

## Role of Magnesium Sulphate In Management of Preterm Labor

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### Introduction

Preterm labor remains one of the last frontier of present day obstetrics. Preterm birth is a condition that occurs in 6.0-15% of all deliveries and is the most frequent cause of fetal & neonatal death and morbidity. Preterm birth is defined as birth before 37 weeks of gestation. Late preterm births between 34 weeks and 0 days and 36 weeks and 6 days account for about 74% of all preterm births while the very preterm less than 32 weeks has remained relatively constant during the last two decades. The incidence of preterm births ranges between 10 and 15% .and 75% of all perinatal deaths occur in preterm infants.

The incidence of PNMR in India varies from 40 and 150 per 1000 births in contrast to 10-20 in the developed countries. Despite advances in perinatal medicine in recent decades, problem of preterm delivery continues to frustrate satisfactory reproductive outcome, with little progress having been made in reducing frequency of preterm births.

Problem of neurological handicap in groups below thirty four weeks has decreased considerably in western countries. Same cannot be said of developing countries. We have to think in terms of instituting more neonatal intensive care units which are limited to a few tertiary centers. Therefore solution lies in improving antenatal care and preventing preterm labor.

Preterm labour is defined as initiation of regular painful contractions that occur usually with increasing frequency and intensity associated with progressive cervical changes of effacement and dilatation culminating in delivery of preterm infant.

**Keywords:** Preterm Labor, Magnesium Sulphate

Date of Submission: 02-04-2018

Date of acceptance: 17-04-2018

### I. Aetiology

There are four main direct reasons for preterm birth

1. Delivery for maternal or fetal indications – 30-35%
2. Spontaneous unexplained preterm labour with intact membranes – 40-45%
3. Idiopathic preterm premature rupture of membranes – 30-35%
4. Twins and higher order multifetal births

Of preterm births, 30 to 35% are indicated, 40-45% are due to spontaneous preterm labour and 30 to 35% follow PROM (Goldenberg and colleagues 2008b). PROM and spontaneous preterm labour together lead to 70-80% of preterm births. According to data from Martin and Co-workers (2006), approximately one in six preterm births in United States are from twins or higher order multifetal pregnancies.

Ananth and Vintzileos (2006) used Missouri birth data from 1989 to 1997 to analyse factors leading to indicated birth before 35 weeks. Preeclampsia, fetal distress, small for gestational age and placental abruption were the most common indications for medical intervention resulting in preterm birth. Other less common causes were chronic hypertension, placenta praevia, unexplained bleeding, diabetes, renal disease, Rh isoimmunisation and congenital malformations. Contributing factors are like Maternal: Low socioeconomic status, Smokers, age less than 18 or greater than 40 years, prior preterm birth, acute diseases like Vaginal infections, UTI, Toxoplasmosis, over distension of uterus, Uterine anomalies, PROM, Abruption placenta, Placenta previa and congenital anomalies of foetus.

### II. Physiology And Factors Responsible For Onset Of Preterm Labor

Preterm birth has major human consequences – after congenital anomalies, it is the greatest cause of neonatal morbidity and mortality. Spontaneous preterm labor with intact fetal membranes is the most common cause of preterm delivery and accounts for about half of preterm births. In another quarter, preterm premature rupture of membranes is almost always followed by preterm delivery. Many factors increase the likelihood of preterm delivery. Some of these are genetics, infection, nutrition, behaviour and the environment.

The common pathway of parturition has three components – cervical ripening, activation of the myometrium, and activation of fetal membranes.

In normal term birth these components are activated simultaneously. In preterm birth, it is not unusual to have predominant activation of one or two of the components, resulting in variations in symptoms and signs . Premature ripening of the cervix is the predominant feature in women with incompetent cervix, premature activation of the membranes is the key component in women with preterm rupture of membranes and premature activation of the myometrium is the cardinal feature in women with preterm labour and intact membranes.

### III. Identification Of Women At Risk Of Preterm Labor

**RISK SCORING SYSTEMS** – Decided by Papiermik modified by Greasy, 1980. There has been considerable interest in risk scoring systems to identify women at greatest risk for preterm birth.

