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Research Article

ISOXSUPRINE AS A TOCOLYTIC AGENT IN PRETERM LABOUR

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ABSTRACT
Preterm delivery is an important cause of perinatal morbidity and mortality. Prematurity and its prevention continue to be a major challenge for both the obstetrician and neonatologist. Despite all advances in neonatology, the delivery of a preterm neonate is a clinical crisis that threatens the life and health of the infant. So the obstetrician faces the challenge of affecting the delivery in a way so as to optimize the status of fetus-infant at birth. Neonatal intensive care is the most expensive health care service present in the health care delivery system. Isoxsuprine is one of the most commonly used drugs to arrest preterm labour. A total of 50 pregnant ladies between gestational age 28-37 weeks, regular uterine contraction $\geq$ 2 per 10 minute each lasting for $\geq$ 30 sec, cervical dilatation not more than 3 cm, cervical effacement not more than 50% with intact membranes were enrolled. All the patients were closely monitored and observed for uterine quiescence and maternal side effects. Isoxsuprine is an effective, safe and reasonably well tolerated tocolytic agent.

***Keywords*:** *Isoxsuprine, Preterm Labour, Tocolytic Agents, Hypotension, Tachycardia*

INTRODUCTION
Preterm labour is the most common obstetrical complication associated with perinatal death (Kaltreider and Johnson, 1976). Prematurity and its prevention continue to be a major challenge for both the obstetrician and neonatologist. Prematurity accounts for 75% of perinatal mortality and morbidity (Fuchs, 1976). Prematurity accounts for 75% to 80% of perinatal deaths not caused by congenital anomalies (How *et al.,* 1995). Preterm labour is defined as the onset of regular, painful uterine contractions, two or more per 10 minutes each lasting for at least 30 seconds with cervical effacement upto 50% or cervical dilatation upto 3 cm between 28-37 completed weeks of gestation. Despite all advances in neonatology, the delivery of a preterm neonate is a clinical crisis that threatens the life and health of the infant. Although survival of preterm infants exceeds 90% by 30 completed weeks of gestation and 90% of otherwise uncomplicated preterm births occur between 30 and 36 weeks of gestation, neonatal morbidity assumes paramount importance during this latter period of preterm gestation (Creasy, 1993). There are a number of demographic, social and medical characteristics of pregnancy with preterm delivery (Meis *et al.,* 1995). Faulty placentation, intrauterine infection, immunological factors, maternal factors, cervical incompetence, uterine factors, trauma and fetal anomalies are various group of possible causes that lead to preterm labour (Lettieri *et al.,* 1993). Increasing rate of preterm labour could be due to artificial reproductive techniques, psycosocial stress or medically induced prematurity (Singh *et al.,* 2011). Underlying causes are unknown in nearly 50% of cases (Das, 1969). Preterm delivery effects almost 23% pregnancies in developing countries like India (Bagum *et al.,* 2003). Estimates of preterm birth range from a relative stable 5-10% in developed countries to as high as 25% in some of the worst hit developing countries (PJ Steers, 2005). It is far more preferable to prevent the initiation of preterm labour than once the cascade of events has already been established (Creasy and Merkatz, 1990). The currently used method to arrest preterm labour is by inhibiting uterine contractions with tocolytic agents. Tocolytic agents delay the delivery and permit the use of glucocorticoids to facilitate the transfer of pregnant lady to a unit where intensive neonatal care facilities are available (Kitchen *et al.,* 1992; Singh *et al.,* 2015). Over the years treatment protocols have achieved tocolysis with beta-sympathomimetics like ritodrine, isoxsuprine, salbutamol and terbutaline (Leveno, 1992), magnesium sulphate (Gordon, 1995), calcium channel blockers especially nifedipine (Van Dijk, 1993) and nicardipine (Larmon *et al.,* 1999), potassium channel openers (Morrison *et al.,* 1993), oxytocin antagonist-atosiban (Goodwin *et al.,* 1994) and nitric

