PROSTAGLANDINS IN CONGENITAL HEART DISEASE

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MJAFI 2001; 57 : 134-138

KEY WORDS : Congenital heart disease; Prostaglandins.

Introduction

Prior to the use of prostaglandins (PGE₁) many infants with ductus arteriosus dependent congenital heart disease (CHD) born outside tertiary care centres did not survive the period from diagnosis to inter-hospital transportation for surgery. Development in the area of neonatal cardiac surgery has increased the importance of rapid diagnosis and stabilisation of infants with CHD. Survival after cardiac defect repair has increased in the past decade. Perhaps an important factor in this increase appears to be the early use of PGE₁ to provide a more clinically stable patient for surgery [1]. Therapy with PGE₁ can effectively maintain an infant's cardiovascular function until palliative or corrective procedure can be performed. At present many hospitals do not maintain a supply of PGE₁ mainly because of its expense and limited use due to the various side effects.

Pharmacology of the Ductus Arteriosus

To appreciate the importance of PGE₁ therapy it is necessary to briefly review the physiology of the ductus and its relevance to infants with CHD. In the foetus ductus arteriosus connects pulmonary artery to descending aorta. Endogenous prostaglandins produced during gestation keep the ductus patent, as a result, majority of the blood passes from pulmonary artery through the ductus by passing the lungs and going directly to the aorta where it is transported to placenta for oxygenation. At birth, an increase in arterial oxygen saturation and a decrease in amount of endogenous prostaglandins, both stimulate an alteration of vascular integrity promoting ductal closure. Exogenous prostaglandins like PGE₁ can be used to maintain the patency of the ductus in neonates where bypassing a defective vessel or continued mixing of oxygenated and unoxygenated blood is needed to provide adequate

systemic circulation [2].

The constricted ductus arteriosus is unusually sensitive to PGE₁ responding with dilation at dosage rates below those required for altering systemic or pulmonary pressure or resistance. Ductal preservation by infusion of PGE₁ can be life saving in neonates with heart disease characterised by severe restriction of pulmonary blood flow, poor arterial venous admixture and severe systemic hypoperfusion.

Indications

a) Restriction of pulmonary blood flow.

Prior to the advent of PGE₁ early management of neonates with pulmonary atresia or other anomalies associated with marked limitation of pulmonary blood flow represented one of the major problems in neonatal cardiology. Patients were usually critically ill in the first few days of life as the ductus constricted and without intervention they generally died within the first few weeks of life. In rare instances the ductus rapidly constricts and pulmonary blood flow diminishes markedly. As a result overwhelming acidosis develops, and infant becomes critically ill. A majority of these children are lost due to delay in reaching a tertiary care centre. Even those who reach are too sick to withstand anaesthesia with the attendant risks of prolonged hypoxemia.

Since mid 1970s the use of PGE₁ to maintain ductal patency has significantly improved the outlook of neonates with CHD characterised by marked restriction of pulmonary blood flow. Dilatation of the ductus is manifest by an immediate rise in PO₂ often by as much as 20 to 30 mmHg. Selective aortograms have revealed wide dilatation of the ductus minutes after an infusion of PGE₁ in prescribed dosage [3].

Infants improve clinically and since hypoxemia and acidosis is reversed, pertinent diagnostic studies can

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be implemented and the patient transferred to a tertiary care centre in a stable condition. PGE₁ has been shown to dilate pulmonary vascular bed and PGE₁ infusion may improve pulmonary blood flow by reducing pulmonary vascular resistance as well [4]. It has been seen that infants older than 96 hours were significantly less responsive than younger infants [5]. Patients with the lowest arterial PO₂ before infusion demonstrate the greatest response. Some patients have been maintained on PGE₁ for days and even weeks during which time right ventricular compliance improves [6]. Efficacy of PGE₁ in improving pulmonary blood flow was evaluated by change in PaO₂ and the value obtained one hour after therapy used to gauge the response. In a multicentre trial conducted over 56 centres in USA, it was observed that the mean PaO₂ increased from 26.7 to 38.5 mmHg after infusion of PGE₁. Infants with an initial PaO₂ of less than 20 mmHg had the greatest improvement as compared to those with an initial PaO₂ of more than 40 mmHg who had virtually no response. If a rise in the PaO₂ of 10 mmHg is considered to define clinically significant improvement 77% of such babies less than 96 hours old showed a favourable response whereas very few babies more than 96 hours old showed clinically significant improvement [5].

b) Poor arterio-venous admixture

Patients with transposition of the great arteries and an intact ventricular septum present in the early neonatal period with severe hypoxemia. The favoured approach to management of such anomalies is the arterial switch operation within the first two weeks of life. PGE₁ is used in these sick neonates to ensure continuing patency of the ductus pending this procedure and serves as an important mixing site prior to surgery. In certain centres balloon atrial septostomy (BAS) is carried out to ensure mixing of blood at the atrial level. In addition to BAS, prostaglandins are advocated to achieve additional ductal shunting, however, increased fragility of ductal tissue among infants who have received prostaglandins has been described and may be a complicating factor in the surgical ligation of ductus while performing arterial / atrial switch operation [7].

