Echocardiographic flow pattern of patent ductus arteriosus: a guide to indomethacin treatment in premature infants

Bai-Horng Su, Ching-Tien Peng, Chang-Hai Tsai

Abstract

**Aim**—To compare the efficacy and safety of an indomethacin treatment strategy based on serial echocardiographic measurement of patent ductus arteriosus (PDA) flow pattern with a standard protocol.

**Methods**—Neonates weighing less than 1500 g at birth, who required respiratory support, and who had developed symptomatic PDA, were studied. PDA was confirmed in all infants using colour Doppler echocardiography, and serial observations of the ductal flow pattern were made. Infants randomly assigned to receive conventional indomethacin treatment (protocol group) were given an initial dose of 0.2 mg/kg, followed by 0.1 or 0.2 mg/kg, depending on age, 12 hourly for two further doses, and were eligible for a second course. Those randomly assigned to the ductal flow pattern assessment (ECHO group) received further doses of indomethacin after 24 hours, only if their flow pattern was “pulsatile” or “growing.”

**Results**—There was no significant difference in the primary outcome measures between the two groups. The closure rate was 89.1% and 87.2%, respectively, in the protocol and ECHO groups. The mean (SD) doses of indomethacin were significantly higher in the protocol group: 3.2 (1.4) doses compared with 1.6 (0.9) doses. There was a significantly higher incidence of hypoglycaemia, impaired urine output, and gastrointestinal bleeding in the protocol group.

**Conclusions**—An indomethacin treatment strategy for PDA based on measurement of the ductal flow pattern is associated with a reduction in the total doses of indomethacin administered, and a reduced rate of complications, compared with a conventional protocol. There is no difference in closure rate.

Keywords: echocardiographic measurement; PDA flow pattern; indomethacin; very low birthweight

Successful pharmacological closure of patent duc tus arteriosus (PDA) with indomethacin was first reported in 1976. Since then indomethacin treatment has become the standard or prophylactic treatment for clinically significant PDA in premature infants. We have dealt with premature infants who received an incomplete indomethacin course because of complications or contraindications following the first doses of indomethacin, but in whom the ductus eventually closed. On the other hand, closure failures have been observed in infants who received a complete or even repeat courses of indomethacin treatment.

Ductal tissues are sensitive to the dilating effects of prostaglandins, and increased concentrations of prostaglandins have been associated with ductal patency in premature infants. However, a recent report by Gonzalez et al revealed that the increased risk of failed closure of PDA in infants with infection was not associated with an incomplete course of, or the absence of, indomethacin. This suggests that a complete course of indomethacin might not be warranted if the ductus can be closed after the first or second dose of indomethacin. This led us to explore which indicator could be used to determine the need for additional doses of indomethacin in infants. Using pulsed Doppler echocardiography, we have already reported that there is an association between pulsatile and growing patterns of PDA shunt flow and the development of clinically significant PDA.

This study aimed to test the reliability of the assessment of PDA shunt flow pattern as a guide to the need for indomethacin treatment. We hypothesised that pulsatile and growing patterns might indicate the need for indomethacin treatment, and that the closing and closed patterns indicate that subsequent indomethacin doses could be withheld.

Methods

The study was conducted at the Tokyo Metropolitan Tsukiji Maternity Hospital, Japan, from August 1995 to December 1996, and at the China Medical College Hospital, Taichung, Taiwan, from February to October 1997. Premature infants weighing less than 1500 g at birth, who required assisted ventilation, and had a symptomatic PDA, were enrolled. General guidelines for the treatment of very low birthweight infants were similar in Tokyo and in Taichung. The fluid supply was 60–70 ml/kg on the first day, increasing by 10 ml/kg daily, and adjusted to maintain serum electrolytes within the normal range, until intake reached 120 ml/kg within the first week of life. Respiratory distress syndrome (RDS) was diagnosed according to clinical and chest radiographic findings consistent with RDS and requirements for inspired oxygen of >40% and for mechanical ventilation. The surfactant

