RESEARCH ARTICLE

Comparison between Blood Electrolyte and Ketonuria Pre- and Post- 5% Dextrose—Ringer's Lactate Rehydration Compared with Ringer's Lactate on Grade II Hyperemesis Gravidarum

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Abstract

Aim and objective: To compare 5% dextrose–Ringer's lactate against Ringer's lactate solution in the intravenous rehydration of grade II hyperemesis gravidarum.

Materials and methods: The research was conducted in Wahidin Sudirohusodo Hospital and the network education hospitals, using the prospective cohort method. The total samples were 66 subjects meeting the criteria and randomly assigned to receive either the 5% dextrose–Ringer's lactate or Ringer's lactate group by intravenous infusion at a rate of 125 mL/hour over 24 hours in a randomized clinical trial. All participants received neurotropic and antiemetics intravenously as well. Oral intake was not allowed. Primary outcomes were resolution of blood electrolytes and ketonuria after 24 hours.

Results: There was a significant increase of the levels of blood electrolyte (hyponatremia, hypokalemia, and hypochloremia) and resolution of ketonuria after the first 24 hours of both groups. Yet, the mean increase of the levels of the blood electrolyte and resolution of ketonuria was insignificant for both groups; however, the increase of the blood electrolyte potassium level was greater in the group treated with 5% dextrose–Ringer's lactate. At the value of 95% CI, the mean increase of the blood potassium levels in the 5% dextrose–Ringer's lactate group and Ringer's lactate was 0.31 and 0.20 mmol/L, respectively (*p* 0.044).

Conclusion: Intravenous rehydration with 5% dextrose–Ringer's lactate or Ringer's lactate solution in women hospitalized for grade II hyperemesis gravidarum produced similar outcomes, other than that for the greater value of potassium electrolyte in 5% dextrose–Ringer's lactate group.

Keywords: Hyperemesis gravidarum, Randomized clinical trial, Rehydration therapy, Ringer's lactate, Ringer's lactate—5% dextrose.

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Introduction

About 50–90% of all pregnancies are accompanied by nausea and vomiting. The condition is usually self-limiting and peaks at around 9 weeks' gestation. At 20 weeks, symptoms typically cease. However, in up to 20% of cases, nausea and vomiting may continue until delivery. In about 35% of women who have this condition, nausea and vomiting are clinically significant, resulting in lost work time and negatively affecting family relationships. In a small minority of patients, the symptoms lead to dehydration and weight loss requiring hospitalization. This condition called hyperemesis gravidarum, and characterized by persistent vomiting, weight loss of >5%, ketonuria, electrolyte abnormalities (hypokalemia), and dehydration.[1] The reported incidence of hyperemesis gravidarum is 0.3–2%, causing the women to be hospitalized. Hyperemesis gravidarum rarely cause death, but the incidence is still high.[2]

The etiology of hyperemesis in pregnancy is unknown, although some biological, and psychological as well as sociocultural factors are thought to be contributory factors. Human chorionic gonadotropin (hCG) is the most likely endocrine factor which accounts for the development of HG. This conclusion is based on observed associations between increased production of hCG (as in molar or in multiple pregnancies) and the fact that the incidence of hyperemesis is highest at the time when hCG production reaches its peak during pregnancy (around 9 weeks' gestation). Women with multiple pregnancies or hydatidiform mole pregnancy are known to have higher hCG level than the other pregnant women with worse nausea and vomiting symptoms.[3,4] Several hormones may cause hyperemesis. Estrogen is also thought to cause nausea and vomiting by inhibiting gastric motility and smooth muscle contraction rhythm. Decreased thyroid-stimulating hormone (TSH) level on early pregnancy is also associated with hyperemesis gravidarum, even though the exact mechanism is still unknown.[5]

Prolonged vomiting accompanied by decreased water intake can cause dehydration and electrolyte imbalance, such

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as decreased sodium, chloride, and potassium level, resulting in metabolic alkalosis state (hypochloremia with hyponatremia and hypokalemia), so it is important to measure electrolyte level on hyperemesis gravidarum. If continues, the patient can suffer from shock. Prolonged dehydration can also inhibit fetal growth.[4] Severe hyperemesis gravidarum can make the patient cannot consume oral intakes, so the carbohydrate reserves will be used up for tissue energy needs, as the result body fat/lipid will be oxidized. Ketonemia and resultant ketonuria is the consequence of the switch to an alternative energy source when dietary glucose is insufficient for metabolic needs.[6]

Hyperemesis gravidarum can seriously impact mothers and fetus health. Its main management is rehydration with physiological fluids (sodium chloride) or Ringer's lactate and food termination for 24–48 hours, and given antiemetics as needed. The addition of glucose, multivitamins, magnesium, pyridoxine, or thiamine should be considered. Treatment with dextrose fluid can stop lipid oxidation.[7] Management should be continued until the patient can tolerate oral fluids and there is improvement in laboratory results.[8]

