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Original Article

Obstetrics and Gynaecology Section

Abbreviated (8 hours) versus Traditional (24 hours) Postpartum $MgSO_4$ Prophylaxis in Severe Preeclampsia: A Randomised Control Trial

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ABSTRACT

Introduction: Preeclampsia is a multisystem disorder affecting pregnancy after 20 weeks of gestation featured by hypertension and proteinuria. Magnesium Sulphate ($MgSO_4$) has been used for 24 hours following delivery to prevent eclampsia in patients with severe preeclampsia.

Aim: To determine the need to continue magnesium sulphate therapy 8 hours following delivery.

Materials and Methods: The double blinded randomised controlled study was performed in the Department of Gynaecology and Obstetrics at R.G. Kar Medical College, Kolkata, West Bengal, India, from 1st July 2015 to 30th June 2016. Total 90 patients with severe preeclampsia were randomised in two group. In group A $MgSO_4$ was discontinued 8 hours following delivery (abbreviated group) and in the group B it was continued for 24 hours following delivery (traditional group). The primary objective of study was to determine the need to continue $MgSO_4$ therapy 8 hours following delivery. Secondary objectives were monitoring time by doctors, nursing care time, postpartum ambulation time, duration of urinary catheterisation, minor complication like urinary tract infection, duration and total dose of $MgSO_4$ therapy. In order to calculate statistical significance of the different variables in between two groups, Student's independent sample's t-test was used for normally distributed numerical values and Chi-square test or Fischer's-exact test was used for unpaired proportion data.

Results: In abbreviated group, the number of patients (n=1) who did not need to continue $MgSO_4$ therapy beyond 8 hours following delivery as safety measures were statistically significant (p-value <0.0001) in comparison to traditional group. Total duration and dose of $MgSO_4$ therapy were significantly less (p-value <0.0001) in the abbreviated group. There was statistically significant reduction in time from delivery to postpartum ambulation and duration of indwelling urinary catheter in the abbreviated group.

Conclusion: The abbreviated (8 hours) regime of postpartum $MgSO_4$ for seizure prophylaxis is a suitable alternative to the traditional (24 hours) regime.

Keywords: Imminent eclampsia, Magnesium sulphate total dose, Postpartum ambulation

INTRODUCTION

Preeclampsia is a multisystem disorder affecting pregnancy after 20 weeks of gestation featured by hypertension and proteinuria [1]. The incidence of preeclampsia is 2-8% of all pregnancies [2-4]. The most dreaded complication of severe preeclampsia is eclampsia, which may occur in antepartum, intrapartum and postpartum period and it may result into various adverse outcomes affecting both mother and foetus [5-8]. Magnesium Sulphate is the drug of choice for prevention of eclampsia in severe preeclamptic patients and its use in severe preeclampsia improves prognosis [9]. $MgSO_4$ reduces the risk of seizures and maternal mortality by 50%, when used judiciously in preeclampsia [2,10-12], but the ideal duration of $MgSO_4$ therapy is yet to be decided [13]. To prevent eclampsia $MgSO_4$ has traditionally being used for 24 hours following delivery [2,14].

The decision of duration of $MgSO_4$ therapy in women with preeclampsia has been taken depending on clinical criteria in some non randomised studies [15,16]. Shorter duration of $MgSO_4$ therapy may help in early postpartum ambulation, less frequent monitoring by healthcare worker and better newborn care. Some women with this shorter treatment regime required a prolongation or re-institution of therapy as shown in a systemic review [17]. The 24 hours postpartum use of $MgSO_4$ in women with preeclampsia for prevention of eclampsia in economically developing country like India is a burden on healthcare system and might preclude kangaroo care practice [18]. Thus, the primary objective of the study was to determine the need to continue magnesium sulfate therapy 8 hours following delivery. The secondary objectives were to compare monitoring time by medical personnel, postpartum ambulation time, duration and total dose of $MgSO_4$ therapy, duration of urinary catheterisation between two groups of patients receiving $MgSO_4$ injection for 8 hours and 24 hours following delivery.

MATERIALS AND METHODS

The double blinded randomised controlled study was conducted at R.G. Kar Medical College, Kolkata, West Bengal, India, in Department of Obstetrics and Gynaecology from 1st July 2015 to 30th June 2016 after obtaining Institutional Ethical Clearance.

Sample size calculation: With the presumption that the $MgSO_4$ treatment duration would be 18±9 hours in the abbreviated group and 24±6 hours in 24 hours group (traditional group) the sample size needed was 35 in each group (for detection of 6 hour difference with statistical power of 90% and a two-sided p-value<0.05). Considering probability of drop-outs of 20% the ultimate sample size was increased to 45 in each group (total 90).

