ORIGINAL ARTICLE

Comparative Study of Efficacy of Magnesium Sulfate and Nifedipine in Suppression of Preterm Labour

SHAGUFTA TABASSUM[1], UZMA SHAHZADI[2], AMMARA KHALID[3]

ABSTRACT

Aim: To compare the efficacy of magnesium sulfate versus nifedipine for prevention of preterm labour.
Methods: A total of 250 patients of preterm labour, 18 to 45 years of age with singleton pregnancy of gestational age between 28 to 36^{+6} weeks (assessed on LMP) were included. Patients with severe pre-eclampsia, eclampsia, multiple gestation and Premature rupture of membrane were excluded. The selected patients were placed randomly into two groups i.e. Group A (magnesium sulfate) & Group B (oral nifedipine), by using lottery method. The efficacy was assessed if preterm labour was prevented and woman with preterm labour did not require an alternative tocolysis for 48hours.
Results: The mean age of women in group 1 was 29.54±6.67 and in group 2 was 30.48±6.08 years. The mean gestational age in group 1 was 32.47±2.41 weeks and in group 2 was 32.69±2.41 weeks. Preterm labour was prevented for 48hrs in group one (88.80% patients) while in Group 2, it was prevented 74% patients. So, efficacy was 88.80% in group 1 (magnesium sulfate) and 74.40% in group 2 (oral nifedipine) with p-value of 0.003.
Conclusion: This study concluded that magnesium sulfate is associated with higher efficacy for prevention of preterm labour as compared to oral nifedipine.
Keywords:- Preterm labour, calcium blocker, magnesium sulphate.

INTRODUCTION

Preterm labour is defined as the presence of regular, effective uterine contractions of sufficient frequency and intensity leading to progressive effacement and dilatation of the cervix after age of viability (28weeks) and prior to 37 completed weeks of gestation[1]. Preterm birth is a global issue, irrespective of region or the level of resources[2]. In a latest World Health Organization report on preterm, Pakistan is ranked 4th country in the world in term of highest preterm birth rates of 7, 48,100 in year 2010[3]. Pakistan has an infant mortality rate of 65 per 1000 live births[4], with prematurity being one of the leading causes of death[5].

The pathogenesis of preterm labor is not well understood, and it is often not clear whether preterm labor represents early idiopathic activation of the normal labor process or results from a pathologic mechanism. Several theories exist regarding the initiation of labor, including 1) progesterone withdrawal, 2) oxytocin initiation, and 3) premature decidual activation[7]. The most likely pathway to the initiation of preterm labor probably involves premature decidual activation. Although decidual activation may be mediated in part by the fetal-decidual paracrine system, and potentially by intrauterine bleeding, in many cases, especially those involving early preterm labor, it appears that this activation occurs in the context of an occult upper genital tract infection[6].

Tertiary interventions are aimed at women who are about to go into preterm labor, or rupture of membranes or bleed preterm. The use of the fibronectin test and ultrasonography improves the diagnostic accuracy and reduces false-positive diagnosis[7]. While treatments to arrest early labor where there is progressive cervical dilatation and effacement will not be effective to gain sufficient time to allow the fetus to grow and mature further, it may defer delivery sufficiently to allow the mother to be brought to a specialized center that is equipped and staffed to handle preterm deliveries[8].

A wide variety of agents have been advocated as suppressing uterine contractions. Those in current use include beta-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, nitric oxide donors, and oxytocin receptor antagonists. There is little reliable information about current clinical practice but it is likely that ritodrine hydrochloride, a beta-agonist, remains the most widely used in Europe[9]. The tocolysis used to prevent perterm labour basically aims to prolong the pregnancy at least for 48hours, so as to provide adequate time to administer doses of corticosteroids which would help in preventing respiratory distress syndrome in the newborn. It will also provide opportunity to transfer

[1,2]Senior Registrar, Gynaecology, Nishtar Hosital, Multan,
[3]PGR, Gynaecology, Nishtar Hospital, Multan. .
Correspondence to Dr. Shagufta Tabassum Email: dr.shaguftatabassum@hotmail.com; Cell: 0333-6101915)

the woman to a tertiary care centre where adequate neonatal intensive care unit facilities are available[10].

Different tocolytic agents are used to delay or suppress preterm labour. Ideally, tocolytics should minimize maternal and fetal morbidity while delaying delivery during the administration of antenatal steroids to enhance fetal lung maturity. Some currently used tocolytics are Magnesium sulfate, Ritodrine, Terbutaline, Nifedipine and Indomethacin. The use of magnesium sulfate as a tocolytic agent was first described by Steer and Petrie in a randomized study of 71 women with preterm labour in 1977[11]. Another agent Nifedipine was also used for preterm labour suppression in 1980[12].

