CLINICAL PROFILE AND MANAGEMENT OF SYMPTOMATIC PATENT DUCTUS ARTERIOSUS IN PREMATURE INFANTS

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ABSTRACT

Twenty cases of symptomatic patent ductus arteriosus (PDA) in preterm inborn infants were studied retrospectively. The diagnostic criteria were a systolic or a systolodiastolic murmur, tachycardia (>160 per minute), hyperdynamic precordium, collapsing arterial pulses, cardiomegaly or a need for intermittent positive pressure ventilation or continuous distending airway pressure. The incidence was found to be 2.48/1000 live births and 1.5% of SCBU admission. All babies were less than 35 weeks gestation and 18/20 weighed less than 1750 g at birth. Ten babies were treated with indomethacin (0.2 mg/kg) and two of these babies died before the course of treatment was completed. Ten babies were treated with conservative therapy. They could not be administered indomethacin because two died of fulminant sepsis soon after the diagnosis was made; two babies had sepsis and DIC but recovered from it, three had thrombocytopenia, one had azotemia, two babies had hyperbilirubinemia requiring exchange transfusion. The two groups of babies matched in respect to gestational age, sex, age at presentation, birth weight and associated illnesses. Two babies in each group died soon after diagnosis. Of the eight babies in each group, six babies closed the ductus on indomethacin therapy as against two on conservative therapy. This difference was significant ($p<0.05$). The babies who responded to indomethacin were all treated within two weeks of age. None of them showed any complication of drug therapy or recurrence of PDA. We conclude that intragastric indomethacin given early in the management of symptomatic PDA in term infants is a safe and effective modality.

Key words: *Patent ductus arteriosus, Indomethacin.*

Patent ductus arteriosus (PDA) is probably the commonest heart lesion in the preterm newborn infant. Freed (1984) has estimated the incidence of 40% in babies weighing less than 1000 g at birth(1). Many reasons have been postulated for the failure of the ductus to close normally in preterms(2). Failure to close the ductus causes significant hemodynamic stress to the preterm infant. In a sick preterm baby the PDA can thus be the cause of considerable morbidity and contribute towards mortality. The immature left ventricle of the preterm has lesser reserve than that of the term newborn, and hence is unable to cope effectively with a patent ductus(3). The resultant clinical manifestations can be congestive heart failure, increased oxygen requirement, delay in or resistance to weaning from the ventilator, recurrent apnea, or a predisposition to germinal matrix hemorrhage and broncho-pulmonary dysplasia. Indomethacin has been

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established as a safe and effective non-surgical modality in the management of patent ductus arteriosus especially when given early(1). We report herewith our experience in the management of PDA in premature babies on neonatal intensive care.

Material and Methods

The data was generated from a review of case records of the babies admitted between January 1, 1987 and September 30, 1989 in the Special Care Baby Unit (SC BU) of Nehru Hospital, Postgraduate Institute of Medical Education and Research, Chandigarh. Twenty infants were diagnosed to have a symptomatic PDA based on the following criteria: (*i*) Murmur, systolic or systolodiastolic; (*ii*) Presence of at least one of the following: (*a*) Elevated basal heart rate (>160/min), (*b*) Hyperdynamic precordium, (*c*) Collapsing arterial pulses; (*iii*) Cardiomegaly as defined by CT ratio more than 0.6; and (*iv*) Need for intermittent positive pressure ventilation and/or continuous distending airway pressure. Similar criteria have been postulated by others(4,5).

Information regarding the basic disease, patient characteristics, mode of therapy and outcome was elicited. Two types of therapeutic modalities were noted to have been used: conservative management and intragastric indomethacin (0.2 mg/kg/dose ×2-3 doses at twelve hourly intervals). The drug formulation was prepared into satchets from commercially available indomethacin capsules. Ten babies could not be given indomethacin and were managed conservatively. Of these four had septicemia and two died within a few hours of diagnosis; three babies had thrombocytopenia, two hyperbilirubinemia requiring exchange transfusion and one baby had azotemia, hence contraindicating indomethacin therapy. The babies given the two therapeutic modalities were compared with respect to gestational age, sex, age at diagnosis and basic illness. The babies receiving indomethacin were monitored for evidence of thrombocytopenia, bleeding tendency and azotemia. The outcome of the two therapeutic modalities were compared using the Chi square test.

