كلية الطب
جامعة عين شمس
٢٠٠٩

IBUPROFEN VERSUS INDOMETHACIN IN EARLY TREATMENT OF PDA IN VERY LOW BIRTH WEIGHT INFANTS

Thesis

Submitted for Partial Fulfillment of
Master Degree in Pediatrics

By

Ehab Fol Faheem
M.B.B.Ch-Assuit University

Under Supervision of

Prof. Dr. Adham Mohamed Hegazy
Professor of pediatrics
Faculty of Medicine
Ain Shams University

Dr. Maha Hassan Mohamed
Lecturer of pediatrics
Faculty of medicine

Ain Shams University

Faculty of Medicine
Ain Shams University
٢٠٠٩

Dedication

To my Father and Mother
who supported me in my
whole life

Acknowledgment

First and foremost, thanks are all to "**ALLAH**".

Moreover I would like to express my sincere and profound gratitude to professor Doctor/Adham Mohamed Hegazy, professor of pediatrics, Faculty of Medicine, Ain Shams University for this meticulous supervision, loyal encouragement and valuable advises throughout the work.

I am also grateful to Doctor /Maha Hassan Mohamed, Lecturer of pediatrics, Faculty of Medicine, Ain Shams University for her unique effort, continuous guidance, assistance and knowledge she offered me throughout the performance of this work.

My special thanks for Doctor/Hala Gaber El Rabei, for her support, guidance and for dedicating mush of her time to accomplish this work.

Also I should not forget to express my great thanks to the NICU, Maternity Hospital. Whom I work with and they all give me their advice, assistant and support.

Last but not least, I convey my thanks to my patients, their parents and to anyone who helped me to complete this work.

CONTENTS

LIST OF TABLES

LIST OF TABLES (Cont...)

LIST OF FIGURES

LIST OF FIGURES (Cont...)

LIST OF FIGURES (Cont...)

LIST OF ABBREVIATIONS

Abbrev.	Meaning
ΔP	: Pressure gradient
٢D	: Two dimensional
Cox	: Cyclo-oxygenase
Cox-١	: Cyclo-oxygenase-١ enzyme
Cox-٢	: Cyclo-oxygenase-٢ enzyme
CPAP	: Continuous positive air way pressure
CTG	: Cardiotocography
DA	: Ductus arteriosus
ECG	: Electrocardiogram
Echo	: Echocardiography
EDV	: End-diastolic volume
EF	: Ejection fraction
ESV	: End-systolic volume
GI	: Gastrointestinal
GIT	: Gastrointetinal tract
Hct	: Hematocrite
IPPV	: Intermittent positive pressure ventilation
IVH	: Intraventricular hemorrhage
LA	: Left atrium
LA-AO	: Left artrial to aortic root ratio
LV	: Left ventricle
NCPAP	: Nasal continuous positive air way pressure
NEC	: Necrotizing enterocolitis
NICU	: Neonatal intensive care unit
PA	: Pulmpnary artery
PDA	: Patent ductus arteriosus
PEEP	: Positive end expiratory pressure
PG	: Prostaglandin
PT	: Prothrombin time
PTT	: Partial thromboplastin time
TxA٢	: Thromboxane A٢
VSD	: Ventricular septal defect

INTRODUCTION

The ductus arteriosus is derived from the sixth aortic arch and normally extends from the main or left pulmonary artery to the descending aorta just distal to the origin of the left subclavian artery. Normally in full term neonates, it closes within several days of birth ***(Ewert, ٢٠٠٥).***

Functional closure of the ductus arteriosus occurs by constriction of the medial smooth muscle in the ductus within ١٠ to ١٥ hours after birth. Anatomic closure is completed by two to three weeks of age by permanent changes in the endothelium and subintimal layers of the ductus ***(Carey, ٢٠٠٣).***

Oxygen, prostaglandins E٢ levels and maturity of the newborn are important factors in closure of the ductus ***(Ivey and Srivastava, ٢٠٠٦).***

A postnatal increase in oxygen saturation of the systemic circulation (from PO٢ of ٢٥ mmHg in utero to ٥٠ mmHg after lung expansion is the strongest stimulus for constriction of the ductal smooth muscle which leads to closure of the ductus ***(Riggst et al., ٢٠٠٠).***

The responsiveness of the ductal smooth muscle to oxygen is related to gestationl age of the newborn. Important problems that premature infants may face is that

the ductus arteriosus is more likely to remain open as preterm infant's ductal smooth muscle layer doesnot have a fully developed constrictor response to oxygen .Clinical evidence of patent ductus arteriosus (PDA) appears approximately in ٣١% in infants whose birth weight between ٥٠٠-١٥٠٠ gm ***(Poon, ٢٠٠٧).***

Indomethacin and more recently ibuprofen have been used to treat hemodynamically significant PDA in preterm infants. Both are cyclo-oxygenase blockers, but seem to have different influence on regional circulation ***(Lago et al., ٢٠٠٢).***

