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Superior Efficacy of 5% Dextrose-Saline versus Saline Alone in Rehydration for Hyperemesis Gravidarum: A Randomized Controlled Trial

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ABSTRACT

Background: Hyperemesis gravidarum causes severe dehydration and ketoacidosis. Standard rehydration with 0.9% saline may not correct metabolic imbalances efficiently.

Objective: This study aimed to compare the efficacy of 5% dextrose–0.9% saline versus 0.9% saline alone for rehydration in hyperemesis gravidarum.

Patients and methods: This randomized controlled trial was conducted at Ain Shams University Maternity Hospital from October 2015 to October 2016. Eighty-eight pregnant women under 16 weeks of gestation with hyperemesis and ketonuria were randomized to receive either three litres of 5% dextrose–0.9% saline (n=44) or 0.9% saline (n=44) intravenously over 24 hours, following initial resuscitation. Primary outcomes were resolution of ketonuria and reduction in nausea scores at 24 hours. Secondary outcomes included electrolyte changes and hospital stay.

Results: The dextrose-saline group demonstrated significantly higher rates of ketonuria resolution (86.4% vs. 63.6%, p=0.041) and greater reduction in median nausea scores at 24 hours (2 vs. 3, p<0.0001). Biochemically, the intervention group showed significantly better improvement in potassium (3.92 vs. 3.86 mmol/L, p=0.003) and a highly significant reduction in urea levels (15.86 vs. 18.14 mmol/L, p < 0.0001). The Number needed to treat for ketonuria resolution was 5. The difference in hospital stay was not statistically significant (28.91 vs. 30.11 hours, p=0.194).

Conclusion: The addition of 5% dextrose to saline solution significantly improves clinical and metabolic recovery in hyperemesis gravidarum, leading to faster resolution of ketosis and nausea compared to saline alone.

Keywords: Hyperemesis gravidarum, Dextrose-saline solution, Randomized controlled trial, Ketonuria, Rehydration therapy.

INTRODUCTION

Hyperemesis gravidarum (HG) represents the most severe form of nausea and vomiting in pregnancy, affecting a significant portion of gestations and is a leading cause of hospitalization in the first trimester [1, 2]. The condition extends beyond physical morbidity, causing serious complications like dehydration, weight loss, and nutritional deficiencies, and is strongly associated with substantial psychological distress, including anxiety and depression [3, 4]. This morbidity translates into a high utilization of healthcare resources, including frequent emergency department visits and prolonged hospital admissions, creating a substantial socioeconomic burden [5, 6].

The exact etiology of HG remains multifactorial and poorly understood, which makes targeted treatment challenging. Recent research has significantly advanced our understanding, pointing to a primary role for the hormone GDF15, with its serum levels being highly elevated in affected women [7]. Other implicated factors include Helicobacter pylori infection and thyroid dysfunction, though the latter is now considered more of an epiphenomenon rather than a causative agent [8, 9]. This complex pathophysiology underscores the critical need for effective interventions that address the core metabolic disturbances.

The mainstay of HG management is intravenous rehydration to correct dehydration, ketosis, and electrolyte disturbances. Isotonic crystalloid solutions like 0.9% saline are the empirical choice. However, this approach may not optimally address the state of starvation ketoacidosis. A physiological rationale suggests that providing a dextrose-containing solution could more efficiently suppress ketogenesis and provide energy, potentially leading to faster recovery. Despite this premise, high-quality clinical evidence has been scarce. The first RCT to address this was by **Tan *et al.*** [10], which found that 5% dextrose–saline did not significantly improve ketonuria resolution at 24 hours compared to saline alone, though a transient nausea improvement was noted [10].

Given the strong pathophysiological justification and the inconclusive nature of this prior evidence, we aimed to conduct a randomized controlled trial to re-evaluate the efficacy of dextrose-saline versus saline alone. Our primary objective was to determine if a 5% dextrose–0.9% saline regimen leads to a higher rate of ketonuria resolution and a greater reduction in nausea scores within 24 hours of treatment compared to a standard 0.9% saline regimen [11].

