B-type natriuretic peptide concentrations to guide treatment of patent ductus arteriosus

J T Attridge, D A Kaufman, D S Lim

ABSTRACT

Objective: To determine whether b-type natriuretic peptide (BNP) concentrations can guide treatment of patent ductus arteriosus (PDA) to reduce the number of indomethacin doses without increasing morbidity.

Design: Prospective, randomised, controlled trial.

Setting: Single-centre referral neonatal intensive care unit.

Patients: Infants with echocardiographic diagnosis of PDA. Infants with congenital heart disease or renal insufficiency were excluded.

Interventions: BNP measurement and echocardiography were performed in all subjects before and after indomethacin treatment. The investigational group had BNP concentrations measured 12 and 24 h after the first dose (before the 2nd and 3rd doses of indomethacin). Indomethacin dosing was withheld in the BNP-guided group if the 12 or 24 h BNP concentrations were found to be <100 pg/ml.

Main outcome measures: Number of doses of indomethacin given during the primary course of treatment (three doses every 12 h).

Results: Sixty patients were randomly assigned to control (n = 30) and BNP-guided (n = 30) treatment groups. There was no difference between the groups with respect to gestational age (26+3 vs 25+5 weeks, respectively), Apgar scores, delivery method, gender or indomethacin prophylaxis. Median baseline and 48 h BNP concentrations did not differ between the groups (0 h: 500 vs 542 pg/ml; 48 h: 85 vs 126 pg/ml; control and BNP-guided groups, respectively). During primary indomethacin treatment, the BNP-guided group received fewer doses of indomethacin than controls (70 vs 88 doses, p<0.05). The rate of PDA ligation, intestinal perforation and chronic lung disease did not differ between groups.

Conclusions: BNP-guided treatment reduced the number of primary indomethacin doses. There was no increase in PDA persistence or associated morbidity.

What is already known on this topic

- Rapid B-type natriuretic peptide (BNP) assays have been used as in clinical algorithms to determine the aetiology for adult patients presenting with respiratory distress.
- BNP concentrations are raised in infants with a patent ductus arteriosus (PDA).

What this study adds

- BNP concentrations fall during the course of indomethacin therapy for PDA.
- BNP concentrations may be used clinically to reduce the number of indomethacin doses during the first course of treatment; however, this study is not powered to detect a difference in the rates of PDA ligation or other comorbidities of a PDA or indomethacin treatment.

A variety of dosing regimens have been tried, with current recommendations for a primary course of treatment being three doses of 0.2 mg/kg (0.25 if >1 week) given 12 h apart. The optimal dosing of indomethacin for a PDA remains controversial, and some investigations have brought into question both the dosage and timing of PDA treatment. Other investigators have raised the question of whether asymptomatic PDA should be treated in these infants. Given these controversies, any adjuvant test that would limit the side effects of indomethacin without losing the beneficial effects may be clinically useful.

B-type natriuretic peptide (BNP) is a protein secreted from cardiac myocytes in response to increased wall stress, which in premature infants may be related to volume overload from the PDA. BNP has been used in adults to distinguish heart failure from other non-cardiac aetiologies in the evaluation of dyspnoea. Previous paediatric investigators have examined the use of BNP concentrations to predict the presence of a PDA and its response to therapy, but none have used them as a tool to guide length of treatment. BNP concentrations have been found to be raised in the presence of a haemodynamically significant PDA, and to decrease in response to PDA closure. The present investigation was undertaken to determine if BNP concentrations could be used to guide the length of indomethacin treatment for a PDA.
Specifically, we hypothesised that BNP concentrations can be used during the initial course of indomethacin treatment to reduce the number of indomethacin doses without increasing morbidity.

**DESIGN/METHODS**

This was a single-centre, prospective, randomised controlled trial undertaken at the University of Virginia Health System neonatal intensive care unit. The study was approved by the institutional review board/human investigations committee at the University of Virginia, and informed, written consent was obtained from the family of all subjects before enrolment. Inclusion criteria for the study included echocardiographic diagnosis of PDA with intent to treat with indomethacin. Clinical indications of a PDA—widened pulse pressures, palmar pulses and a new murmur—were used to determine which infants should have an initial screening echocardiogram. Infants were treated with indomethacin if they were found to have a PDA on echocardiography and were also receiving positive pressure ventilation, had a feeding intolerance, or a high requirement for supplemental oxygen (≥40% fractional inspired oxygen). Exclusion criteria were the presence of any other congenital structural heart defect or renal insufficiency defined as baseline creatinine concentration >2.0 mg/dl. There was no guideline for the use of prophylactic indomethacin; practice varied depending on the attending physician caring for the child at birth, and no explicit criteria were used to determine the timing of the initial echocardiography.

