Magnesium sulfate, as an alternative to sildenafil in treatment of persistent pulmonary hypertension of the new born in Egypt

Thesis

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Abstract

Persistent pulmonary hypertension of the newborn (PPHN), it is characterized by failure of the normal postnatal fall in pulmonary vascular resistence, it can cause both immediate and long term complication.

There are various modalities for treatment of PPHN. ECMO & INO are effective in treatment of PPHN but not available in developing countries.

Our study was done to light the comparison between the effects of oral sildenafil and magnesium sulfate in the treatment of PPHN.

Our study is prospective cohort review included 20 neonates. The neonates were divided into two groups: the first group represented 10 neonates treated with sildenafile, whereas the second group represented 10 neonates treated with magnesium sulfate. We found a statistically significant difference (P value 0,014) in estimated pulmonary artery pressure after another 3 days of treatment by sildenafil or magnesium sulfate. We also revealed that good improvement in Sao2&ABG with two groups but earlier in sildenafil group. Limited side effects and good outcome was observed in both groups.

Conclusion: we concluded that $MgSo_4$ can be used as an alternative treatment to sildenafil in treatment of PPHN in Egypt.

Keywords: Persistent pulmonary hypertension of the newborn (PPHN), sildenafil, Magnesium sulfate ($MgSo_4$).

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List of Abbreviation

AaDo2	**:**	Alveolar- to arterial oxygen gradient
ABG	**:**	Arterial Blood gases
ACD	**:**	Alveolar Capillaries dysplasia
AMP	**:**	Adenosine monophosphate
ANP	**:**	A – type natriuretic peptide
AVMS	**:**	Arterio- venous malformations
BMP	**:**	Bone morphogenic protein
BMPR II	**:**	Bone morphogenic protein receptor II
BNP	**:**	B- type natriuretic peptide
CAM	**:**	Congenital adenomotoid malformation
CAMP	**:**	Cyclic adenosine monophosphate
CBC	**:**	Complete Blood count
CDH	**:**	Congenital Diaphragmatic hernia
CGMP	**:**	Cyclic guanosine mono phosphate
CS	**:**	Cesarean section
CVP	**:**	Centeral venous pressure
ECMO	**:**	Extra-corporeal membrane oxygenation
ETA	**:**	Endothlin receptor A
ET-1	**:**	Endothelin -1
ETB	**:**	Endothelin receptor B
FIO2	**:**	Inspired oxygen concentration
GMP	**:**	Guanosine mono phosphate
GC	**:**	Guanylate cyclase
INO	**:**	Inhaled nitric oxide
IP3	**:**	Inositol triphosphate
IVC	**:**	Inferior vena cava

LA	**:**	Left atrium
LV	**:**	Left ventricle
LVO	**:**	Left ventricular out put
MAP	**:**	Mean air way pressure
MAS	**:**	Meconium aspiration syndrome.
MPAP	**:**	Mean pulmonary artery pressure
No	**:**	Nitric oxide
NOS	**:**	Nitric oxide synthetase
NSAID	**:**	Non steroidal Anti-inflammatory drug
OI	**:**	Oxygenation index
PA	**:**	Pulmonary artery
PAP	**:**	Pulmonary artery pressure
PAPs	**:**	Pulmonary artery sysotic pressure
Pao2	**:**	Partial pressure of arterial oxygen
PDA	**:**	Patent ductus arterious
PDE5	**:**	Phospho diesterase 5
PEDP	**:**	Pulmonary End diastolic pressure
PFC	**:**	Persistent Fetal circulation
PFO	**:**	Persistent foramen oval
PGI2	**:**	Prostacyclin
PIP	**:**	Peak inspiratory pressure
PKA	**:**	CAMP- dependend protein Kinase
PKC	**:**	Protein Kinase C
PKG	**:**	CGMP – dependend protein kinase
PPHN	**:**	Persistent pulmonary hypertension of newborn
PPM	**:**	Part per million
PVR	**:**	Pulmonary vascular resistence
RA	**:**	Right atrium
RDS	**:**	Respiratory distress syndrome