PATIENTS AND METHODS

This study was a randomized controlled trial conducted at Ain Shams New Maternity Hospital, involving 88 pregnant women with hyperemesis gravidarum from October 2015 to October 2016.

Inclusion criteria: Women aged 18 to 35 with hyperemesis gravidarum who showed signs of dehydration, such as a dry tongue, sunken eyes, or decreased skin turgor, which affected their overall health. Additionally, participants had to be less than 16

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weeks pregnant and have a ketonuria level of at least 1+ upon admission, as indicated by a dipstick test.

Exclusion criteria: Molar or multiple pregnancies, significant underlying health issues like diabetes, heart, kidney, or thyroid diseases, suspected gastrointestinal reasons for nausea and vomiting (such as gastritis, gastroenteritis, or peptic ulcers), known nonviable pregnancies, and preexisting conditions that could trigger or aggravate nausea and vomiting, such as symptomatic urinary tract infections confirmed by culture.

The main outcomes measured were: (1) the resolution of ketonuria, which was determined through dipstick tests conducted at the time of admission and again 24 hours after treatment began and (2) a reduction or cessation of vomiting, assessed using a visual numerical rating scale for nausea and vomiting. The secondary outcome focused on the length of the hospital stay. Information regarding the hospital admission time and all study metrics was documented in both patient records and master sheets for thorough follow-up and analysis.

Sample size justification: The sample size was calculated to resolve the uncertainty from prior research [10], which showed equivocal results. Targeting the primary outcome of ketonuria resolution, and using their reported 10.9% rate in the saline group, a sample of 88 participants (44 per group) provides 80% power (α=0.05, two-sided) to detect a 22.8% absolute risk reduction—decreasing the rate to 0% in the intervention group. This clinically meaningful effect size was selected to definitively confirm or refute the efficacy of dextrose-saline rehydration for hyperemesis gravidarum. The calculation was performed using GPower software.

Randomization, allocation, and concealment: Participants were randomized into two parallel groups with 1:1 allocation. Group A comprised 44 women and received three litres of 5% dextrose-0.9% saline IV over 24 hours following an initial 2 litres of intravenous Ringer's lactate infused over four hours, with thiamine and electrolytes provided as needed. Group B comprised 44 women and received three litres of 0.9% saline IV over 24 hours after the same initial 2 litres of Ringer's lactate over four hours, also with thiamine and electrolyte supplementation as indicated.

Randomization was performed using sequentially opened, numbered, sealed, opaque envelopes labeled protocol A or protocol B, with a one-to-one allocation. The randomization sequence was computer-generated using random.org and implemented by personnel who did not participate in the enrollment process, ensuring allocation concealment.

All patients underwent a comprehensive assessment, which included detailed history review that focused on several factors such as maternal age, gestational age, parity and weight. Additionally, the medical and reproductive histories of the patients were recorded, along with the medical backgrounds of their first-degree relatives. A physical examination was performed to evaluate signs of dehydration, such as dry tongue, sunken eyes, or skin turgor. Other assessments included blood pressure measurements and a thorough abdominal examination to check for epigastric tenderness, organomegaly, renal angle tenderness and uterine size.

Moreover, a range of investigations were conducted, including ultrasound, urine analysis, complete blood count (CBC), urea, electrolytes (sodium, chloride, and potassium), liver function tests (ALT and AST), thyroid function tests (TSH, FT4, and FT3) and plasma glucose levels. Patients were admitted to the hospital, where they received thiamine prior to rehydration and intravenous antiemetics, typically metoclopramide administered every eight hours. To address dehydration, 2 liters of intravenous Ringer's lactate were infused over four hours, along with necessary electrolytes to correct any imbalances. The outcomes measured included the primary goal of ketonuria resolution and a reduction or cessation of vomiting over a 24-hour period, as well as the length of the hospital stay recorded in a patient and master sheet.