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INDOMETACIN TREATMENT FOR PATENT DUCTUS ARTERIOSUS

Protocol group

Colour Doppler echocardiographic examination was performed daily 12–24 hours after birth until the ductus arteriosus closed. Infants were examined at least twice daily for clinical signs of PDA, and diagnosis and treatment protocols were made by the attending clinician. The management protocol for a symptomatic PDA in both units included fluid restriction and intravenous administration of indomethacin (0.2 mg/kg for the first dose, then 0.1 mg/kg in infants less than 48 hours old, 0.2 mg/kg in infants over 48 hours, every 12 hours for another two doses) if not contraindicated. A follow up echocardiogram was obtained 24 hours after completion of the course of indomethacin treatment. If the PDA remained open, as documented on colour Doppler echocardiography, a second course of indomethacin was given and the echocardiogram was repeated 24 to 36 hours afterwards, and then every 24 hours until closure. If the PDA had not closed and the patient remained symptomatic after the second course of indomethacin, surgical ligation was considered. Surgery was also performed in infants with symptomatic PDA in whom indomethacin was contraindicated.

ECHO group

Infants in this group also received colour Doppler echocardiographic and clinical assessments. Similarly, indomethacin was given when a symptomatic PDA was diagnosed. Pulsed Doppler echocardiography was performed immediately before indomethacin treatment to determine the PDA flow pattern. A follow up echocardiogram was obtained 24 hours after the start of the first dose of indomethacin. The echocardiographer (BHS) was blinded to the clinical status of the infants. PDA flow pattern and the treatment regimen were decided by the attending clinician. Subsequent doses of indomethacin were given only if the pulsatile or growing PDA flow pattern persisted on follow-up echocardiography. If PDA was present, the pulsed Doppler gate was placed in the pulmonary end of the ductus, taking care to ensure the angle of insonation was below 20 degrees, and the flow pattern of the shunt was recorded.

The PDA flow was classified as follows: (1) pulmonary hypertension pattern, which has a bi-directional flow profile with a predominant right to left shunt (downward away from the baseline); (2) growing pattern, which also has a bi-directional flow but with a predominant left to right shunt; (3) pulsatile pattern, which has a left to right shunt with a pulsatile profile of peak flow velocity about 1.5 m/second; and (4) closing pattern, which also has a left to right shunt, but with a characteristic continuous profile of peak flow velocity of about 2 m/second (fig 1).4

In Taichung the infants were studied using an Acouson 128XP/10 scanner with 5 or 7 MHZ colour and pulsed Doppler transducer. The ductus arteriosus was imaged as in Tokyo.

Echocardiographic data collection

In Tokyo, the infants were studied using a Hewlett-Packard 77020A or an Aloka SSD-2000 scanner fitted with a probe which incorporated a 5 MHZ colour and pulsed Doppler transducer. The first echocardiographic study confirmed cardiac normality and the ductus arteriosus was imaged from the high left parasternal view using colour Doppler echocardiography. If PDA was present, the pulsed Doppler gate was placed in the pulmonary end of the ductus, taking care to ensure the angle of insonation was below 20 degrees, and the flow pattern of the shunt was recorded.

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TABLE 2 Clinical results after indomethacin treatment

<table>
<thead>
<tr>
<th></th>
<th>Protocol group (n=46)</th>
<th>ECHO group (n=47)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at treatment (days)</td>
<td>2.6 (1.9)</td>
<td>2.3 (1.1)</td>
<td>0.999</td>
</tr>
<tr>
<td>Doses of indomethacin</td>
<td>3.2 (1.4)</td>
<td>1.6 (0.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Closure rates</td>
<td>41 (98.1%)</td>
<td>41 (97.2%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Reopening rates</td>
<td>4 (8.7%)</td>
<td>5 (10.6%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Ligation rates</td>
<td>5 (10.9%)</td>
<td>5 (10.6%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>21 (45.7%)</td>
<td>10 (21.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Necrotising enterocolitis</td>
<td>4 (8.7%)</td>
<td>4 (8.5%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Impaired urine output</td>
<td>26 (56.5%)</td>
<td>12 (25.5%)</td>
<td>0.0046</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>18 (39.1%)</td>
<td>8 (17.0%)</td>
<td>0.03</td>
</tr>
<tr>
<td>IVH (all grades)</td>
<td>9 (19.6%)</td>
<td>9 (19.1%)</td>
<td>0.999</td>
</tr>
<tr>
<td>IVH (grades 3 and 4)</td>
<td>3 (6.4%)</td>
<td>3 (6.4%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>9 (19.6%)</td>
<td>9 (19.2%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Chronic lung disease in survivors</td>
<td>9 (24.3%)</td>
<td>10 (26.3%)</td>
<td>0.999</td>
</tr>
</tbody>
</table>

