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ملاحظات:

ملاحظات:



COMPARATIVE STUDY BETWEEN NICORANDIL AND NIFEDIPINE FOR THE TREATMENT OF PRIMIGRAVIDAS PRESENTING BY MODERATE PRETERM LABOR

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LIST OF ABBREVIATION

3βHSD	: 3beta-hydroxysteroid dehydrogenase
ACOG	: American College of Obstetricians and Gynecologists
ACTH	: Adrenocorticotrophic hormone
AFI	: Amniotic fluid index
ATP	: Adenosine triphosphate
BMI	: Body mass index
BPD	: Bronchopulmonary dysplasia
Bpm	: Beat per minute
Ca⁺⁺	: Calcium
cAMP	: Cyclic adenosine monophosphate
CAPs	: Contraction-associated proteins
CBC	: Complete blood count
CCBs	: Calcium channel blockers
Cm	: Centimeter
CNS	: Central nervous system
COX	: Cyclooxygenase enzymes
CP	: Cerebral palsy
CRH	: Corticotropin-releasing hormone
CRL	: Crown-rump length
CS	: Cesarean section
CTG	: Cardiotocography
DHEAS	: Dehydroepiandrosterone sulfate
DM	: Diabetes mellitus
DVT	: Deep vein thrombosis
FDA	: Food and Drug Administration
Fetal hpa	: Fetal Placental Hypothalamic-Pituitary-Adrenal Axis
FIP	: Focal intestinal perforation
GA	: Gestational age
GIT	: Gastrointestinal tract
HDACs	: Histone deacetylase corepressor complex
ICU	: Intensive care unit
IL	: Interleukin
IQR	: Interquartile range

IUFD	: Intrauterine fetal death
IVH	: Intraventricular hemorrhage
K⁺	: Potassium
KCO	: Potassium channel opener
MCA	: Middle cerebral artery
MgSO₄	: Magnesium sulfate
miR-200	: Micro rna
MMP	: Matrix metalloproteinase
mTORC1	: Mammalian target of rapamycin complex 1
NEC	: Necrotizing enterocolitis
NICU	: Neonatal intensive care unit
NSAIDs	: Non-steroidal anti-inflammatory drugs
NTG	: Transdermal Nitroglycerin
NVD	: Normal vaginal delivery
PDA	: Patent ductus arteriosus
PG	: Prostaglandin
PGF2α	: Prostaglandin f2 α
PROM	: Premature rupture of membranes
proMMP-1, proMMP-2	: Procollagenase and prostromelysin
PSF	: Protein-associated splicing factor
PTBs	: Preterm births
PTGS	: Post-transcriptional gene silencing
PTL	: Preterm labor
PVL	: Periventricular leukomalacia
RCT	: Randomized controlled clinical trial
RDS	: Respiratory distress syndrome
RH	: Rhesus factor
ROP	: Retinopathy of prematurity
RU-486	: Mifepristone
Sc	: Side-chain cleavage
SD	: Standard deviation
TIMP-1	: Tissue inhibitor of matrix metalloproteinase 1
TLRs	: Toll-like receptors
TNF-α	: Tumour necrosis factor α

Trp53	: Transformation-related protein 53
US\$: United states dollar
USA	: United states of America
ZEB1	: Zinc finger e-box binding homeobox protein 1

ABSTRACT

Objective: To compare the effectiveness of the potassium channel opener nicorandil with the calcium channel blocker nifedipine for tocolysis in moderate preterm labour in primigravidas. **Methods:** A randomized clinical trial of 230 pregnant women in preterm labour was conducted at Ain Shams University Hospital, Egypt. Eligible women were assigned at random into two groups: 115 women received nicorandil and 115 women received nifedipine. Prolongation of pregnancy for 48 hours was the primary outcome measure. Maternal and neonatal outcomes were also assessed. **Results:** Nicorandil was comparable to nifedipine for prolongation of pregnancy for 48 hours. Women treated with Nifedipine were significantly more likely to experience palpitation, hypotension, headache, nausea or vomiting and maternal tachycardia, (14.6%, 23.3%, 18.4%, 22.3% and 21.4% of cases, respectively) compared with women treated with nifedipine ($p < 0.001$). No differences in neonatal outcome regarding NICU admission were observed between the two groups ($P > 0.05$). **Conclusions:** Nicorandil is as effective as nifedipine for tocolysis in preterm labour with less maternal side effects, but unfortunately nicorandil is more expensive and not always available in Egyptian pharmacies. Larger studies are needed to assess safety and efficacy of Nicorandil as tocolysis in very preterm and in multiparous women.