Points	Socioeconomic factors	Previous medical history	Daily habits	Aspects of current pregnancy
1	Two children at home, low socioeconomic status	Abortion x 1 less than 1 yr since last birth	Works outside	Unusual fatigue
2	Maternal age < 20 yr Or > 40 yr Single parent	Abortion x 2	Smokes >10 cigarettes per day > 3 flights of stair without elevator	Gain of < 5 kg by 32 wk
3	Very low socioeconomic status Height < 150 cm Weight < 45 kg	Abortion x 3	Heavy or stressful work that is long and tiring, Long daily commuting Extensive traveling	Breech at 32 wks weight loss Head engaged at 32 wks febrile illness
4	Maternal age < 18 yr	Pyelonephritis		•Bleeding after 12 wks short cervix Opened internal os Uterine irritability
5		Uterine anomaly second – trimester abortion DES exposure cone biopsy		Placentapraevia Hydramnios
10		Preterm delivery, repeated second trimester abortion		Twins, Abdominal surgical procedure

In their review, Hueston and associates (1995) found no benefits of this programmatic approach. Mercer and colleagues (1996) concluded that risk assessment failed to identify most women who deliver preterm neonates. In another study , Klerman and co-workers (2001) randomly assigned 619 women with a modified risk assessment score for preterm delivery of 10 or higher to receive augmented or customary prenatal care. Mean birth weight and incidence of preterm delivery and low birth weight were similar in both groups and in the general obstetrical population.

### MANAGEMENT OF PRETERM LABOR

Goals of obstetric patient management of preterm labor should include Early identification of risk factors associated with preterm birth, Timely diagnosis of preterm labor, Identifying the etiology of preterm labor, Evaluating fetal well-being, Providing prophylactic pharmacologic therapy to prolong gestation and reduce the incidence of respiratory distress syndrome(RDS) and intra-amniotic infection(IAI), Initiating tocolytic therapy when indicated, and Establishing a plan of maternal and fetal surveillance with patient.

Preterm labor may be difficult to diagnose and a potential exists for overtreatment of uterine irritability. The risk of neonatal mortality and morbidity is low after 34 completed weeks of gestation; although a trial of acute tocolysis may be initiated, aggressive tocolytic therapy is generally not recommended beyond 34 weeks, due to potential maternal complications. Between 24 and 33 weeks gestation, benefits of tocolytic therapy are generally accepted to outweigh the risk of maternal and/or fetal complications and these agents should be initiated provided no contraindications exist.

### **Diagnosis**

Contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix at 24-37 weeks' gestation are indicative of active preterm labor. If the diagnosis of preterm labor is suspected, but not confirmed, it may be prudent to first obtain a vaginal fetal fibronectin (FFN) sample before pelvic cervical examination. If the diagnosis of preterm labor becomes obvious after the pelvic examination, the FFN specimen can be subsequently discarded. However, if the diagnosis remains in doubt, the FFN specimen can be sent to the lab for analysis.

Criteria that indicate consideration of tocolytic therapy include more than 6 contractions per hour resulting in a demonstrated cervical change or presumed prior cervical change (transvaginal cervical length <2.5 cm, >50% cervical effacement, or cervical dilation  $\geq$  2 cm). If contractions are present without cervical change, management options include continued observation or therapeutic sleep (eg, morphine sulphate 10-15 mg subcutaneous). If the FFN is negative and the contractions abate, the patient may be sent home with appropriate follow-up evaluation.

### **TOCOLYTIC AGENTS**

Various tocolytics like Betamimetics(Terbutaline,Ritodrine,Isoxsuprine),Prostaglandin Synthase Inhibitors(Indomethacin,Sulindac),Calcium channel Blockers(Nifedipine,Nicardipine),Oxytocin Antagonists(Atosiban),Nitric Oxide Donors(Glyceryl Trinitrate) and Magnesium Sulphate are being used for management of preterm labor.

Criteria for Ideal uterine inhibiting agents

- should be efficient in inhibiting uterine activity
- should not alter maternal and foetal hemodynamics
- should be free from the side effects on mother and foetus
- should not later the course of labor
- should be free from 3<sup>rd</sup> stage complications like post partum hemorrhage

### **MAGNESIUM SULPHATE**

Magnesium Sulphate has been used for many years in the prophylaxis of convulsions in the women with pre eclampsia. The use of this drug for treatment of preterm labor originated in the observation that it causes the decrease in frequency and intensity of contractions in pre eclamptic women in labor. Magnesium sulphate is widely used as primary tocolytic agent because it has similar efficacy to terbutalin with far better tolerance.

