ORIGINAL RESEARCH

A Clinical Trial of Oral Hydration Therapy for the Management of Very Preterm Nonsevere Preeclampsia

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Abstract

Background and objectives: To compare the effectiveness of oral hydration therapy compared with controls in decreasing mean arterial pressure and extending the duration of pregnancy in very preterm preeclampsia.

Materials and methods: Forty-five cases of preterm preeclampsia between 20 and 34 weeks of gestation who were admitted to the Department of Obstetrics and Gynaecology, KIMS, Hubballi, were included in the study. They were randomized into two groups and intervened with oral hydration therapy and a control group, which was not on any intervention. Both groups were given adequate antihypertensives for control of BP. Outcome measures were a fall in BP, prolongation of pregnancy, and improved maternal and neonatal outcomes.

Results: It was observed that diastolic BP significantly reduced in oral hydration group after 5 days of starting treatment ($p = 0.020$). The average weight of babies in oral hydration therapy group was 2.5 kg ($p = 0.011$) and 2 kg in controls. Mean prolongation of pregnancy among oral hydration group was 38.6 days ($p = 0.037$) and 26.7 days ($p = 0.249$) in controls.

Conclusion: Oral hydration therapy was more useful to improve fetal outcome compared with maternal outcome. It was useful to prolong pregnancy and to increase fetal birth weight. It was not found as useful for improving maternal outcome or in decreasing mean arterial pressure. Though most of the outcomes were better in oral hydration therapy clinically, it was not statistically significant. Hence, larger studies maybe required to prove their difference in outcome.

Keywords: Mean arterial pressure, Oral hydration therapy, Preterm preeclampsia, Prolongation of pregnancy.

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Introduction

Preeclampsia is a devastating human-specific disorder of pregnancy. Preterm preeclampsia comprises a significant group of women with a financial and emotional burden on the community in terms of pregnancy wastage, neonatal intensive care, and long-term effects of preterm birth and IUGR associated with preeclampsia.

Hypertensive disorders in pregnancy are the second most common direct cause of maternal mortality worldwide – comprising 14% of all causes. In South Asia, 10.3% of all deaths are on account of hypertension.[1]

Of the estimated 2.6 million stillbirths annually, approximately 16% occur in pregnancies complicated by hypertensive disorders in pregnancy. Neonatal morbidities occur 10–20 times more often than neonatal deaths. About 1 in 250 primigravidae give birth prior to 34 weeks due to preeclampsia.[2]

Objectives of the Study

To determine the effectiveness of oral hydration therapy compared with controls in decreasing mean arterial pressure and extending the duration of pregnancy in very preterm nonsevere preeclampsia.

Materials and Methods

Source of Data

Patients presenting to Obstetrics and Gynaecology Department, KIMS Hubballi, with preterm nonsevere preeclampsia.

Method of Collection of Data

Time period: November 2017 – April 2019.

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Source of support: Nil

Conflict of interest: None

Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

Type of study: Randomized controlled study, randomized by envelope method.

Sample size: 50 subjects.

Inclusion Criteria

Pregnant women with singleton pregnancy with less than 34 weeks of gestational age with nonsevere preeclampsia.

Exclusion Criteria

- Patients with features of severe preeclampsia.
- Patients with other complications of preeclampsia at the time of diagnosis.

Methodology

Informed consent of the subjects was taken.
Study subjects were randomized to two groups:

- Group I: Oral hydration therapy: Women in this group were advised to take plenty of oral fluids and produce a targeted urine output of >2500 mL/day. Daily urine output of all women was noted.
- Group II: Routine treatment was given as followed in the institute. Routine treatment included controlling BP with tablet Nifedipine and/or tablet Labetalol in adequate doses at required intervals in both the groups.
  - Preeclampsia was diagnosed as per the standard criteria. CRL or LMP gestational ages were recorded (whichever available) at the time of first diagnosis of preeclampsia in both cases and controls. The gestational ages at the end of pregnancies in every woman were recorded in all groups.
  - The duration of pregnancy that could be continued from initial diagnosis to delivery was calculated.
  - Periodic assessment of blood pressure, serum Na+, and serum K+ was considered for analysis.
  - The average values of these parameters were calculated.
  - Mean arterial pressure (MAP) was calculated from average blood pressure in each case.
  - The reasons for termination of pregnancies were recorded in both cases and controls.

