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GAUGING THE SAFETY AND EFFICACY OF NITROGLYCERINE USED TRANSDERMALLY AS A TOCOLYTIC AGENT IN FEMALES WITH PRETERM LABOR

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ABSTRACT

Background: Preterm delivery is a persistent difficulty for obstetricians and has been a prevalent worry with rising frequency internationally. Approximately 8–10% of births are complicated by preterm birth. Preterm delivery has a significant related burden and its aetiology is yet unclear.

Aim: The purpose of this study is to evaluate the safety and effectiveness of transdermal nitroglycerine as a tocolytic drug in pregnant women.

Methods: Two hundred women experiencing premature labour were evaluated for this prospective clinical trial.

These 200 female individuals were split into two groups of 100 each, and each group was randomly assigned to either bed rest alone or nitroglycerine patch. Six months were spent doing the study.

Results: 6% (n=6) of the research individuals had their pregnancy extended by less than 48 hours, 8% (n=8) by 48–72 hours, 22% (n=22) by 73–96 hours, and 56% (n=56) by more than 7 days. Induced tocolysis in 100 Group I patients resulted in 94% (n=94) of subjects successfully and 6% (n=6) of study subjects unsuccessfully. Group I had considerably fewer resuscitation demands and Apgar scores of less than 7 at five minutes (p=0.02). In group I, there were 10 and 14 low-birth-weight patients with weights of ≤1.8 kg and 1.9-2.1 kg, respectively, compared to group II, which included 16 and 34 subjects.

Conclusion: The current study suggests that other frequently used tocolytic drugs are not as effective as nitroglycerine when applied transdermally to females experiencing premature labour. For patients experiencing preterm labour, nitroglycerine is the preferred medication for the acute relaxation of the uterus.

Keywords: transdermal nitroglycerine, ritodrine, tocolytics, nitroglycerine, premature labour

INTRODUCTION

Preterm labour (PTL) is the term used to describe the start of labour after 20–24 weeks of gestational age but before 37 weeks of pregnancy are completed.1. Preterm labor's precise mechanism and aetiology are unclear, but they are most frequently linked to the premature or early onset of a normal, physiological uterine contraction or any disease that causes uterine contractions and causes preterm births in the affected people.

.[2] Preterm delivery, which affects 7% to 12% of pregnant women and results in 7% to 80% of newborn deaths and morbidities, is a major public health problem.The improved survival rates after 34 weeks of gestation are a result of recent developments in feto-maternal medicine.3

Intraventricular haemorrhage, respiratory distress syndrome, retinopathy of prematurity, periventricular leukomalacia, necrotizing enterocolitis, sepsis, and patent ductus arteriosus are the main causes of newborn fatalities.4 Long-term research have shown that neonates born preterm have an increased risk of neurodevelopmental disabilities, including blindness, hearing loss, and cerebral palsy. Preterm newborns are also known to have a range of intellectual disabilities. Chronic lung illnesses and the general development of newborns might be compromised by long-term sequelae of non-neurological origin.[5]

The primary focus of treatment for preterm labour is on tocolytic drugs, which enable the administration of prenatal corticosteroids to increase the fetus's lung maturity and permit the mothers to be transferred to a tertiary care facility with a neonatal intensive care unit (NICU).Six One medication with a high liver first-pass inactivation rate is nitroglycerine. The liver's glutathione-dependent organic nitrate reductase enzyme quickly breaks down the active ingredient in nitroglycerine. In situations of premature labour, transdermal application of nitroglycerine is recommended to bypass this metabolism. This method delivers the medication at a steady and consistent pace, enabling it to achieve a smooth plasma concentration free from variations.7.

The purpose of the current study was to evaluate the safety and effectiveness of transdermal nitroglycerine as a tocolytic drug in pregnant women.

MATERIALS AND METHODS

The goal of the current prospective randomised controlled clinical trial was to evaluate the safety and effectiveness of transdermal nitroglycerine as a tocolytic drug in pregnant women. Following approval from the relevant ethics committee, the study was conducted on Subjects from the Department of Obstetrics and Gynaecology made up the study population. All subjects gave their informed permission in writing and verbally after being fully told about the study's design.

Two groups of 100 individuals each were randomly assigned to the trial, which comprised 200 females with premature labour. Group I received a transdermal nitroglycerine patch, whereas Group II was recommended to rest in bed due to preterm labour.The treatments that the participants received were hidden from them. Subjects with intact membranes, cervical dilatation up to 3 cm, 80% or more progressive cervical effacement, two contractions lasting 40 seconds each in a 10-minute period, evaluation on ultrasonography and clinical examination, and gestational ages between 28 and 34 weeks were the inclusion criteria for the study.

