Section: Obstetrics and Gynaecology

Original Research Article

COMPARATIVE STUDY OF TOCOLYTICS IN MANAGEMENT OF PRETERM LABOUR WITH ISOXSUPRINE, NIFEDEPINE AND TRANSDERMAL NITROGLYCERIN

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Abstract

Background: Preterm birth, defined as birth at less than 37 weeks of gestation, is the most important single determinant of adverse infant outcome in terms of both survival and quality of life. It is the leading cause of neonatal deaths and second leading cause of death after pneumonia in children under five years. Three-quarters of them could be saved with current, cost-effective interventions even without intensive care facilities. **Material and Methods:** The study was a prospective comparative study undertaken in the Department of Obstetrics and Gynaecology in a tertiary care hospital in Visakhapatnam, over a period of 18 months from January 2020 to June 2021. The study group consists of equal number of antenatal women admitted with preterm labour at 28-35 weeks gestation, selected to receive Nifedepine or Isoxsuprine or Transdermal Nitroglycerin. Written informed consent was taken from the subjects recruited in the study. They were evaluated thoroughly by detailed history, clinical examination and ultrasonography. Amniotic membrane status was noted on vaginal examination. The study group was formulated after the inclusion and exclusion criteria were taken into account. **Results** The total number of deliveries during the study period were 8597 and the total number of preterm deliveries during the study period were 637. Incidence of preterm births at the Institute of study in Visakhapatnam was 7.4%. Out of the 90 women with singleton pregnancies who enrolled for the study, 30 were assigned to Isoxsuprine group, 30 to Nifedepine group and 30 to Nitroglycerin group (NTG). The patient was regarded as being booked if she had antenatal care in this institute and unbooked if she did not receive antenatal care in this institute and was referred from private clinic, maternity home, peripheral centre or presented herself without any referral. In this study 50 cases (55.5%) were unbooked (referral cases) and only 40 cases (44.4%) were booked cases.. **Conclusion:** Prematurity continues to be the major contributor to the perinatal morbidity and mortality. Prevention and treatment of preterm labour is essential to reduce adverse neonatal and infant outcome and to improve survival and quality of life. These approaches will have great impact on society and long-term public health care costs. Tocolysis remains the predominant modality for the treatment of preterm labour. None of the currently available tocolytic agents are ideal. Calcium channel blockers (Nifedepine) are safer and more effective than other tocolytics.

INTRODUCTION

Preterm birth, defined as birth at less than 37 weeks of gestation, is the most important single determinant of adverse infant outcome in terms of both survival and quality of life.[1] It is the leading cause of neonatal deaths and second leading cause of death after pneumonia in children under five years. Three-quarters of them could be saved with current, cost-effective interventions even without intensive care facilities.[2]

Approximately 15 million babies are born preterm according to WHO statistics updated in November, 2013. Over one million babies die annually from preterm birth complications.[2] Preterm births account for 13% of all live births in India. Inequalities in survival rates among low and high income settings has led to publication of global

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action report "Born to soon",[3] in May 2012. This report was issued by the WHO and partners, and aimed to save 16 million lives by 2015.[3]

Prematurity is multifactorial and the mechanisms for preterm labour are still unclear. It could be associated either with a premature activation of the physiological contracting process or with a pathological factor responsible for uterine contractions, leading to preterm delivery.[4]

Tocolytics are the drugs used to inhibit uterine contractions. These drugs have been available for several decades but their actions are directed toward the effects and not the causes of preterm labour. There is no clear evidence regarding the usage of tocolytic drugs in preterm labour. Women most likely to benefit from use of a tocolytic drug are those who are in very preterm labour, those needing transfer to a hospital which can provide neonatal intensive care and those who have not yet completed a full course of corticosteroids.[5]

In the present study the efficacy of tocolytics in delaying delivery for atleast 48hrs and the maternal and fetal complications associated with their usage and their safety profile were compared.

Aims and Objectives of the study

To compare the efficacy of Isoxsuprine, Nifedepine and Transdermal Nitroglycerin in management of preterm labour.

