บทฟื้นฟูวิชาการ

Treatment of patent ductus arteriosus in the low birth weight infant

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สุวิมล สรรพวัฒน์. การรักษา Patent ductus arteriosus ในทารกน้ำหนักน้อย จุฬาลงกรณ์เวชสาร 2526 กรกฎาคม ; 27 (4) : 251–257

ภาวะ ductus arteriosus เปิด เป็นภาวะที่พบบ่อยในเด็กน้ำหนักน้อย ในระยะหลังคลอด ductus arteriosus ขนาดเล็ก มักไม่ทำให้มีปัญหา แต่พวกที่มีขนาดกลางและขนาดใหญ่ จะทำให้เลือดแดงจำนวนมากไหลลัดเข้าสู่ pulmonary artery ซึ่งเป็นระบบเลือดดำ ทำให้เกิดการคั่งของเลือดในปอดและมีภาวะหัวใจวายตามมา การรักษาตามอาการและรักษาแบบประคับประคองนั้น ใช้วิธีจำกัดจำนวนน้ำที่ให้ ให้ยาขับปัสสาวะเป็นครั้งคราว ให้ digitalis และการใช้เครื่องหายใจในบางราย ส่วนการรักษาเฉพาะทำได้โดยการปิด ductus arteriosus ซึ่งอาจใช้วิธีผ่าตัดหรือใช้ยา

การผ่าตัดปิด ductus arteriosus ให้ผลที่แน่นอน และมีอัตราเสี่ยงน้อยมาก ในกรณีที่ไม่อาจทำผ่าตัดได้ อาจปิดโดยวิธีใช้ยา indomethacin ซึ่งมีฤทธิ์ระงับการสร้าง prostaglandin ที่เป็นตัวทำให้ ductus arteriosus เปิดอยู่ในทารกในครรภ์ ขนาดของ indomethacin คือ 0.2 มิลลิกรัม ต่อ กิโลกรัมของน้ำหนักตัว ให้ได้ทุก 8–24 ชั่วโมง ผลเสียจากการให้ยานี้ คือ ปัสสาวะลดน้อยลง BUN, creatinine pH. โปแตสเซียมเพิ่ม โซเดียม และ PCO_2 ลดและกดหน้าที่ของเพลทเล็ตชั่วคราว การติดตามผลระยะยาวในกลุ่มที่ใช้ยาเปรียบเทียบกับที่ใช้วิธีผ่าตัด ไม่พบว่ามีความแตกต่างในด้านการเจริญเติบโต ทั้งทางร่างกาย จิตใจ ประสาทสมอง การได้ยิน หรือการเห็น ในระหว่างกลุ่มทั้งสอง

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The survival of the newborn infants of low birth weight with or without hyaline membrane disease has increased due to modern technology and ICU care. Management of those who developed heart failure and pulmonary edema because of left to right shunting through the ductus arteriosus during the first few days of life by therapeutic closure of the ductus, responsible for the increase in survival. The purpose of this paper is to review different methods in treating patent ductus arteriosus especially by using indomethacin. The pharmacokinetics, dosage and side effects of indomethacin along with two cases treated with this medication are presented.

Physiology

The ductus arteriosus, arising from the 6th. aortic arch, is well developed by the 6th. week of gestation and forms a connection between the left pulmonary artery and the dorsal aorta.

Patency of the fetal ductus arteriosus is sustained by prostaglandins, which are biosynthesized from dihomo-γ-linoleic acid and arachidonic acid, both of which are derived from the essential dietary fatty acids. Arachidonic acid, through the classical cyclooxygenase pathway, yields ThromboxaneA_2 (TXA_2), prostacyclin (PGI_2), the primary prostaglandins (PGE_2, PGF_2, PGD_2) and the intermediate compounds, the prostaglandin endoperoxides (PGG_2, PGH_2).[1] The prostaglandins that relax the ductus are formed intramurally and exert their actions locally on the muscle cells. The marked sensitivity of the tissue to PGE_2 probably makes it the most important one in relaxing the ductus arteriosus.[1,2]

Closure of the ductus arteriosus after birth occurs in two stages.[2] Functional closure in the first few days of life is from contraction of the smooth muscle in the ductus wall. Permanent closure is from destruction of the endothelium, proliferation of the subintimal layers, formation of the connective tissue and eventually obliteration of the lumen.

