A comparative study of magnesium sulphate &isoxsuprine in threatened preterm labour– an interventional study in Karad

EdavallySuhasini[1], Nitin S. Kshirsagar[2*], Sanjaykumar Patil[3], Yamini Patil[4]

Abstract

Background: Preterm labour associated with perinatal mortality and its prevention continues to be a major challenge to the obstetricians. In the interest to safeguard both maternal and child health tocolytic agentsare preferred. The current study proposed to evaluate the effectiveness of Isoxsuprine with MgSO4, in management of threatened preterm labour.

Methods:Aninterventional non-randomized study was conducted among 100 participants sorted into Group 1 (Isoxsuprine group; n=50, received a 40 mg of the Isoxsuprine)and Group 2 (MgSO4 group; n=50, received a 4gm-6mg of the MgSO4 I.V. bolus of the drug to 500 ml of 5% dextrose drip). Patients in both groups were monitored for tocolytic index, mean prolongation, pregnancy outcome, maternal and foetal side effects.Data was analysed using the Chi-square test wherein the p≤ 0.05 indicated statistical significance.

Results: The mean prolongation of pregnancy was observed to be p<0.05 between two groups.Association between the pregnancy outcome and the groups (p=0.0345) and cost of treatment (p=0.001) was observed. While the maternal adverse effects were observed in 22% in Group I and 48% in Group II, foetal complications were noted in 8% of Group I and 18% of Group II.

Conclusions: The Isoxsuprine group showed better outcomes with less maternal and foetal complications than MgSO4 group in the management of threatened preterm labour. The drug Isoxsuprine is safe, cost effective and less toxic to MgSO4 in management of preterm labor.

KeyWords: Isoxsuprine - Magnesium Sulfate -Pregnancy Outcome - Premature Obstetric Labor - Tocolytic Agents
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Introduction

Preterm labour is the 'delivery before 37 full weeks of gestation' and is one of the principal challenges for obstetricians.[1]Pretermlabour or 'preterm' by definition is the onset of regular, painful uterine contractions, (around 4 episodes in 20 minutes or 8 in 60 minutes) with cervical effacement (80%) or more cervical dilatation (>1 cm) between 28-37 completed weeks of gestation. According to WHO in 2005, 12.9 million births, or 9.6% of all births worldwide were preterm.[1]It is further grouped into early (baby is born before 33 weeks) and late preterm (baby is born between 34 and 36 weeks).The prevalence of this condition ranges from 11% in developed countries like the USA; however, its twice as much as that (23.3%) in India.2 The preterm labour is accountable for 40–75% of neonatal deaths in India.[2]The raise in the incidence of preterm labour shows increasing trend, in countries owing to the psychosocial stress, assisted reproductive techniques or combination of multiple factors.[3-5]

The multiple factors enlisted as risk factors of the preterm labour are age <18 or >40, low body mass index/poor nutrition, vaginal bleeding/infection, substance use, smoking, placental

Corresponding author: Nitin S. Kshirsagar
Address: [1]Post Graduate Student, Department of Obstetrics &Gynaecology, Krishna Institute of Medical Sciences, Karad-415110, Maharashtra, India;[2] Professor, Department of Obstetrics &Gynaecology, Krishna Institute of Medical Sciences, Karad-415110, Maharashtra, India, [3] Professor, Department of Obstetrics &Gynaecology, Krishna Institute of Medical Sciences, Karad-415110, Maharashtra,India, [4] Associate Professor, Department of Obstetrics &Gynaecology, Krishna Institute of Medical Sciences, Karad- 415110, Maharashtra,India

abruption, placenta previa, history of preterm birth or abortion, inadequate prenatal care, foetal developmental issues, oligohydramnios, premature preterm rupture of membranes (PPROM) and stress.[6]

The diagnosis of pre-term labour is achieved by medical examinations like vaginal examination, cervix length measurement by trans-vaginal ultrasonography, cardiotocography and abdominal ultrasonography of the foetus.[7] The history and risk factors and above diagnostic tools must be adapted for a timely diagnosis, to avoid complications. Preterm labour has been associated with maternal complications such an increased risk for maternal cardiovascular mortality and impaired infantile neurodevelopment.[8]Theneonatalcomplications like intraventricular haemorrhage, weak growth necrotizing enterocolitis, congenital anomalies are also well documented.[8]