In a recent study in which these two tocolytic agents Magnesium sulfate and Nifedipine were compared in terms of efficacy in preterm labour. The primary outcome was arrest of preterm labour, defined as prevention of delivery for 48 hours. Results showed that more patients assigned to magnesium sulfate achieved the primary outcome (87% compared with 72%, *P*=0.01). While comparing two drugs fewer maternal side effects were noticed with nifidipine[13].

But toxicity of magnesium sulfate can be reversed by its antidote (Calcium Gluconate). Magnesium sulfate may help to reduce the risk of cerebral palsy in babies who are born preterm[14].

The objective of the study was to compare the efficacy of magnesium sulfate versus nifedipine for prevention of preterm labour.

MATERIAL AND METHODS

This randomized controlled trial was carried out in the Department of Obstetrics & Gynecology, Nishtar Hospital, Multan from May 2015 to November 2015. A total of 250 patients of preterm labour, 18 to 45 years of age with singleton pregnancy of gestational age between 28 to 36^{+6} weeks (assessed on LMP) were included. Patients with severe pre-eclampsia, eclampsia, multiple gestation and Premature rupture of membrane were excluded. The selected patients were placed randomly into two groups i.e. Group-A (magnesium sulfate) & Group-B (oral nifedipine), by using lottery method. The efficacy was assessed if preterm labour was prevented and woman with preterm labour did not require an alternative tocolysis for 48hours.

Data was analyzed with statistical analysis program (SPSS version18). Numerical variables like age, gestational age were presented in the form of mean +SD. Outcome variable like efficacy was presented as percentages. Chi-square test was applied to compare efficacy in both groups. Effect modifiers like age, obesity, previous preterm labour, Gestational age and Inter pregnancy interval were controlled by stratification. Post stratification chi-square test was applied to see their effect on outcome. P-value equal or less than 0.05 was considered as significant

RESULTS

Age range in this study was from 18 to 45 years with mean age of 29.94±6.35 years. The mean age of women in group 1 was 29.54±6.67 and in group 2 was 30.48±6.08 years. Majority of the patients 118(47.20%) were between 26 to 35 years of age as shown in Table II.

Gestational age was from 28 to 37 weeks with mean age of 32.52±2.41 weeks. The mean gestational age in group 1 was 32.47±2.41 weeks and in group 2 was 32.69±2.41 weeks. Majority of the patients 103 (41.20%) were between 34 to 37 weeks of gestation as shown in Table III. %age of patients according to obesity in both groups has shown in Table IV. Table V & VI have shown the %age of patients according to previous history of preterm labour and inter-pregnancy interval.

There was prevention of preterm labour for 48 hours in 111(88.80%) patients in Group 1 while in Group 2, it was seen in 93 (74.40%) patients respectively. So, efficacy was 88.80% in group 1 (magnesium sulfate) and 74.40% in group 2 (oral nifedipine) with p-value of 0.003 as shown in Table VII.

Stratification of efficacy between two groups in terms of age and gestational age is shown in Table VIII & IX respectively while Table X & XI have shown the stratification of efficacy with respect to obesity and previous preterm labour respectively. Stratification of efficacy with respect to inter pregnancy interval in both groups is shown in Table XII.

Table-I: Age distribution for both groups

Age (years)	Group 1 (n=125)		Group 2 (n=125)	
	n	%age	n	%age
18-25	37	29.6	38	30.4
26-35	58	46.6	60	48.0
36-45	30	24.0	27	21.60
Mean ± SD	29.54 ± 6.67		30.48 ± 6.08	

Table-II: %age of patients according to Gestational age in both groups.

Age (weeks)	Group 1 (n=125)		Group 2 (n=125)	
	n	%age	n	%age
28-30	28	22.4	28	22.4
31-35	46	36.8	45	36.0
34-37	51	40.8	52	41.6
Mean ± SD	32.47 ± 2.41		32.69 ± 2.41	

Table III: %age of patients according to obesity in both groups.

Obesity	Group 1 (n=125)		Group 2 (n=125)	
	n	%age	n	%age
Yes	59	47.2	57	45.6
No	66	46.6	68	54.4

Table IV: %age of patients according to previous preterm labour in both groups.

Preterm labour	Group 1 (n=125)		Group 2 (n=125)	
	n	%age	n	%age
Yes	43	34.4	46	36.8
No	82	65.6	79	63.2

Table V: %age of patients according to interpregnancy interval in both groups.