Increase oxygen tension is the most important factor for ductal closure.[3] The other factors may be the level of circulating prostaglandins, the muscle mass, changes in the pulmonary and systemic circulations and the release of vasoactive substances. At birth, the increased pulmonary blood flow causes an effective removal of prostaglandins in the lungs, thus constricts the ductus arteriosus. In vitro experiments have also implicated constriction effect by bradykinin, catecholamine, low pH and acetylcholine.[4]

Nonsteroidal antiinflammatory substances, such as, acetyl salicylic acid and indomethacin, constrict the ductus arteriosus in premature infants[6] by inhibiting prostaglandin synthesis.

Patent ductus arteriosus (PDA)

Isolated PDA is common, accounting for 3.9% of all newborns symptomatic with heart disease.[4] It also often coexists hyaline membrane disease (HMD), most

prevalent in female, prematures and in infants born at high altitude.[4] Premature infant's ductus tends to respond to oxygen less than that of the full term,[5] and causes the delayed closure. The other factor is the increased sensitivity to the dilating influence of prostaglandin.[21]

A small right to left or bidirectional shunt may occur during the first hours after birth. But with the fall in pulmonary vascular resistance and an increase in systemic resistance, a left to right shunt develops. Persistence of the ductus may produce no symptom or severe hemodynamic changes, depending on the size. In the moderate and large sized ductus arteriosus, left to right shunting causes significant increased pulmonary blood flow and congestive heart failure which occurs about 3–6 weeks in the full term infant, while in premature infant it occurs much earlier.

Congestive heart failure in these low birth weight (LBW) infants may cause deterioration of pulmonary function in the already compromised lungs, such as, surfactant deficiency, pneumonia, Wilson–Mikity syndrome, apnea and bradycardia. Prolonged ventilatory support may be required while awaiting spontaneous closure of the ductus arteriosus.

Treatment of symptomatic PDA

Most clinicians agree that a trail of conventional treatment should precede the other form of therapy. These include fluid restriction, digoxin, added diuretic when necessary, ventilatory support and packed red cell tranfusion to keep the hematocrit above 40%.[7] The response to decongestive therapy was equivocal, and digoxin administration in the premature infants is not without risk. Johnson et al.[8] demonstrated that digoxin, as low as that of the initial loading dose of 0.020–0.030 mg/kg over 24–36 hr. and maintenance dose of 0.003–0.005 mg/kg every 12 hr., could cause complication in the seriously ill LBW infants. Clinical deterioration felt to be related to digoxin in their study included bradycardia, cardiac arrhythmia, and feeding difficulties; all of which disappeared after digoxin was discontinued. Prolongation of P–R interval by more than 50% of the control value was also seen and serum digoxin level usually exceeded 4.5 ng/ml.

If signs of circulatory congestion persist or digoxin toxicity develops, closure of the patent ductus arteriosus should be carried out by surgical or medical intervention.

Surgical ligation. The first report of successful ligation of the ductus was by Gross and Hubbard in 1939.[9] Since then, several reports have supported the operative intervention to relieving respiratory distress and terminating cardiac failure resistant to conservative management. Surgical ligation of the ductus arteriousus often produces dramatic improvement, and the mortality rate is very low in skillful hands. Complications of surgery include Horner's syndrome, injury to the recurrent laryngeal nerve

or lymphatic duct, transient hypertension, atrial fibrillation and iatrogenic coarctation of aorta.

Although ligation of PDA is a definite treatment, the appropiate timing of surgery has not been cleary defined. Smith, Cook et al.[10] suggested that the opitmal timing of surgery should be within the second week of life in their study.

Indomethacin Recent experiences indicate that indomethacin, a prostaglandin synthetase inhibitor, has been effective in inducing constriction or closure of the ductus arteriosus.[6,22] There has been a great variability of report findings concerning the use of indomethacin, of which its result may be influenced by the actual age at the time of treatment, concomittent drug therapy or circulating prostaglandin levels.

Originally indomethacin was given for the treatment of symptomatic PDA in infant who failed to respond to standard supportive management and in whom surgical ligation was not available. Recently many infants were treated even earlier. Merrit et al.[11] reported that infants undergoing early intervention had significantly reduced occurrence of broncopulmonary dysplasia and mortality by 6 months of age. Jacob et al.[12] has indicated a relationship between PDA and the development of severe hyaline membrane disease, and suggested very early pharmacological closure of PDA as an adjunct to the treatment of the premature especially those less than 1200 gm.