### **PHARMACOLOGY**

Magnesium sulfate is  $MgSO_4 \cdot 7H_2O$  and not simple  $MgSO_4$ . At high serum concentrations Mg is a potent vasodilator, muscle relaxant and sedative. Magnesium is the second most common intracellular cation. One half of body Mg is in bone, one-fourth is in muscle and one-fourth is in soft tissue.

About 25% to 30% of total plasma Mg is bound to protein, 10% to 15% circulates in complex form and 55% to 60% is ionized. Readily crosses the placenta and is distributed in mothers milk, however breastfeeding is not contraindicated.

### **HALFLIFE**

An elimination half life of 43.2 hours has been reported in newborn infants whose mothers received magnesium sulphate. The elimination rate is the same for both preterm and infants.

### **TOXICOLOGY**

Parenterally administered magnesium is cleared almost totally by renal excretion, and magnesium intoxication is unusual when the glomerular filtration rate is maintained or only slightly decreased. Adequate urine output usually correlates with preserved glomerular filtration rates. That said, magnesium excretion is not urine flow dependent, and urinary volume per unit time does not, per se, predict renal function. Thus, serum creatinine levels must be measured to detect signs of declining glomerular filtration rate.

Patellar reflexes disappear when the plasma magnesium reaches 10 meq/L-about 12 meq/L-presumably because of a curariform action. This sign serves to warn of impending magnesium toxicity. When

plasma levels rise above 10meq/L breathing becomes weakened, and at 12meq/L or more, respiratory paralysis and respiratory arrest follow. Somjen and colleagues (1966) induced marked hypermagnesemia in themselves by intravenous infusion and achieved plasma levels upto 15meq/L. Predictably, at such high plasma levels, respiratory depression developed that necessitated mechanical ventilation but depression of the sensorium was not dramatic as long as hypoxia was prevented.

#### **CVS EFFECTS:**

Direct toxic effects on the myocardium from high levels of magnesium are uncommon. It appears that the cardiac dysfunction associated with magnesium is due to respiratory arrest and hypoxia. With appropriate ventilation, cardiac action is satisfactory even when plasma levels are exceedingly high (Mc Cubin and co-workers, 1981).

#### **RENAL EFFECTS:**

Because magnesium is cleared almost exclusively by renal excretion, the dosages described will become excessive if glomerular filtration is decreased substantively. The initial 4-g loading dose of magnesium sulfate can be safely administered regardless of renal function. It is important to administer the standard loading dose and not to reduce it under the mistaken conception that diminished renal function requires it. This is because after distribution, a loading dose achieves the desired therapeutic level and the infusion maintains the steady-state level. Thus only the maintenance infusion rate should be altered with diminished glomerular filtration rate. Renal function is estimated by measuring plasma creatinine. Whenever plasma creatinine levels are >1.0 mg/mL, serum magnesium levels are used to adjust the infusion rate. Magnesium decreased systemic vascular resistance and mean arterial pressure, and at the same time increased cardiac output without evidence of myocardial depression. These findings were incidental with transient nausea and flushing, and the cardiovascular effects persisted for only 15 minutes despite continued magnesium infusion.

#### **CNS EFFECTS:**

There was a small and highly significant increase in total magnesium concentrate in the cerebrospinal fluid with magnesium therapy. The magnitude of the increase was directly proportional to the corresponding serum concentration.

#### **FETAL EFFECTS**

Magnesium administered parenterally promptly crosses the placenta to achieve equilibrium in fetal serum and less so in amniotic fluid (Hallak and co-workers, 1993). Levels in amniotic fluid increase with duration of maternal infusion (Gortzak-Uzen and associates, 2005). Elevated levels in the newborn may persist for upto 7 days with an elimination half-life of 43.2 hours. Magnesium sulphate helps in preventing cerebral palsy (Grether and associates, 2000; Nelson and Grether, 1995; Beams study-Rouse and colleagues, 2008)

#### **MECHANISM OF ACTION**

It acts by competitive inhibition to calcium ion either at the motor end plate or at the cell membrane reducing calcium influx. It decreases acetylcholine release and its sensitivity at the motor end plate. It has direct depressant action on the uterine muscle.

**Side effects are** Muscular weakness, Pulmonary congestion, Respiratory depression, Neurotoxicity, Neonatal depression (rarely), Neonatal hypotonia, Neonatal hypocalcemia.

### **IV. Aims And Objectives Of Study**

To study the effectiveness of intravenous magnesium sulphate in arrest of preterm labor. The following factors were taken into consideration

1. Time taken for uterine contractions to subside after starting intravenous magnesium sulphate
2. Number of days gained in utero after treatment with drug.
3. Side effects and toxicity to drug
4. Birth weights and APGAR scores of babies in treatment failure and success groups.