BNP measurement and echocardiography were carried out on all subjects just before initiation of indomethacin treatment (study time 0 h) and after completion of the initial course of treatment at study time 48 h. The investigational group also had BNP measured at 12 and 24 h (before the 2nd and 3rd doses of indomethacin). Indomethacin dosing was withheld in the BNP-guided group if the 12 or 24 h BNP concentrations were found to be <100 pg/ml. At the time of study inception, data on BNP concentrations for infants were lacking, and this cut-off point was chosen as it had been used to rule out congestive heart failure in adults, implying that a condition of cardiac overload mimicked by a PDA and resultant ventricular overload. BNP assays were run as a standard clinical specimen by the University of Virginia Department of Clinical Pathology (specimens were collected and sent to the laboratory for immediate processing), and clinicians were not blinded to the BNP results. The assay used for the initial 33 patients was the BioSite Triage BNP assay on whole blood; the assay used for the final 27 patients was Abbott AxSym on plasma.

Echocardiographic measurements were performed at baseline to ensure that the two groups had similar sonographic presentations. All scans were reviewed by one investigator (DSL), who was unaware of the randomisation group at the time of review. No specific echocardiographic criteria other than ductal patency were required to make the diagnosis of PDA. Echocardiographic indices of volume overload (secondary to shunting from the PDA) included left atrial/aortic ratio (LA/Ao), left ventricular end diastolic diameter (LVEDD) and left atrial volume (LAV). LA/Ao was measured from the parasternal long-axis view, using m-mode measurements through the aorta and left atrium. LVEDD was also measured using m-mode measurements through the left ventricle from the parasternal long-axis view. LAV was determined using the ellipsoid method, with the left atrial superior–inferior dimension and the mediolateral dimensions measured in the two-dimensional echocardiographic apiacal four-chamber view, and the anterio–posterior dimension in the parasternal long-axis view.

The primary outcome for the study was the number of indomethacin doses given during the initial treatment course. Secondary outcomes were rate of PDA ligation, rate of isolated intestinal perforation (as defined by the attending neonatologist at the time of diagnosis), rate of chronic lung disease (defined as the need for supplemental oxygen at 36 weeks’ corrected gestation age), post-treatment creatinine concentrations, and death. For this study, intestinal perforation was defined as

![](image_url)

**Figure 1** Flow chart of infants enrolled in this trial. Infants with a patent ductus arteriosus (PDA) were randomised to B-type natriuretic peptide (BNP)-guided or control therapy for their first course of indomethacin (INDO) treatment. The number of doses of indomethacin given is summarised in the bottom two boxes.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n = 30)</th>
<th>BNP-guided (n = 30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated gestational age</td>
<td>26 (25–28)</td>
<td>25 (24–27)</td>
<td>0.248</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>922 (731–985)</td>
<td>801 (562–970)</td>
<td>0.16</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>27.2 (23–32)</td>
<td>24.6 (19–39)</td>
<td>0.086</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>20 (67%)</td>
<td>17 (57%)</td>
<td>0.5959</td>
</tr>
<tr>
<td>Male</td>
<td>17 (57%)</td>
<td>21 (70%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Inborn</td>
<td>27 (90%)</td>
<td>24 (80%)</td>
<td>0.471</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>13 (43%)</td>
<td>10 (33%)</td>
<td>0.5959</td>
</tr>
<tr>
<td>Aggar 1 min*</td>
<td>6 (4–7)</td>
<td>5 (3–7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Aggar 5 min*</td>
<td>7.5 (6–8)</td>
<td>7 (6–8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Completed steroids</td>
<td>16 (53%)</td>
<td>18 (60%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Chorio</td>
<td>10 (33%)</td>
<td>10 (33%)</td>
<td>1.0</td>
</tr>
<tr>
<td>PROM &gt;24 h</td>
<td>4 (13%)</td>
<td>5 (17%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>2 (7%)</td>
<td>7 (23%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, values are number (%) or mean (interquartile range).