Results

There were 8087 live births between the period January 1, 1987 and September 30, 1989 and 1279 babies were admitted to the SCBU. The criteria for admission to the SCBU have been highlighted in our previous communication(6). Twenty babies were found to have symptomatic PDA giving an incidence of 2.48/1000 live births and 1.5% of all admissions to SCBU.

Table I gives the break-up of total live births and babies having PDA by birth weight and gestation during the study period. The incidence decreased with improving birth weight and gestational age. PDA was found to be in 4.8, 3.6 and 1.5% in the babies less than 1000 g, 1000-1499 g and 1500-1749 g weight groups, respectively. The mean birth weight of babies with PDA was 1331.5 g (±341.5 g) and mean gestation was 30.9 weeks (±2.36 weeks).

There was marked female preponderance among the subjects, and only seven babies(35%) were male. All the babies were sick and had multiple associated problems. *Table II* gives the incidence of these problems. Septicemia, birth asphyxia, recurrent apnea and hyaline membrane disease were the major associated diseases in order of frequency.

TABLE I —*Distribution of Babies Having PDA and Live Births According to Birth Weight and Gestation*

Birth weight (g)	Gestational age (in weeks)					Total	(%)
	≤28	29-30	31-32	33-34	≥35		
≤999	1/33	2/12	0/9	0/4	0/0	3/63	(4.8%)
1000-1499	2/17	4/73	3/88	2/62	0/63	11/303	(3.6%)
1500-1749	0/1	1/18	1/52	1/85	0/109	3/265	(1.5%)
1750-2249	0/1	0/2	0/34	3/78	0/835	3/950	(0.3%)
≥2250	0/0	0/0	0/0	0/87	0/6410	0/6497	
Total	3/52	7/105	4/183	6/316	0/7417	20/8078	
	(5.8%)	(6.7%)	(2.2%)	(1.9%)		(0.24%)	

* Number of babies with symptomatic PDA/number of live births.

TABLE II —*Incidence of Associated Problems in Babies Included in the Study*

	Problem	No.	%
1.	Septicemia	12	60
2.	Severe birth asphyxia	10	50
3.	Recurrent apnea	8	40
4.	Hyaline membrane disease	7	35
5.	Pneumonia	6	30
6.	Hyperbilirubinemia	5	25
7.	Intracranial bleed	4	20
8.	Disseminated intravascular coagulation	3	15

TABLE III—*Clinical Features of Babies with PDA*

	Clinical sign	No.	%
1.	Systolic murmur	19	95
2.	Collapsing pulses	8	40
3.	Hepatomegaly (>3 cm)	7	35
4.	Recurrent apnea	5	25
5.	Cardiomegaly	2	10
6.	Increasing oxygen requirement	2	10

The PDA was detected around the end of the first week (mean 6± 3.9 days). *Table III* gives the clinical features of babies with PDA. A systolic murmur was the presenting feature in 19(95%) of the babies. A collapsing pulse, hepatomegaly and cardiomegaly were the other significant clinical findings. Two babies while on ventilator presented with increasing oxygen requirements when the PDA was detected. Five babies (25%) presented with recurrent apnea and two of them required ventilatory support in addition to the therapy for PDA.

Ten babies were managed conservatively without indomethacin. Seven babies were managed with fluid restriction (120 ml/kg) alone, one with fluid restriction and frusemide (1 mg/kg) and two babies with digoxin and frusemide in addition to fluid restriction. Fluids were administered on the basis of birth weight, and appropriate amounts of extra fluids were administered

in case the baby was under a radiant warmer or phototherapy. Two babies were severely ill and died soon after the diagnosis of PDA was made. The others showed a symptomatic improvement and in two the murmur disappeared after 96 hours and 14 days of therapy. In spite of clinical improvement the murmur remained audiable in other six babies. The overall closure rate of PDA for babies treated with conservative management was 25%(2 out of 8).