Inclusion criteria: All postpartum women with severe preeclampsia admitted in the Department of Obstetrics and Gynaecology were included.

Exclusion criteria: Women with eclampsia, those with HELLP (Haemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome [12], patients with diabetes mellitus, seizure disorder, renal compromise, allergy to magnesium sulfate and reduced urinary output (25 mL/hour) were excluded from the study.

By definitions preeclampsia is characterised by hypertension and proteinuria typically developing after 20 weeks of gestation, on the contrary in gestational hypertension there is development of

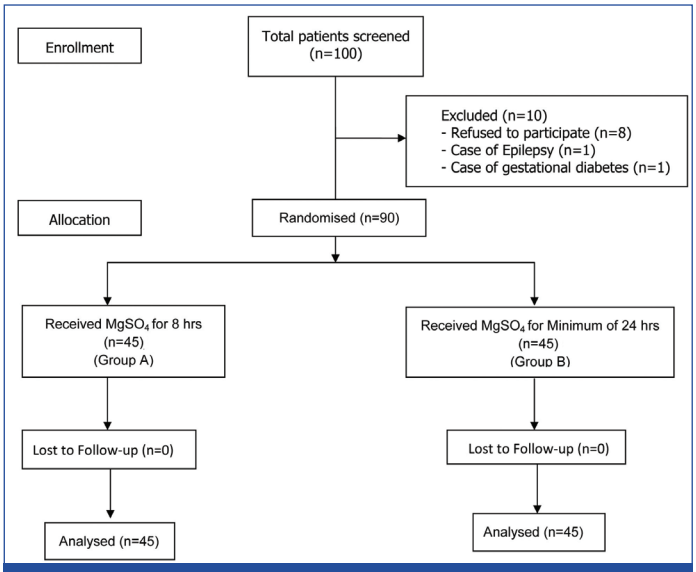
hypertension after 20 weeks gestation and/or within the first 24 hours postpartum without proteinuria or other signs of preeclampsia [19]. In chronic hypertension the raised blood pressure is documented before or within 20 weeks of pregnancy, and persists longer than 12 weeks after delivery. Superimposed preeclampsia is a term to define the development of preeclampsia on pre-existing chronic hypertension [19]. Preeclampsia is considered severe when systolic blood pressure is ≥160 mmHg and/or diastolic blood pressure is ≥110 mmHg, with or without the following characteristics such as 1) proteinuria of 5 g or higher in a 24-hour urine specimen or 3+ or greater on two random urine samples collected at least 4 hours apart, 2) oliguria (<500 cc in 24 hours), 3) thrombocytopenia (platelet count <100,000/mm^3), 4) elevated liver enzymes with persistent epigastric or right upper quadrant pain, 5) pulmonary oedema, 6) persistent, frontal or occipital headache with or without visual disturbances [19]. In mild preeclampsia systolic blood pressure is ≥140 mmHg but ≤160 mmHg and/or a diastolic blood pressure is ≥90 mmHg but ≤110 mmHg without any dangerous signs and symptoms as stated above.

Procedure

In this study $MgSO_4$ was started with the following Pritchard Regime [20], with the loading dose of 4 gm intravenous (i.v) slowly followed by 5 gm intramuscular (i.m.) in each buttock. Maintenance dose of 5 gm i.m. 4 hourly in alternate buttocks.

In the study all women were started magnesium sulfate intrapartum or shortly before that. Postpartum, all participants receive $MgSO_4$ for 8 hours. Approximately 4 hours after delivery, patients with written informed consent were enlisted and allotted a randomisation number.

A total of 100 women [Table/Fig-1] were approached but 10 women were excluded as 8 of them refused to participate, 1 was a known case of epilepsy and another 1 was also a known case of gestational diabetes. The participants were randomised 1:1 to receive an abbreviated regime (8-hour) (group A) or ongoing regime (24-hour) (group B) of $MgSO_4$.



[Table/Fig-1]: CONSORT flowchart of participants.

Randomisation was done by using computer generated random numbers ranging from 1 to 45. The group assignment was done by non transparent, sealed, sequentially numbered envelopes, which was opened only after 8 hours of completion of the initial period of magnesium sulfate. Those who were assigned to 24 hours $MgSO_4$ continuation (traditional) group were treated with the same drug for another 16 hours or more but in the other group (abbreviated group) the dose was completed within 8 hours. In rare occasion if a woman who was assigned to the abbreviated $MgSO_4$ protocol, was having systolic blood pressure ≥180 mmHg and/or a diastolic blood pressure ≥120 mmHg and/or any other signs of imminent eclampsia, magnesium sulfate was continued even after 8 hours with the discretion of her attending doctor. Every woman was followed for 24 hours with clinical assessment (blood pressure, heart rate, respiratory rate, urine output) in every 4 hours and data was tabulated. Laboratory tests like haemoglobin (gm/dL), platelet count, serum Lactate Dehydrogenase (LDH), urea, creatinine, total Bilirubin, Asparate Transaminase (AST), urine for protein were evaluated initially and after 24 hours.