MATERIALS AND METHODS

The study was a prospective comparative study undertaken in the Department of Obstetrics and Gynaecology,in a tertiary Hospital in Visakhapatnam, over a period of18 months from January, 2020 to June, 2021. The study group consists of equal number of antenatal woman (90) admitted with preterm labour at 28-35 weeks gestation, selected to receive Nifedepine or Isoxsuprine or Transdermal Nitroglycerin. Written informed consent was taken from the subjects recruited in the study. They were evaluated thoroughly by detailed history, clinical examination and ultrasonography. Amniotic membrane status was noted on vaginal examination. The study group was formulated after the inclusion and exclusion criteria were taken into account.

Inclusion Criteria

- Gestational age between 28-35 weeks
- Painful uterine contractions
- 4 uterine contractions in 20minutes
- 8 uterine contractions in 60 minutes
- Intact amniotic membranes
- Changes in cervical effacement and dilatation

Exclusion Criteria

- Signs of chorioamnionitis
- Documented rupture of membranes
- Hypertensive disorders of pregnancy
- Polyhydramnios
- Heart disease causing moderate to severe functional impairment.
- Cases of antepartum hemorrhage selected for conservative management
- Severe Anemia in pregnancy
- Hypersensitivity to Isoxsuprine, Nifedepine, Nitroglycerine
- Cervical dilatation more than 3cms
- Maternal medical conditions such as Renal and Hepatic insufficiency
- Multifetal gestation
- Non-reassuring fetal status
- Fetal demise
- Major fetal congenital malformations

Treatment Protocol

ISOXSUPRINE GROUP (GROUP- 1): Group -1 constituted subjects who were given Isoxsuprine intravenous infusion as 40-60mg diluted in 500ml of 5% dextrose at the rate of 0.2 - 0.5 mg per minute over 3-3.5 hrs depending on the status of uterine contractions and maternal and fetal side effects. Infusion was continued up to 12-48hrs.

NIFEDEPINE GROUP (GROUP – 2): Group -2 constituted subjects who were given 20mg of oral Nifedepine initially, if contractions persist after 90mins, another dose of 20mg Oral Nifedepine was given, followed by 20mg at 6 hourly intervals for 48 hours. Nifedepine dosage administered was according to standard RCOG guidelines [6].

TRANSDERMAL NITROGLYCERIN GROUP (GROUP 3):

Group-3 constituted subjects,to whom 10mg Transdermal Nitroglycerin patch was applied to the skin of the abdomen. If there was no reduction in contraction strength after one hour, second 10mg patch was applied. Maximum dose was 20mg for 24 hours. Patches were changed for every 24 hours upto 48 hours.

In the three groups, subjects were strictly monitored for uterine contractions, maternal pulse rate, blood pressure, respiratory rate, fetal heart rate as most of the tocolytics were associated with side effects like hypotension, tachycardia in mother and fetus, pulmonary edema, Hence vital data were monitored pre and postdrug administration after 2hours. In case of any serious side effects, the respective drug would be stopped.

All women with preterm labour were investigated for infection by complete hemogram, urine microscopy and culture, vaginal swab culture.

Prophylactic oral antibiotics, Oral Ampicillin / Amoxycillin 500mg TID were given.

Women with gestational age less than 34 completed weeks were given 12mg Injection Betamethasone intramuscularly which was repeated after an interval of 24 hours.

The goal of tocolysis was to delay delivery for 48 hours for completion of Betamethasone dosage to achieve fetal lung maturity.

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Patients in whom delivery was delayed for at least 48 hours were transferred to antenatal ward for observation.

- Treatment was considered successful, if there was abolition of uterine contractions, no progression of cervical dilatation and she did not deliver within 48hrs of onset of therapy.
- Treatment was deemed failure, despite maximal dose mentioned for the three groups, if uterine relaxation was not achieved or patient or fetus developed some significant side effects that necessitated discontinuation of therapy.
- Data regarding efficacy of drugs in terms of maximum dosage required for subsidence of contractions pre and post drug administration vitals (after 2hrs of onset of therapy), number of patients delivered inspite of tocolytic usage, maternal and fetal side effects were recorded.
- The investigation reports of hemogram, urine microscopy and culture, vaginal swab culture and sensitivity were noted to study the role of infection as a risk factor for preterm labour.
- Details of APGAR scores, birth weight and early neonatal complications of babies born preterm as a result of failure of tocolysis were noted.