Neonatal outcomes like birth weights, NICU admissions, and reason for admission to the NICU were recorded in all subjects.

- Antenatal steroids were given whenever needed.

Primary Outcome Measures

- Fall in blood pressure.
- Prolongation of pregnancy.

Secondary Outcome Measures

- Neonatal outcome.
- Maternal outcome, i.e., occurrence of complications like eclampsia, imminent eclampsia, abruption, etc.

Statistical Analysis

Data were collected and tabulated in the Microsoft Excel. The data were analyzed using EpiData Analysis software version 2.1.1.2. The continuous variables were described using mean and standard deviation. The categorical variables were described using percentages. The association between continuous variables and group was analyzed using *t*-test or analysis-of-variance test. The association between categorical variables and the groups was analyzed using Chi-square test. The *p*-value of less than 0.05 was considered as statistically significant.

Results

Phases of enrolment for intervention and follow-up of cases in the study are described in Figure 1.

The daily urine output of patients was more than 2.5 liters.

Baseline characteristics of cases are mentioned in Table 1.

When the groups were matched by gestational age, the maximum number of participants were in the 26–29-week 6-day category in the oral hydration group, making 55% of the total 20 participants. The control group had a maximum number of participants of all groups, including 12 in the 26–29-week 6-day category and 11 in the 30–33-weeks 6-day category.

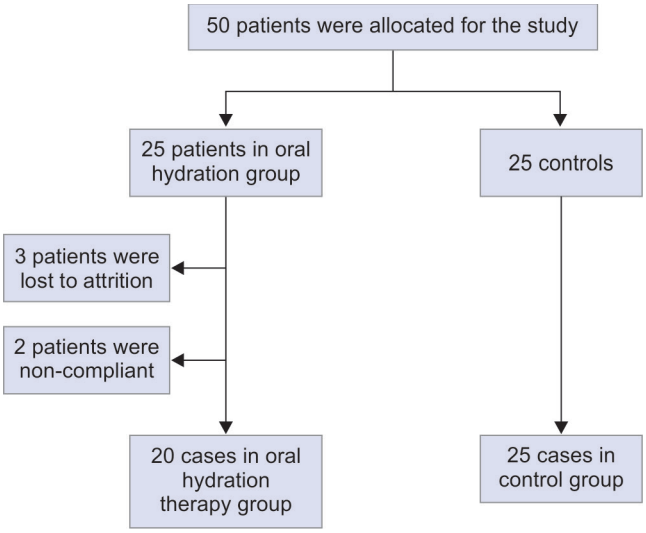

Fig. 1: Consort flow diagram

Table 1: Baseline characteristics of cases included in the study were as mentioned below

	OHT		*Control*	
	Mean	*SD*	*Mean*	*SD*
Age (in years)	26.5	4.6	24.5	4.1
Nulliparous	9 (45%)		16 (64%)	
Gestational age (in days)	214.7	12.6	212.6	16.7
SBP (mm Hg)	140.4	9.1	136.4	7.5
DBP (mm Hg)	93.7	9.8	93.1	11.4
MAP (mm Hg)	109.3	7.2	107.5	6.7

Of the total 50 patients, 4 patients were referred as hypertensive disorders in pregnancy. About 27 were detected as hypertensive during regular ANC visits. Others were diagnosed after admission.

The majority of the patients in each group did not have any significant past history. Some known hypertensive patients were also included in the study, who had superimposed nonsevere preeclampsia. Three patients were diabetics, two among them were in oral hydration group.