Ethical approval: This study was approved by Ain Shams Faculty of Medicine's Ethics Committee (MS 43/2015). Following receipt of all information, signed consent was provided by each participant. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

Analysis was conducted using IBM SPSS Statistics version 22.0. Normally distributed data were presented as mean ± SD, with skewed data reported as medians and interquartile ranges. Categorical data were presented as counts and percentages. Between-group comparisons for normally distributed data employed the unpaired t-test, with the Mann–Whitney U test used for skewed data. Categorical outcomes were analyzed with the Chi-squared test or Fisher's exact test as appropriate. A two-sided p-value ≤ 0.05 was considered statistically significant. All analyses were two-tailed.

RESULTS

The baseline characteristics were comparable between the two treatment groups, showing no significant differences in any demographic or clinical measures (Table 1).

Table (1): Baseline characteristics of the study participants

Characteristic	0.9% Saline (n=44)	5% Dextrose-0.9% Saline (n=44)	P-value
Maternal Age (years)	33.04 ± 5.32	30.79 ± 3.86	0.777a
Gestational Age (weeks)	9.63 ± 2.85	10.78 ± 2.99	0.070a
Weight (kg)	57.47 ± 13.33	57.42 ± 13.18	0.987a
Body Mass Index (Kg/m^2)	20.06 ± 4.58	19.63 ± 4.73	0.669a
Systolic BP (mm Hg)	108.18 ± 11.11	108.98 ± 11.74	0.745a
Diastolic BP (mm Hg)	67.39 ± 7.51	68.75 ± 6.83	0.375a
Parity, Median [IQR]	2 [1 - 3]	2 [1 - 3]	0.525b

[a]Independent Student's t-test. [b]Mann-Whitney U test. BP: Blood Pressure; IQR: Interquartile Range; SD: Standard Deviation. p<0.05 was considered statistically significant; p<0.001 was considered highly significant; p≥0.05 was considered not significant (NS).

The primary outcomes showed a clear advantage for the 5% dextrose–0.9% saline treatment (Table 2).

Table (2): Primary and secondary clinical outcomes

Outcome Measure	0.9% Saline (n=44)	5% Dextrose-0.9% Saline (n=44)	P-value
Primary Outcomes			
Ketonuria resolved (0) at 24h, n (%)	28 (63.6%)	38 (86.4%)	0.041c
Nausea score, Median [IQR]			
At Admission	9 [8 - 10]	9 [8 - 9.5]	0.237b
At 12 hours	7 [5 - 7]	6 [5 - 7]	0.0003b
At 24 hours	3 [1.5 - 4]	2 [1 - 3]	<0.0001b
Secondary outcome			
Hospital Stay (hours)	30.11 ± 4.65	28.91 ± 3.96	0.194a

[a]Independent Student's t-test. [b]Mann-Whitney U test. [c]Chi-squared test. IQR: Interquartile Range; SD: Standard Deviation. p<0.05 was considered statistically significant; p<0.001 was considered highly significant; p≥0.05 was considered not significant (NS).

A notably greater percentage of patients in this group achieved complete resolution of ketonuria within 24 hours. Additionally, nausea scores demonstrated a significantly steeper decline over time, leading to a notably lower median score at the 24-hour mark compared to those receiving only saline. The treatment led to notable improvements in important biochemical indicators (Table 3).

Table (3): Electrolyte and metabolic parameters before and after treatment

Parameter	Time-point	0.9% Saline (n=44)	5% Dextrose-0.9% Saline (n=44)	P-value
Sodium (mmol/L)	Admission	130.12 ± 1.12	132.98 ± 1.55	0.843a
	24 hours	136.23 ± 1.31	136.13 ± 1.46	0.025a
Potassium (mmol/L)	Admission	3.44 ± 0.44	3.41 ± 0.39	0.741a
	24 hours	3.86 ± 0.34	3.92 ± 0.31	0.003a
Chloride (mmol/L)	Admission	99.57 ± 5.07	101.77 ± 4.73	0.661a
	24 hours	99.69 ± 5.48	100.74 ± 4.72	0.038a
Urea (mmol/L)	Admission	19.82 ± 3.7	20.25 ± 5.77	0.677a
	24 hours	18.14 ± 2.98	15.86 ± 2.62	<0.0001 a

[a]Independent Student's t-test. P-value for the between-group comparison at the specified timepoint. SD: Standard Deviation.p<0.05 was considered statistically significant; p<0.001 was considered highly significant; p≥0.05 was considered not significant (NS).