It has been observed that infants with transposition have a lower preinfusion PaO₂ although the overall increase in PaO₂ is similar to that in other infants with reduced pulmonary blood flow. Freed et al [5] reported that infants older than age 4 days and weighing more than 4 Kg at birth did not have a clinically significant rise in PaO₂.

c) Ductal dependent systemic blood flow

Infants with various forms of hypoplastic left heart syndrome, including aortic atresia, critical aortic stenosis, interrupted aortic arch and severe juxtaductal coarctation of the aorta may depend on patency of the duct for survival during the early neonatal period. Natural constriction of the ductus results in low systemic cardiac output, shock, acidosis and death. Prostaglandins infusion has allowed such infants to remain viable for a longer period of time, so that potentially operable lesions can be identified and corrected. PGE₁ usually improves descending aortic blood pressure and blood flow in infants with interruption of the aortic arch of juxtaductal coarctation and a closing ductus arteriosus. In a study where PGE₁ was infused in 107 infants with duct dependent systemic flow, when the ductus was considered closed during cardiac catheterisation before the infusion of PGE₁ reopening could not be accomplished, regardless of age (range 3 days - 5 months) [5]. An irreversibly closed ductus, acidosis and collapse are usually associated with a lower success rate with PGE₁ infusion [8-10]. Improvement occurs in the majority in whom the ductus is partially constricted [5]. Clinically this is reflected by increased perfusion of the lower limbs, increased urine output and reduced metabolic acidemia. It has also been observed that cyanotic infants achieve a maximal beneficial response within 30 minutes of starting the infusion whereas maximal response occurs 1.5 hours (range 15 min to 4 hours) later in infants with acyanotic congenital heart disease [11].

d) Refractory Severe Hypertension

PGE₁ infusion is a possible therapeutic alternative for babies with idiopathic arterial calcification complicated by severe hypertension refractory to conventional treatment [13].

Prostaglandin Therapy

Since prostaglandin is metabolised rapidly infusion must be continuous. Over two thirds of the circulating prostaglandin is metabolised in a single pass through the lungs, and the metabolites are excreted by the kidneys within 24 hours. Hence, the agent should be infused through a pump delivery system at an initial intravenous infusion of 0.05 micrograms/kg/min although to avoid side effects lower dosages (0.005-0.01 micrograms/Kg/min) have been recommended by some workers with equal efficacy [5]. A ductus that has functionally closed but is anatomically capable of reopening may respond to prostaglandins, however, results are better when the agent is administered as early as possible so that the infant is not subjected to a

period of severe hypoxemia. The decreased response of the ductus to PGE₁ infusion after 96 hours of age suggests that either anatomical closure is complete or there is irreversible functional closure due to lack of responsiveness of prostaglandin receptors by this age. However patients with cyanotic CHD have responded as late as 36 days of age [11].

There have been reports on newborn children, in whom only prostaglandins E₂ was used to perform a better lung or kidney perfusion by opening ductus arteriosus. The diagnosis of the children were pulmonary atresia, hypoplastic left heart syndrome, transposition of the great arteries with or without ventricular septal defect, coarctation of the aorta and tetralogy of Fallot. The dose of prostaglandins E₂ infusion used was 0.1 microgram/kg body weight/min and consecutive reduction depending on the capillary pO₂. An oral prostaglandin preparation E₂ has also been administered. The effectiveness and simplicity of oral PGE₂ administration have advantages over intravenous administration, especially for long-term treatment. The duration of treatment ranged between 15 min and 37 days. There was a significant increase of capillary pO₂ under prostaglandin E₂ treatment (p less than 0.0001), the increase of capillary pO₂ correlated negatively with the initial pO₂ before treatment (p less than 0.05), but was not dependent on the age of children [14,15].

Side Effects

In several large studies the incidence of side effects has been reported to vary from 21.5 to 53% [11-12]. The common side effects are cutaneous vasodilatation, apnoea or hypoventilation, seizures or jitteriness, pyrexia and diarrhoea. However, using the suggested dosage range, significant complications are rare. Flushing has been reported in 10% of patients [5]. Severe vasodilatation of an upper extremity secondary to arterial infusion in the arch of the aorta is usually not seen.