OInter-pregnancy interval	Group 1 (n=125)		Group 2 (n=125)	
	n	%age	n	%age
<2 years	71	46.8	73	58.4
>2 years	54	43.2	52	41.6

Table VI: Comparison of Efficacy between both Groups (n=250).

Efficacy	Group 1 (n=125)		Group 2 (n=125)	
	n	%age	n	%age
Yes	111	88.8	93	74.4
No	14	11.2	32	25.6

Table VII: Efficacy

		Group 1 (n=125)		Group 2 (n=125)	
		n	%age	n	%age
EFFICACY	Yes	111	88.80	93	74.40
	No	14	11.20	32	25.60

P value is 0.003 which is statistically significant.

Table VIII: Stratification of efficacy of both groups according to age.

Age of patients	Group A (n=125)		Group B (n=125)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
18-25	32 (86.49%)	05 (13.51%)	31 (81.58%)	07 (18.42%)	**0.562**
26-35	54 (93.10%)	04 (6.90%)	43 (71.67%)	17 (28.33%)	**0.002**
36-45	25 (83.33%)	05 (16.67%)	19 (70.37%)	08 (29.63%)	**0.244**

Table IX: Stratification of efficacy of both groups according to gestational age.

Gestational age	Group A (n=125)		Group B (n=125)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
28-30 weeks	25 (89.31%)	03 (10.71%)	24 (85.71%)	04 (14.29%)	**0.686**
31-33 weeks	38 (82.61%)	08 (17.39%)	20 (44.44%)	25 (55.56%)	**0.000**
34-37 weeks	48 (94.12%)	03 (5.88%)	49 (94.23%)	03 (5.77%)	**0.980**

Table X: Stratification of efficacy of both groups according to obesity.

Obesity	Group A (n=125)		Group B (n=125)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
Yes	54 (91.53%)	05 (8.47%)	41 (71.93%)	16 (28.07%)	**0.006**
No	57 (86.36%)	09 (13.64%)	52 (76.47%)	16 (23.53%)	**0.142**

Table XI: Stratification of efficacy of both groups according to previous preterm labour.

Previous preterm labour	Group A (n=125)		Group B (n=125)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
Yes	38 (88.37%)	05 (11.63%)	37 (80.43%)	09 (19.57%)	**0.304**
No	73 (89.02%)	09 (10.98%)	56 (70.89%)	23 (29.11%)	**0.004**

Table XII: Stratification of efficacy of both groups according to inter-pregnancy interval.

Inter-pregnancy interval	Group A (n=125)		Group B (n=125)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
≤2 years	63 (88.73%)	08 (11.27%)	52 (71.23%)	21 (28.77%)	**0.009**
>2 years	48 (88.89%)	06 (11.11%)	41 (78.85%)	11 (21.15%)	**0.159**

DISCUSSION

Despite the introduction of new diagnostic and therapeutic technologies, there has been little reduction in the incidence of preterm birth over the past 30 years. While no treatment has proven highly effective in preventing preterm delivery in women who experience preterm labor, diagnosis at an early stage allows the use of interventions that may delay delivery for 48 hours or more. Tocolytics are drugs given to inhibit uterine contractions. Acute tocolysis is used to decrease or stop uterine contractions and slow or halt cervical change in women during preterm labor. Maintenance tocolysis refers to medication administered after acute tocolysis, in women with arrested preterm labor, to prevent a recurrence of preterm labor.

Since uterine contractions are the most frequently recognized symptom and sign of preterm birth, inhibition of uterine contractions with tocolytic agents (to prolong pregnancy and reduce neonatal complications) has been the focus of treatment of preterm labor. Tocolytic agents are intended to arrest uterine contractions during an episode of preterm labor (acute tocolysis) or maintain uterine quiescence after an acute episode (maintenance tocolysis). Several agents have been used for the inhibition of preterm labor but, unfortunately, it is still not clear what the first-line tocolytic agent should be 1) β_2-adrenergic-receptor agonists reduce the risk of delivery within 48 hours of initiation of treatment[19], Nevertheless, there is no evidence that this delay in the timing of birth leads to improvements in neonatal outcomes, and maternal adverse events are substantial 2) magnesium sulfate is effective in delaying birth or preventing preterm birth, and its use could be associated with decreased risk of cerebral palsy of neonate[19]3) there is not enough evidence of whether prostaglandin-synthesis inhibitors reduce the risk of preterm birth because studies have limited sample size[20];4) the oxytocin receptor antagonist, atosiban, was found to increase the proportion of patients remaining undelivered and not requiring an alternate tocolytic at 7 days when compared with placebo; yet, this was not associated with an improvement in neonatal outcomes which has been attributed to the complex design and interpretation of trials of tocolysis that involve a rescue maneuver[21].

