blocks of size 4 stratified by a nurse that is not involved in the study to 2 treatment arms. The intervention group received OIS, and the control group received oral plain water which were put into identical tumbler. None of the researchers knows what the tumbler contains. The volume of oral fluids received was *ad libitum*. The OIS beverage composed of Na⁺ 21 mEq/L, K⁺ 5 mEq/L, Ca²⁺ 1 mEq/L, Mg²⁺ 0.5 mEq/L, Cl⁻ 16 mEq/L, citrate³⁻ 10 mEq/L, and lactate 1 mEq/L, which is a standard formulation from a company.^[9] To anticipate sudden changes of blood pressure, both groups received 500 ml of maintenance Ringer Lactate intravenously per day and continued until subjects were discharged. During hospitalization, if any of the subjects have one or more of these signs (inadequate oral intake, bleeding, increased hematocrit tendency, shock, seizure, decreased consciousness, and thrombocyte count < 100,000/ μ L), they will be treated according to the 2005 Indonesian Ministry of Health Guidelines for DHF. Tolerability was determined by observing nausea, vomiting, bloating, and oral fluid intake; efficacy was determined by body temperature, hematocrit, mean arterial pressure (MAP), fluid balance (oral and parenteral fluid intake minus urine output), Na⁺, and K⁺ every 24 h. For hematocrit, more frequent measurements were done if there was a tendency to increase.

Laboratory assays

Dengue NS1 antigen test (Panbio) was used to diagnose dengue. Detection of DENV RNA was performed with reverse transcription-PCR method as previously described.^[10] RNA was extracted from 140 μ l of plasma using QIAamp viral RNA mini kit (Qiagen, Germany) according to the manufacturer’s instructions. Examination of blood parameters was performed using an automatic hematology analyzer (Sysmex, Japan).

Blood electrolytes were determined using an automatic chemical analysis Cobas 501 (Roche, Germany).

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (IBM, USA) and presented into descriptive and analytical approaches through General Linear Model to assess daily measurement results, and unpaired-*t*, Mann–Whitney, and Chi-square tests to confirm the differences of the effect of intervention. Figures were made with GraphPad Prism version 5.01 (GraphPad Software, Inc., USA). Data were presented as an absolute number due to the small sample size.

Ethical approval

The study protocol was approved by the Medical Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia–Cipto Mangunkusumo Hospital (No. 429/H2.F1/ETIK/2013). Each patient received information before giving signature of consent according to the Helsinki Declaration of 1975.

RESULTS

General characteristics of study participants

Twenty-four participants were included in this study. General characteristics of the subjects can be found in Table 1. The length of stay of the control group was longer than the intervention group. There were seven patients in the control group and five patients in the intervention group classified as DHF. There was neither drop out patient nor deteriorated into shock or death during hospitalization.

Clinical outcome differences

There were some differences in gastrointestinal signs and symptoms between groups although not statistically significant.

Table 1: General characteristic of the study groups at admission

Variables	Control group (n=12)	Intervention group (n=12)	P
Age (years)	23.9 \pm 6.5 [#]	21.5 (18-52)*	0.443 (mw)
Gender			
Female	8	6	0.408 (x)
Male	4	6	
Length of stay (days)	6.1 \pm 2.4 [#]	5.7 \pm 0.9 [#]	0.582 (t)
Diagnosis			
DF	5	7	0.684 (x)
DHF	7	5	
Body temperature ($^{\circ}$ C)	37.5 \pm 0.6 [#]	38.0 \pm 0.7 [#]	0.091 (t)
Mean arterial pressure (mmHg)	83.3 (80–93)*	88.7 \pm 10.1 [#]	0.443 (mw)
Hemoglobin (mg/dl)	13.4 \pm 1.6 [#]	13.6 \pm 1.7	0.832 (t)
Hematocrit (vol%)	38.6 \pm 4.3 [#]	39.2 \pm 4.4 [#]	0.735 (t)
Sodium (mEq/l)	135 (124-138)*	134.9 \pm 3.6 [#]	0.378 (mw)
Potassium (mEq/l)	3.3 \pm 0.3 [#]	3.0 \pm 0.29 [#]	0.034 (t)

[#]Mean \pm SD, *Median (minimum–maximum). mw: Mann-Whitney test, t: Unpaired *t*-test, x: Chi-square test, DF: Dengue fever, DHF: Dengue hemorrhagic fever, SD: Standard deviation

Nausea and vomiting were less frequent in the intervention group compared to the control group. On the other hand, bloating was more frequent in the intervention group compared to the control group.

The differences in body temperature between groups were not significant ($P = 0.218$). Body temperature in the control group was higher compared to the intervention group up to the 5th day of fever [Figure 1a]. Meanwhile, the intervention group's initial average temperature was 37.83°C and subsequently decreased to a normal limit.

There were no significant differences in MAP values between groups ($P = 0.711$) although the intervention group had a slightly higher and stable values [Figure 1b]. In addition, there were no significant differences in fluid balance [Table 2]. The amount of oral fluid intake in the intervention group showed an increment pattern. The Intervention group received fewer intravenous fluid and higher oral fluid intake compared to the control group. In general, the intervention group had a greater positive fluid balance in comparison, especially from day 2 to day 5 of illness.