There was no statistical difference between cases and controls in terms of serum sodium and serum potassium between patients at recruitment and on 5th day after initiation of treatment ($p = 0.392$; $p = 0.772$). These results show that hydration therapy does not produce electrolyte imbalance.

It was observed that diastolic BP significantly reduced in oral hydration group after 5 days of starting treatment. There was no significant difference in mean BP 5 days after starting treatment in the oral hydration group (Table 2). There was no significant difference between systolic blood pressure (SBP), diastolic blood pressure (DBP) and MAP at the termination of pregnancy in both groups.

Severe preeclampsia, hemolysis, elevated liver enzymes, low platelet count (HELLP), partial HELLP, imminent eclampsia, eclampsia, and oligohydramnios were considered as PIH-related indications. Fetal compromise, Post datism, PROM, PPROM, previous

Table 2: Comparison of systolic, diastolic, and mean arterial blood pressure of the study participants in the intervention and control groups at 5th day after initiation of treatment ($N = 68$)

BP (in mm of Hg)	*OHT*			*Control*		
	Mean	*SD*	*p-value*	*Mean*	*SD*	*p-value*
SBP	129.4	16.4	0.766	128.1	13.2	0.789
DBP	79.6	7.5	**0.020**	81.9	12.7	0.571
MAP	96.2	9.4	0.241	97.3	12.2	0.700

Significant of *p*-value is <0.05

LSCS,Spontaneous onset of labor were considered non-PIH-related indications for termination of pregnancy.

Indications for termination of pregnancy included 70% due to non-pregnancy-induced hypertension (PIH)-related indications in oral hydration therapy. Among controls, 44% were terminated due to non-PIH indications and 56% due to PIH-related indications.

About 60% of participants in oral hydration and 52% in the control group had good outcomes, and a maximum number of maternal complications like severe preeclampsia, imminent eclampsia, eclampsia, HELLP, partial HELLP, and CVT were seen in the control group.

There was a significant difference between oral hydration group and controls in terms of birth weight of babies with *p*-value of 0.011. The mean birth weight of the oral hydration group was 2.5 kg, and that of the control group was 2 kg.

About 60% (12) of participants in oral hydration and 52% (13) in control group had good outcomes of the mother just post delivery.

Good outcomes included those cases who had mild preeclampsia or their BP became normal after delivery. Bad outcomes were those patients who developed severe preeclampsia, imminent eclampsia, eclampsia, CVT, HELLP, partial HELLP, or died.

There was no significant difference between the groups in terms of fetal outcomes statistically, but the maximum proportion of babies (16%) had died in the control group compared with 10% in oral hydration group.

There was a significant difference between oral hydration group and control in terms of the prolongation of pregnancy. Mean prolongation of pregnancy in oral hydration group was 38.6 days and in the control group was 26.7 days ($p = 0.037$).

Discussion

Imbalance between angiogenic and antiangiogenic factors causes preeclampsia. Antiangiogenic factor, soluble fms-like tyrosine kinase1 (sFlt-1) induces preeclampsia-like phenotype in experimental models, and circulates at high levels in preeclampsia.[3] Extracorporeal removal of circulating sFlt-1 by dextran-sulfate apheresis reduces proteinuria and stabilizes blood pressure without apparent adverse effects on the fetus and mother.[4]

Samartha Ram et al. concluded that oral hydration therapy with urine output 3962 ± 989 mL/24 hrs helps to prolong very preterm preeclamptic pregnancies to term with good perinatal outcome. Continuation of pregnancy in cases was 7.51 ± 5.22 weeks, and in controls, it was 1.38 ± 1.18 weeks ($p = 0.000$). Significant decrease in RDS, NICU admission days ($p = 0.000, 0.001$), and increase in birth weights and take-home babies ($p = 0.000, 0.041$) were observed in cases. The limitation of the study was blood, and urine sflt level was not measured in the study.[5] Hereby referred to as reference study/index study.

