Effectiveness of 2nd Course of Oral Ibuprofen in Closure of Patent Ductus Arteriosus After Failure of Initial Treatment in Preterm Infants

Thesis

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أعوذ بالله من الشيطان الرجيم

بسم الله الرحمن الرحيم

" قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إلاَّ مَا عَلَّمْتَنَا إنَّكَ أَنتَ العَلِيمُ الحَكِيمُ "

صدق الله العظيم

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To all those I say:

جزاكم الله خيرا ووفقكم لما يحبه ويرضاه

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ABBREVIATIONS

ALT	Alanine Transferase
ASD	Atrial Septal Defect
AST	Aspartate Transaminase
BPD	Bronchopulmonary Dysplasia
BUN	Blood urea nitrogen
CHF	Congestive Heart Failure
CLD	Chronic Lung Disease
COA	Coarcitation of Aorta
COX	Cyclo-Oxygenase
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
ELBW	Extremely Low-Birth-Weight
FIO2	Fraction Of the Inspired Oxygen
FO	Foramen Ovale
GA	Gestation age
GFR	Glumerular Filtration Rate
IVC	Inferior Vena Cava
IVH	Intra-Ventricular Heamorage
LVH	Left Ventricular Hypertrophy
MRI	Magnetic Resonance Imaging
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
NO	Nitric Oxide
NSAID	Non-Steroidal Anti-inflammatory Drugs
PAO2	Pressure Of Arterial Oxygen
PDA	Patent Ductus Arteriosus
PEEP	Peak-End-Expiratory-Pressure
PGS	Prostaglandins
PIP	Positive Inspiratory Pressure
PLT	Platelets
PVOD	Pulmonary Vascular Obstructive Disease
PVR	Pulmonary Vascular Resistance
RDS	Respiratory Distress Syndrome
RVH	Right Ventricular Hypertrophy
S1	1st Heart Sound
S2	2nd Heart Sound
SIMV	Synchronized Intermittent Mandatory Ventilation
SVC	Superior Vena Cava
TLC	Total leukocytic Count
UOP	Urine Output
VSD	Ventricular Septal Defect

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ABSTRACT

Key words:

Patent ductus arteriosus- PDA - oral ibuprofen- - Preterm- second course.

The objective of this study was to determine the efficacy and safety of 2nd course of oral ibuprofen in closure of hemodynamically significant PDA in preterm infants after failure of the initial course. The study included 100 preterm neonates ≤ 34 weeks gestational age admitted to Kasr Al-Ainy hospital, NICU units, Cairo University between Jan. and Sept. 2009 whom had clinically significant PDA, they received initial oral ibuprofen course of 10, 5, 5 mg/kg/dose at 24h intervals. Seventy six neonates had their PDA closed after 1st course with closure rate of 76%, nineteen neonates were eligible to receive 2nd course of 20, 10, 10 mg/kg/dose at 24hr intervals. Nine of total 19 infants had their PDA closed with closure rate of 47.46%. Monitoring of urine output, renal function, hematological parameters, gastrointestinal symptoms, neurological and hepatic function showed no significant adverse effects related to treatment.

Conclusion: 2nd course of ibuprofen is safe and effective in closure of PDA in preterm infants with cumulative closure rate of 89.4%.

INTRODUCTION

Patent ductus arteriosus (PDA) is a postnatal communication, usually between the main pulmonary trunk and the descending thoracic aorta that's due to the persistent patency of fetal ductus arteriosus **(David et al., 2006)**.

The incidence of isolated persistent patency of ductus arteriosus has been estimated to be 1:2000 to 1:5000 births or about 10-12% of all varieties of congenital heart disease **(Friedman & Silverman, 2001).** The persistence of the PDA in preterm infants is inversely related to gestational age and birth weight. The incidence of PDA is 70% in preterm infants weighing less than 1000 g and 29 weeks gestational age. Although spontaneous closure of the ductus will occur in approximately 34% of these extremely low-birth-weight (ELBW) infants, failure of the ductus to close in remaining infants can result in potentially life-threatening sequelae **(Sekar & Corf, 2008).**

The clinical consequences of PDA are related to the magnitude of the left-to-right shunt through the PDA with its associated change in blood flow to the lung, kidneys, and intestine **(Clyman, 2005).**

The typical presentation of PDA begins with harsh systolic ejection murmur heard over the entire pericardium but loudest at the left upper sternal border and left infraclavicular area. The peripheral pulse increases in amplitude (bounding pulses). The respiratory status of the patient deteriorates leading to tachypnea, apnea, CO2 retention and increased need to mechanical ventilation **(Wechsler and Wernovskey, 2004).**

In some centers, conservative measures including fluid restriction, diuretics, and Digoxin have been advocated to treat the symptoms associated with a PDA. Although

excessive fluid administration has been associated with an increased incidence of PDA, fluid restriction is unlikely to cause ductus closure. In addition, the combination of fluid restriction and diuretics frequently leads to electrolyte abnormalities, dehydration, and, most important, caloric deprivation. Digoxin and other inotropes would not be expected to be very useful because myocardial contractility is increased rather than reduced in infants with PDA **(Clyman 2005).**

Pharmacotherapy of PDA involves the use of COX inhibitors, which have been shown to be safe and effective in the majority of treated infants (**Sekar & Corf, 2008).**