When considering the use of prostaglandins in a patient, who is to have surgical manipulation in the region of the ductus, it is important the surgeon be aware of increased risk of surgically induced rupture of the ductus [11]. It has been reported that mucopolysaccharides are increased throughout the ductus. These changes produced increased fragility of the ductal and juxtaductal structures, thus increasing the likelihood of spontaneous aneurysms and rupture, or of tearing or rupture at the aortic and pulmonary junctions at the time of surgical closure of the ductus. Unusual fragility of the ductus, pulmonary artery, and

aorta has been observed during ligation of the ductus following prostaglandin E infusion lasting seven and ten days. Additionally, another patient who had received prostaglandins E infusion for six days has been reported to have aneurysmal fullness of the ductus arteriosus at autopsy. The histologic findings and intraoperative experience in this study suggest that there may be a real danger of spontaneous or surgically related rupture of the ductus arteriosus after prolonged infusion of prostaglandins [16,17].

Hyperpyrexia and apnoea that occur in 10-15% of cases are the most severe complications with prostaglandin infusion. These episodes are known to cease after the infusion is discontinued. Sudden onset apnoea may require immediate intubation and ventilation during treatment; hence ventilatory support should be available before a neonate is started on PGE₁. The question of whether apnoea attacks are dose related remains controversial however in the multicentre trial side effects like apnoea, jitteriness and pyrexia did not appear to be dose related [5].

Short and long term prostaglandins infusion in neonates is also reported to be associated with cortical proliferation throughout the skeletal system. Total resolution of these changes has occurred in seven patients described to date; other reports did not note either the time or the regression of these changes. Skeletal changes may occur within 9 days of initiation of prostaglandins therapy and include widened fontanelles, pretibial and soft-tissue swelling, and swelling of the upper and lower extremities. These reactions may last up to 38 weeks following discontinuation of therapy. Alkaline phosphates (AP) concentrations have been shown to be increased in 4 cases, as well as in 1 retrospective analysis. Although these were not prospective studies, evaluation of AP may provide a means to monitor neonates receiving prostaglandin therapy [18]. The periostitis was associated with limb pain and considerable swelling of the extremities in all children. Periostitis improved on cessation of prostaglandin infusion, and by 6 weeks after cessation of the drug, periostitis decreased significantly. Periostitis seemed more dependent on the duration of administration of prostaglandins than on dosage of prostaglandins administered. Awareness of this entity is essential not only for the team caring for these infants but also for consultant paediatric orthopaedists to avoid excessive investigation for infection, metabolic disease, or vitamin deficiencies that resemble prostaglandin induced periostitis [18-21].

Two cases of neonatal acute gastric outlet obstruction related to prostaglandin induced gastric foveolar

hyperplasia, which developed following infusion of prostaglandins E₁ (PGE₁) for treatment of hypoplastic left heart syndrome have also been reported [22,23].

Experience with PGE₁

The drug is commercially available in India since April 1995. Author has recorded the outcome of use of PGE₁ in 61 infants [24]. Age at time of starting PGE₁ infusion ranged from 18 hours to 50 days. 41 of these were more than a week of age, 18 were more than 14 days, and 2 were above one month. PGE₁ was started in an initial dose of 0.05mcgm/Kg/min, decreased to 0.005-0.01 mcgm/Kg/min for maintenance. Desired response was obtained in all except one infant. The indications for use of PGE₁ were to increase pulmonary blood flow in 32 cases with pulmonary atresia (PA_t), tricuspid atresia or critical pulmonary stenosis with or without a BT shunt (Gp I). The other indications were to increase systemic blood flow in 15 cases with coarctation of aorta (CoA), hypoplastic left heart or interrupted aortic arch (IAA) (GP II); to improve mixing in 12 cases of transposition of great vessels (TGA) (GP III) and to improve the left ventricular volume by keeping the duct open in 2 cases of TGA with intact ventricular septum (IVS). The efficacy of the drug was assessed by a rise in SPO₂ determined non-invasively. A rise in SPO₂ > 10% within the first half an hour of starting prostaglandins was considered favourable for GP I and III, and the appearance of lower limbs pulse in GP II. Left ventricular volumes were serially measured by echocardiography in cases where PGE₁ was given in TGA-IVS after balloon atrial septostomy (BAS). The drug was successful in 59 of the 61 cases. The mean (range) of increase in SPO₂ in GP I was 33 ± 14 (28-43)% and GP III it was 21 ± 12(14-32)%. The 2 failures were a 39 day old baby with PA_t and a seven day old baby with COA and renal failure. Side effects included apnoea in 5(9%) of 56 spontaneously breathing patients. NEC and hyperpyrexia occurred where PGE₁ was used in a dose higher than 0.2 mcgm/kg/min. Jitteriness was seen in 1. 4 patients died. 2 were related to PGE₁, 1 due to failure, another due to its side effects. Definitive procedures were performed in 49 cases electively. PGE₁ was used upto 13 days with sustained benefit.

PGE₁ is a major addition to medical management before, during and even after palliative or corrective surgery in infants with ductus arteriosus dependent heart disease. Although many of these infants are older than 4 days of age when diagnosed, PGE₁ appears to be effective and therefore should be used regardless of age to dilate ductus arteriosus and improve

perfusion.

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