*Median (interquartile range).

Chorio, chorioamnionitis (defined histologically); PROM, premature rupture of the membranes.

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**Table 1** Details of infants with a patent ductus arteriosus assigned to a control or B-type natriuretic peptide (BNP)-guided indomethacin treatment group.
pneumoperitoneum without radiographic or surgical evidence of pneumatosis.16

All patients enrolled were analysed in their assigned treatment groups. An investigator (DSL) generated a randomisation sequence using a standard random number generator to assign a subject to the experimental or control treatment group: no stratification was used for this study. Group assignments were then placed in sequentially numbered sealed envelopes, which were opened by one of the three authors after the patient’s family had consented to treatment. Consent could be obtained by any of the three investigators, and neither the investigators nor the patient’s family group were blinded to the allocation.

Statistical analysis
Continuous variables were compared using the t test or Wilcoxon rank sum as appropriate. Dichotomous outcomes were analysed using the Fisher exact test. It was estimated that BNP-guided treatment would be able to reduce the number of indomethacin doses from three to two for a quarter of subjects and from three to one for a quarter of subjects (ie, the other patients in the BNP-guided group would receive a full three-dose schedule). This would result in a three-quarter dose difference between the two groups in the mean number of indomethacin doses. To detect this difference, with an assumed power of 0.8, \( \alpha \) of 0.05, and standard deviation of one dose, 56 infants (29 in each group) were required. Given the lack of previous data using this assay, a planned interim analysis of the data was performed after the study period; the primary closure rate (after the initial course of indomethacin) was 41% (37% vs 43%, for control and BNP-guided groups, respectively) (table 5). There was no difference in the change in creatinine concentration (baseline to 48 h) between the two treatment groups despite the fact that the BNP-guided group received fewer doses of indomethacin. After the study period, infants received an additional dose of indomethacin if the PDA remained open. The number of subsequent doses was left to the judgement of the clinician treating the infant and was not directed by protocol. The rate of PDA ligation, total number of indomethacin doses, intestinal perforation and chronic lung disease did not differ between the groups (table 5).

RESULTS

There were 117 infants admitted to our neonatal intensive care unit from April 2004 to October 2006 who were diagnosed with a PDA by echocardiography and treated with indomethacin. Sixty of these infants received consent for randomisation. The study population was randomly assigned to either a control (n = 30) or BNP-guided (n = 30) treatment group (fig 1). Table 1 summarises details of these infants.

Table 2. Treatment variables for infants with a patent ductus arteriosus assigned to a control or B-type natriuretic peptide (BNP)-guided indomethacin treatment group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 30)</th>
<th>BNP-guided (n = 30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic indomethacin</td>
<td>9 (30%)</td>
<td>3 (10%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Baseline LA/Ao ratio</td>
<td>1.67 (1.33–1.92)</td>
<td>1.72 (1.30–2.10)</td>
<td>0.72</td>
</tr>
<tr>
<td>Post-treatment LA/Ao ratio</td>
<td>1.44 (1.18–1.72)</td>
<td>1.29 (1.10–1.47)</td>
<td>0.10</td>
</tr>
<tr>
<td>Baseline LAV (cm³)</td>
<td>0.50 (0.22–0.69)</td>
<td>0.55 (0.22–0.76)</td>
<td>0.66</td>
</tr>
<tr>
<td>Post-treatment LAV (cm³)</td>
<td>0.35 (0.19–0.43)</td>
<td>0.31 (0.16–0.37)</td>
<td>0.55</td>
</tr>
<tr>
<td>Baseline LVEDD (cm)</td>
<td>1.19 (0.99–1.41)</td>
<td>1.10 (0.89–1.29)</td>
<td>0.22</td>
</tr>
<tr>
<td>Post-treatment LVEDD (cm)</td>
<td>1.12 (1.02–1.24)</td>
<td>1.00 (0.81–1.18)</td>
<td>0.07</td>
</tr>
<tr>
<td>Timing of initial BNP (h of life)</td>
<td>63 (40–87)</td>
<td>67 (42–102)</td>
<td>0.32</td>
</tr>
<tr>
<td>Baseline (0 h) BNP (pg/ml)</td>
<td>500 (160–1550)</td>
<td>542 (119–1736)</td>
<td>0.91</td>
</tr>
<tr>
<td>48 h BNP (pg/ml)</td>
<td>85 (39–431)</td>
<td>126 (37–265)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Values are number (%) or mean (interquartile range). LA/Ao, left atrial/aortic ratio; LAV, left atrial volume; LVEDD, left ventricular end diastolic diameter.

