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Use of paracetamol for ductus closure in preterm neonates

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ABSTRACT

Patent ductus arteriosus (PDA) is more common in preterm newborns. Risk factors are mechanical ventilation, lack of antenatal steroids, surfactant useand metabolic acidosis. It is a significant cause of morbidity and mortality in preterm infants. Medical treatment modalities included indomethacin and ibuprofen. Both are cyclo-oxygenase inhibitor and associated with renal, hematological, gastrointestinal side effects. Recently few studies has shown that paracetamol is effective in duct closure and also has better side effect profile. It has also low cost and both preparation (oral and IV) is available. Yet further compartiverandomized clinical trials are needed for recommendation. © 2014 Trade Science Inc. - INDIA

INTRODUCTION

Patent ductus arteriosus (PDA) is a persistent communication between the descendingaorta and the pulmonary artery. It is because of failure of the ductus arteriosus (DA) to close within 48-96 hours of birth. This is more likely to happen in premature neonates. Treatment modalities for PDA are fluid restriction, indomethacin, ibuprofen and surgical closure. Both indomethacin and ibuprofen are associated with side effects. Recently paracetamol found to be effective for ductus closure.

PHYSIOLOGY

Oxygen and endothelin are very strong vasoconstrictors and prostaglandins E2 and I2 arestrong vasodilators of the DA. Lower oxygen concentrations in utero and high circulating PGE2 and PGI2 levels help in keeping the ductus patent. Sudden elevation in circulating oxygen tension and fall in prostaglandin levels soon after delivery results in strongvasoconstriction and functional closure of the DA soon after delivery.

DUCTUS ARTERIOSUS IN PRETERM NEONATES

Preterm babies are more prone for PDA because (a) Increasedsensitivity of ductus to prostaglandins as compared to term neonates (b) Sensitivity toprostaglandins is sustained for a longer period (c) Higher incidence of hypoxia andacidosis (d) Defective smooth muscle migration resulting in compromised anatomicalclosure.

RISK FACTORS FOR PDA IN PRETERM NEONATES

The incidence of PDA is inversely related to gestational age and birth weight. Ahemodynamically significant PDA has been reported in 40% of infants lessthan 1000 grams and 20% of infants between 1000-1500 grams[1,2,3] Respiratory distresssyndrome (RDS), ventilation, surfactant, lack of antenatal steroids, presence of sepsis, and liberal fluidtherapy

Review

are additionalrisk factors for PDA.

HEMODYNAMIC CONSEQUENCES OF PDA

Shunting of blood from the systemic circulation to the pulmonary circulation results incongestive cardiac failure, pulmonary edema/hemorrhage. These newborns are more prone to bronco pulmonary dysplasia (BPD), acute renal failure (ARF), necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH).

CLINICAL FEATURES

Hyper dynamic circulation, wide pulse pressure (>25 mm Hg), prominent precordial pulsations, bounding pulsesand pan systolic/ continuous murmurbest heard at the 2nd left parasternal area[4]. Indicators of ductus opening on a ventilated baby are:Metabolic acidosis, deteriorating respiratorystatus after a period of relative stability, increasing ventilatory requirements, unexplained CO2 retention, fluctuating FiO2 requirements and recurrentapneas in a ventilated baby.

INVESTIGATIONS

(a) Chest xray

Findings may be non-specific, usually includes cardiomegaly, upturned left bronchus due to left atrial enlargement andpulmonary plethora.

(b) Echocardiography

Echocardiographic criteria include (a) Left atrial dilatation (Left atrial: Aorticroot>1.6) (b) Diastolic turbulence on doppler in the pulmonary artery and (c) Direct imaging to measure the diameter of PDA. A hemodynamically significant PDA is diagnosed in the presence of a ductus diameter>1.5mm and absent/ retrograde diastolic flow in the post ductal aorta.

STRATEGIES OF MANAGEMENT[5]

(a) Prophylactic treatment

In this treatment is started before the appearanceof PDA, usually within the first 24 hours of birth. Itwas found to decrease symptomatic PDA and IVH, yet not associated with decrease in long-term outcome. Moreover, indomethacin hasalso been found to decrease cerebral and renal blood flow and hence is not recommendedas a prophylactic agent[6]. Trials with prophylactic ibuprofen arestill going on.

(b) Early symptomatic

In this strategy, treatment is started as soon as the PDA isdetected even if it is not hemodynamically significant.

(A) Weight <1000 grams

Among neonates detected to have a PDA, 80% of neonateswould progress to develop a hemodynamically significant shunt. Hence, it isrecommended to treat PDA in this group early even though it may not behemodynamically significant (hs PDA).

(B) Weight >1000 grams

Early treatment is not recommended in this group asprogression to symptomatic PDA is less common and spontaneous closure are knownto occur in this group[7].

(c) Late symptomatic

Only hemodynamically significant PDA is treated in this strategy and it is therecommended approach for neonates >1000 grams.

MANAGEMENT

(a) General measures

Fluid restriction, avoidance of hypoxia and acidosis. Furosemide should be used only in intractable cases (dose of 1 mg/kg/dose 12 hourly).

(b) Medical management

(A) Indomethacin

The mechanism of action is an inhibition of cycloxygenase (COX) enzymein the prostaglandin pathway. Indomethacin has a greater affinity for COX 1 (renal) asagainst COX 2 (extra-renal). Due to this greater affinity for renal COX1, the incidence ofrenal complications is higher with indomethacin as compared to other inhibitors ofprostaglandin synthesis.