### **V. Materials And Methods**

In this study 50 patients admitted in labor wards of obstetrics and gynaecology department, Victoria General Hospital, Visakhapatnam from September, 2016 to October 2017 with a diagnosis of preterm labor between 28 to 36 weeks period of gestation were included. After admission each patient was assessed clinically and ultrasonically for period of gestation. After excluding congenital anomalies, uterine contraction, cervical effacement and dilatation were assessed.

### **INCLUSION CRITERIA**

1. uterine contractions occurring at least twice in every 10 minutes regularly synchronizing with pain.
2. Dilatation of cervix varying from 1-4 cms and cervical effacement 50% or more.
3. Women were considered suitable for inclusion if they had pregnancies with intact membranes between 28-36 weeks gestation.
4. No evidence of infection (Cases of urinary tract infections were treated with antibiotics).

### **EXCLUSION CRITERIA**

1. Cervical dilatation > 4 cms
2. Women with polyhydramnios, ruptured membranes, chorioamnionitis, twin pregnancies, abruption placenta & placenta previa
3. Irregularity of fetal heart rate- indicating fetal distress, fetal malformation, IUGR, IUFD
4. Maternal medical condition like PIH, cardiac disease, diabetes, myasthenia gravis

**Preliminary investigations** are Complete blood count, CRP, Serum Creatinine, Urine Analysis-C/S and Ultrasound.

### **VI. Methods Of Administration**

- Administer loading dose of intravenous magnesium sulfate 4 gm bolus over 20mins followed by 2g/hr infusion, until uterine quiescence was achieved
- Drip was maintained for 12 hrs if uterine contractions were abolished within 2 hrs.
- Those patients who continued to have uterine contraction with progressive Cx dilation even after 2 hrs after commencement of Rx were allowed to progress.
- Catheterise patient and maintain Mg So<sub>4</sub> Chart including level of consciousness, PR, RR, BP, Lung sounds, DTR, Urine output, uterine contractions
- All patients should receive 2 doses of 12 mg of betamethasone im 24 hrs apart
- Add 20 gms Mg So<sub>4</sub> in 500 ml 5% dextrose
- Start drip rate at 75 drops per minute for 20 minutes. For maintenance infusion adjust drip rate @ 12 to 15 drops per minute for next 12 hrs.

### **MONITORING**

- Blood Pressure- systolic, diastolic, Pulse rate, Respiratory rate, Heart, Lungs, urine output, knee jerk were monitored every thirty minutes
- Uterine contractions- By noting hardening of uterus on abdominal palpation number of contractions in 10 min / duration were noted.
- Fetal Heart Rate every 15min with pinard's fetoscope because of non availability of sophisticated fetal monitoring equipment (whenever doubtful doppler verification was done). Side effects of drugs noted.

Patients were kept in hospital for a week after completion of therapy and then discharged. At the time of discharge general condition of patient was checked regarding Pulse Rate, Blood Pressure, Fetal Heart Rate.

Patient was asked to come for follow up every week or to report to hospital when she gets backache or pain abdomen. At every Antenatal visit, general condition of mother and growth of fetus were assessed clinically and for some cases by ultrasound. After delivery gestational age of fetus and weight were assessed.

Treatment to delivery time, baby weight, APGAR score, neonatal mortality were noted after delivery

### **Success of Tocolysis**

- 1) Tocolysis was considered successful if there was no recurrence of uterine contractions and no cervical dilatation and pregnancy was prolonged for more than forty eight hours .

### **Failure of Tocolysis**

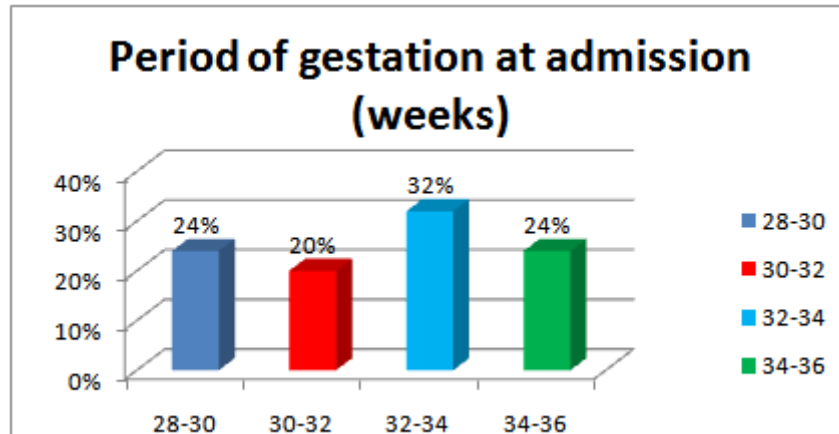
- 1) Cases delivering within 48hrs [Minimum time for action of corticosteroids].
- 2) No cessation of uterine contractions within therapeutic dosage limit

