

# **Effectiveness of 2<sup>nd</sup> Course of Oral Ibuprofen in Closure of Patent Ductus Arteriosus After Failure of Initial Treatment in Preterm Infants**

## **Thesis**

**Submitted for fulfillment  
of the M.Sc. degree  
in Pediatrics**

By

**Ahmed Ibrahim Amin**

Resident of Pediatrics  
The national institute of health insurance

*Under supervision of*

**Prof. Dr. Zahraa Mohammed Ezzeldin**

Professor of Pediatrics,  
Head of NICU unit,  
Faculty of Medicine,  
Cairo University

**Prof. Dr. Amira Esmat Al-Tantawy**

Assistant Professor of Pediatrics,  
Faculty of Medicine,  
Cairo University

**Dr. Hanan Zekri Khaled**

Lecturer of Pediatrics,  
Faculty of Medicine,  
Cairo University

**2010**

أَعُوذُ بِاللَّهِ مِنَ الشَّيْطَانِ الرَّجِيمِ  
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

“ قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا  
إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ ”

صدق الله العظيم

” سورة البقرة آية (٣٣) ”

# ACKNOWLEDGEMENT

First of all, I would like to thank **ALLAH**, the merciful and compassionate for making all this work possible and for granting me the best teachers, family, colleagues that many people would wish and dream to have.

I am honored to have Prof. Dr. Zahraa Mohammed Ezzeldin, professor of pediatrics and neonatology, Faculty of Medicine, Cairo University as a supervisor on this work. I am greatly indebted to her for her valuable supervision and kind guidance.

Also I would like to thank Prof. Dr. Amira Esmat Al-Tantawy, assistant professor of pediatrics, Faculty of Medicine, Cairo University, for her patience, guidance and her helpful advice throughout my research work. I will never forget her great effort with me.

Words cannot express my deep gratitude and sincere appreciations to Dr. Hanan Zekri Khaled, lecturer of pediatrics, Faculty of Medicine, Cairo University, who assisted me in the most of the practical work. I would like to express all the feelings of respect and appreciation toward her. I am extremely fortunate to work under her supervision.

The completion of this work wouldn't be possible without the help support and encouragement of my Parents, brother Mohammed and sister Asmaa.

I would like to send special thanks to my dear wife for her great patience, support and help.

To all those I say:

جزاكم الله خيرا ووفقكم لما يحبه ويرضاه

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# ABBREVIATIONS

<b>ALT</b>	Alanine Transferase
<b>ASD</b>	Atrial Septal Defect
<b>AST</b>	Aspartate Transaminase
<b>BPD</b>	Bronchopulmonary Dysplasia
<b>BUN</b>	Blood urea nitrogen
<b>CHF</b>	Congestive Heart Failure
<b>CLD</b>	Chronic Lung Disease
<b>COA</b>	Coarctation of Aorta
<b>COX</b>	Cyclo-Oxygenase
<b>CPAP</b>	Continuous positive airway pressure
<b>ECG</b>	Electrocardiogram
<b>ELBW</b>	Extremely Low-Birth-Weight
<b>FI<sub>O2</sub></b>	Fraction Of the Inspired Oxygen
<b>FO</b>	Foramen Ovale
<b>GA</b>	Gestation age
<b>GFR</b>	Glomerular Filtration Rate
<b>IVC</b>	Inferior Vena Cava
<b>IVH</b>	Intra-Ventricular Hemorrhage
<b>LVH</b>	Left Ventricular Hypertrophy
<b>MRI</b>	Magnetic Resonance Imaging
<b>NEC</b>	Necrotizing Enterocolitis
<b>NICU</b>	Neonatal Intensive Care Unit
<b>NO</b>	Nitric Oxide
<b>NSAID</b>	Non-Steroidal Anti-inflammatory Drugs
<b>PA<sub>O2</sub></b>	Pressure Of Arterial Oxygen
<b>PDA</b>	Patent Ductus Arteriosus
<b>PEEP</b>	Peak-End-Expiratory-Pressure
<b>PGS</b>	Prostaglandins
<b>PIP</b>	Positive Inspiratory Pressure
<b>PLT</b>	Platelets
<b>PVOD</b>	Pulmonary Vascular Obstructive Disease
<b>PVR</b>	Pulmonary Vascular Resistance
<b>RDS</b>	Respiratory Distress Syndrome
<b>RVH</b>	Right Ventricular Hypertrophy
<b>S<sub>1</sub></b>	1 <sup>st</sup> Heart Sound
<b>S<sub>2</sub></b>	2 <sup>nd</sup> Heart Sound
<b>SIMV</b>	Synchronized Intermittent Mandatory Ventilation
<b>SVC</b>	Superior Vena Cava
<b>TLC</b>	Total leukocytic Count
<b>UOP</b>	Urine Output
<b>VSD</b>	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 2<sup>nd</sup> 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  $\leq$  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 1<sup>st</sup> course with closure rate of 76%, nineteen neonates were eligible to receive 2<sup>nd</sup> 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:** 2<sup>nd</sup> 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, CO<sub>2</sub> 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 2<sup>nd</sup> course of oral Ibuprofen in closure of patent ductus arteriosus after failure of 1<sup>st</sup> initial treatment in preterm infants.