(1) Indications for indomethacin use

(i) Early symptomatic treatment of PDA in <1000 grams (ii) Late symptomatic treatment of PDA in > 1000 grams (iii) Re-treatment after failure of the first course of Indomethacin (iv) Recurrence of PDA after the first course of indomethacin.

(2) Oral medication

Due to non-availability of the IV formulation, oral indomethacinis being used forclosure of PDA.

Side effects and monitoring:Adverse effects include renal compromise, bleeding tendency, increased risk of necrotizing enterocolitis andpoor neuro-developmental outcome. Urine output, renal function andPlatelet counts should be monitored.

Contraindications for use of indomethacin:Urine output< 0.6 ml/kg/h[8], blood urea>30 mg/dl, creatinine>1.8 mg/dl, Bleeding from IV sites; gastrointestinal bleeding, enlarging or evolvingintraventricular hemorrhage (IVH); platelet count < 60,000/mm3, necrotizing enterocolitis and bloody stool

Efficacy:The closure rate with indomethacin is 80%. The full course should be completed even if closure is achieved before thethird dose.

(B) Ibuprofen

Ibuprofen is also an inhibitor of prostaglandin synthesis and is effective in closing theductus. It has an equal efficacy as compared to indomethacin with fewer side effects[9,10]. Its use is associated with a lower incidence of oliguria, renal compromise, lesser effect on mesenteric and cerebral blood flow as compared toindomethacin. The dose is 10 mg/kg stat followed by 5 mg/kg/dose x 2 doses at 24 hourintervals given orally.

(C) Paracetamol

There are few studies, shown the effect of paracetamol in ductus closure.Rahul Sinha, VandanaNegi, SS Dalal studied oral paracetamol for patent ductus closure in preterm neonates with significant PDA who had contraindication for Brufen/ Indomethacin[11]. There were total 18 preterm neonates, who had significant PDA, out of these oral brufen was given to 8 preterm neonates and 10 were given oral Paracetamol @ 15 mg/kg 8 hourly for 48 h. The ductal closure was achieved in all neonates by 48 h of administration and was confirmed with repeat echocardiography after 72 h of administration of oral paracetamol. These neonates didnot suffer any complication related to paracetamol.Oncel M.Y., Yurttutan S.' Degirmencioglu H.et al evaluated the efficacy of intravenous paracetamol in preterm infants with hsPDA whose feeding was contraindicated or had feeding intolerance[12]. A total of 10 preterm infants were included in the study with a median gestational age of $27^{4/7}$ weeks and a median birth weight of 775 gm. Intravenous paracetamol resulted in successful closure of PDA in all patients. This study is the first case series in the literature which used intravenous paracetamol treatment for PDA. Authors believe that intravenous paracetamol could be used as an alternative drug for infants. Cathy Hammerman, Alona Bin-Nun, EinatMarkovitch, et al has presented preliminary datathat support paracetamol'sefficacy inclosing PDAs over a wide range of postnatalages[13]. Jasani B et al reported a case series of 6 neonates of hs PDA[14]. Out of them 3 neonates did not respond to Indomethacin and one to ibuprofen treatment. In two others treatment with indomethacin/ibuprofen was contraindicated. Treatment with oral paracetamol was started in these cases at a dose of 15 mg/kg every 6 hourly for 7 days. Further follow-up echocardiography was performed to see ductus closure. Median age at paracetamol administration was 128 hours (range 62-214 hr). The median duration of therapy was 82.5 h. (range 56-102 hr) and median age at closure of ductus was 209.5hr (range 130-210 hr). Complete closure was observed in 6/6 (100%) of babies. None of the babies had any adverse effect. Pre and post-treatment levels of liver enzymes were normal in all neonates. KarelAllegaert, Brian Anderson, Sinno Simons et alconcludedthat paracetamol remains a need for alternative medical treatments for PDA closure in extreme preterm neonates because of therapeutic failure and adverse effects associated with non-selective cyclooxygenase inhibitors[15]. Dang D et al studied the comparison of oral paracetamol versus ibuprofen in premature infants (d"34 weeks) with Patent Ductus Arteriosus. It was a randomized controlled trial. A total of 249 infants were enrolled in

Review

the study. The study revealed that oral paracetamol was comparable to ibuprofen in terms of the rate of ductal closure and even showed a decreased risk of hyperbilirubinemia or gastrointestinal bleeding. Therefore, paracetamol may be accepted as a first-line drug treatment for PDA in preterm infants.

Nevertheless, wecaution that these are merely preliminaryobservations that must be testedand validated in further prospective studies and randomized control trials. If confirmed, paracetamolcould offer several important therapeuticadvantages over existing therapies:(1) it has no peripheral vasoconstrictiveeffect (2) it can be given toinfants with clinical contraindicationsfor non-steroidal anti-inflammatorydrugs; and (3) it seems to be effectiveafter some ibuprofen treatment failureswhen the only other therapeuticoption is surgery.

(c) Surgical ligation

The indications for surgical therapy include a contraindication to medical therapy andfailure of a second course of indomethacin[16].

CONCLUSIONS

PDA has been has been reported in 40% of preterm's lessthan 1000 grams and 20% of infants between 1000-1500 grams.

Medical Management includes indomethacin and ibuprofen, but have higher rates of side effects.

Recently paracetamol has been found to effective for ductus closure in preterm babies and is better in terms of availability of both intravenous and oral preparation, cost and fewer side effects than indomethacin and brufen.

However safety for PDA closure is uncertain because there are a limited number of observation in this specific subpopulation so far.

Further prospective studies and randomized controlled trials are needed to establish both the effectiveness and safety for further recommendation.

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