Ten babies were administered intragastric indomethacin (0.2 mg/kg/dose). Two babies in this group died within a few hours of diagnosis before full indomethacin therapy could be completed; one of these died of septicemia and the other of pulmonary hemorrhage. Of the remaining eight, two received two doses and six received three doses of indomethacin at 12 hourly intervals. Six (75%) of them closed their ductus and became totally asymptomatic within 12-96 hours (mean 46 hours) of administration of the first dose. The drug was administered at a mean age of 7 days (±2 days). The two nonresponding babies received the drug on day 4 and day 23. There was no difference in the gestation, birth weight or basic illness between the babies who responded to indomethacin and those who did not.

The babies who had been managed with conservative therapy, were compared with the babies who had received indomethacin, after excluding the terminally ill babies from both the groups. There was no difference in the gestational age, birth weight, age at presentation, sex and basic illness between the two groups. The rate of closure of the ductus was significantly higher ($p < 0.05$) in the indomethacin treated babies as compared to the babies treated conservatively.

No side effect was noticed in the 8 babies administered the drug. None of the babies who responded to indomethacin reopened their ductus at a later date.

Discussion

This study clearly shows that symptomatic PDA is a significant problem in babies admitted to our SCBU. The incidence noted was 2.48 cases per 1000 live births. The incidence in 13 major centres caring for VLBW infants in USA(5) was however much higher, *i.e.*, 42, 21 and 7% in the less than 1000, 1000-1500, 1500-1750 g birth weight groups, respectively, as compared to our figures of 4.8, 3.6 and 1.5%, respectively. The differences may be due to many factors–the very high mortality (57%) in babies below 1000 g most of whom die within the first two days of life, and our conservative policy of administering IV fluids to preterm and sick babies (40 ml/kg) till adequate diuresis is achieved.

In spite of the above mentioned observations we feel that the incidence of symptomatic PDA in our experience has been very much lower than expected and needs a much more systematic study.

The diagnosis of PDA in this study was clinico-radiological as our earlier experience at this Institute(7) shows that echocardiographic estimation of LA/Ao ratio has a low specificity in diagnosing PDA. Similar opinion about the role of echocardiography in diagnosing PDA has also been expressed by Ellison *et al.*(5). However, Ellison *et al.*(4) have shown Doppler to be a much more sensitive modality to diagnose PDA. Unfortunately this modality was unavailable to us at the time of the study. The criteria for diagnosis of PDA adopted by us are similar to those used by other workers(4,5). The age of

presentation was also near the end of the first week, a characteristic feature in the preterm infants. The low pulmonary vascular resistance leads to rapid increase in the magnitude of the left to right shunt, coupled with poor compensatory mechanisms in the prematures leads to the presentation of PDA in the first 1 to 2 weeks of life(3).

PDA is a well known complication of hyaline membrane disease(8). It may manifest as increasing oxygen requirements(9) as was seen in two of our babies. It may also manifest as failure to wean from the ventilator or with manifestations of early broncho-pulmonary dysplasia. These manifestations were not seen in our study.

Recurrent apnea was the presenting feature of PDA in five babies. The mechanism postulated has been increased circulation in the pulmonary vasculature causing decreased lung compliance(2).

Septicemia with Gram negative organisms was a problem found in 12 (60%) of the babies. Four of these babies (two in each group) were preterminal when the diagnosis of PDA was made. Three of them died of sepsis and one had pulmonary hemorrhage soon after developing symptomatic PDA. These four babies have been excluded while analysing the results of therapy.

Restricted fluid intake (120-150 ml/kg/day) is recommended as the first line of management for PDA(10). In our study, among the conservative management group, two babies responded to fluid restriction alone while all other babies showed a decrease in their symptoms except the murmur.

Indomethacin is a proven drug for inducing pharmacological closure of the ductus(11,12). We found successful closure of PDA in 75% of babies who received adequate indomethacin therapy. The success rate with indomethacin has been reported between 18 and 86%(13). The indications for therapy have been a symptomatic PDA as was the case in our study. It has also been tried by others for prophylaxis against PDA in VLBW infants(14). However, we have no experience with this mode of therapy. It has also been shown that therapy with indomethacin, if delayed, beyond 2-3 weeks of age, can result in poor response(15,16). All except one baby who responded to indomethacin had received the drug within the first one week. Of the two babies who failed to respond, one received the drug at 23 days age, and hence may explain the treatment failure. The babies treated conservatively did not differ from those treated with indomethacin in gestational age, sex, birth weight, or age at detection of PDA. The indomethacin treated group showed a significantly better PDA closure rate ($p < 0.05$). No side effects of drug therapy were noted in this group. This underlines the fact that early administration of indomethacin to premature infants with symptomatic PDA should be the treatment modality of choice.