Erythroblastosis, oligohydramniosis, polyhydramniosis, congenital abnormalities, IUGR (intrauterine growth restriction), foetal distress, foetal mortality, and multiple gestations are among the exclusion criteria for the research of foetal variables.

Acute respiratory distress syndrome (ARDS), asthma, pulmonary or renal disorders, prior caesarean section, heart disease, hypertension, pregnancy-induced hypertension, antepartum haemorrhage, cervical dilatation greater than 3 cm, infection, and ruptured membranes were among the maternal factors taken into consideration for exclusion. Following final inclusion, each participant had a thorough history taken, which was followed by a clinical assessment. Gender, age, medical history, and menstruation history were among the information entered. Urine analysis, complete blood counts, vaginal swabs, and ultrasounds were the studies performed. Participants in Group I received a transdermal nitroglycerine patch (NTG-10), which releases 10 milligrammes of nitroglycerine every 24 hours. The abdominal wall was covered with the patch.

An additional patch of the same amount was administered to the individuals, and both patches were retained for 24 hours, if, after one hour, there was no change in the length, frequency, or strength of the contractions. If, despite applying a 20 mg nitroglycerine patch, the uterine contraction persisted for more than 24 hours, the treatment was stopped; patients with premature rupture of membranes (PROM), a heart rate greater than 100 beats per minute, and blood pressure lower than 90/60 mmHg were also excluded. The bed rest was suggested for Group II individuals. Two intramuscular (12 mg) doses of betamethasone (IM) spaced 24 hours apart were administered to subjects in both groups.

Adverse medication responses, delivery method, gestational age at delivery, finishing the course of maternal steroids, lengthening the duration of pregnancy, effective tocolysis—defined as tocolysis lasting longer than 48 hours—and the cessation of uterine contractions were among the maternal outcomes that were evaluated. Neonatal mortality and NICU hospitalisation were the foetal outcomes measured in this study (neonatal ICU).

Multivariate statistical methods and logistic regression were used to statistically evaluate the gathered data. Two forms were used to show the data: tabular and descriptive. Fisher exact test, chi-square, and SPSS version 22.0, 2013, Armonk, NY: IBM Corp. were used. With a significance threshold of 0.05%, the results were presented as percentages, numbers, mean, and standard deviations.

RESULTS

Two groups of 100 participants each were randomly assigned to the trial, which comprised 200 female subjects with premature labour. Group I received a transdermal nitroglycerine patch, whereas Group II was recommended to rest in bed due to preterm labour. Group I and II had similar mean ages (28.86±6.36 and 27.58±5.71 years, respectively; p=0.27). Group I and II ladies' steroid courses were similar throughout (p=0.21). With 64% (n=64) of Group I participants and 62% (n=62) of Group II individuals, the bulk of the subjects were between 29 and 32 weeks gestation. With p=0.56, gestational age was likewise comparable.

With p=0.53, 46% (n=46) and 40% (n=40) of the individuals in Groups I and II, respectively, had previously had abortions. In groups I and II, 10% (n = 10) and 4% (n = 4) of the individuals had positive preterm labour histories (p = 0.42). With p=0.48, parity between the two groups was likewise comparable (Table 1).

Haemoglobin was 11.85±0.94 and 11.81±0.99 gm/dl for Groups I and II according to the laboratory parameters; p=0.82 indicated that these values were not significant. Additionally, there was comparability in the creatinine, with p=0.7 and respective values of 0.83±0.17 and 0.82±0.12 mg/dl in groups I and II. With a p-value of 0.25, the mean urea in Groups I and II was 29.98±9.06 and 27.88±8.15 mg/dl, respectively.

10% (n=10) and 8% (n=8) of the individuals in groups I and II, respectively, had positive urine cultures; this difference was not statistically significant (p=1.00). In 6% (n = 6) and 10% (n = 10) of the research patients, vaginal cultures were positive (p= 0.74). For 40% (n=40) of the group I participants and 56% (n=56) of the group II subjects, the Rh factor was positive (p=0.13). As shown in Table 2, ABO grouping between the two groups was also equivalent with p=0.33.

Regarding the mother outcomes in the Group I subject treated with nitroglycerine, it was observed that pregnancy was prolonged by less than 48 hours in 6% (n = 6) of the subjects, 48–72 hours in 8% (n = 8), 73–96 hours in 22% (n = 22), and more than 7 days in 56% (n = 56) of the research subjects.

Induced tocolysis in 100 Group I patients resulted in 94% (n=94) of subjects successfully and 6% (n=6) of study subjects unsuccessfully. As shown in Table 3, the adverse effects of nitroglycerine for tocolysis were evaluated. Of the subjects, 66% (n=66) reported no side effects, 4% (n=4) reported patch site irritation, 6% (n=6) reported vomiting, 10% (n=10) reported hypotension, and 14% (n=14) reported headaches.