Of the 57 patients who were not enrolled, five parents declined, five met exclusion criteria, 32 received their first dose of indomethacin before being approached for the study, and the final 15 were missed as the primary investigator (JTA) was unavailable. There was no significant difference between the groups with respect to gestational age, Anpgar scores, delivery method, gender, chorioamnionitis (defined histologically), pre-eclampsia, or rate of antenatal steroid use. The timing of the initial BNP assay did not differ between the groups (median 63 h vs 67 h of postnatal age; table 2). Median baseline and 48 h BNP concentrations did not differ between the groups (0 h: 500 vs 542 pg/ml; 48 h: 85 vs 126 pg/ml; control and BNP-guided groups, respectively) (table 2, fig 2).

During the study period (initial treatment course of indomethacin), the BNP-guided group received fewer doses of indomethacin than the control group (70 vs 88 doses, p<0.05) (table 3). Three patients in the BNP-guided group died compared with none in the control group; this difference did not reach statistical significance.

Baseline echocardiographic measurements of volume overload from the FDA showed no difference in the LA/Ao ratio, LAV or LVEDD measurements between treatment groups (table 2). Indomethacin treatment resulted in a decrease in both BNP concentration and echocardiographic indices associated with PDA (LA/Ao ratio, LAV and LVEDD). The LA/Ao ratio decreased from a mean (SD) of 1.7 (0.6) to 1.3 (0.3) (p<0.05) in the BNP-guided treatment group and from 1.7 (0.5) to 1.4...
outcomes (PDA ligation and chronic lung disease) would remain
sample would be needed to determine if the rate of binary
difference in the number of indomethacin doses, a much larger
sample. Whereas a sample size of 60 was able to detect a
would be a difference in secondary outcomes with a larger study
doses were administered. It remains to be seen whether there
the BNP-guided group, so it is not surprising that fewer study
reduced during the study period with this method without any
increase in complications. This study only examined the
predictive ability of BNP concentration for the number of
indomethacin doses.

DISCUSSION
Successful medical treatment of a haemodynamically significant
PDA remains a primary goal for healthcare professionals caring
for premature infants. The definition of a haemodynamically
significant PDA and the timing and methods of closure remain
controversial. This pilot study tested the hypothesis that BNP-
guided treatment for a PDA was safe and efficacious. Much of
the literature on BNP is about its use as a marker of congestive
heart failure in adult patients. A recent meta-analysis found
BNP concentration to be highly predictive in its ability to rule
out congestive heart failure in adults. BNP concentrations have
been used in neonates to screen for persistent pulmonary
hypoventilation of the newborn and PDA, and have been followed
in patients after heart surgery. This is the first report of a
randomised controlled trial using BNP concentration to guide
treatment of PDA. The number of indomethacin doses was
reduced during the study period with this method without any
increase in complications. This study only examined the
predictive ability of BNP concentration for the number of
indomethacin doses.

The shortcomings of this trial include the lack of blinding of
the investigators to the study arm, and the possibility of a type
II error for important secondary outcomes. The study was
designed so that fewer doses would only be able to be given in
the BNP-guided group, so it is not surprising that fewer study
doses were administered. It remains to be seen whether there
would be a difference in secondary outcomes with a larger study
sample. Whereas a sample size of 60 was able to detect a
difference in the number of indomethacin doses, a much larger
sample would be needed to determine if the rate of binary
outcomes (PDA ligation and chronic lung disease) would remain
unchanged using BNP to guide PDA therapy. Other limitations
include a high rate of PDA ligation and the change in type of
assay used during the study. The rate of PDA ligation was high
for the infants included in this trial; however, there was no
difference between the two treatment regimens. This higher
rate of ligation may have arisen because of the relative
infrequency (20%) of indomethacin prophylaxis in this cohort.
This high rate of surgical intervention is obviously of concern,
especially in the light of recent data suggesting that infants who
undergo PDA ligation may be at higher risk of neurodevelop-
mental sequelae later in life. It is unclear whether a larger
study would bring this rate more in line with recent national
assessments, with PDA ligation rates in the range 18–26%.