REFERENCES

1. Freed MD. Congenital cardiac malformations. *In:* Schaffer's Diseases of the Newborn, 5th edn. Eds Avery MA, Taeusch WH Jr. Philadelphia, WB Saunders Company, 1984, pp 278-281.

2. Gittenberger de Groot AC. Patent ductus arteriosus: Most probably a primary congenital malformation. Br Heart J 1977, 39: 610-618.

3. Rowe BD, Freedom RM, Mehrizi A, Bloom KR. Patent ductus arteriosus in a neonate. *In:* The Neonate with a Congenital Heart Disease, 2nd edn. Ed

Schaffer AJ. Philadelphia, WB Saunders Co, 1981, p 273.

4. Mellander M, Larsson LE, Ekstiom-Jodal B, Sabel KG. Prediction of symptomatic PDA in preterm infants using Doppler and M mode echocardiography. Acta Pediatr Scand 1987, 76: 553-559.
5. Ellison RC, Peckham GJ, Lang P, *et al.* Evaluation of the preterm infants for patent ductus arteriosus. Pediatrics 1983 71: 364-372.
6. Bhakoo ON, Khajuria R, Desai A, Narang A. Lessons from improved neonatal survival at Chandigarh. Indian Pediatr 1989, 26: 234-240.
7. Narang A, Bhakoo ON, Bidwai PS. Medical management of patent ductus arteriosus–Indian Experience (Personal communication).
8. Friedman WF, Fitzpatrick KM, Kerrit TA, Feldman BH. The patent ductus arteriosus. Clin Perinatol, 1978, 5: 411-436.
9. Cotton RB. Patency of the ductus arteriosus–its etiologic and pathogenetic relationship to respiratory distress syndrome. *In:* Hyaline Membrane Disease. Pathogenesis and Pathophysiology, 2nd edn. Ed Stern L. New York, Grune and Stration, 1984, pp 175-210.
10. Stevenson JG. Fluid administration in association with PDA complicating respiratory distress syndrome. J Pediatr 1977, 90: 257-261.
11. Yanagi RM, Wilson A, Newfeld EA, Azia KU, Hunt CE. Indomethacin treatment for symptomatic patent ductus arteriosus: A double blind control study. Pediatrics 1981, 67: 647-652.
12. Rudd P, Montanez P, Hallidie-Smith K, Silverman M. Indomethacin treatment for patent ductus arteriosus in very low birth weight infants: Double blind trial. Arch Dis Child 1983, 58: 267-270.
13. Olley PM, Coceani F. Mechanism of closure of the patent ductus arteriosus. *In:*Pediatric Cardiology, Vol 2. Eds Godman MJ, Marquis RM. Edinburgh, Churchill Livingstone, 1979, p 37.
14. Vincer M, Allen A, Evans J, *et al.* Early intravenous indomethacin prolongs respiratory support in very low birth weight infants. Acta Pediatr Scand 1987, 76: 894-897.
15. McCarthy JS, Zies LC, Gelband H. Age dependent closure of patent ductus arteriosus by indomethacin. Pediatrics 1978, 62: 706-712.
16. Cooke RWT, Pickering D. Poor response to oral indomethacin therapy in very low birth weight infants. Br Heart J 1979, 41: 301-303.

NOTES AND NEWS

XV NATIONAL CONFERENCE OF INDIAN ASSOCIATION FOR COMMUNICABLE DISEASES, HYDERABAD

The XV National Conference of Indian Association for Communicable Diseases, Hyderabad is being held under the auspices of Indian Association for Communicable Diseases on March 9th and 10th, 1991 at the Institute of Tropical Diseases, Nallakunta, Hyderabad-500 044. A pre-conference CME will be held on 8th March, 1991. For further details please contact Dr. Dinesh Raj Mathur, Organizing Secretary.