INTRODUCTION

Preterm labor (PTL), which has been defined as birth in <37 weeks of gestation, categorizes into four major types: late preterm (Birth between 34 weeks to 37 weeks of gestation), moderate preterm (Birth between 32 weeks to 34 weeks of gestation), very preterm (Birth between 28 week to 32 weeks of gestation), and extremely preterm (birth before 28 weeks of gestation) (*WHO, 2012*).

In the world, about 15 million preterm infants are born every year (*Blencowe H et al., 2012; Ferrero et al., 2016*). In many industrialized countries, preterm birth had increased until around 2005, but it has declined slightly in recent years. In the USA, it was 12.7% in 2007, but it decreased to 11.4% in 2013 (*Matthews TJ, MacDorman MF, & ME., 2015*). Premature birth is the most important cause of increasing neonatal morbidity and mortality (*Ferrero et al., 2016; Heron et al., 2010; Onishi, 2020*).

Risk factors for PTL include previous spontaneous preterm delivery, previous cesarean section or hysterotomy (being at risk for rupture of uterus) and short inter-pregnancy interval (less than 6 months) (*Ferrero et al., 2016; Rodrigues & Barros, 2008*). Certain medical conditions such as chronic hypertension, diabetes, renal, autoimmune diseases and blood clotting problems may put

the patients at high risk of PTL (*Di Renzo, Tosto, & Giardina, 2018; Menon, 2012*). Also, specific conditions that occur during the current pregnancy such as urinary tract infections, vaginal infections are also risk factors for preterm labor. (*Nadeau, Subramaniam, & Andrews, 2016; R. Romero, Dey, & Fisher, 2014*).

Diagnosis of preterm labor is made when the symptoms of preterm labor are associated with cervical changes (*Shivkumar, Priyadarshani, & Choksi, 2020*). Vaginal bleeding and/or ruptured membranes in this setting increase diagnostic certainty, using the following specific criteria:

Uterine contractions (≥ 4 every 20 minutes or ≥ 8 in 60 minutes) **Plus** one of the following:-

- Cervical dilation equal or more than 3 cm
- Cervical length less than 20 mm on transvaginal ultrasound
- Cervical length between 20 to less than 30 mm on transvaginal ultrasound and positive fetal fibronectin test (*Chao, Bloom, Mitchell, McIntire, & Leveno, 2011; Shivkumar et al., 2020*).

Tocolytics are used to decrease uterine activity for a short time (up to 48 hours) in women with uncomplicated pregnancies. This gives time for action of corticosteroids or magnesium sulfate

or for arranging transfer of women to institutions with specialty care centers for preterm infants (*Shivkumar et al., 2020*).

Nifedipine is a calcium channel blocker that inhibits the entry of calcium through channels in the cell membrane and causes smooth muscle relaxation. It is the tocolytic of choice (*A. Conde-et al., 2011; King et al., 2003*).

Atosiban is an oxytocin analog that acts as a competitive antagonist of oxytocin-induced contractions. Atosiban is offered to women in whom nifedipine is contraindicated (*Tsatsaris, Carbonne, & Cabrol, 2004*).

Beta adrenergic receptor agonists as terbutaline and ritodrine react with β -adrenergic receptors to reduce intracellular ionized calcium levels and prevent activation of myometrial contractile proteins (*Shivkumar et al., 2020*).

Indomethacin inhibits the synthesis of prostaglandin by blocking the enzyme prostaglandin synthase. Though it is effective in delaying preterm birth, associated side effects like oligohydramnios, patent ductus arteriosus, necrotizing enterocolitis, and intraventricular hemorrhage limit its use (*Shivkumar et al., 2020*).

Nicorandil is a potassium channel opener with smooth muscle relaxation effect. Its distinctive pharmacological effect is to open ATP- 153 sensitive potassium channels. It is used in the prevention and long-term treatment of angina pectoris (***Rezk, Sayyed, Masood, & Dawood, 2015***).

This study aims to assess the efficacy of Nicorandil (potassium channel opener) compared with Nifedipine (calcium channel blocker) as a tocolytic agent in delaying labor for 48 hours following its administration.

AIM OF THE WORK

To assess the efficacy and safety of Nicorandil (Randil[®], a potassium channel activator) compared with Nifedipine (Epilat[®], a calcium channel blocker) as a tocolytic agent in delaying labor for 48 hours following its administration when used in primigravidas presenting by moderate preterm labor (from 32 to less than 34 weeks).