**V. Results And Analysis**

A total of 50 cases were taken up for evaluation of magnesium sulphate in the management of preterm labor of them, 2 cases did not come for follow-up and treatment was curtailed in 2 cases due to toxicity features. The treatment was deemed successful if contractions were abolished and no further cervical dilation occurred during treatment and there was no recurrence of contractions within 48 hrs of stopping the treatment.

**TABLE-1 PERIOD OF GESTATION**

Period of gestation at admission (weeks)	No. of patients	Percentage
28-30	12	24%
30-32	10	20%
32-34	16	32%
34-36	12	24%

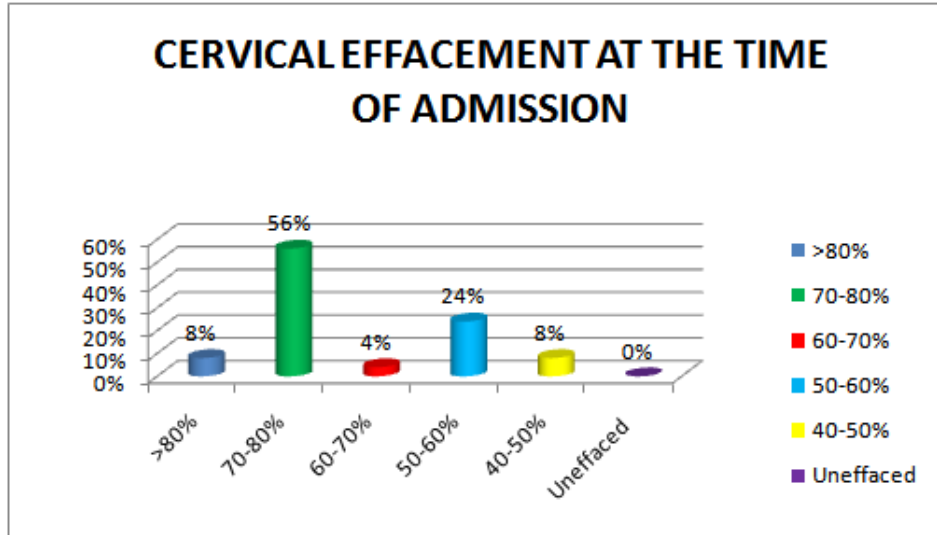


Most of the patients were between 32-34 weeks period of gestation. 66% of patients in this study belong to gestational age >32 weeks. Birth weight in these fetuses will be >1.5kgs and with proper preterm labor management and good neonatal support, many fetuses can survive.

**TABLE-2 Cervical Effacement At The Time Of Admission**

Cervical effacement	No. of patients	Percentage
>80%	4	8%
70-80%	28	56%
60-70%	2	4%
50-60%	12	24%
40-50%	4	8%
Uneffaced	0	0%

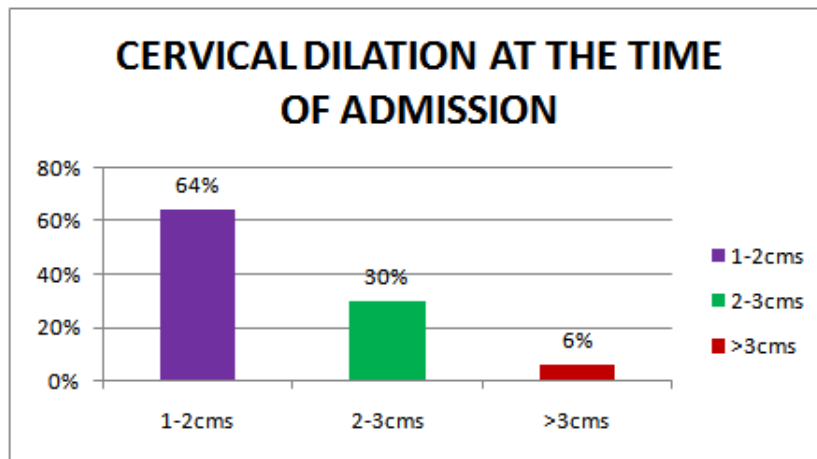
Out of 50 cases studied, 28 (56%) were with cervical effacement of 70-80%. Almost all cases had cervical effacement >50%. Therefore in patients with history of PTL, antenatal examination of cervix - PV/ultrasound can be a predictor of PTL.