Preterm labour before 34 weeks needs to be arrested for at least 48 h so that foetal pulmonary maturity is attained. The β-adrenergic receptor blocking agents (Isoxsuprine hydrochloride and calcium channel blocker nifedipine) are commonly used tocolytic agents in India..[2]The efficacy of Isoxsuprine [1-(4-hydroxyphenyl)-2-(1-methyl-2-phe-noxyethylamino)-1-propanol], in both preterm labour and risk of abortion is well establihsed.[9,10]The other drugs used in the medical management of preterm labour includes use of Oxytocin-receptor antagonists, Inhibitors of prostaglandin synthesis, Nitric oxide donors and Magnesium).[8,9]The prenatal administration of glucocorticoids before the end of 34thweek of pregnancy is employed additionally for the prevention of serious complications in the neonate.Magnesiumsulphate (MgSO4) is reported to have the ability to non-specifically displace calcium from the voltage-dependent calcium channels of myometrial cell membrane.[7] The treatment with this drug is controversial (owing to foetal effects like protection form cerebral palsy while causing motor / cognitive functional disorder later) among various studies.[11,12]A meta-analysis from a pooled data of 23 clinical trials had reported that magnesium sulphate to be ineffective in delaying birth, preventing preterm births, and associated with an infant increased mortality.[12]

Thus, the pre-term labour is constantly presenting issue in hospital settings and many medications are used for preventing it, but their effectiveness is not clearly known and those with better neonatal outcomes need further evaluations regarding their efficacy and safety. The current study was planned to evaluate the efficacy of Isoxsuprinewith magnesium sulphate (MgSO4)for maternal and foetal parameters in threatened preterm labourinKarad, Maharashtra. The study also comparatively analysed maternal and perinatal complications associated with these tocolytic agents.

Methodology

Study Settings And Sample

AnInterventional, non-randomized, open-label study was conducted from May 2016 to May 2017(a period of 12months)ata tertiary care hospital in Karad.The approval of the Institutional Ethics Committee (Reference number: KIMSDU/IEC/02/2016)and Informed patient consent wasobtainedbefore initiating the study.

The sample size was calculated by using the formula

$$n = \frac{2\left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2}{d^2} \; where, \; d = \frac{|\mu_1 - \mu_2|}{\sigma},$$

where μ1 is mean of the first group, μ2 is mean of the second group, σ^2 is the common error variance, $Z_{\alpha/2}$value is 1.96 for 95% confidence level and Z_{β} value is 1.645 for 95% power.Here we assumed that, there is considerable difference between the two groups.

Hence, the value of Cohen's d is 0.75. By using above formula, the sample size was obtained to be 48 subjects per each group. Total sample size required is 48 x 2 = 96 subjects.As sample size increases, accuracy of result increases. So, 100 subjects were considered in this study (i.e.50 in each group).

Patients with pregnancies between 20 to 36 weeks with intactmembranes, presenting with threatened or established preterm labourdiagnosed on the basis of painful uterine contractions, at least onceevery 10 minutes, with every minimal cervical changes in the form ofeffacement and dilatation (not exceeding 3 cm) were included in this study. The participants with severe preeclampsia and eclampsia, antepartum, haemorrhage, hydramnios, chorioamnionitis, cardiac disease, thyroid disorder and advanced labour were excluded. The foetal factors for exclusion were severe intrauterine growth restriction ,intrauterine contraceptive device, oligohydramnios or any foetal anomalies incompatible with life.

The methodology of the study included the

following interventions were given for each group respectively. Group 1 (Isoxsuprine group; n=50) :A 40 mg of the Isoxsuprine (500 ml of 5% dextrose drip) was started with 8 drops per minute and was increased as required. It was given for 24 hours.Group 2 (MgSO4 group; n=50): A 4gm-6mg of the MgSO4I.V. bolus of the drug to 500 ml of 5% dextrose drip was given at 2 gm/ hour. It was continued for 72 hours.