STATISTICAL ANALYSIS

All data were analysed by Statistical Package for the Social Sciences (SPSS) version 20.01 and GraphPad Prism version 5 software. Data have been summarised as mean and standard deviation for numerical variables and count and percentages for categorical variables. The median and the interquartile range have been stated for numerical variables that are not normally distributed. Student's independent sample's t-test was applied to compare normally distributed numerical variables between groups, Unpaired proportions were compared by Chi-square test or Fischer's-exact test, as appropriate p-value <0.05 is considered to be statistically significant.

RESULTS

Baseline variables of both traditional and abbreviated groups like age (in years), parity, gestational age at delivery (weeks), and mode of delivery (vaginal/instrumental/caesarean section) were compared and no statistically significant differences were found [Table/Fig-2].

Variables	Group A (n=45) {Mean (SD)}	Group B (n=45) {Mean (SD)}	p-value
Age (years)	19.84 (2.66)	19.93 (2.38)	0.8680*
Primipara (n, %)	33 (73.3)	39 (86.7)	0.1183*
Multipara (n, %)	12 (26.7)	6 (13.3)	
Gestational age at delivery	35.85 (0.89)	35.79 (0.94)	0.7487*
Chronic hypertension (n, %)	1 (2.2)	1 (2.2)	0.8415 Chi-square test
Gestational hypertension (n, %)	2 (4.4)	1 (2.2)	
Preeclampsia (n, %)	42 (93.3)	43 (95.6)	
Caesarean section (n, %)	36 (80)	33 (73.3)	0.7481 Chi-square test
Instrumental delivery (n, %)	2 (4.4)	3 (6.7)	
Vaginal delivery (n, %)	7 (15.6)	9 (20)	
Haemoglobin (gm/dL)	11.51 (0.43)	11.50 (0.40)	0.996*
Heart rate (beats per minutes)	86.44 (69)	86.57 (4.48)	0.8780*
Respiratory rate	15.88 (1.55)	16.02 (1.33)	0.6641*
Urine output {Mean(SD)}	81.88 (15.56)	81.22 (15.78)	0.8406*
Platelet count (lacs/cmm)	2.08 (0.21)	2.14 (0.26)	0.2425*
Serum creatinine (mg/dL)	0.51 (0.08)	0.53 (0.07)	0.3861*
Serum LDH (mg/dL)	265.64 (8.70)	264.04 (8.79)	0.3880*
AST (U/L)	23.20 (4.74)	23.0 (4.30)	0.8345*
Total bilirubin (mg/dL)	0.44 (0.16)	0.46 (0.17)	0.6165*
Duration of urinary catheter			
8 hours	44	0	<0.0001 Fischer-exact test was used
24 hours	1	45	

[Table/Fig-2]: Baseline characteristics between both the groups.
LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase; *Student's independent sample's t-test, Chi-square test, Fischer-exact test; p-value <0.05 is considered to be statistically significant

$MgSO_4$ was continued for only one woman beyond 8 hours, out of 45 women (2.2%) in the intervention group (p-value <0.001) [Table/Fig-3].

Authors need not to discontinue the therapy in any women for any untoward effects of the drugs. There was no incidence of eclampsia, pulmonary oedema, renal or liver complications, thromboembolic

Variables	Group A (n=45, %)	Group B (n=45,%)	p-value
Need to continue $MGSO_4$ therapy beyond 8 hours {n(%)}	1 (2.2)	45 (100)	<0.0001

[Table/Fig-3]: Comparison of need to continue $MGSO_4$ therapy beyond 8 hours. Chi-square test was used for statistical analysis; p-value <0.05 is considered to be statistically significant

features like disseminated intravascular coagulation or cerebrovascular accident. No maternal deaths were documented in any of the groups during the study. Minor complications like urinary tract infection were found statistically significant among the women receiving $MgSO_4$ for 24 hours [Table/Fig-4]. The duration of anticonvulsant therapy was significantly shorter among the women receiving $MgSO_4$ for 8 hours resulting in reduction of total dose of $MgSO_4$. Similar results with significant reduction in time from delivery to postpartum ambulation were seen among the women receiving $MgSO_4$ for 8 hours [Table/Fig-4].