**TABLE-3** Cervical Dilatation At The Time Of Admission

Cervical dilatation (in cms)	No. of patients	Percentage
1-2cms	32	64%
2-3cms	15	30%
>3cms	3	6%

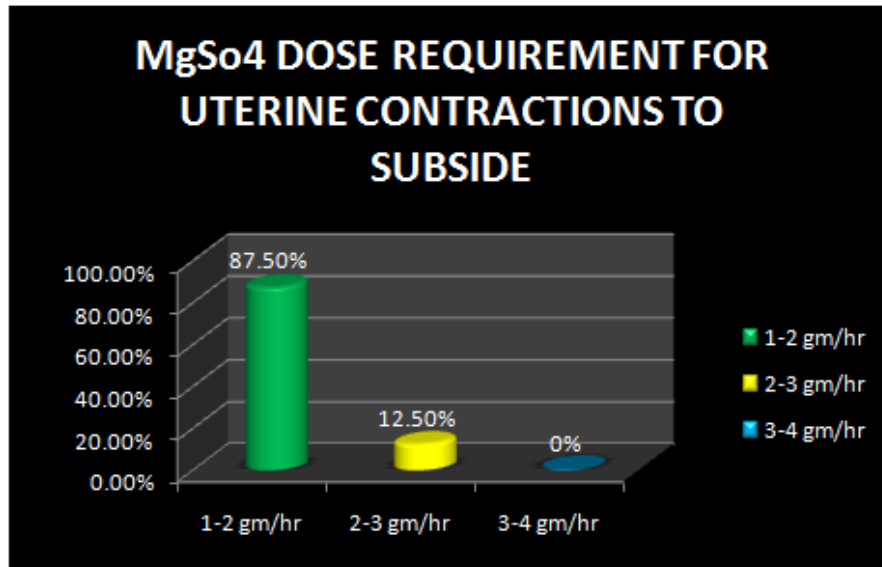
Out of 50 cases studied, 32 (64%) were with cervical dilatation in the range of 1-2cms. Majority of patients in the present study were in latent phase of labor, where tocolysis is helpful.



**TABLE-4** Mgso<sub>4</sub> DOSE REQUIREMENT FOR UTERINE CONTRACTIONS TO SUBSIDE

MgSo <sub>4</sub> Maintenance dose (gm/hr)	No. of patients	Percentage
1-2 gm/hr	42	87.5%
2-3 gm/hr	6	12.5%
3-4 gm/hr	0	0%

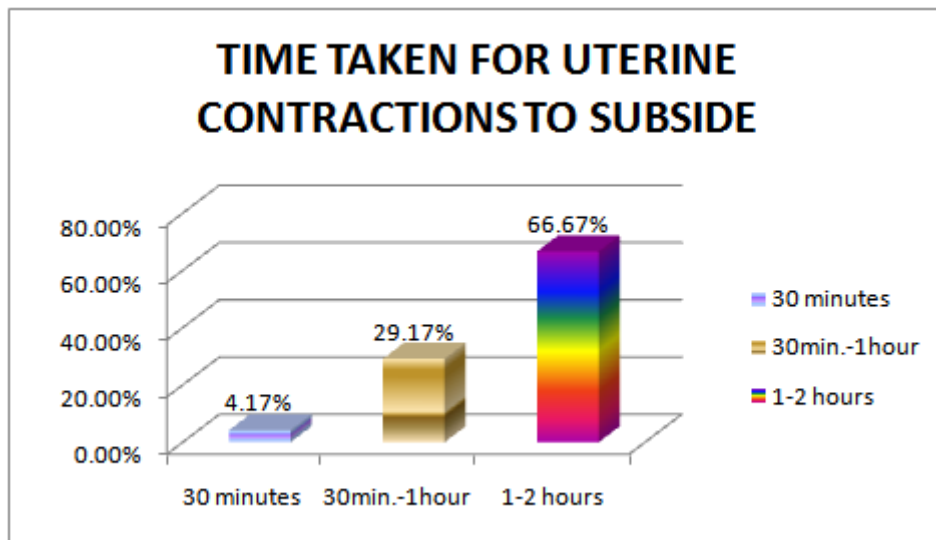
Most of the patients in this study required MgSo<sub>4</sub> maintenance dose at 1-2 gm/hr – 42 (87.5%) and none required dose >3gm/hr.