RESULTS

- Total number of deliveries during the study period - 8597
- Total number of preterm deliveries during the study period -637
- Incidence of preterm births at Study Institute in Visakhapatnam -7.4%

Out of the 90 women with singleton pregnancies who enrolled for the study, 30 were assigned to Isoxsuprine group, 30 to Nifedepine group and 30 to Nitroglycerin group. (NTG)

Group 1 – Treated with Isoxsuprine
Group 2 – Treated with Nifedepine
Group 3 – Treated with NTG

CHARACTERISTICS OF STUDY POPULATION

In the present study, patients were between 17-33 years of age. About 80% of the patients were between 20 - 30 years. Majority of the cases were in the age group of 20 – 25 yrs (54.4%). Minimum and maximum age in Isoxsuprine group was 18 and 33 years respectively, Nifedepine group was 17 and32 years respectively and Nitroglycerin group was 18 and 32 years respectively.

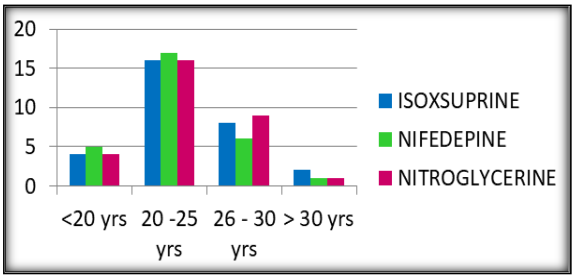

Figure 1: Distribution of Patients According to Maternal Age

The patient was regarded as being booked if she had antenatal care in this institute and unbooked if she did not receive antenatal care in this institute and was referred from private clinic, maternity home, peripheral centre or presented herself without any referral. In this study 50 cases (55.5%) were unbooked (referral cases) and only 40 cases (44.4%) were booked cases. [Table 2]

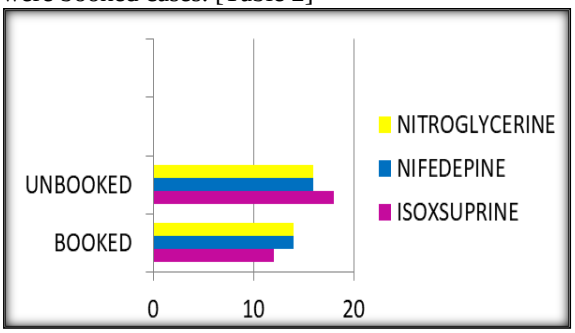

Figure 2: Distribution of Patients According to Prenatal Care

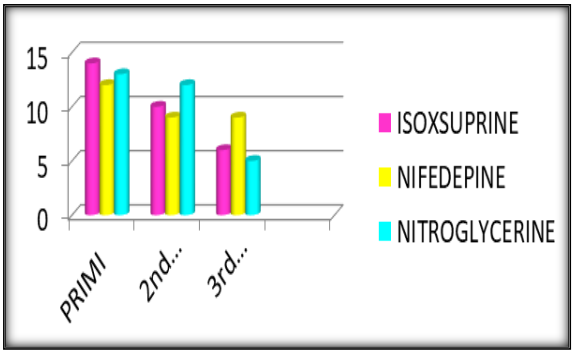

Figure 3: Distribution of Patients According to Parity

Most of the cases in the three study groups were of normal weight (61.1%).21.1% were overweight and 4.4% were obese. [Table 4]

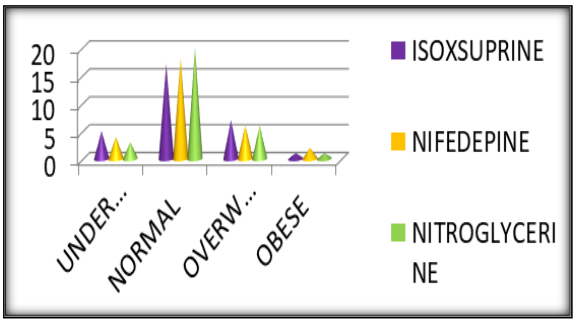

Figure 4: Distribution of Patients According to BMI

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All of the patients in this study presented with abdominal pain (100%).25% of the patients had low back ache and20% of the patients presented with symptoms of urinary tract infection. [Table 5]