oxide donors (Jones and Poston, 1997). The activity in the uterine muscle is mediated by alpha and beta-adrenergic receptors. Alpha receptors mediate stimulant effect on myometrium and beta-receptor stimulation inhibits uterine contractions (Alquist, 1948). There are two types of beta-receptors in the humans: $beta_1$ and $beta_2$. $Beta_2$–receptors predominate in the smooth muscles of the uterus, blood vessels, diaphragm and bronchioles (Higby *et al.,* 1993). Using radioligand binding technique it has been found that there is a comparable concentration of beta-adrenoreceptors in the uterine fundus and lower uterine segment in normal pregnant women (Berg *et al.,* 1985). Of all the group of tocolytic drugs, beta-sympathomimetics have been investigated and used most frequently to arrest preterm labour. Various sympathomimetic agents used are isoxsuprine, fenoterol, ritodrine, salbutamol, terbutaline and orciprenaline. Isoxsuprine hydrochloride was the first beta-agonist used to arrest preterm labour (Bishop and Woutersz, 1961). Isoxsuprine is a drug of beta-phenylethylamine group of epinephrine like compounds (Hendricks *et al.,* 1961). A variety of troublesome side effects like hypotension and tachycardia were reported in patients treated with isoxsuprine (Schenken *et al.,* 1980). In general, while the choice of the best first line short term tocolytic drug is not clear, it is evident that the use of these agents has a clear place in current obstetric therapeutics (Haas *et al.,* 2014).

MATERIALS AND METHODS

This study was carried out in the Department of Obstetrics and Gynaecology, Government Medical College and Rajindra Hospital, Patiala. The study included 50 women with preterm labour admitted in labour room who were put on isoxsuprine.

Selection Criteria

1. Gestational age 28-37 weeks.
2. Regular uterine contractions, 2 or more than 2 per 10 minutes each lasting for at least 30 seconds.
3. Cervical dilatation not more than 3 cm.
4. Cervical effacement not more than 50%.
5. Membranes intact.

Exclusion Criteria

1. Multiple pregnancy
2. Ante-partum haemorrhage
3. Hydramnios
4. Pregnancy with heart disease and diabetes mellitus
5. Fetal malformations.

After selecting the patients, the following details were noted: age of the patient, parity, number of abortions and history of preterm deliveries, exact date of last menstrual period, duration of pregnancy and time of onset of preterm labour. Detailed history and clinical examination of the patients was done which included record of vitals, systemic examination and per-vaginum examination. The investigation which were carried out in all the patients were haemoglobin, bleeding time, clotting time, ABO Rh grouping, urine complete examination, vaginal swab for culture and sensitivity and urine for culture and sensitivity. After selecting the patients, they were given intravenous infusion of isoxsuprine. 4 ampoules (40 mg) of isoxsuprine hydrochloride were added to 500 ml of 5% dextrose giving a concentration of 0.8 mg/ml. Drop rate was set at 8 drops/minute (0.04 mg/minute). The drop rate was increased by 8 drops/minute after every 15 minutes until uterine quiescence was attained or patient developed adverse effects in the form of maternal tachycardia (heart rate more than 130/minute) or hypotension (systolic blood pressure less than 80 mmHg or diastolic blood pressure less than 40 mmHg), intolerable nausea and vomiting or foetal tachycardia (foetal heart rate greater than 160 beats/minute). The infusion was discontinued then. The intravenous drip was tapered over next 12 hours after uterine quiescence was achieved. After 15 minutes of stoppage of infusion, intramuscular injection of isoxsuprine hydrochloride 10 mg 6 hourly was given for 24 hours. 30 minutes before discontinuing the intramuscular therapy, one tablet (10 mg) of isoxsuprine was given 8 hourly and it was continued till 37^{th} completed week or delivery. Treatment was considered successful if the uterine quiescence was maintained for at least 48 hours. Treatment was

considered a failure if uterine quiescence could not be achieved or maintained for at least 48 hours inspite of maximum drug dosage or if the patient experienced intolerable side effects requiring discontinuation of the therapy. In all the cases, duration of pregnancy, total duration of delay in labour, mode of delivery, fetal outcome i.e. birth weight of newborn, apgar score at 1 minute and 5 minute were noted.

RESULTS AND DISCUSSION

Results

In the present study isoxsuprine was able to attain tocolysis for at least 2 days in 66% of patients. Furthermore, isoxsuprine was able to attain tocolysis for at least 7 days in 50% of patients as shown in Table -1.

Table 1: Table Showing 2 Day Success and 7 Day Success Rate of Isoxsuprine

Parameter	No. of Cases	%Age
2 day success	33/50	66
7 day success	25/50	50

As the cervical dilatation increased, the chances of successful tocolysis decreased. Successful tocolysis was attained in 80% of cases with cervical dilatation up to 1 cm at the time of presentation. The success rate was marginally lower at 73% in patients who presented with cervical dilatation between1-2 cm. The success rate dropped to 22.22% in patients with cervical dilatation of more than 2 cm at the time of presentation as shown in Table-2.