Foetal death was seen in 6% (n=6) and 16% (n=16) research individuals, respectively, which was comparable between the two groups (p=0.13). These findings were based on an assessment of the foetal outcomes in the two groups of study subjects.

It was also comparable that 6% (n=6) and 12% (n=12) of the participants in groups I and II, respectively, required mechanical ventilation (p=0.47). With p-values of 0.47 and 0.18 for the ICU and ARDS, respectively, the two groups' requirements for admission were likewise similar. With 22% (n=22) of the participants on bed rest and 6% (n=6) of the subjects receiving nitroglycerine, Group I's resuscitation needs were noticeably lower (p=0.02). A substantially smaller foetus was also seen with Apgar scores of less than seven at five minutes in 6% (n = 6) of Group I participants and in 22% (n = 22) of Group II subjects, which was significantly higher with p = 0.02.

Table 4 indicates that there were considerably fewer Low-birth-weight participants (10 and 14) in Group I compared to 16 and 34 in Group II, with a weight of ≤1.8 kg and 1.9-2.1 kg.

DISCUSSION

Two groups of 100 participants each were randomly assigned to the trial, which comprised 200 female subjects with premature labour. Group I received a transdermal nitroglycerine patch, whereas Group II was recommended to rest in bed due to preterm labour. Group I and II had similar mean ages (28.86±6.36 and 27.58±5.71 years, respectively; p=0.27). Group I and II ladies' steroid courses were similar throughout (p=0.21).

With 64% (n=64) of Group I participants and 62% (n=62) of Group II individuals, the bulk of the subjects were between 29 and 32 weeks gestation. With p=0.56, gestational age was likewise comparable. With p=0.53, 46% (n=46) and 40% (n=40) of the individuals in Groups I and II, respectively, had previously had abortions. In groups I and II, 10% (n = 10) and 4% (n = 4) of the individuals had positive preterm labour histories (p = 0.42). With p=0.48, parity between the two groups was likewise comparable. These findings were contrasted with research

conducted in 2019 by Bashir B et al. and in 2015 by Baker E et al., in which the authors evaluated participants whose demographics were similar to those of the current study.

Haemoglobin levels were non-significant (p=0.82), with values in Groups I and II being 11.85±0.94 and 11.81±0.99 gm/dl, respectively, according to the assessment of the laboratory parameters. Additionally, there was comparability in the creatinine, with p=0.7 and respective values of 0.83±0.17 and 0.82±0.12 mg/dl in groups I and II. With a p-value of 0.25, the mean urea in Groups I and II was 29.98±9.06 and 27.88±8.15 mg/dl, respectively. 10% (n=10) and 8% (n=8) of the individuals in groups I and II, respectively, had positive urine cultures; this difference was not statistically significant (p=1.00). In 6% (n = 6) and 10% (n = 10) of the research patients, vaginal cultures were positive (p= 0.74). For 40% (n=40) of the group I participants and 56% (n=56) of the group II subjects, the Rh factor was positive (p=0.13). With p=0.33, ABO grouping between the two groups was likewise equivalent.

These results were in line with research published in 2018 by Pimenta JM et al. and in 2020 by Tavassoli F et al., who proposed similar blood urea, creatinine, positive vaginal and urine cultures, and ABO grouping as of the current investigation.

The study's findings demonstrated that the Group I subject's maternal outcomes were improved by using nitroglycerine; among the participants, pregnancy was extended by less than 48 hours in 6% (n = 6), 48–72 hours in 8% (n = 8), 73–96 hours in 22% (n = 22), and more than 7 days in 56% (n = 56) of the subjects. When tocolysis was produced in 100 Group I individuals, 94% (n=94) of the patients responded well, whereas 6% (n=6) of the research subjects did not respond well.

When the side effects of nitroglycerine for tocolysis were evaluated, it was found that 66% (n=66) of the subjects experienced no side effects, 4% (n=4) experienced patch site irritation, 6% (n=6) experienced vomiting, 10% (n=10) experienced hypotension, and 14% (n=14) experienced headaches. These outcomes were consistent with trials conducted by Goyal N et al. in 2020 and Kaur P et al. in 2021, whose authors reported high success rates of nitroglycerine tocolysis along with longer pregnancy durations and fewer adverse effects.