**TABLE-5** Time Taken For Uterine Contractions To Subside

Time	No. of patients	Percentage
30 minutes	2	4.17%
30min.-1hour	14	29.17%
1-2 hours	32	66.67%

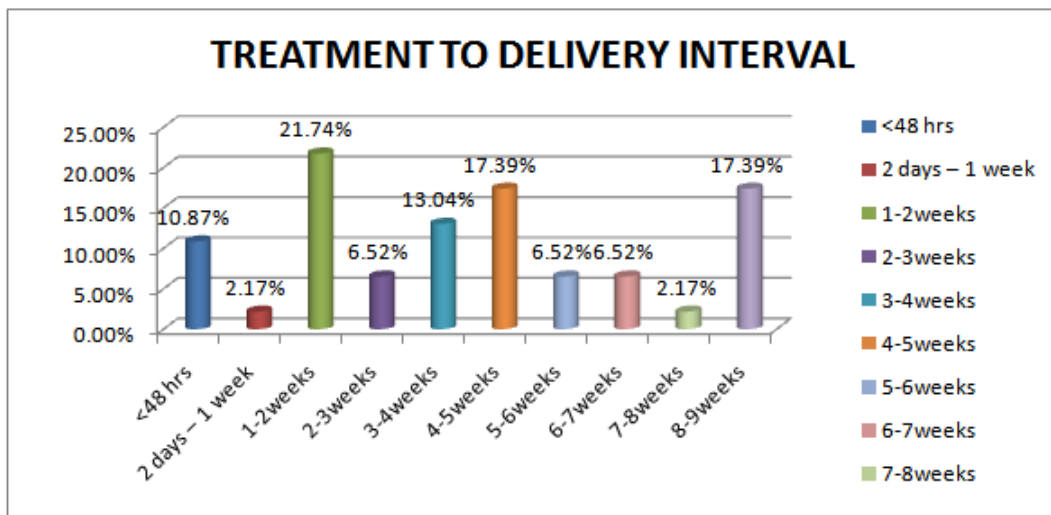
Out of 50 cases, treatment was stopped in 2cases due to toxicity features. Out of remaining 48 cases, 32 (66.67%) cases took 1-2 hours for uterine contractions to subside after commencing treatment.





**TABLE-6 Treatment To Delivery Interval**

Duration of Prolongation of pregnancy	No. of patients	Percentage
<48 hrs	5	10.87%
2 days – 1 week	1	2.17%
1-2weeks	10	21.74%
2-3weeks	3	6.52%
3-4weeks	6	13.04%
4-5weeks	8	17.39%
5-6weeks	3	6.52%
6-7weeks	3	6.52%
7-8weeks	1	2.17%
8-9weeks	8	17.39%

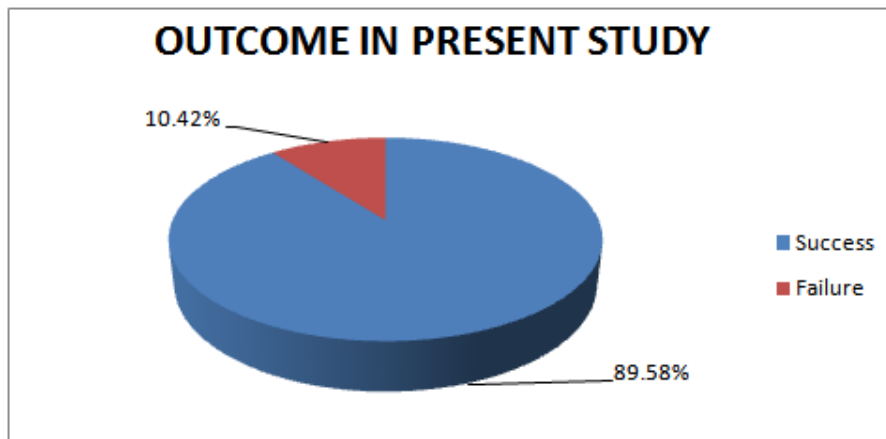


**TABLE-7 Outcome In Present Study**

Outcome	No. of patients	Percentage
Success	43	89.58%
Failure	5	10.42%

In present study labor was deferred for 48 hrs in 43 patients (89.58%) which was considered to be success rate. Out of remaining 5 (10.42%), which comes under failure, 3 delivered within 2 hours of starting treatment and the other 2 cases delivered within 8 hours of starting treatment.