Data collection details

The data for both groups corresponding to the demographic and history of pregnancy was recorded. The clinical findings on general examination, investigations and treatment/ follow-up data were also recorded.

Outcome parameters

The essential demographic and clinical data[Ex: age, pregnancy status (primi/multi para), anaesthesia type (general / local use)] along with parameters like mean prolongation (in days), pregnancy outcome in treatment groups, frequency of pregnancy outcome in failure cases, frequency of maternal side effects, frequency of perinatal complication and total cost effectiveness (in rupees) between groups was recorded and compared between groups.

Patients in both groups were monitored for these standard parameters [pulse/Blood pressure /Foetal Heart Sounds/ urine output /respiration/ knee jerk] and adverse effects. The data between the groups was compared by statistical analysis.

Statistical analysis

Data was analysed using statistical software R (version 4.0.1). The categorical variables were represented by frequency tables, the continuous variables in the form of Mean ± Standard Deviation. The Chi-Square test was used to check the association between attributes. P-value less than or equal to 0.05 indicated statistical significance.

Results

The mean age of participants was 23.62 ± 3.95 years for group 1 and 23.48 ± 2.46 years for group 2. A significant difference ($p<0.05$) was noted in the meanduration of prolongation of pregnancy i.e.34.78±20.19 days for group 1 and 30.28±11.84 days for group 2. The success in propagation (of duration of pregnancy) upto 34-36 weeks was obtained in 98% (n=49) of cases in group 1 and 86% of cases (n=43) in group 2. The failure rate was 2% (n=1) for group 1 as opposed to 14% (n=7), which was significantly different ($p<0.05$) between groups.A significant association was present between the pregnancy outcome and the groups ($p=0.0345$) and cost of treatment ($p=0.001$).The strength of association was low. Table 1 shows comparison of few maternal parameters in both groups.

The strength of association was high. Likewise, a significant difference in distribution of cost over the two groups ($p=0.001$). See Table 1.It is observed that, the cost involved in MgSO4 (431.2 ± 64.42 rupees) is more compared to Isoxsuprine(357.2 ± 29.49 rupees), the difference was significant between the groups ($p<0.001$; Mann Whitney U test).

Considering the maternal side effects, around 8% (n=4) had hypotension and 10% (n=5) had tachycardia in group 1. The major maternal side effects in group 2 were 9 %(n=18) vomiting and 2 %(n=1) hot flushes. See Table 2. The foetal complications when compared between the groups, showed that birth asphyxia was common in group 1, while preterm and foetal complications due to obstetrical causes were common side effects in group 2.See Table 3.

Discussion

Threatened preterm labour (TPL) is the progression of cervical dilatation and ripening caused by uterine contractions occurring before 37 weeks of pregnancy, resulting in preterm birth.Pretermlabour is when the 'delivery before full term of gestation' occurs with maternal and foetal complications. [13, 14]The complications of this condition could be maternal, infantile or neonatal. [8, 13]The tocolytic agents are often used along with glucocorticoids for the prevention of serious complications. Magnesium sulphate (MgSO4) is reported to have both positive and negative effects on the outcome of preterm labour. [11-14].Theefficacy of magnesium sulphate and routinely used Isoxsuprine in threatened preterm labour were compared in the current study, among the subjects of Karad.

The mean age of participants was 23.62 ± 3.95 years for group 1 and 23.48 ± 2.46 years for group 2which is line with study by Ahankari et al which showed a mean age of 22 years.[13]The incidence of preterm delivery was foundto be more in the age group of 20-26 years in the present study. Ahankari et al showed that 75% of preterm deliveries

occurred in women above 22 years, [13] of age which is in line with current findings.Considering the costs, a significant association was noted between the cost involved and the groups (p=0.001). The strength of association was high. Singh et al noted that Isoxsuprine had better outcomes than Nifedipine,whileIsoxsuprine was superior to MgSO4 in the current study. [2]