In our study, we have compared the magnesium sulfate with oral nifedipine for prevention of preterm labour. The mean age of women in group 1 was 29.54 ± 6.67 and in group 2 was 30.48±6.08 years. Majority of the patients 118(47.20%) were between 26 to 35 years of age. These results were much higher compared to Taherian AA et al[22] study who had a mean age of 26 years for both groups. The mean gestational age in group 1 was 32.47±2.41 weeks and in group 2 was 32.69±2.41 weeks in our study while Taherian AA et al[22] had found mean gestational age for magnesium sulfate group as 32.06 weeks and for oral nifedipine group as 32.23 weeks.

In our study, preterm labour was prevented for 48 hours in 111(88.80%) patients in Group 1 while in Group 2, it was seen in 93(74.40%) patients respectively. So, efficacy was 88.80% in group 1 (magnesium sulfate) and 74.40% in group 2 (oral nifedipine) with p-value of 0.003. In a study by Naz S et al[24] showed that the efficacy of oral nifedipine as a tocolytic agents in stopping uterine contractions for 48 hours was 74.1% while Kawagoe Y et al[25] showed that after magnesium sulfate infusion, 90% patients prolonged their pregnancy for >48 hours. In a recent study in which these two tocolytic agents Magnesium sulfate and Nifedipine were compared in terms of efficacy in preterm labour[16]. The primary outcome was arrest of preterm labour, defined as prevention of delivery for 48 hours. Results showed that more patients assigned to magnesium sulfate achieved the primary outcome (87% compared with 72%, P=0.01)[16].

A case-series report of 192 women without a comparison group concluded that, the present study demonstrates the effectiveness of magnesium sulfate as a tocolytic agent to treat premature labor[26]. Another retrospective case series report on 355 patients (without a control group) reached a similar untenable conclusion, MgSO4 was found to be a successful, inexpensive, and relatively nontoxic tocolytic agent that had few side effects[27].

Five trials contributed data which included 556 women. There was no overall difference between nifedipine and magnesium sulfate for delivery within 48 hours of treatment, or before 34 or 37 weeks of gestation, gestational age at birth or in time from trial entry to delivery. Nifedipine was associated with a significant reduction in maternal adverse events (23.5% vs 35.6%; RR, 0.63; 95% CI, 0.48–0.82%=48%; NNT for benefit, 8; 95% CI, 5–19)28.[101] In addition, one trial[28] reported that severe maternal adverse effects were significantly less frequent among women receiving nifedipine than among women receiving magnesium sulfate (10.0% vs 21.7%; RR, 0.46; 95% CI, 0.23–0.93). There were no significant differences between the groups in the risk of major adverse neonatal outcomes, although a significant reduction was seen in the risk of admission to NICU (37.3% vs 51.9%; RR, 0.72; 95% CI, 0.53–0.97; NNT for benefit, 7; 95% CI, 4–69) and NICU length of stay (WMD, −2.2 days; 95% CI, −3.4 to −1.1; I^2=42.0%) in the nifedipine group compared with the magnesium sulfate group.

Glock JL et al[102] in his comparative trial had found that both these drugs were equally effective in arresting labor and delaying delivery > 48 hours, 92% versus 93%. Both study groups had a similar incidence of side effects, although four (10%) of magnesium sulfate-treated patients required drug discontinuation because of severe symptoms. A recent multicenter prospective cohort study from the Netherlands and Belgium, in which an independent panel evaluated the recorded adverse events without knowledge of the type of tocolytic used, reported that among 542 women treated with nifedipine, five (0.9%) had a serious adverse side effect and six (1.1%) had a mild adverse side effect[29].

So, this study concluded that magnesium sulfate was associated with higher efficacy for prevention of preterm labor as compared to oral nifedipine and gives some benefit from prolongation of pregnancy by enabling corticosteroid administration to accelerate fetal lung maturation which would help to reduce perinatal mortality and morbidity of both mother and fetus.

CONCLUSION

This study concluded that efficacy of Magnesium sulfate is higher than Nifedipine in prevention of preterm labour. So, we recommend that magnesium sulfate should be used as a first line agent for the prevention of preterm labour and thus some benefit could be achieved from prolongation of pregnancy by enabling corticosteroid administration to accelerate fetal lung maturation which would help to reduce perinatal mortality and morbidity of mother & fetus.

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