In the present study, all failure cases belong to gestational age <32 weeks and with cervical effacement >80% and cervical dilation  $\geq$ 3cms.



### VI. Discussion

Magnesium sulphate has been used by obstetricians for more than 25 years to treat preterm labor. Magnesium sulphate is effective in delaying delivery for atleast 48 hours in patients with preterm labor when used in higher dosages. There do not seem to be any harmful effects of the drug on the fetus, and indeed there is a neuroprotective effect in reducing the incidence of cerebral palsy in premature newborns weighing less than 1,500gms (Elliot, John P.MD, 2009, American college of obstetricians and Gynecologists). In the present study, pregnancy continued for greater than 2 days in 43 cases (89.58%) out of 48 cases. These 2 days are important as this is the minimum time interval considered sufficient to allow benefit if corticosteroids are administered to decrease the possibility of respiratory distress syndrome developing in premature infants. The mean treatment delivery interval in success group was 33 days with a maximum prolongation of pregnancy upto 64 days.

#### Prolongation of pregnancy >48 hours compared with other studies

Studies	Prolongation of pregnancy > 48hrs
ZaZhi et al	76.67%
Morales W.J	85%
Lyell, Deirdre J.M.D	87%
Present study	89.58%

#### Prolongation of pregnancy >48 hours compared with other tocolytics

Drug	Prolongation of pregnancy >48 hours
Nifedipine (Lyell et al)	72%
Indomethacin (Madhav.H. et al)	90%
Present study	89.58%

In the present study, 32 cases (66.67%) took 1-2 hours for uterine quiescence after starting treatment. The mean time taken for uterine contractions to subside was 74 minutes with minimum time taken being 30 minutes after starting treatment. In a prospective trial, (Stephen J. Schorr) gestational age <32 weeks with preterm labor received magnesium sulphate and time taken for uterine quiescence was 6.22 hours compared to 74 minutes in the present study where 66% were of gestational age > 32 weeks.

In the present study, mean birth weight was 2.52 kgs with a minimum birth weight of 1.3 kgs and maximum birth weight of 3.5 kgs. In the present study admission in neonatal intensive care unit was 4.65% in success group, of which one was admitted for neonatal sepsis and the other was admitted for neonatal jaundice. None of the cases were admitted for magnesium sulphate toxicity. Almost all mothers experienced side effects to magnesium sulphate, which were mild and not life threatening. In only 2 cases, treatment was discontinued due to toxicity features.

### VII. Summary

A total of 50 patients were included in this present study. 2 cases did not come for follow-up and treatment was curtailed in 2 cases due to toxicity features.

1. 66% of cases in the study were of gestational age >32 weeks.
2. Success rate was 89.58%, which is defined as treatment to delivery interval >48 hours.
3. The mean treatment to delivery interval was 32 days, which again depends on cervical effacement and dilation and other risk factors.
4. The mean time taken for uterine quiescence was 74 hours after starting treatment.
5. Dosage requirement for uterine quiescence was 1-2 gms/hour in 87.5% cases.
6. All mothers experienced side effects but they were mild and none were as serious as to discontinue the drug.
7. Toxicity features were observed in 4% of cases, which need to discontinue the drug.
8. Neonatal deaths occurred in 2 of 43 successful cases and none were implicated to drug toxicity.

### VIII. Conclusion

Intravenous magnesium sulphate is effective in postponement of preterm labor atleast for 48 hours, which is the minimum time considered sufficient to allow benefit if corticosteroids are administered to decrease the possibility of respiratory distress syndrome in premature infants. It is more effective in gestational age >32 weeks and is less effective to arrest preterm labor in gestational age <32 weeks. There was a significant correlation of cervical dilation at the onset of treatment to success of controlling preterm labor. The side effects to the mother, fetus and the neonates were mild and not prominent.

Effect of Magnesium Sulphate given for Neuroprotection before preterm birth\_ (JAMA and RCT of magnesium sulphate for the prevention of cerebral palsy) \_the potential clinically important improvement in pediatric outcomes from magnesium sulphate given to women immediately before very preterm birth for neuroprotection urgently needs confirmation in further trials.

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