Table 2: Table Showing Relationship Between Cervical Dilatation and Success Rate

Cervical Dilatation (cm)	No. of Cases	Successful Cases	%Age
0-1	15	12	80.00
1-2	26	19	73.08
2-3	9	2	22.22

The successful tocolysis was achieved in 76.92% cases with cervical effacement upto 20%. The success rate declined to 54.55% with cervical effacement between 30-40%. A further decline in the success rate to 50% was recorded with increase in cervical effacement to 40-50%. 73.91% patients had vaginal delivery and 26.09% cases had a caesarean section. The mean time gained was 16.21$\pm$ 10.45 days. The commonest adverse effects seen in this study were fetal tachycardia (18%) and hypotension (18%). palpitation/tachycardia (14%), headache (8%) and nausea (8%) were the other common side effects experienced by patients as shown in Table-3. Fetal tachycardia and hypotension necessitated cessation of treatment in 2 (4%) patients.

Table 3: Table Showing Adverse Effects of Isoxsuprine

Side Effects	No. of Cases	% Age
Fetal tachycardia	9	18
Lethargy	1	2
Hypotension	9	18
Palpitation/Tachycardia	7	14
Nausea	4	8
Dry mouth	1	2
Headache	4	8
Dizziness	1	2

The 1 minute apgar score was in the range of 0-4 in 4.35% cases. 1 minute apgar score was in the range of 8-10 in 65.22% cases. None of the newborns had 5 minute apgar score in the range of 0-4. 5 min apgar score of 8-10 was observed in 80.43% cases.

Discussion

Prematurity and its prevention continue to be a major challenge for both the obstetrician and neonatologist. The currently used method to arrest preterm labour is by early detection and inhibition of uterine contractions by tocolytic agents. In the present study the mean age of patients was 24.44 $\pm$ 2.82 years which is comparable to other studies (Csapo and Herezeg, 1977; Schenken *et al.*, 1987; Patki *et al.*, 1993; Sirohiwal et al., 2001). In the present study 44% patients were nullipara, 40% patients were primipara and 16% had a parity status of > 2 which is comparable to other studies (Gulati and Rai, 1993; Patki *et al.*, 1993; Brazy *et al.*, 1981). In the present study 16% patients had a history of previous preterm birth and 22% had a history of abortions in the past. This supports the fact that preterm labour has a high chance of recurrence (Hollander *et al.*, 1987; Kalita *et al.*, 1998; Sirohiwal *et al.*, 2001). In the present study the mean gestational age at the onset of preterm labour was 33.76$\pm$1.87 weeks. These results are similar to other studies (Hollander *et al.*, 1987; Ridgway *et al.*, 1990; Sirohiwal *et al.*, 2001). Isoxsuprine was able to attain tocolysis in 66% cases. The results of this study are consistent with other studies (Nagendrappa *et al.*, 2012; Yogol *et al.*, 2009; Raymajhi *et al.*, 2003; Sirohiwal *et al.*, 2001; Kalita *et al.*, 1998; Bhide *et al.*, 1995). In the present study delivery was successfully delayed for 7 days or more in the patients receiving isoxsuprine in 50% cases. These results are similar to results of other studies. (Vaja and Goyal, 2014; Singh *et al.*, 1987). In the present study successful tocolysis was obtained in 80% cases with cervical dilatation up to 1 cm. As the cervical dilatation increased, the success rate came down. In patient with cervical dilatation between 2-3 cms, the success rate was 22.22%. These results are comparable to results of other studies. (Singh *et al.*, 1990). In the present study the mean time gained was 16.21$\pm$ 10.45 days. These results are similar to the results of other studies (Nagendrappa *et al.*, 2012; Raymajhi and Pratap, 2003; Sirohiwal *et al.*, 2001; Kalita *et al.*, 1998; Patki *et al.*, 1993; Gulati and Rai, 1993). In the present study fetal tachycardia and maternal hypotension were the commonest side effects each occurring in 18% cases. Palpitations and tachycardia were the next common adverse effects experienced by 14% patients while headache and nausea/vomiting occurred in 8% cases each. Isoxsuprine had to be discontinued in 4% patients due to severe fetal tachycardia and in another 4% patients due to maternal hypotension. These results are similar to results of other studies (Nagendrappa *et al.*, 2012; Sirohiwal *et al.*, 2001; Kalita *et al.*, 1998).

Conclusion

Prematurity continues to be the major contributor of perinatal morbidity and mortality. Isoxsuprine is a safe, effective, well tolerated and easily available tocolytic agent. Hypotension and tachycardia are its commonest side effects.

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