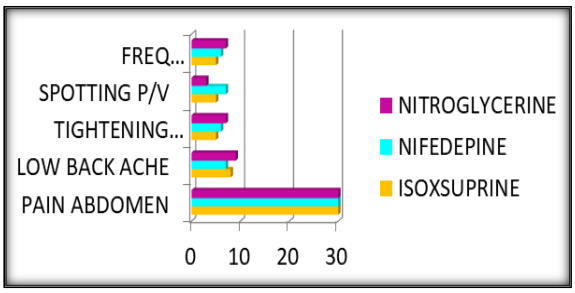

Figure 5: Distribution of Patients According to Symptoms

Majority of the patients in the present study were between 31-35 weeks of gestation, in Isoxsuprine group (73.3%), Nifedepine group (69.9%) and NTG group (73.35%). The mean gestational age in Isoxsuprine group, Nifedepine group and NTG group was 31.7 wks,32 wks and 31.6wks respectively. There was no statistically significant difference in the three study groups with respect to gestational age. [Table 6]

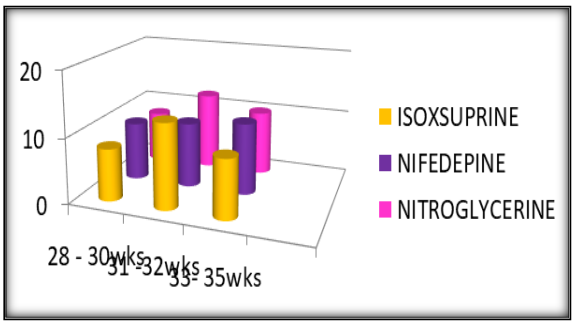

Table 6: Distribution According to Gestational Age

INFECTION -23 (25.5%)
UTI - 19 cases (21.1%), URTI - 2 cases (2.2%), GASTROENTERITIS -1 case (1.1%)
H/O FEVER (12.1%)
UTI with FEVER - 4 cases (4.4%), VIRAL FEVER -6 cases (6.6%)
MALARIA FEVER - 1 case (1.1%)
No risk factor was identified in majority of the cases (33.3%). Genitourinary infections were the most common risk factor associated with preterm delivery (37.7%). Previous history of preterm delivery and abortions constitute 29.9% followed by Anemia (20%). [Table 7]

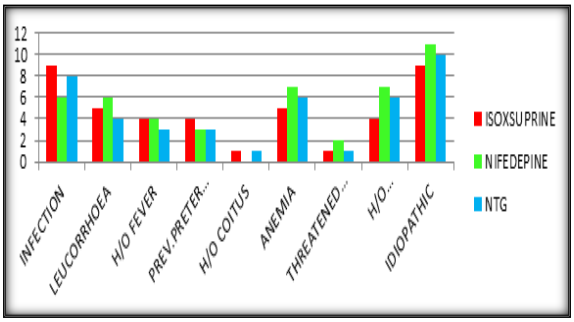

Figure 7: Distribution According to Risk Factors for Preterm Delivery

Drug Administration

In the present study a significant fall in systolic blood pressure was observed in Isoxsuprine group post drug administration which was statistically significant (p value<0.05). Nifedepine and Nitroglycerin patch were not associated with significant hypotension.

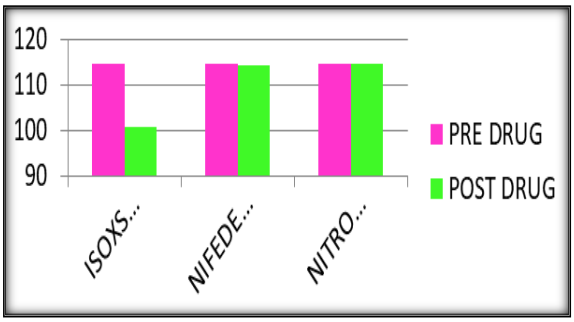

Figure 8: Changes Insystolic Blood Pressure Pre and Post Drug Administration

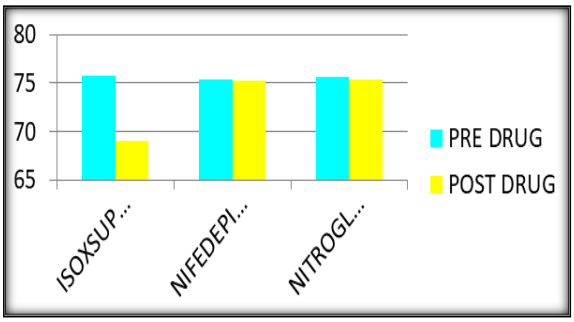

Figure 9: Changes in Diastolic Blood Pressure Pre and Post Drug Administration

Statistically significant maternal tachycardia was observed following Isoxsuprine administration compared to Nifedepine and NTG. Statistically significant fetal tachycardia was observed following Isoxsuprine administration compared to Nifedepine and NTG. [Table 10]