Pharmacokinetics The mean plasma half life of indomethacin varied from 11–90 hours. Half life was related to the postnatal age and birth weight,[13] but not to the route of adminstration. Correlation between gestational age of the infants and the half life has been contradicted.[14,15]

The mean clearance ranged from 7–20 ml/kg/hr, and was related to postnatal age when the drug was given[13,14,16] and to birth weight.[13] This probably reflects the reduced hepatic metabolism in the infants.

The volume of distribution was similar in all babies with same extrauterine age, but a significant greater value was found in babies with the greater birth weight as compared to that of the smaller infants.

The serum indomethacin level also bore a direct relationship to postnatal age. Yaffe et al.[13] found significantly a higher value in infants of less than 48 hours, when compared to those of more than 7 days old.

Dosage Indomethacin has been given ranging from 0.1–5.0 mg/kg. Recently the recommended dose has been 0.2 mg/kg orally or intravenously. Repeated dose can be given 8–24 hours later. Altered subsequent dose according to the age of the baby at the time of the initial administration was recommended at 12 hours interval.[15] Brash et al.[14]

suggested that plasma indomethacin levels during the 6–24 hours after the initial dose would serve to adjust the repeated dose to reach the effective plasma level. Intravenous route has the advantage over oral adminstration in obviating the problem of GI absorption.

Successful rate Evidence of indomethacin induced PDA constriction has been as few as 20%[17] and as many as 97% of treated infants.[14] The satisfactory constriction or closure in most reports were between 60–70%. Ductus in an infant of older postnatal age is less likely to respond to the treatment. Infants treated before 8–14 days old had better result compared to those more than 14 days old, irrespective of birth weight and gestational age(18). Response of the ductus to indomethacin was also related to the plasma concentration of the drug 24 hours after the dose was given.[14] There is no difference in response between oral or intravenous administration.

Some infants have only transient closure of the ductus arteriosus and develop left to right shunt 3–14 days later. In this latter circumstance further management is not required due to a nonsignificant hemodynamic change and spontaneous closure of the ductus may be expected. Some of these infants respond to a second course of indomethacin, while others may require a lifesaving surgical ligation.

Recently two babies with symptomatic PDA were treated with indomethacin in our nursery. Both weighed over 1800 gm., were about 32–34 weeks by gestational age and had no response to decongestive therapy. The first baby treated at 14 days of age had premanent closure of PDA. The second baby, who also had hyaline membrane disease, treated at 21 days old, had only transient constriction and the PDA reopened 7 days later. The average urine output recorded 3–24 hours after the first dose of indomethacin was at 2.5 ml/kg/hr.

Side effects and complications It is apparent that side effects of indomethacin, if properly used, are transient. Reduced urine output was common[18,19] and mostly seen within 8 hours after treatment. Subsequent increase in serum creatinine concentration was thought to be related to the degree of oliguria.[18] The other changes included rising of BUN, hyponatremia, hyperkalemia, a reduction in p CO_2 and an increase in pH; all occurred even in the absence of ductal closure.[18] Study of the effect of indomethacin on renal function revealed a decrease in urine flow rate, fractional excretion of Na, Cl and urinary kallikrien, but no significant change in GFR,[19] which is in contrast to the previous report.

Indomethacin inhibits platelet function but bleeding rarely occurs. There was no change of platelet count after therapy.[18] There has been no obvious increased incidence of intracranial hemorrhage, necrotizing enterocolitis or sepsis.

A follow-up study of patients receiving either indomethacin or under-

going surgical ligation at one year revealed no significant difference in growth, major neurological sequelae, serious multiple handicaps, mental and motor status, hearing or vision.

Summary Significant left or right shunt through the ductus arteriosus causes some degree of deterioration to the already compromised lungs in the low birth weight infants. Although spontaneous closure of PDA may eventually occur, the infants may have to depend on prolonged ventilatory support and subject to its complications, or develop drug toxicity. The benefit from surgical or pharmacological interventions outweighs the risk in these infants.

PDA = patent ductus arteriosus
LBW = low birth weight
HMD = hyaline membrane disease

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