Laboratory parameters

There were no significant differences in the hematocrit level

between groups ($P = 0.60$) [Figure 1c]. The Control group's initial level (38.61 vol%) was lower from intervention group (39.22 vol%) and both groups experienced fluctuation of hematocrit level during the study.

Differences in the blood electrolytes were not significant between groups (sodium $P = 0.707$; potassium $P = 0.581$). Nevertheless, the intervention group showed a consistent upward trend after a mild hyponatremia at the beginning [Figure 1d]. Both groups showed an increase trend lasting till the end of the treatment for the potassium levels from a hypokalemic state [Figure 1e].

DISCUSSION

This present study evaluated several parameters regarding the tolerability and efficacy of OIS versus plain water in dengue. According to the 2009 WHO guidelines, group A and a portion of group B dengue patients do not require intravenous fluid therapy and are able to receive oral fluid therapy.^[3] In the 2011 guidelines, dengue patients are advised to take several oral solutions instead of plain water as a fluid treatment.^[7] Nevertheless, there is a lack of evidence to support this recommendation.

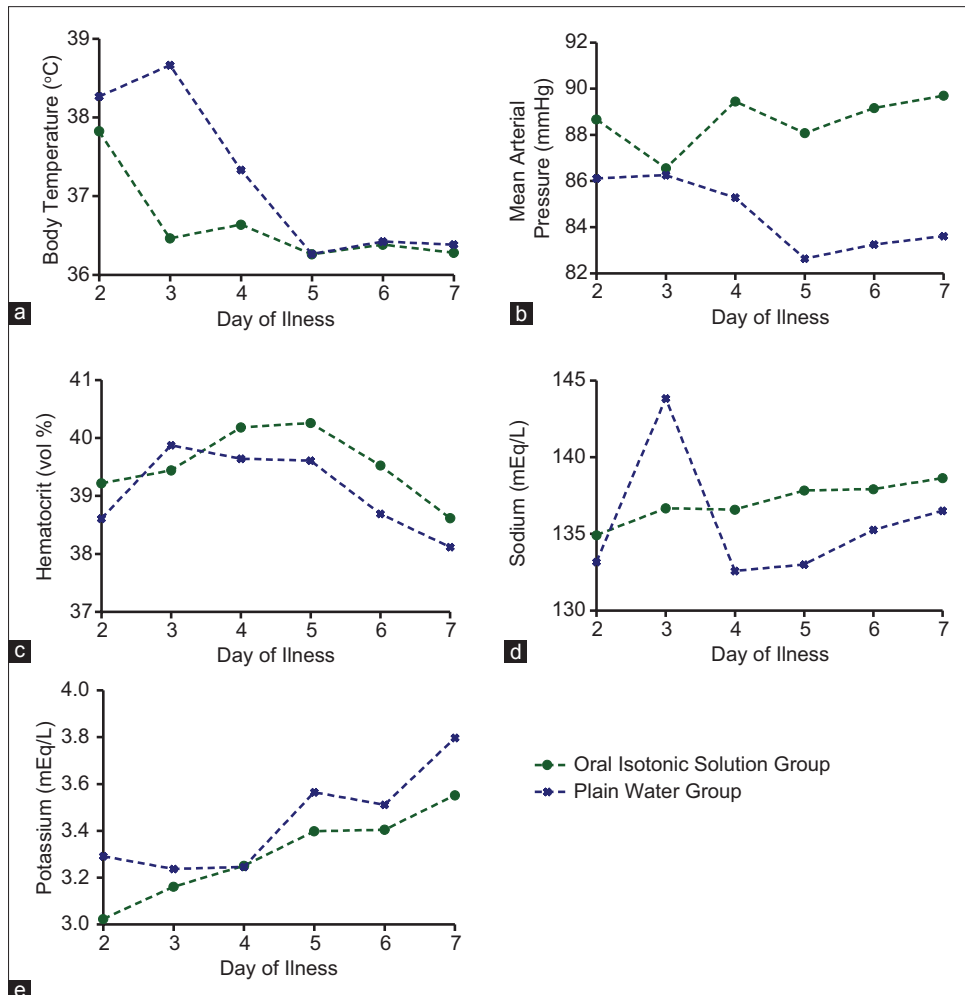


Figure 1: Clinical and laboratory parameters of dengue patients treated with oral isotonic solution (OIS) or plain water. (a) Body temperature, (b) mean arterial pressure, (c) hematocrit, (d) sodium, and (e) potassium levels were evaluated from day 2 till day 7 of the disease. Data are depicted as mean