Considering the side effects, hypotension and tachycardia were common in group 1 while heat and vomiting were common in group 2. An Indian study had reported that Poor progress Pre-term labour, Hypertensive disorder, Retained products and obstructed labour to be common maternal side effects.[15]Another study had reported that 7.3% of the women (n=1,927) who gave birth in the local hospitals had a severe complications ofhaemorrhage, hypertension, infection, anaemia and dystocia while 16.1% had a less-severe complication.[16]The major maternal complications reported in the study were like hypotension and tachycardia in group 1 and vomiting in group 2. The foetal complications when compared between the groups, showed that birth asphyxia was common in group 1, while preterm and foetal complications due to obstetrical causes were common side effects in group 2. The foetal complications as per a rural Indian study were Foetal distress, Breech presentation and post-deliveryconditions(PDC). [15]

The drug Isoxsuprine was not effective as a maintenance treatment in preventing pre-term births or in delaying delivery until after 34 weeks and most acceptable drug for preterm labour. The findings of the current study also favour group 1 (Isoxsuprine) over group 2(MgSO4) which is in line with other studies. [2,4,7]group 2(MgSO4) was less efficient and showed more complications in the current study which is also reported by a Cochrane meta-analysis of 23 trials on a total of 2036 patients which also showed a 2.82-fold elevation of perinatal mortality. The review showed that MgSO4failed to document efficacy for the prolongation of pregnancy by 48 hours. [12]Themagnesium sulphate cannot be recommended as a treatment due to considerable maternal side effects as per exiting reports and guidelines.[17-19] The treatment with this drug is controversial among various studies.[11,12]The efficacy of Isoxsuprine, on the other hand, is well established and endorsed by high quality secondary research.[9,10]

The strengths of the study lie in analysing efficiency of two commonly used drugs for rural Indian population. This weakness lies in simplicity of design and smaller sample. The future directions include large scale, meta-centric studies evaluating multiple parameters for maternal and foetal complications.

Conclusion

The Isoxsuprine group showed better outcomes with less maternal and foetal complications than MgSO4 group in the management of threatened preterm labour.The drug Isoxsuprine is safe, cost effective and less toxic compared to MgSO4 in the management of preterm labor.

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Conflicting Interest

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Conflict of Interest

None

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Table 1: Comparison of distribution of different variables over the groups

Variable	Sub-Category	Isoxsuprine	MgSO4	p-value (Cramer's V)
Age (years)	Mean ± SD	23.62 ± 3.95	23.48 ± 2.46	0.8322W
Gravida	Primi	20 (40%)	16(32%)	0.4047C
	Multi	30(60%)	34(68%)	
Gestational Age (Weeks)	Mean ± SD	32.06 ± 2.88	31.9 ± 2.53	0.7738W
Hospital stay (days)	Median (Min, Max)	3 (1, 60)	4 (2, 9)	0.2452MW
Pregnancy Outcome (success/ failure)	Failure	1 (2%)	8 (16%)	0.0345MC* (0.2446)
	Successful	49 (98%)	42 (84%)	

Abbreviation: W – Welch t test; C - Chi square test; MW – Mann Whitney U test; $p<0.05$ is considered as significant.

Table 2: Comparison of frequency of maternal complications between the groups

Side Effects	Group 1 (Isoxsuprine) Frequency (%)	Group 2 (MgSO4) Frequency (%)
Tachycardia	4 (8%)	2 (4%)
Hypotension	5 (10%)	0 (0%)
Headache	0 (0%)	1 (2%)
Nausea	0 (0%)	3 (6%)
Vomiting	0 (0%)	9 (18%)
Hot flushes	0 (0%)	1 (2%)
PPH	0 (0%)	1 (2%)
Giddiness	1 (2%)	3 (6%)
Heat	0 (0%)	4 (8%)
CMP	1 (2%)	0 (0%)

Table 3: Comparison of frequency of perinatal complication between the groups

Side Effects	Group 1 (Isoxsuprine) Frequency (%)	Group 2 (MgSO4) Frequency (%)
Birth asphyxia	2 (4%)	1 (2%)
Hypotonia	0 (0%)	1 (2%)
Preterm	1 (2%)	4 (8%)
DAMA	1 (2%)	0 (0%)
Foetal tachycardia	0 (0%)	1 (2%)
Foetal complications due to obstetrical causes	0 (0%)	2 (4%)