Foetal outcomes in the two study subject groups were observed, and it was found that foetal death occurred in 6% (n = 6) and 16% (n = 16) of research subjects, respectively. These numbers were comparable between the two groups (p=0.13). It was also comparable that 6% (n=6) and 12% (n=12) of the participants in groups I and II, respectively, required mechanical ventilation (p=0.47). With p-values of 0.47 and 0.18 for the ICU and ARDS, respectively, the two groups' requirements for admission were likewise similar. With 22% (n=22) of the participants on bed rest and 6% (n=6) of the subjects receiving nitroglycerine, Group I's resuscitation needs were noticeably lower (p=0.02).

A substantially smaller foetus was also seen with Apgar scores of less than seven at five minutes in 6% (n = 6) of Group I participants and in 22% (n = 22) of Group II subjects, which was significantly higher with p = 0.02. With 10 and 14 participants respectively, Group I had a considerably smaller number of low-birth-weight subjects (weight of ≤1.8 kg and 1.9-2.1 kg) than Group II, which had 16 and 34 subjects. These findings were consistent with the earlier research conducted by Jamil M et al. in 2020 and Akhtar Z et al. in 2020, where the authors found comparable foetal outcomes after nitroglycerine as of the current study.

CONCLUSION

Considering its limitations, the present study concludes that Nitroglycerine used transdermally in females with preterm labor has equal efficacy as other commonly used tocolytic agents. Nitroglycerine is a drug of choice for the acute relaxation of the uterus in subjects with preterm labor. Also, transdermal nitroglycerine was found to be a non-invasive, cost-effective, well-tolerated, effective, safe, and promising mode of tocolysis. The limitations of this study were smaller considered population, shirt monitoring, and biased related to the geographic location warranting further long-term studies planned longitudinally.

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TABLES

Characteristics	**Group I (nitroglycerine group) % (n=100)**	**Group II (bed rest) % (n=100)**	**p-value**
Mean age (years)	28.86±6.36	27.58±5.71	0.27
Complete course of steroids (>34 weeks)	78 (78)	66 (66)	0.21
Gestational age at delivery (weeks)			
29-32	64 (64)	62 (62)	0.56
33-34	12 (12)	18 (18)	
35-37	20 (20)	16 (16)	
>37	2 (2)	0	
Abortion history			
Yes	46 (46)	40 (40)	0.53
No	54 (54)	60 (60)	
Preterm labor history			
Yes	10 (10)	4 (4)	0.42
No	90 (90)	96 (96)	
Parity			
0 (primigravida)	18 (18)	24 924)	0.48
1	16 (16)	16 (16)	
2	20 (20)	28 (28)	
≥3	46 946)	32 (32)	

Table 1: Demographic characteristics of the study participants

Laboratory investigations	Group I (nitroglycerine group) % (n=100)	Group II (bed rest) % (n=100)	p-value
Hemoglobin (gm/dl)	11.85±0.94	11.81±0.99	0.82
Creatinine (mg/dl)	0.83±0.17	0.82±0.12	0.7
Urea (mg/dl)	29.98±9.06	27.88±8.15	
Urine culture			
Positive	10 (10)	8 (8)	1.00
Negative	90 (90)	92 (92)	
Vaginal culture			
Positive	6 (6)	10 (10)	0.74
Negative	94 (94)	90 (90)	
ABO group			
A	24 (24)	22 (22)	0.33
B	28 (28)	26 (26)	
AB	14 (14)	28 (28)	
O	34 (34)	24 (24)	
Rh Factor			
Positive	40 (40)	56 (56)	0.13
Negative	60 (60)	44 (44)	

Table 2: Laboratory investigations in the two groups of study subjects

Maternal Outcome with nitroglycerine	Percentage (%)	Number (n)
Duration of pregnancy prolongation		
<48 hours	6	6
48-72 hours	8	8
73-96 hours	22	22
97-<7 days	8	8
≥7 days	56	56
Tocolysis success		
Success	94	94
Failure	6	6
Nitroglycerine side-effects		
None	66	66
Patch site irritation	4	4
Vomiting	6	6
Hypotension	10	10
Headache	14	14

Table 3: Maternal outcomes with nitroglycerine patch in Group I subjects

Fetal Outcome with nitroglycerine	Group I % (n=100)	Group II % (n=100)	Number (n)
Death	6 (6)	16 (16)	0.13
Mechanical ventilation need	6 (6)	12 (12)	0.47
NICU admission	6 (6)	12 (12)	0.47
ARDS	4 (4)	14 (14)	0.18
Required resuscitation	6 (6)	22 (22)	**0.02**
Apgar score <7 at 5 minutes	6 (6)	22 (22)	**0.02**
Birth weight (kg)			
≤1.8	10 (10)	16 (16)	**0.001**
1.9-2.1	14 (14)	34 (34)	
2.2-2.4	36 (36)	34 (34)	
>2.4	40 (40)	16 (16)	

Table 4: Fetal outcomes in the two groups of study subjects