The values are mean (SD) or number of infants (percentage).

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The mean doses of indomethacin, the age at first dose, PDA outcomes and complication rates, as well as neonatal mortality and the incidence of chronic lung disease among survivors. Among the major complications associated with indomethacin treatment, there was no significant difference in the incidence of necrotising enterocolitis, but significant differences were noted in the incidences of hypoglycaemia, impaired urine output, and gastrointestinal bleeding. There were no significant differences in the incidences of any grade of IVH or grades 3 and 4 IVH between the two groups.
**Discussion**

The overall closure rate of 88% (82/93) in this series is consistent with that of a previous report. Among the infants in whom PDA flow pattern was used as a guide to indomethacin treatment (ECHO group) and who did not complete the full course of three doses, the closure rate was 87.2%. This study showed that indomethacin treatment guided by the PDA flow pattern is as good as our standard indomethacin treatment protocol in terms of PDA closure.

The introduction of surfactant replacement therapy means that PDA is diagnosed earlier and more frequently in premature infants. In our study 88% (82/93) infants received surfactant treatment. Our diagnosis of symptomatic PDA was made by combing through prospective daily echocardiography data and clinical findings.

A common indomethacin treatment strategy is one dose every 12 hours over a course of three doses. Clinically, there is a relatively high incidence of complications associated with indomethacin treatment, including hypoglycaemia, necrotising enterocolitis, decreased urine output and gastrointestinal haemorrhage. A more selective policy of indomethacin treatment would be a more effective way of reducing complications. However, it is difficult to predict those infants who will not require indomethacin, those in whom the duct will close after one or two doses of indomethacin, and those who will fail to respond to the full course of treatment. Colour Doppler echocardiography, on the other hand, is a useful tool to assess the patency of duc tus arteriosus and the direction of PDA shunt flow. Actual size of shunt flow and haemodynamic changes are, however, difficult to measure. Methods for calculating the PDA shunt volume from both ventricular outputs to predict a clinically significant PDA are complicated.

We classified PDA shunt flow into four patterns using pulsed Doppler echocardiography, and showed that serial changes in the pattern can be used to predict the risk of developing clinically significant PDA. Our previous study suggested that the pulmonary hypertension pattern is common in early postnatal life, and reflects a bi-directional shunt, with only a little left to right shunting in the presence of a high pulmonary artery resistance. After the fall in pulmonary artery resistance, the left to right shunting through a constricted ductus produces a very rapid velocity, characterised by the closing pattern. In contrast, growing and pulsatile patterns are primarily evidence of falling pulmonary artery resistance, in the presence of a ductus which is not completely restricted and becomes clinically significant.

In this study we used PDA flow pattern analysis as a guide to indomethacin treatment, and this allowed us to use significantly fewer doses of indomethacin than normal, but without a higher incidence of closure failure. Furthermore, fewer doses were associated with a reduced incidence of complications, including hypoglycaemia, impaired urine output, and gastrointestinal bleeding. There was no obvious effect on neonatal morbidity or the incidence of chronic lung disease.

In conclusion, although PDA flow pattern assessment is a useful guide to the use of indomethacin treatment in infants with a PDA, it does require an operator who is skilled in the use of colour Doppler echocardiography. Moreover, the operator would need to be available on a daily basis, the implications of which have been discussed before.

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