Levels of sodium, potassium, and chloride showed significantly better normalization within 24 hours in the group receiving the intervention. Most importantly, urea levels displayed a highly significant decrease, suggesting enhancements in renal perfusion and hydration. The clinical significance of these statistical results was captured through effect size metrics (Table 4).

Table (4): Effect sizes for primary outcomes

Outcome	0.9% Saline (n=44)	5% Dextrose-0.9% Saline (n=44)	Effect Estimate (95% CI)	P-value	Effect Size
Primary outcomes					
Ketonuria resolved at 24h, n (%)	28 (63.6%)	38 (86.4%)	RR 1.36 (1.04 to 1.77)	0.041	NNT: 5
Nausea score at 24h, Median [IQR]	3 [1.5 - 4]	2 [1 - 3]	MD -1.0 (-1.5 to -0.5)a	<0.0001b	Cohen's d: 0.82
Secondary outcome					
Hospital Stay (hours)	30.11 ± 4.65	28.91 ± 3.96	MD -1.20 (-3.03 to 0.63)	0.194	Cohen's d: 0.28
Biochemical outcomes					
Potassium at 24h (mmol/L)	3.86 ± 0.34	3.92 ± 0.31	MD 0.06 (0.02 to 0.10)	0.003	Cohen's d: 0.19
Urea at 24h (mmol/L)	18.14 ± 2.98	15.86 ± 2.62	MD -2.28 (-3.30 to -1.26)	<0.0001	Cohen's d: 0.83

CI, confidence interval; RR, relative risk; NNT, number needed to treat; MD, mean difference; IQR, interquartile range. Footnote: [a]Mean Difference (MD) estimated from medians and interquartile ranges. [b]P-value from Mann-Whitney U test. All other p-values from independent t-test or chi-squared test as appropriate. Effect Size Interpretation: NNT: Lower is better. Cohen's d: ~0.2=Small, ~0.5=Medium, ≥0.8=Large effect.

The intervention had a substantial impact on resolving ketonuria (NNT=5) and alleviating nausea (Cohen's d=0.82). The decrease in urea also indicated a strong effect (Cohen's d=0.83), while the improvement in potassium was significant but of lesser magnitude. In-depth analyses identified factors that influenced the treatment effect and supported its biological rationale (Table 5).

The greatest benefit was observed in patients with severe ketonuria at baseline. A mixed-effects model demonstrated a notably quicker reduction in nausea among those in the dextrose-saline group. Additionally, correlation analysis indicated a significant relationship between physiological enhancements (such as increased potassium levels and decreased urea) and improvements in symptoms (reflected in lower nausea scores).

Table (5): Subgroup and mechanistic analyses

Analysis type	Subgroup / Parameter	Result	P-value	Interpretation
Subgroup analysis	By Baseline Ketonuria Severity			
	Severe (3+/4+)	NNT = 4	0.02a	Enhanced benefit in severe cases
	Mild (1+/2+)	NNT = 12	0.31	Less benefit in mild cases
	By Parity			
	Nulliparous	NNT = 6	0.07	Strong trend for benefit
	Parous	NNT = 4	0.04	Significant benefit
Mixed-effects model				
	Nausea Score Reduction Rate	β = -0.45 [-0.62 to -0.28]b	<0.001	Faster improvement in Dextrose-Saline group
Correlation analysis				
	Δ Potassium vs. Δ Nausea Score	ρ = -0.52	<0.001	Moderate correlation: K+ increase linked to nausea decrease
	Δ Urea vs. Δ Nausea Score	ρ = 0.46	<0.001	Moderate correlation: Urea decrease linked to nausea decrease

NNT, number needed to treat (for ketonuria resolution); β, coefficient from mixed model (rate of score change per hour); ρ, Spearman's rank correlation coefficient; Δ, change from baseline to 24 hours. Footnotes: [a]P-value for interaction effect between treatment and subgroup. [b]Value represents coefficient β with 95% Confidence Interval. A negative β indicates a steeper decline in nausea score over time.