Table 3: Comparison of prolongation of pregnancy in different studies

	Prolongation of pregnancy	*p-value*
Samartha Ram et al.[5]	6 weeks	0.00
Current study	1 week 5 days	0.037

Table 4: Comparison of fetal outcomes with other studies

Number of IUDs	*Cases*	*Controls*	*p-value*
Samartha Ram et al.[5]	1	6	0.041
Current study	2 (one died due to hypoglycemia)	4	0.368

The current study was done in a tertiary care institute, which caters to a large number of deliveries with a high prevalence of preeclampsia with significant morbidity and noticeable mortality. Going by large numbers, as there is no proven method to prolong pregnancy and perinatal outcomes, we decided to try a different method and compare it to currently followed treatment at our institute, in terms of maternal and neonatal outcomes.

A wide range of unproven interventions are available to treat or prevent preeclampsia. But, there is a need for low-cost, simple, easy, and practicable interventions. In this study, we have compared controls with one such modality, i.e., oral hydration therapy, which is an intervention with the least-possible cost. With this, we wanted to test the hypothesis that oral hydration therapy may significantly reduce clinical symptoms and may also help to continue pregnancies to viability, as enhanced renal excretion of sFlt1 is possible.

There was also a significant difference between prolongation of pregnancy between oral hydration therapy group and controls ($p = 0.037$) (Table 3).

In oral hydration group, of the two neonatal deaths, one could be attributed to hypoglycemia as the mother was diabetic. In the control group, 4 babies died due to LBW leading to sepsis and/or respiratory distress. Thus, though there was a difference clinically, there was no statistical difference on analysis (Table 4).

Current study showed that oral hydration therapy significantly decreased diastolic blood pressure when compared with controls after 5 days of intervention, i.e., the group consuming antihypertensives only ($p = 0.02$) as seen in Table 5.

There was no statistical difference between cases and controls in terms of serum sodium and serum potassium between patients at recruitment and on the 5th day after initiation of oral hydration therapy ($p = 0.392$, $p = 0.772$). Even in the reference study, there was no statistically significant difference in serum sodium and potassium levels between cases and controls ($p = 0.072$, $p = 0.201$). These results show that hydration therapy does not cause electrolyte imbalance.

When termination of pregnancy was considered, in this study, 30% were terminated due to PIH-related indications in oral hydration therapy. Among controls, 56% were terminated due to PIH indications. Whereas in reference study, 75% of the controls were terminated due to PIH-related indications and only 5% of subjects on oral hydration therapy were terminated due to PIH-related indications (Table 6).

In this study, there was a significant difference between oral hydration group and controls in terms of birth weight of babies as in Table 7.

Table 5: Comparison of systolic and diastolic blood pressures between cases and controls before starting treatment and on the 5th day after initiation of therapy

	Samartha Ram et al.[5]			*Current study*		
	Cases	*Control*	*p-value*	*Cases*	*Control*	*p-value*
SBP (mm Hg)	No data	No data	No data	129.4	128.1	0.766
DBP (mm Hg)	No data	No data	No data	83.1	81.9	0.020
Mean BP (mm Hg)	104.86	115.99	0.00	96.2	97.3	0.241

Table 6: Comparison of indications of termination with other studies

	Oral hydration therapy (in percentage)	*Controls (in percentage)*
	Termination due to PIH-related indications (in %)	*Termination due to PIH-related indications (in %)*
Samartha Ram et al.[5]	5	75
Current study	30	56

Limitations of the Study

- Urine output per day was maintained to be more than 2500 mL but the average urine output of all the days was not calculated.
- sFlt levels in blood and/or urine could not be calculated as the facility is not available in this institution.
- Blinding was not possible as one arm of the study included drinking water in large amounts, which could not be blinded.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable with ethical standards.

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Table 7: Comparison of average birth weight compared with other studies

	Average birth weight	*p-value*
Samartha Ram et al.[5]	2.54 kg	0.00
Current study	2.5 kg	0.011

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