To the best of our knowledge, intravenous rehydration regimes in the management of hyperemesis gravidarum have not been previously studied. There is only one study conducted by Tan et al. in 2013 at Kuala Lumpur University Hospital, Malaysia which compares dextrose saline (NaCl 0.9% and D5%) and normal saline (NaCl 0.9%) with no differences in outcome. This research is expected to provide scientific information about blood electrolyte level and ketonuria in patients with hyperemesis gravidarum and eventually can be a consideration material in giving appropriate fluid management. Based on those background, this study's objective is to evaluate the effect of blood electrolyte level and ketonuria in hyperemesis gravidarum patients treated with either Ringer's lactate or Ringer's lactate combined with dextrose 5%.

Materials and Methods

Location and Study Period

This research was conducted in Obstetrics and Gynecology Department of Hasanuddin Medical Faculty, Dr Wahidin Sudirohusodo Hospital and the network education hospital in Makassar. The study was conducted from February 2015 until the number of samples are met.

Design

This research use the double-blind randomized clinical trial design.

Population and Sample

Participants were recruited by healthcare providers as they were admitted to the gynecology ward. Research population were all patients diagnosed with grade II hyperemesis gravidarum and hospitalized in Dr Wahidin Sudirohusodo Hospital, Makassar and the network education hospitals. Study samples were all patients diagnosed with grade II hyperemesis gravidarum who fulfilled the inclusion criteria and have signed informed consent to participate in the study. The number of samples is 66 people, divided into two groups of pregnant women who were treated with Ringer's lactate or Ringer's lactate combined with D5%.

The inclusion criteria of this study: voluntarily participate in the study; aged ≥18 years with gestational age <20 weeks (Naegele formula); single, alive pregnancy; not a hydatidiform mole pregnancy; do not suffer from diarrhea; body mass index (BMI) 18.5–22.9 kg/m^2; blood glucose level ≤200 mg/dL; ketonuria ≥+1; and no history of gastritis and drug abuse. The exclusion criteria: the blood sample lysis; incomplete data and does not follow the entire procedure; or if the patients had a specific reason to resign from the study.

Data Collection Method

Subjects who met the criteria will be stratified by its clinical stage. Researchers then explain the purpose and the objective of the research to the patients who participated in the study. Participants who agreed to participate signed the informed consent and fill out the questionnaire sheet that has been provided which consist of history taking, physical examination, and additional examinations. Urine sample obtained by taking 30 cc of patients' urine which were accommodated in a tube. Blood sample is obtained by taking 5 cc of blood from the antecubital vein using a disposable syringe without the use of anticlotting agent and then sent to the laboratory.

Data Analysis

We performed statistical analysis using paired *t* test, independent *t* test, and Mann–Whitney test with significance level of *p* value < 0.05 (data processing using SPSS for Windows).

Results

We have conducted double-blind randomized clinical trial to evaluate the effect of fluid therapy using Ringer's lactate and Ringer's lactate combined with dextrose 5% on blood electrolyte level and ketonuria in patients with hyperemesis gravidarum. The study involved 66 people which then divided into two groups. Based on the age, majority of the events was found in age group 20–35 years (72.7%). In terms of education, the majority of the study sample are educated, with the majority result is senior high school educated (45.5%). Based on gravidity, the majority is primigravida (48.5%). While the majority of the gestational age is 9–10 weeks (30.3%) (Table 1).

Majority of patients suffered from hyponatremia conditions (87.9%), hypokalemia (53%), normochloremia (80.3%), and all levels of ketonuria are not normal (100%) with the majority is +2 (Table 2).

Figure 1 demonstrated a significant reduction in ketonuria level after treatment either with Ringer's lactate as well as Ringer's lactate + D5% (*p* 0.000 and *p* 0.009). Respondents who have abnormal ketonuria level reduced from 33 respondents (100%) to 6 (18.2%) and 9 respondents (27.3%).

Table 3 described the significant increase in electrolytes level (sodium, potassium, and chloride) in blood before and after treatment either with Ringer's lactate or Ringer's lactate + D5% (*p* 0.000 and *p* 0.001). Based on those results, we found that there was not any differences in the mean increase of sodium and chloride blood level and decreased ketonuria level in Ringer's lactate and Ringer's lactate + D5% (*p* 0.348 and *p* 0.545). While the average increase in blood potassium level differs between Ringer's lactate therapy and Ringer's lactate + D5%, where the improvement was higher in Ringer's lactate + D5% therapy. This table shows that there is no differences in ketonuria level decrement either from Ringer's lactate and Ringer's lactate + D5% therapy (*p* 0.108) (Table 4).