RV	:	Right ventricle
RPEP	:	Right ventricle pre- ejection period
RVO	:	Right ventricular out put
RVET	:	Right ventricular ejection time
Sao2	:	Oxygen saturation
SERT	:	Serotonin transporter
SGC	:	Soluble guanyle cyclase
SMC	:	Smooth muscle cell
SSRIs	:	Selective serotonine reuptake inhibitors
SVC	:	Superior vena cava
TGF-B	:	Transforming growth factor-B
TPV	:	Time to peak velocity
TR	:	Tricuspid regurgitation
TTF-1	:	Thyroid transcription factor 1
V-A	:	Veno- arterial
VC	:	Vasoconstriction
V-V	:	Veno-venous
WBC	:	White blood cell

INTRODUCTION

Persistent pulmonary hypertension in the newborn (PPHN) is a neonatal emergency due to the failure to achieve normal cardiopulmonary adaptation following delivery. PPHN still remains a challenging condition with high morbidity and mortality. **(*Kleigman et al., 2007*)**

The aim of treatment is to lower pulmonary vascular resistance, maintain systemic blood pressure, reverse right to left shunt, and improve arterial oxygen saturation. ***(*Abman et al., 2004)***

A variety of treatment include hyperventilation, pressor agents surfactant, sedation, Alkalinization, vasodilatation e.g (tolazoline, inhaled nitric oxide, Magnesium sulfate, Adenosine, sildenafil) and Extracorporeal membrane oxygenation ECMO ***(Donn et al., 2007)***.

PPHN can occur as a primary condition or be secondary to meconium aspiration, respiratory distress syndrome, infection or congenital diaphragmatic hernia ***(Finer 2004)***.

PPHN occurs in approximately 1.9 per 1000 new born and may be more frequent in developing countries. There is strong evidence for the use of inhaled nitric oxide (INO) and ECMO in the treatment of PPHN. However, many developing countries do not have access or the technical expertise required for these expensive therapies ***(Chambers et al., 2006)***.

$MgSo_4$ is a natural Ca channel blocker that antagonizes Ca ion entry into smooth muscle cell thus promoting vasodilatation. $MgSo_4$ is a safe and chaper alternative for 1^{st} line treatment in moderate PPHN and was chosen to be alternative therapy for PPHN when other conventional treatments fail, are contraindicated or are not available ***(Chandran, 2004)***.

Sildenafil is a potent and selective inhibitor of cGMP-specific PDE5. This isoenzyme metabolizes cGMP which is the Second-Messenger of NO and a principle mediator of smooth muscle relaxation and vasodilatation. By inhibiting the hydrolytic breakdown of CGMP, sildenafil prolongs the action of CGMP. This results in augmented smooth muscle relaxation and cause pulmonary vasodilatation. ***(Reffelmann and Kloner, 2003)***. Inhibition of PDE5 lead to increase the concentration of cyclic-AMP and GMP locally, which in turn leads to relaxation of pulmonary vasculature smooth muscles so sildenafil decreases pulmonary vascular resistance in pulmonary hypertensive neonate.**(Humbert,2004)**

AIM OF THE WORK

The aim of this study was to compare the use of sildenafil versus magnesium sulfate as pulmonary vasodilator in the treatment of persistent pulmonary hypertension of the newborn in addition to the conventional therapy in these newborn. Duration to improvement, degree of improvement, side effects and outcome were compared.

EMBRYOLOGICAL DEVELOPMENT OF PULMONARY ARTERIAL VASCULATURE:-

Development of pulmonary arteries:

The vascular supply to lung buds arises from the paired sixth aortic arches, which arises from truncus arteriousus, the upper end of bulbus cordis, as it represents the most cranial part of heart tube.