# REVIEW

# Anatomy

## Patent Ductus Arteriosus (PDA)

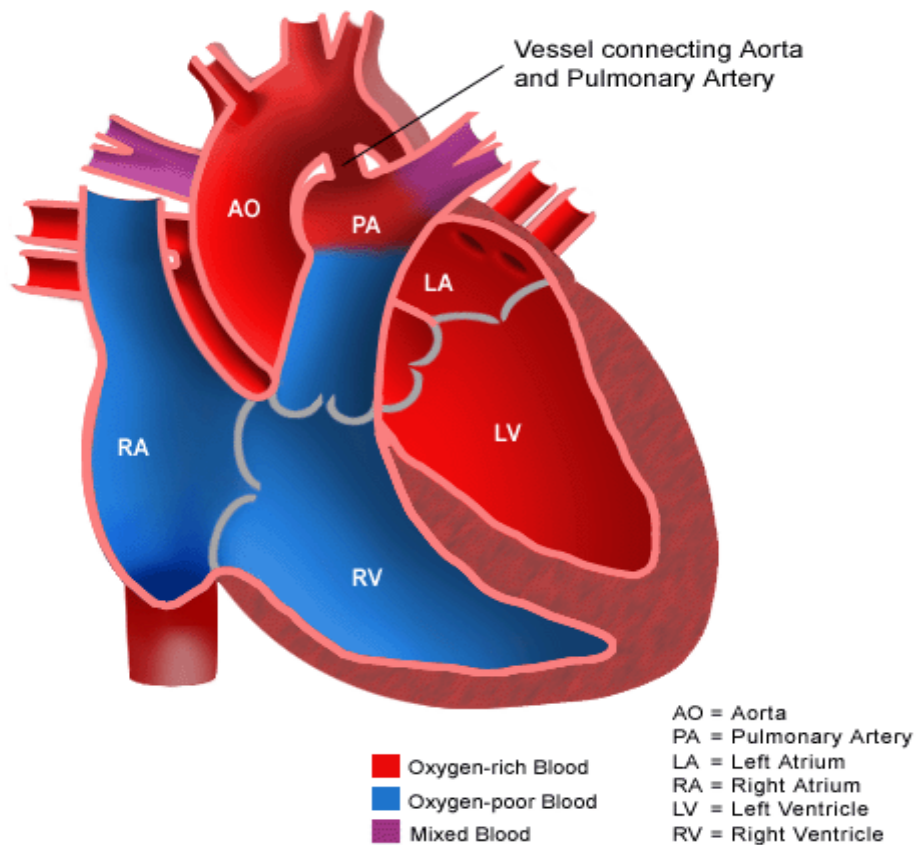


Fig (1): Anatomy of PDA

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**).