Discussion

This study shows various characteristic distributions of grade II hyperemesis gravidarum patients. Most patients with hyperemesis come from the age group 20–35 years. This result consistent with research conducted by Bailit that the average age of patients who

Table 1: Respondents' characteristics distribution

	Group						
	RL		RL + D5%		Total		
Characteristic	*n*	*%*	*n*	*%*	*n*	*%*	*p value*
Age group (years)							
<20	4	12.1	0	0.0	4	6.1	0.115
20–35	22	66.7	26	78.8	48	72.7	
>35	7	21.2	7	21.2	14	21.2	
Education							
Bachelor degree	9	27.3	13	39.4	22	33.3	0.532
Senior high school	17	51.5	13	39.4	30	45.5	
Junior high school	7	21.2	7	21.2	14	21.2	
Gravid							
1	17	51.5	15	45.5	32	48.5	0.926
2	9	27.3	12	36.4	21	31.8	
3	3	9.1	3	9.1	6	9.1	
4	2	6.1	2	6.1	4	6.1	
>4	2	6.1	1	3.0	3	4.5	
Gestational age (weeks)							
<9	6	18.2	6	18.2	12	18.2	0.899
9–10	10	30.3	10	30.3	20	30.3	
11–12	7	21.2	10	30.3	17	25.8	
13–14	6	18.2	4	12.1	10	15.2	
>14	4	12.1	3	9.1	7	10.6	
Body mass index (mean ± SD)	20.22 ± 1.22		20.72 ± 1.33				0.117

Table 2: Blood electrolyte level and ketonuria distribution, pretreatment

	Group					
	RL		RL + D5%		Total	
Pretreatment	*n*	*%*	*n*	*%*	*n*	*%*
Sodium level						
Normal	5	15.2	3	9.1	8	12.1
Abnormal	28	84.8	30	90.9	58	87.9
Potassium level						
Normal	20	60.6	11	33.3	31	47
Abnormal	13	39.4	22	66.7	35	53
Chloride level						
Normal	27	81.8	26	78.8	53	80.3
Abnormal	6	18.2	7	21.2	13	19.7
Ketonuria						
Normal	0	0.0	0	0.0	0	0.0
Abnormal	33	100	33	100	66	100

experience nausea and vomiting during pregnancy is 27 years.[9] In terms of education, the majority of the samples are well educated, mostly with senior high-school education. In terms of gravidity, the majority is primigravida. These predisposition factors may be due to women with primigravida yet to adapt to estrogen and chorionic gonadotropin hormone which is suspected to be the cause of hyperemesis gravidarum.[10] While the most common gestational age is 9–10 weeks. This result appropriate with Gunawan et al. and Niebyl, that nausea and vomiting in pregnancy usually begins in 9th until 10th week of pregnancy and ends 11 weeks afterward. Only in 1–10% of pregnancies, the symptoms continue past the 20th until 22nd week.[8,11]

This study found that the electrolyte level examined pretreatment is in various levels. Majority of the patients suffering from hyponatremia conditions (87.9%), hypokalemia (53%), and normokalemia (80.3%). Majority level of ketonuria is +2 (31.8%). According to Tan et al., hyponatremia usually occurs in approximately 43–49% of patients and hypochloremia in 33–40% of patients. Chloride level in this study is mostly normal (hypochloremia only occurred in 19.7% of cases), due to chloride intake and abnormal loss

outside of the kidneys and its excretion can occur without depends on the sodium. In dehydration condition, chloride conservation in the kidney is adequate as a result of kidney efficient regulation.[12] In the proximal tubule of the kidney, a certain portion (60–70%) of filtrated chloride will be absorbed back, which causes the chloride level remained within normal limit.[13]

There was a statistically significant difference of the blood electrolyte level examination (sodium, potassium, and chloride) posttreatment in both groups receiving therapy with Ringer's lactate or Ringer's lactate + D5%. Hyponatremia incidence was decreased from 87.9 to 34.8%. Hypokalemia incidence decreased from 53 to 13.6%. And hypochloremia incidence decreased from 19.7 to 7.6%. While the ketonuria level was significantly decreased in both Ringer's lactate group and Ringer's lactate + D5% group. Abnormal ketonuria level reduced from 100 to 22.7%. These results indicate that intravenous rehydration is a mainstay of management in hyperemesis gravidarum, while rehydration is the easiest method to be given, and this reduces the symptoms experienced by patients with severe hyperemesis.[1] Unfortunately, there has not been any literature mentioning specific fluid used for this treatment.[6] And in recent study, there has not been any intravenous rehydration regimen for the treatment of patients with hyperemesis gravidarum.