The paired sixth aortic arches give off branches to developing lung each one divides into ventral (medial) & dorsal (lateral) segment. The ventral segment of the right 6th aortic arch forms the proximal part of the right pulmonary artery which enters the right lung bud while its dorsal segment disappear (loses its connection within dorsal aorta). The ventral segment of the left 6th aortic arch forms the main pulmonary artery and the proximal part of left hilar branches which enters the left lung bud while the dorsal segment persists during the intrauterine life forming the ductus arteriosus which forms a connection between the left pulmonary artery and the arch of the aorta. The aortic arches connect the aortic sac ventrally with the 2 dorsal aorta dorsally which fuses together form common dorsal aorta. ***(Risau et al., 1990)***.

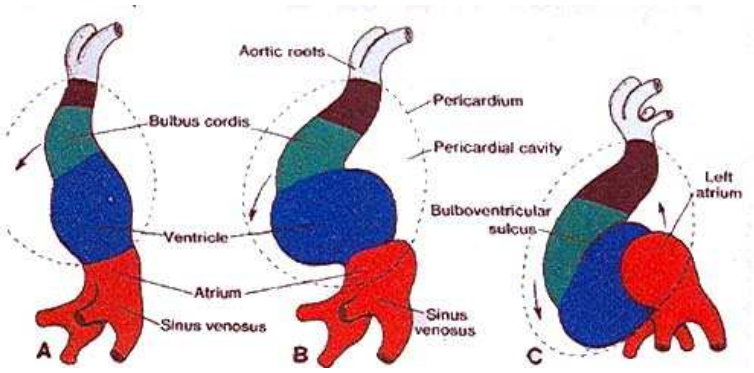

Figure (1): Formation of cardiac loop
A: 22 days, B; 23 day, C: 24 day
Broken Line: pericardium

(Sadler, 2004)

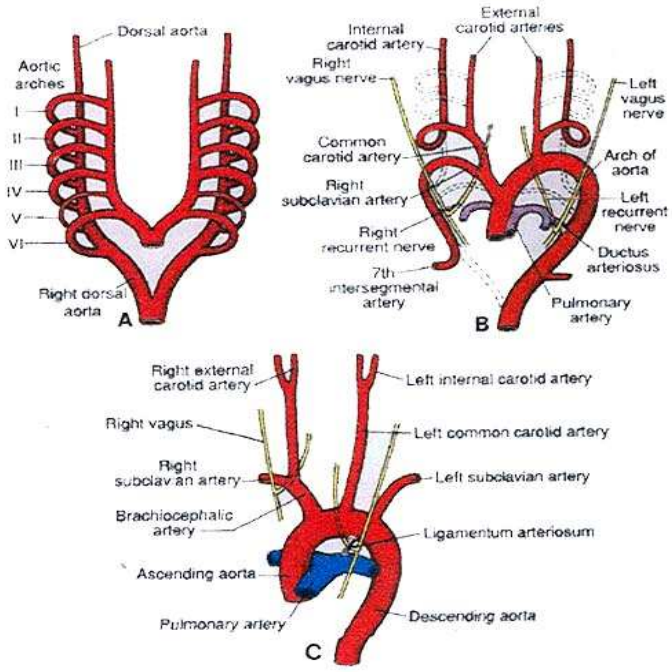

Fig (2):-A. Aortic arches and dorsal aortae before transformation into the definitive vascular pattern. B. Aortic arches and dorsal aortae after the transformation .Broken lines, obliterated components. Note the patent ductus arteriosus and position of the seventh intersegmental artery on the left C.The great arteries in the adult. Compare the distance between the place of origin of the left common carotid artery and the left subclavian in B and C. After disappearance of the distal part of the sixth aortic arch (the fifth arches never form completely), the right recurrent laryngeal nerve hooks around the right subclavian artery. On the left the nerve remains in place and hooks around the ligamentum arteriosum (Sadler, 2004).

Besides the different origin of pulmonary artery segment, two other processes probably contribute to the development of lung vasculature: Angiogenesis and vasculogenesis ***(Morin and stermark, 1995)***.

Course of Pulmonary artery in relation to Aorta:

Two ridges called the right & left major bulbar cushions develop inside the distal part of bulbus cordis & descend in the direction of ventricle following a spiral course. Later they fuse together forming aortico-pulmonary septum. The distal part of bulbus cordis become