Two types of assay were used to detect BNP during the study
period. The Biosite assay is run on whole blood, while Assym
is run on plasma. The decision to change assays was taken by the
Department of Clinical Pathology at the University of Virginia
because plasma sample analysis could be automated and protein
stability was up to 24 h in plasma compared with only 3 h in
whole blood. The two assays were run by the Department of
Clinical Pathology, and quality assurance testing before the
change in assay showed a correlation coefficient of 0.90 between
the two assays.

It is important to note that there were three deaths in the
BNP-guided group after study completion. Two infants died
from overwhelming sepsis >10 days after the last dose of
indomethacin and had had their PDA closed on follow-up
echocardiography. The final infant had required a PDA ligation
and then died from fulminant necrotising enterocolitis totalis 5
weeks after randomisation. All deaths and significant side
effects were reported to the institutional review board per
protocol; they were not judged to be associated with the
investigational intervention.

Finally, pharmacological treatment of PDA remains a source
of active inquiry in neonatology. BNP-guided treatment is one
option available at the bedside using minimal amounts of blood.
The short half-life and rapid turnaround make BNP an ideal
marker of left ventricular volume overload secondary to a
significant PDA. It remains to be seen whether more frequent
echocardiography or use of other markers, clinical or laboratory
(pro-BNP concentrations, after serial indomethacin concen-
trations), may become better suited to guide the length of indomethacin
therapy or whether these concentrations can be used to guide
treatment with ibuprofen. Clinicians using this assay must be
aware of other conditions that could increase BNP without an
associated PDA (eg, persistent pulmonary hypertension, other
genital heart defects, or renal difficulties inducing fluid
overload).

Table 3 Primary and secondary outcomes of infants with a patent
ductus arteriosus assigned to a control or B-type natriuretic peptide
(BNP)-guided indomethacin treatment group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>BNP-guided</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of study doses of indomethacin</td>
<td>88</td>
<td>70</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non-study number of doses of indomethacin</td>
<td>84</td>
<td>98</td>
<td>0.51</td>
</tr>
<tr>
<td>Persistent PDA after initial indomethacin</td>
<td>course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDA ligation</td>
<td>11 (37%)</td>
<td>14 (48%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Timing of PDA ligation (days)</td>
<td>19</td>
<td>26</td>
<td>0.03</td>
</tr>
<tr>
<td>Isolated intestinal perforation</td>
<td>3 (10%)</td>
<td>3 (10%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Necrotising enterocolitis (surgical)</td>
<td>1</td>
<td>2</td>
<td>0.60</td>
</tr>
<tr>
<td>Chronic lung disease*</td>
<td>18 (62%)</td>
<td>19 (73%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Died</td>
<td>0</td>
<td>3</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Data available for 57 patients at 36 weeks’ corrected gestational age (three deaths).

PDA, patent ductus arteriosus.

Figure 2 Box and whisker plot showing the decline in B-type
natriuretic peptide (BNP) concentrations (pg/ml) over the course of 48 h
after initial detection and treatment of a patent ductus arteriosus for
control and BNP-guided groups. *Maximal data point in the series.

(0.4) (p<0.05) in the control treatment group. A significant
decrease was also seen in LAV and LVEDD measurements.
There was no difference in left atrial or ventricular measure-
ments between the two groups at the end of the study.
CONCLUSIONS
In this pilot study, the use of BNP-guided therapy allowed the number of indomethacin doses given in the initial course (three doses every 12 h) to be reduced without any change in the rate of PDA closure or complications. However, there was no difference in the total number of doses given to patients (including prophylaxis and follow-up treatment). A larger trial with long-term follow-up on developmental outcomes, which also controlled for the number of subsequent doses, is needed to determine if this approach should become standard practice during the treatment of a PDA.

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Competing interests: None.

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