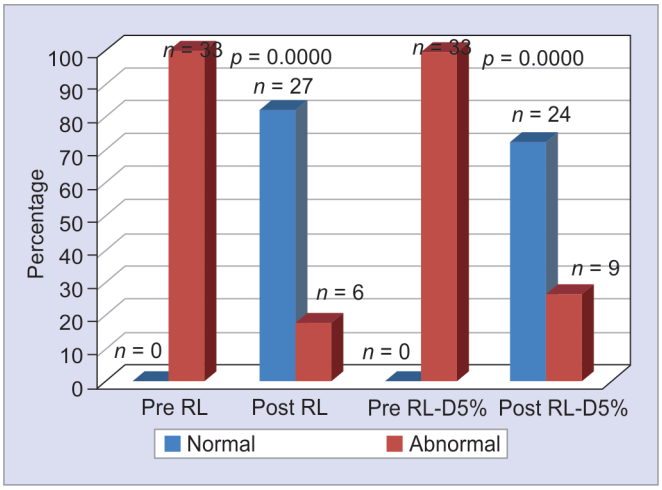

Fig. 1: Ketonuria level before and after therapy on RL and RL + D5% group

There are no studies compare various fluid replacement therapies.[14] This proves that simple fluids, such as Ringer's lactate or Ringer's lactate combined with dextrose 5%, are able to replace fluid loss on hyperemesis gravidarum.

These findings revealed the results of the mean increase of blood sodium and chloride level in group treated with Ringer's lactate or Ringer's lactate + D5% were insignificant. There is also no differences between ketonuria level decrement in both groups. Whereas the difference of blood potassium level was more dominant in Ringer's lactate + D5% treatment group, i.e., 0.31 mmol/L, compared to those receiving only Ringer's lactate therapy (0.20 mmol/L). But the 0.11 mmol/L difference is not clinically significant because it is within normal limits. In therapy treatment with additional dextrose, the condition will be more hyperosmolar, where an increase in extracellular fluid osmolarity will cause osmotic water flow out of the cells. Cellular dehydration state will then raise the intracellular potassium concentration that eventually diffuse into the extracellular compartment. As a result, the extracellular potassium level will increase.[15]

This study revealed no differences in the decrement level of ketonuria. However, this is not in accordance with the theory saying that when carbohydrate reserves in the body has been used up, it will result in lipid oxidation. The lipid cannot be oxidized completely and will cause buildup of acetone–acetic acid, hydroxybutyric acid, and acetone, causing ketosis,[3] so when the patients are treated with intravenous rehydration therapy in addition with dextrose, it will be able to lower the fat-free acid breakdown and ketonuria level that eventually will be able to decrease the incidence of persistent nausea and vomiting.[1,16] This is possibly caused by the uneven ketonuria level distribution in both groups, where in Ringer's lactate—D5% group, majority of ketonuria level is +3 and +4, whereas in Ringer's lactate only group, majority of ketonuria level is +1 and +2. This has become one of the study weaknesses. The results of this study is in accordance with the recent research conducted by Tan et al., in which intravenous rehydration with 5% dextrose–0.9% saline or 0.9% saline solution in women hospitalized for hyperemesis gravidarum produced similar outcomes.

Conclusion

Electrolyte deficiency (hyponatremia, hypokalemia, hypochloremia) and ketonuria can be corrected effectively by either Ringer's lactate

Table 3: Blood electrolyte level before and after therapy

	Na^+ level (mean ± SD) mmol/L			K^+ level (mean ± SD) mmol/L			Cl^- level (mean ± SD) mmol/L		
Group	*Pretest*	*Posttest*	*p value*	*Pretest*	*Posttest*	*p value*	*Pretest*	*Posttest*	*p value*
Ringer's lactate	133.61 ± 2.25	135.94 ± 1.60	0.000	133.61 ± 2.25	135.94 ± 1.60	0.000	99.55 ± 3.35	100.88 ± 2.96	0.000
Ringer's lactate + D5%	133.45 ± 2.09	136.15 ± 2.29	0.000	133.45 ± 2.09	136.15 ± 2.29	0.000	100.21 ± 3.15	101.88 ± 2.20	0.001

Table 4: Mean electrolyte level and ketonuria differences before and after therapy

Group	*Mean Na^+ level difference (mmol/L)*	*p value*	*Mean K^+ level difference (mmol/L)*	*p value*	*Mean Cl^- level difference (mmol/L)*	*p value*	*Mean ketonuria level difference (mmol/L)*	*p value*
Ringer's lactate	2.33	0.348	0.20	0.044	1.33	0.545	1.72	0.108
Ringer's lactate + D5%	2.70		0.31		1.67		2.22	

or Ringer's lactate + dextrose 5%. Therapy using either Ringer's lactate or Ringer's lactate + dextrose 5% gives similar outcome of electrolyte (sodium and potassium) level increment and ketonuria level decrement. The difference of blood potassium level was more dominant in group treated with Ringer's lactate + D5%. Further research is needed to compare other intravenous fluid regiments for hyperemesis gravidarum, apart from Ringer's lactate only or Ringer's lactate + D5%.

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