For years, Indomethacin, a nonspecific prostaglandin synthetase inhibitor has been the drug of choice for the treatment of PDA worldwide. It has been shown to close 90% of PDAs successfully. However, less mature infants and those treated later after birth are less likely to respond **(Evan & Seri, 2003).**

Undesirable adverse effects prompted researchers to seek alternative agents. In April 2006, the US Food and Drug Administration approved the use of ibuprofen for closure of clinically significant PDA in premature neonates **(Grace, 2007).**

Ibuprofen which is a cyclo-oxygenase (COX) inhibitor proved to be effective in closure of the PDA. Moreover it is just effective as Indomethacin in closing PDA in neonates with RDS but with fewer side effects on kidney and brain **(Lago et al., 2002).** Also studies on animals suggest that Ibuprofen may even have a cyto-protective effect on the gastro-intestinal tracts **(Clyman, 2005).**

AIM OF WORK

The aim of our study was to determine the effectiveness of 2nd course of oral Ibuprofen in closure of patent ductus arteriosus after failure of 1st initial treatment in preterm infants.

REVIEW

Anatomy

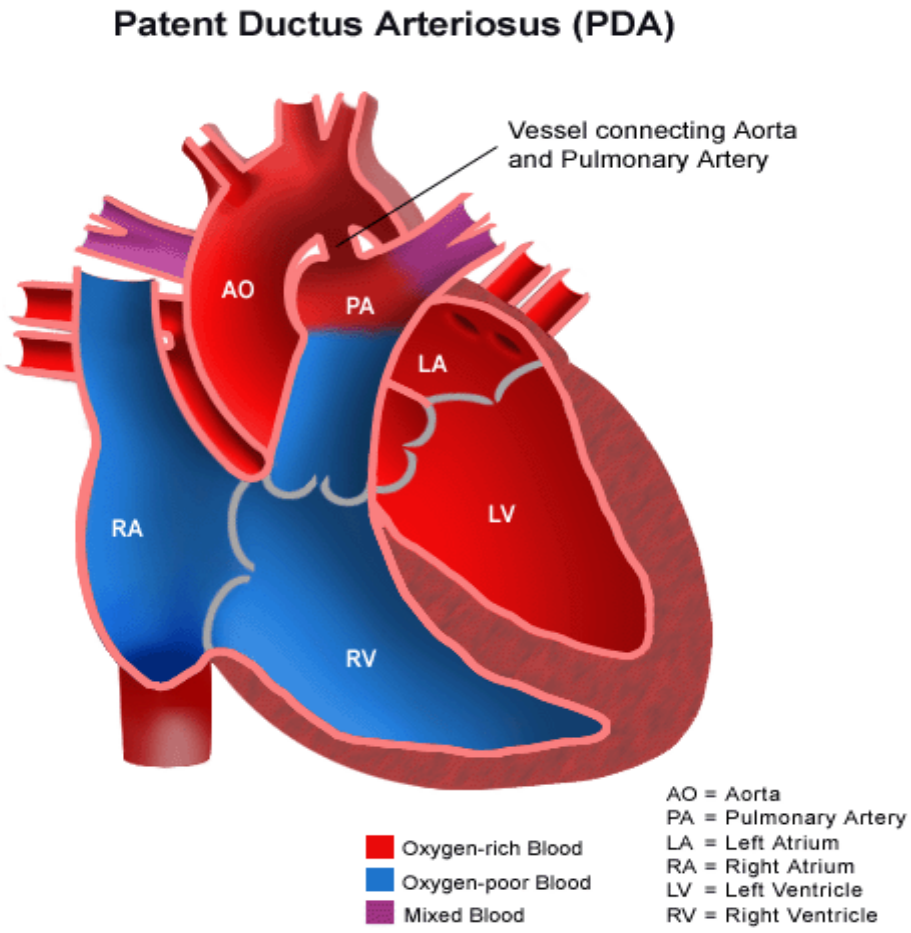

Fig (1): Anatomy of PDA

PDA is a postnatal communication, usually between the main pulmonary trunk and the descending thoracic aorta that's due to the persistent patency of fetal ductus arteriosus **(David et al., 2006)**.

It takes a slight cephalic to caudal direction as it passes from anterior aspect of pulmonary artery to posterior aspect of descending aorta **(Mullins & Pagatto, 1998).** With a right aortic arch the ductus is

usually left sided, although rarely it arises in mirror image **(Musewe & Olley, 1992),** the ductus arteriosus on the right, joining the right pulmonary and right aortic arch just distal to the right subclavian artery **(Moore et al., 2001).** Bilateral ductus is rare **(Musewe & Olley, 1992)**.

The ductus arteriosus may persist in an infinite variety of shapes and sizes **(Mullins & Pagatto, 1998).**

In the fetus, where at least 50%-60% of cardiac output arises from the right ventricle and transverses the ductus on its way to the systemic circulation, the ductus tends to maintain a **short tubular shape (Musewe & Olley, 1992).** The typical persistent ductus has a **conical shape** with a large aortic end tapering toward pulmonary artery with the narrowest area of the ductus close to the junction with the pulmonary artery. The total length of the persistent ductus, regardless of its shape or diameter may vary from millimeters to centimeters, the base of the aortic end of the ductus can vary in size from several millimeters to centimeters **(Mullins & Pagatto, 1998).**

At birth however, the ductus undergoes rapid change in size and shape related to the process of constriction and closure. The persistent ductus may therefore be long and thin or short and large depending on how closure progresses **(Musewe & Olley, 1992).**