Variables	Group A (n=45) {Mean (SD)}	Group B (n=45) {Mean (SD)}	p-value
Monitoring time by doctors (in minutes)	20 (0.82)	30.46 (1.14)	<0.0001
Nursing care time (in minutes)	32.40 (1.72)	88.88 (6.09)	<0.0001
Ambulation time			
8 hours	44	0	<0.0001
24 hours	1	45	
Minor complications {n(%)}*	10 (22.2)	25 (55.6)	0.001
Duration of urinary catheter			
8 hours	44	0	<0.0001
24 hours	1	45	
Duration of $MgSO_4$ therapy (in hours)	9.622 (0.984)	25.889 (0.935)	<0.0001
Total dose of $MgSO_4$ (in gm)	14.222 (1.833)	34.556 (1.439)	<0.0001

[Table/Fig-4]: Comparison of other secondary outcomes.
*Urinary tract infection, mild abdominal distension, flushing;
Student's independent sample's t-test, Chi-square test or Fisher's exact test were used for statistical analysis; p-value <0.05 is considered to be statistically significant

DISCUSSION

In present study, there was no difference in the baseline variables like age, parity, gestational age at delivery and mode of delivery, among the abbreviated (8 hours) regime and traditional (24 hours) regime group. Most clinical and laboratory parameters like heart rate, respiratory rate, blood pressure, urine output, platelet count, serum creatinine, uric acid, serum LDH, AST, total bilirubin, at admission were also similar or comparable. In the present study, $MgSO_4$ was continued for only one woman beyond 8 hours, out of 45 women (2.2%) in the abbreviated group (p-value <0.0001). In a study by Isler CM et al., postnatal clinical symptoms were used as guide to reinstitute $MgSO_4$ therapy in 7.6% participants of the total 503 study women [15]. A more recent randomised controlled trial by Ehrenberg HM and Mercer BM examined disease progression during a 12-hour and 24-hour postpartum $MgSO_4$ regime for mild preeclampsia and reported the need to extend $MgSO_4$ administration among 6.9% of women in the 12-hour group [21].

In a randomised control trial by Darngawn L et al., comparing a shortened 6 hours $MgSO_4$ prophylaxis regime versus 24 hours in preeclamptic women at low risk of eclampsia, only one woman out of 75 (1.3%) in the 6 hours intervention group needed to continue $MgSO_4$ due to increased blood pressure nine hours following delivery [22]. This is in concordance with present study findings. Regarding the secondary outcomes, no eclampsia occurred in either group, which is in accordant with the observation of both studies by both Isler CM et al., and Ascarelli MH et al., [15,16]. The duration of monitoring of women was significantly less in the abbreviated group (8 hours group) (p-value <0.0001). Similarly, time spent by the nurses in giving $MgSO_4$ injections and care was significantly less in the intervention group (p-value <0.0001). In limited resource country like India the manpower saving is also of great significance for the abbreviated group. The reduced duration of keeping the bladder catheter in abbreviated group is also important as it significantly reduced the incidence of urinary tract infection as shown in a study by Maki DG and Tambyah PA [23]. Early ambulation in the abbreviated group is the key factor for prevention of thromboembolic manifestation as suggested by Bates SM et al [24]. Most of the women on $MgSO_4$ therapy have to be kept in high dependency unit or intensive care unit which preclude mother taking care of her baby resulting in all the disadvantages arising from keeping the baby apart. In abbreviated group the early rooming in of the baby with the mother is very advantageous for initiation of breast feeding and its short term and longterm benefits. Further, this study generates the hypothesis for future studies with large sample size, preferably multicentric for standard recommendations. The incidence of eclampsia is comparatively less in India (0.5-1.8%) [25], and statistically only 25% of those occurs post confinement.

Limitation(s)

In this study eclampsia was not included as primary objective. The effects of the regime on morbidity were not assessed in this study by any scales of morbidity. Multicentric study with larger number of preeclamptic women is required before we conclude that the abbreviated regime can be considered as universally accepted protocol. Blinding was not feasible in this study due to study design. Duration and doses of $MgSO_4$ administered prior to delivery was not considered in the study.

CONCLUSION(S)

The present randomised control trial indicates that the abbreviated (8 hours) regime of postpartum $MgSO_4$ for seizure prophylaxis is a suitable alternative to the traditional (24 hours) regime in respect to the prognosis of the patients with a clear advantage of less exposure of drugs in terms of both dose and duration. However, multicentric study with larger sample size of preeclamptic women has to be conducted before drawing any uniform conclusion about the abbreviated protocol.

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