In the present study, hypotension was noted in two patients of Isoxsuprine group as compared to Nifedepine and Nitroglycerin groups where none of them had hypotension. The drug was discontinued in the two patients and intravenous fluids like Ringer lactate and/ or Normal saline were given and Blood pressure returned to normal within 1hr. [Table 11]

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26 babies delivered inspite of tocolysis. Birth weights and the APGAR scores of the babies born were according to the gestational age at which they were born. [Table 13]

Early neonatal complications observed in the study were due to prematurity and not specific to the tocolytic used. [Table 14]

In Isoxsuprine group 8 patients (26.6%) required 40mg dose , where as 13patients (43.3%) required 60 mg dose for subsidence of uterine contractions . 9 patients (23.3%) delivered inspite of drug usage and in 2 patients drug was discontinued in view of side effects and they delivered within 48hrs. [Table 15]

Table 1: Distribution of Patients According to Maternal Age

AGE GROUPS	ISOXSUPRINE	NIFEDEPINE	NITRO GLYCERINE	TOTAL
< 20yrs	4	5	4	13 (14.4%)
20 -25 yrs	16	17	16	49 (54.4%)
26 -30 yrs	8	7	9	24 (26.6%)
>30 yrs	2	1	1	4 (4.4%)
MIN. AGE	18 yrs	17yrs	18yrs	90(100%)
MAX. AGE	33yrs	32yrs	32yrs	

Table 2: Distribution of Patients According to Prenatal Care

	ISOXSUPRINE	NIFEDEPINE	NTG	TOTAL
BOOKED	12	14	14	40(44.4%)
UNBOOKED	18	16	16	50(55.5%)

Table 3: Distribution of Patients According to Parity

	ISOXSUPRINE	NIFEDEPINE	NTG
PRIMI (43.3%)	14	12	13
2NDGRAVIDA (34.4%)	10	9	12
3RDGRAVIDA (22.2%)	6	9	5
TOTAL	30	30	30

In the present study primigravidae were 43.3% and multigravidae were 56.6%

Table 4: Distribution of Patients according to BMI

Table 5: Distribution of Patients According to Symptoms

	ISOXSUPRINE	NIFEDEPINE	NTG
PAIN ABDOMEN (100%)	30	30	30
LOW BACKACHE (25%)	8	7	9
TIGHTENING (18.7%)	5	6	7
SPOTTING P/V (16.6%)	5	7	3
INCREASED FREQUENCY OF MICTURITION (20%)	5	6	7

Table 6: Distribution According to Gestational Age

GA IN WKS	ISOXSUPRINE	NIFEDEPINE	NTG	TOTAL
28-30	8(26.6%)	9(30%)	8(26.6%)	25(27.7%)
31-32	13(43.34%)	10(33.3%)	12(40%)	35(38.8%)
33-35	9(30%)	11(36.6%)	10(33.3%)	30(33.3%)
TOTAL	30	30	30	90
MEAN	31.76	32	31.66	31.8
MIN	28	28	28	28
MAX	35	35	35	35

Table 7: Distribution According to Risk Factors for Preterm Delivery

RISKFACTORS	ISOXSUPRINE	NIFEDEPINE	NTG	TOTAL
INFECTION	9	6	8	23(25.5%)
LEUCORRHOEA	5	6	4	15(16.6%)
H/O FEVER	4	4	3	11(12.2%)
PREV.PRETERM DELIVERY	4	3	3	10(11.1%)
H/O COITUS	1	0	1	2(2.2%)
ANEMIA	5	7	6	18(20%)
THREATENED ABORTION	1	2	1	4(4.4%)
H/O ABORTIONS	4	7	6	17(18.8%)
IDIOPATHIC	9	11	10	30(33.3%)