Table 2: Fluid balance parameters of the participants

Variables at specific day of illness	Control group (n=12)	Intervention group (n=12)	P
Parenteral fluid intake (ml)			
Day 2	500 (500–2000)*	500 (300–3800)*	0.748 (mw)
Day 3	950±734 [#]	1000 (500–4160)*	0.160 (mw)
Day 4	1691±599 [#]	1715±1082 [#]	0.949 (t)
Day 5	1775±539 [#]	1750±969 [#]	0.938 (t)
Day 6	1729±966 [#]	1448±1060 [#]	0.505 (t)
Day 7	1793±949 [#]	1336±839 [#]	0.282 (t)
Oral fluid intake (ml)			
Day 2	2107±1415 [#]	1000 (450–5000)*	0.478 (mw)
Day 3	2807±1514 [#]	2627±1209 [#]	0.750 (t)
Day 4	2570 (1500–5900)*	2870±1089 [#]	0.514 (mw)
Day 5	3325 (2000–6180)*	2700 (1000–8700)*	0.060 (mw)
Day 6	2992±1122 [#]	3276±1718 [#]	0.637 (t)
Day 7	2610 (1950–4090)*	2734±1447 [#]	0.840 (mw)
Urine output (ml)			
Day 2	2037±1182 [#]	1582±902 [#]	0.323 (t)
Day 3	2367±1208 [#]	2024±1006 [#]	0.526 (t)
Day 4	2675±1241 [#]	2379±1325 [#]	0.578 (t)
Day 5	3325±1324 [#]	2649±1758 [#]	0.299 (t)
Day 6	2936±1375 [#]	2986±1499 [#]	0.934 (t)
Day 7	3383±738 [#]	2548±1460 [#]	0.158 (t)
Fluid balance (ml)			
Day 2	800 (100–3100)*	1005±924 [#]	0.880 (mw)
Day 3	1390±1180 [#]	2053±1177 [#]	0.182 (t)
Day 4	2150±967 [#]	2206±1850 [#]	0.927 (t)
Day 5	1875±1646 [#]	2075±1818 [#]	0.781 (t)
Day 6	1785±1304 [#]	1738±1530 [#]	0.937 (t)
Day 7	1725±1034 [#]	1522±1282 [#]	0.718 (t)

[#]Mean±SD, *Median (minimum–maximum). mw: Mann–Whitney test, t: Unpaired t-test, SD: Standard deviation

The use of oral hydration therapy in dengue patients has been previously studied. A study in Nicaragua showed that oral fluid intake during the 24 hours before being seen by a clinician was associated with reduced risk for hospitalization.^[6] Another study also showed that oral hydration may be as effective as intravenous fluid replacement for nonshock DHF adult patients.^[11] Soo^[5] also reported two cases with plasma leakage which were successfully treated with adequate oral fluid therapy during the critical phase. Nonetheless, there is no clinical trial that evaluates different oral fluid solutions for dengue patients.

Our data showed that there are no significant statistical differences between OIS and plain water for dengue. Nevertheless, we describe several noteworthy observations. We found less nausea and vomiting in the intervention group. This group also showed an increase in the fluid intake and a decrease in parenteral fluid administration after day 5 of the illness. These data indicate that most of the subjects were able to tolerate OIS better than plain water. Nevertheless, some patients experienced bloating which may be due to the citrate content.

Body temperature showed a lower trend in the intervention group. Casa *et al.*^[12] showed that OIS caused body temperatures to cool down. They explained that previously cooled fluid taken

with oral route could decrease core body temperature. In our study, the rapid decrease of temperature in the intervention group implies that OIS might decrease fever more effectively than plain water. In addition, we observed that MAP in both groups was within normal limits, which suggest that oral fluid is adequate to maintain blood pressure in dengue. Moreover, MAP in the intervention group was higher and showed more stable curve.

Plasma leakage in dengue may be detected from an increasing of hematocrit levels. Hematocrit of both groups was within normal limits. However, we found that hematocrit levels in the intervention group were higher than the control group. This result may be explained by the higher baseline level of the intervention group compared to the control group.

In dengue patients, sodium level is lower compared to healthy individuals.^[13] Hyponatremia occurs more frequently in DHF than in DF.^[14] Our study observed that the sodium levels of both groups were within normal limits. However, the control group generally had lower sodium levels compared to the intervention group, probably due to the low-sodium content in plain water. Although within normal limits, the intervention group's fluid balance was higher than the control group. Thus, there may be a connection between fluid balance, MAP, and serum sodium levels. The presence of sodium and glucose in OIS increase

water absorption in the small intestine, subsequently increasing the amount of intravascular volume and creating a stable blood pressure. On the other hand, the presence of sodium could increase thirst, prompt more oral intake, and attain quick rehydration.^[15]

Potassium levels in both groups showed hypokalemic state. This is consistent with the previous reports which showed that dengue patients had a significant lower potassium levels compared to healthy individuals.^[3] Inadequate dietary intake as well as release of potassium into the extracellular compartment during infection can cause hypokalemia.^[16] Although the intervention group had lower potassium levels, the values were increasing steadily compared to the control group.

A major limitation in our study is the small sample size. This may explain the nonsignificant differences of the parameters that were evaluated in this study. A larger study is needed to confirm our data.

CONCLUSION

This study broadens the perspective regarding the type of oral fluid used in managing dengue infection. Although the differences were not significant, this small study shows the trend that OIS is well-tolerated and effective for dengue patients compared to plain water. Further study needs to be performed to confirm our findings.

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Conflicts of interest

The authors received consultation fee from PT. Amerta Indah Otsuka.

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