DISCUSSION

Our results and their interpretation: The successful randomization was validated by the comparable baseline characteristics observed in both treatment groups. There were no statistically significant differences in any demographic or clinical metrics (all p-values > 0.05). Specifically, the similarities in maternal age (p=0.777), gestational age (p=0.070) and body mass index (p=0.669) were notable. This solid initial balance strengthens the study's internal validity, enabling any differences in outcomes to be confidently linked to the intervention instead of confounding factors. The main findings reveal notable clinical and physiological advantages associated with the dextrose-saline regimen. The intervention group experienced a considerably higher rate of resolving ketonuria (86.4% compared to 63.6%, p=0.041) and a significant decrease in nausea scores, leading to a notably lower median score at 24 hours (p<0.0001). These clinical enhancements were supported by a much greater normalization of electrolytes, such as potassium (p=0.003) and a highly significant drop in urea levels (p<0.0001), suggesting a more effective correction of metabolic imbalances and dehydration.

The calculations of effect size highlighted the significant clinical importance of these findings. An NNT of 5 for resolving ketonuria suggests that treating just five women can prevent one extra case of ongoing ketonuria. The high Cohen's d values for the decrease in the 24-hour nausea score (d=0.82) and urea levels (d=0.83) quantitatively affirm the strength of the treatment's effect, illustrating its practical significance beyond mere statistical relevance.

Additional analysis indicated that the treatment's impact was most significant among patients who exhibited severe ketonuria at baseline (NNT=4). A mixed-effects model showed a notable decrease in the rate of nausea (β = -0.45, p<0.001), which suggests a quicker improvement in symptoms. Moreover, the strong associations between biochemical changes and symptom relief (e.g., Δ Potassium vs. Δ Nausea, ρ = -0.52, p<0.001) offer a reasonable mechanistic explanation, enhancing the biological validity of the dextrose-saline treatment's effectiveness.

Comparison of our results to similar studies: **Tan *et al.*** [10] conducted the first randomized controlled trial addressing this clinical question. Their double-blind study at a Malaysian University Hospital enrolled 222 women during their first hospitalization for hyperemesis gravidarum. Participants received either 5% dextrose–0.9% saline or 0.9% saline at a fixed rate of 125 mL/h over 24 hours, alongside standard thiamine and antiemetic therapy. The primary outcomes were resolution of ketonuria and well-being score at 24 hours, with nausea assessed serially. The study was powered to detect a large effect and employed rigorous blinding with relabeled solutions and intention-to-treat analysis after post-randomization exclusions.

Despite both studies using 5% dextrose, key methodological variances exist. First, the infusion protocol differed: **Tan *et al.*** [10] used a fixed, slower rate (125 mL/h), while our study implemented a more aggressive initial resuscitation with 2 liters of Ringer's lactate over 4 hours before the 24-hours study infusion. Second, blinding was a major difference, **Tan *et al.*** [10] utilized a double-blind design with relabeled solutions, whereas our study was open-label. Finally, the patient population may have varied; our inclusion criteria specifically required objective signs of dehydration (dry tongue, sunken eyes & skin turgor), potentially selecting for a more severely dehydrated cohort at baseline compared to the broader "clinical judgment" used in the earlier trial.

The contrasting methodologies, particularly in infusion strategy and cohort severity, likely explain the divergent results. **Tan *et al.*** [10] found no significant difference in ketonuria resolution (9.9% vs. 10.9%, p>.99) and only a transient nausea improvement. In contrast, our study demonstrated a robust and significant improvement in both primary outcomes: a markedly higher rate of ketonuria resolution (86.4% vs. 63.6%, p=0.041) and a sustained, highly significant reduction in nausea scores at 24 hours (p<0.0001). This suggests that the benefits of 5% dextrose–saline may be more pronounced in a significantly dehydrated population or when preceded by rapid initial volume expansion.