Table 8: Changes Insystolic Blood Pressure Pre and Post

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Table 9: Changes Indiastolic Blood Pressure Pre and Post Drug Administration

	Isoxsuprine (P Value <0.05)		Nifedepine (P Value>0.05)		Ntg (P Value>0.05)	
Systolic B.P(Mm Of Hg)	Pre Drug	Post Drug	Pre Drug	Post Drug	Pre Drug	Post Drug
Mean	114.6	100.2	114.6	114.4	114.6	114
Minimum	104	82	104	104	104	104
Maximum	130	114	130	130	130	130
DIASTOLIC B.P(mm of Hg)	PRE DRUG	POST DRUG	PRE DRUG	POST DRUG	PRE DRUG	POST DRUG
MEAN	75.8	69	75.4	75.2	75.6	75.4
MINIMUM	64	50	64	64	64	64
MAXIMUM	88	80	88	88	86	86

Table 10: Changes in Maternal Pulserate Pre and post Drug Administration

MPR (BEATS PER MIN)	ISOXSUPRINE (p value<0.05)		NIFEDEPINE (p value>0.05)		NTG (p value>0.05)	
	PRE DRUG	POST DRUG	PRE DRUG	POST DRUG	PRE DRUG	POST DRUG
MEAN	80.2	98.6	80.2	80.4	80.5	80.7
MINIMUM	76	88	74	74	76	76
MAXIMUM	88	122	88	88	88	88

Table 11: Distribution of Patients According to Maternal Side Effects

	ISOXSUPRINE	NIFEDEPINE	NTG
HEADACHE	2	2	2
NAUSEA AND VOMITINGS	1	-	-
FACIAL FLUSHING	1	1	-
IRRITATION OF SKIN		-	1
PALPITATIONS	2	-	-
TACHYPNOEA	1	-	-
REELING SENSATION	2	1	-
TOTAL	9(30%)	4(13.3%)	3(10%)
TACHYCARDIA (MPR>100/min)	9(30%)	-	-
HYPOTENSION (B.P<90/50mm of Hg)	2(6.66%)	-	-

Table 12: Distribution According to Birthweight of the Babies Born Due to Failure of Tocolysis

BIRTH WEIGHT	ISOXSUPRINE	NIFEDEPINE	NTG
1.5 - 2 kgs	4	4	3
2.1 - 2.5kgs	5	1	9
TOTAL	9	5	12

Table 13: Distribution According to Apgar at 1 And 5 Minutes of The Babies Delivered Due to Failure of Tocolysis

APGAR AT 1 MIN:	ISOXSUPRINE	NIFEDEPINE	NTG
<7	3	1	4
>7	6	4	8
APGAR AT 5 MINS:			
<7	2	1	2
>7	7	4	10

Table 14: Distribution According to Neonatal Complications of Babies Delivered Due to Failure of Tocolysis

	ISOXSUPRINE	NIFEDEPINE	NTG
TTN	1	-	-
RDS	2	1	2
JAUNDICE	-	1	2

Table 15: Distribution According to Results of Treatment

	ISOXSUPRINE	NIFEDEPINE	NTG	TOTAL
SUCCESS	21(70%)	25(83.3%)	18(60%)	64(71.1%)
FAILURE	9(30%)	5(16.7%)	12(40%)	26(28.9%)
TOTAL	30	30	30	90

DISCUSSION

Prematurity is the greatest single problem in perinatal medicine. Despite the availability of tocolytic agents, the rate of prematurity has not declined over the past few years for several reasons.

This prospective study was designed to find out the efficacy and safety of Isoxsuprine and Nifedepine in women with preterm labour. Patients were included into the study group in whom uterine contractions continued even after complete bed rest.

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SIGNIFICACE OF MATERNAL AGE, GESTATIONAL AGE AND PARITY ON PRETERM LABOUR

Gestational age in weeks in the present study, in Nifedepine group was 32, 31.76 in Isoxsuprine group and 31.66 in NTG group. While in Kedar et alstudy it was 30.5 ± 3.5 wks in Nifedepine group and 31.4 ± 2.8 wks in Isoxsuprine group and in Rayamajhi R et al study it was 32.22 wks in Nifedepine group and 32.64wks in Isoxsuprine group.[7]

COMPARISION OF TOCOLYTIC DOSAGE ADMINSTERED

In Kedar et al study Isoxsuprine was administered as 40-60 mg added in 5% Dextrose and was initially started at the rate of 0.5 mg/min and increased upto 10 mg/min and after cessation of uterine activity, drip was continued for 12 hours. Subsequently patients received Isoxsuprine injection 10 mg I.M,[8] hrly for 48 hrs followed by oral 10-20 mg, 8 hrly till 36weeks.