Administration of three doses of ibuprofen intravenously within ٣ hours after birth in preterm neonates reduced the incidence of PDA without causing notably early adverse reactions ***(Varvarigou et al., ١٩٩٦).***

Adverse events associated with both drugs include bleeding, skin lesion as irritation, hypoglycemia, adrenal insufficiency and respiratory failure. Intraventricular hemorrhage (IVH) and renal insufficiency have been reported ***(Poon, ٢٠٠٧).***

AIM OF THE WORK

The aim of the study is to determine the safety and efficacy of oral ibuprofen compared with intravenous indomethacin in the prevention and treatment of PDA in premature babies born under ٣٢ weeks gestation with birth weight less than ١٢٥٠ gm.

FETAL AND NEONATAL CIRCULATION

Fetal circulation:

Fetal circulation differs from adult circulation in several ways. Almost all differences are attributable to the fundamental difference in the site of gas exchange. In the adult, gas exchange occurs in the lungs. In the fetus, the placenta provides the exchange of gases and nutrients ***(Park, ٢٠٠٧).***

In the fetus, the most highly oxygenated blood returns via the umbilical vein, ductus venosus and inferior vena cava. The majority of this blood passes across the foramen ovale into left atrium and then through the left ventricle to the descending aorta. Almost all of the superior vena cava return passes through the right atrium and through the tricuspid valve to the right ventricle and main pulmonary trunk. Because of the high pulmonary vascular resistance in the fetus, only a small proportion of this blood passes to lungs, most traversing the ductus arteriosus to reach the ascending aorta. As a result of this arrangement the more highly oxygenated blood is directed to the coronary arteries and the arteries supplying the brain. Blood with the lowest oxygen content passes from the descending aorta to placenta via the paired umbilical arteries which arise from the internal iliac arteries ***(Leonard, ٢٠٠٧).***

Unlike the adult heart which increases its stroke volume when the heart rate decreases, the fetal heart is unable to increase stroke volume when the heart rate falls because it has a low compliance. Therefore the fetal cardiac output depends on the heart rate; when the heart rate drops, as in fetal distress, a serious fall in cardiac output results ***(Park, ٢٠٠٧).*** Fetal circulation is illustrated in figure (١).

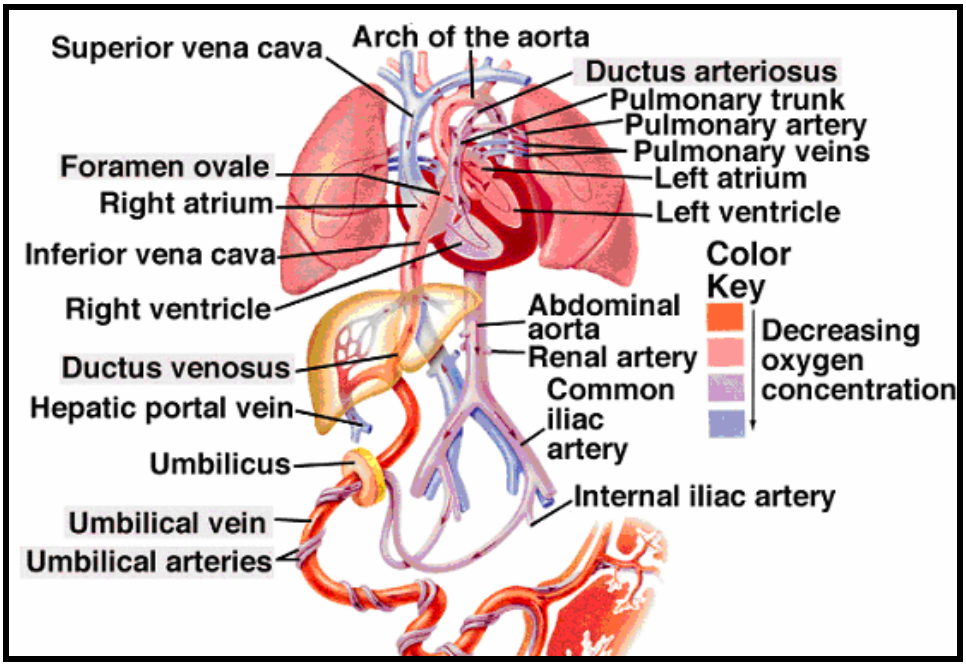

Figure (١): Fetal circulation ***(Leonard, ٢٠٠٧)***

Organ blood flow within the fetus is dependant upon vascular resistance of that organ. Because of the widely patent ductus arteriosus both ventricles eject blood against effectively the same total vascular resistance. In the normal fetal heart the right ventricle ejects about ٦٠% of the combined ventricular output while the left ventricle ejects ٤٠% ***(Leonard, ٢٠٠٧).***