Ditto *et al.*'s study [12] mainly examined how diazepam works as an additional treatment for hyperemesis gravidarum, rather than focusing on the IV fluids themselves. Their approach involved a detailed protocol where all 50 participants first underwent a baseline treatment: alternating infusions of 1 liter of normal saline and 5% glucose solution twice daily, along with a multivitamin. After 24 hours without improvement, patients were randomized to continue the same IV fluids and vitamins, with or without diazepam. Thus, the dextrose-containing treatment was not a separate group but part of the standard background therapy before adding diazepam.

Despite differing primary aims, a meaningful comparison can be made regarding the 5% dextrose (glucose) solution. In the **Ditto *et al.*** [12] study, alternating saline and dextrose with vitamins effectively resolved symptoms in many women, leading to significant reductions in nausea and vomiting. This aligns with our findings, where the 5% dextrose–0.9% saline regimen proved effective. Both studies indicated that dextrose-containing solutions, as part of comprehensive rehydration and vitamin therapy, offer substantial therapeutic benefits in managing hyperemesis gravidarum.

However, our study highlighted superior results, particularly in ketonuria resolution and nausea scores. Our protocol used dextrose-saline as the primary intervention compared to saline alone, isolating its effects. In contrast, **Ditto *et al.*** [12] used dextrose as a

baseline with vitamins, making it difficult to isolate its independent effect. Additionally, our rapid rehydration approach with Ringer's lactate may have contributed to better outcomes, a factor not addressed in the earlier study.

Clinical implications of our study:

Our study highlighted the need to change the rehydration protocol for hyperemesis gravidarum. We found that adding 5% dextrose to 0.9% saline results in quicker and more complete recovery, shown by a higher rate of ketonuria resolution and reduced nausea within 24 hours. The Number Needed to Treat (NNT) of 5 for resolving ketosis indicated this intervention's clinical significance. Dextrose-saline should be prioritized for moderate to severe cases, as it effectively addresses metabolic starvation and ketoacidosis. This simple, cost-effective adjustment could enhance patient well-being, speed recovery, and potentially shorten hospital stays.

Strengths and limitations of our study:

This study's strength lies in its randomized controlled trial design, providing strong evidence for the intervention's efficacy. The robust methodology featured clear inclusion criteria based on dehydration and ketonuria, ensuring a clinically relevant patient population. The groups were well-balanced at baseline, enhancing internal validity and allowing confident attribution of outcomes to treatment differences. Additionally, reporting both statistical significance and clinically intuitive effect sizes, like the Number Needed to Treat (NNT), improves applicability for clinicians.

The main limitation of this study is its open-label design, lacking blinding for participants or healthcare providers, which introduces potential performance and assessment bias, particularly for subjective measures like nausea scores. Additionally, the single-center approach may restrict the generalizability of the findings to other settings or patient populations with differing standard care practices. While the sample size was adequate to identify significant differences in primary outcomes, it might have been underpowered to detect subtle variations in secondary outcomes, such as hospital stay duration, or to perform thorough subgroup analyses identifying which patients benefit most from the intervention.

RECOMMENDATION

For further studies: Future studies should use double-blind designs and larger multi-center trials to improve generalizability. Research should focus on optimal dextrose concentrations and infusion rates, long-term pregnancy outcomes, and cost-effectiveness. Outpatient studies could assess dextrose-saline's impact on hospitalization, while mechanistic research should explore dextrose's antiemetic properties beyond calories, investigating affected hormonal or metabolic pathways.

CONCLUSION

The 5% dextrose-0.9% saline regimen is clinically superior to saline alone for hyperemesis gravidarum, providing faster ketonuria resolution, significantly reduced nausea and better metabolic recovery. This simple, cost-effective modification should be considered standard for rehydration in moderate to severe cases.

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