Nifedepine was administered as loading dose 5mg S/L, repeated every 15 mins, up to a maximum of 8 doses (40 mg) during the first two hours of treatment followed by maintenance dose oral Nifedepine of 10 mg was initiated 3 hrs after the last sublingual dose. Oral Nifedepine was then continued as 10 mg 8 hrly for next 48 hrs. Nifedepine retard tablet 10 mg or 20 mg was then started 12 hrly and continued till 36 weeks.

The maternal side effects observed in the present study were less when compared to Kedar et al, Rayamajhi et al and Amorim et al study. In the present study significant change in BP (hypotension) was observed in two patients in Isoxsuprine group that necessitated discontinuation of therapy. Significant tachycardia was observed following Isoxsuprine administration (30%). Other side effects like headache, reeling sensation, nausea and vomiting, flushing of skin were more with Isoxsuprine compared to Nifedepine and NTG. In the present studyas Nifedepine was given in tablet form instead of gel form via oral route and as it exhibits greater selectivity for inhibition of uterine activity relative to cardiovascular effects, it was not associated with hypotension or tachycardia. Hence the incidence of side effects were less with Nifedepine in the present study compared to Isoxsuprine.[8]

COMPARISION OF RISK FACTORS FOR PRETERM LABOUR

A study was conducted by Alka satija et al, Department of Obstetrics and Gynaecology, Dayanand Medical College and Hospital, Ludhiana published in International Journal of Basic and Applied Medical Sciences in May 2014 to study the risk factors of preterm labour. It was a prospective study conducted between December 2010 and March 2012 on 100 pregnant women presenting to the labour room of Dayanand Medical College and Hospital, Ludhiana between 24 – 37 weeks of gestation with spontaneous preterm labour.

The present study was comparable to the study conducted by Alka satija et al Department of Obstetrics and Gynaecology, Dayanand Medical College and Hospital, Ludhiana published in International Journal of Basic and Applied Medical Sciences in May 2014 to study the risk factors of preterm labour. It was a prospective study conducted between December 2010 and March 2012 on 100 pregnant women presenting to the labour room of Dayanand Medical College and Hospital, Ludhiana between 24 – 37 weeks of gestation with spontaneous preterm labour. The present study was comparable to the study conducted by Alka et al with genitourinary infection(37.7%) being the most common risk factor for preterm labour. 21.1% patients in the three groups had urinary tract infection in the present study. In the study conducted by Alka et al incidence of UTI was 20%. Similar findings were reported by Pandey et al., (2010) [9], Chhabra et al., (2001)10 and Singh et al., (2007) who found an incidence of 20.34%, 14% and8.4% respectively confirming that UTI was an important risk factor for preterm labour.9 But in the present study in majority of the cases, urine culture and sensitivity was sterile and in the cases where urine cultures were positive, Escherichia coli was the most common organism isolated andin the study conducted by Alka et al.[10]

CONCLUSION

In the present situation, results of meta-analysis indicate that amore achievable goal of tocolytic therapy is to delay delivery for at least 48 hours, an important interval during which the mother may be transferred to a tertiary centre for delivery, administer corticosteroids to the mother as well as to treat maternal infection when present. These measures have shown to reduce neonatal morbidity and mortality and aggressive pursuit of these achievable goals may be expected to lead to further improvements in neonatal outcome.

The present study found a favourable outcome with Nifedepine in this aspect (83.3%). In the view of increasing evidence of efficacy and safety, combined with its ease of administration, it appears likely that Nifedipine will play an expanded role in the suppression of preterm labour.

In future better understanding of the pathophysiology of preterm labour may lead to newer and specific approaches for its treatment and prevention. Till then tocolytics continue to be used to prevent preterm labour and to reduce perinatal morbidity and mortality.

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