

When is a second course of indomethacin effective in ventilated neonates with patent ductus arteriosus?

This article reviews the evidence for giving a second course of indomethacin to treat a patent ductus arteriosus in a ventilated preterm neonate after a first course has failed to close the ductus adequately.

Uzma Hafeez

MB ChB, DCH, MRCPCH
Specialist Registrar in Paediatrics
Heart of England NHS Foundation Trust
Neonatal Unit
Birmingham Heartlands Hospital
uzmahafeez@doctors.org.uk

Michael Watkinson

MB BChir, FRCPC
Consultant Neonatologist
Heart of England NHS Foundation Trust
Neonatal Unit
Birmingham Heartlands Hospital

Clinical question

The answer to the following question was sought: "In a ventilated preterm neonate with a patent ductus arteriosus (PDA) that has reopened or remained open after an initial course of indomethacin, when is a second course of indomethacin effective at closing it?"

Literature search

Pubmed, the Cochrane Library and Google Scholar were searched using the key words patent ductus arteriosus and indomethacin. Six papers relevant to the topic were found (**TABLE 1**):

Keller et al, 2003

These authors looked at 32 infants <28 weeks' gestation at birth who received a second course of indomethacin¹. They used echocardiography to assess the response of the PDA after both first (0.2, 0.1, 0.1 mg/kg) and second (0.2, 0.1, 0.1 mg/kg) courses of indomethacin. Their univariate analyses of multiple factors showed that only a persistent Doppler flow through a PDA after a first treatment course, predicted failure of closure after a second course. All nine infants with a persistent Doppler flow needed ligation even after a second course, compared to only nine of 23 (39%) with absent Doppler flow. ($p<0.001$). Those with Doppler detectable flow after the first course developed a haemodynamically significant patent ductus arteriosus (hsPDA) sooner than those with no flow (8 ± 2 v 15 ± 2 days after the first course, $p=0.03$).

Su et al, 1999

Su et al² performed a randomised controlled trial (RCT) looking at 93

ventilated infants <1500g with hsPDA as assessed by Doppler and clinical examination. Randomisation was into two groups:

Group 1 = Protocol group

After a first course of indomethacin (of variable dosage depending upon postnatal age), Doppler studies were performed and a second course (0.2 mg/kg x 3) was given if the PDA was still patent. Subsequent Dopplers were performed 24 hourly after the second course until closure occurred. If a PDA remained open and symptomatic after a second course, then ligation was performed.

Group 2 = Echo Group

Echocardiography was performed prior to the first course and 24 hourly following the first dose. Further doses (within the first 'course') were given only if 'pulsatile' or 'growing' flow pattern was seen on Doppler. Ligation was performed if a 'closing' or 'closed' pattern was not seen on Doppler after six doses of indomethacin. Overall 11 (12%) of the 93 ducts did not close, and a further nine reopened. In all, 10 ducts were ligated. Results showed that using PDA flow pattern analysis as a guide to treatment resulted in significantly fewer doses of indomethacin compared to the protocol group: 1.6 v 3.2 ($p<0.01$), but did not affect ligation rates.

Clyman et al, 1985

This study included 123 premature infants <2500g at birth, who required indomethacin (0.2, 0.1, 0.1 mg/kg) for PDA treatment³. Observations were made on clinical and Doppler evidence of PDA after both first and second courses of indomethacin. Sixteen (13%) of the ducts

Keywords

patent ductus arteriosus; indomethacin; Doppler; echocardiography

Key points

Hafeez, U., Watkinson, M. (2007) When is a second course of indomethacin effective in ventilated neonates with patent ductus arteriosus? *Infant* 3(4): 140-43.

1. No randomised controlled trials were found that specifically addressed the topic.
2. A literature search revealed better prediction of response to a second course of indomethacin can be achieved by considering gestation, birth weight, postnatal age and Doppler evidence of persistent ductal flow.

Authors	Patient group	Outcomes	Key results
Keller R, 2003 USA	374 ventilated newborns <28wks & PDA treated with 1st course of Indo (0.2, 0.1, 0.1 mg/Kg). 32 infants received 2nd course Indo (0.2, 0.1, 0.1 mg/Kg).	Persistence of hsPDA needing ligation after 2nd course of Indo.	18/32 (56%) met criteria for ligation after 2nd course. Persistent Doppler flow through PDA after 1st course in 9/32 (28%) predicted PDA ligation (= failed 2nd course). All 9 ligated. Only 9/23 (39%) with absent Doppler flow after 1st course developed a hsPDA & were ligated after 2nd course ($p<0.001$). Infants with Doppler detectable flow after 1st course had hsPDA sooner than those with no flow after 1st course (8 ± 2 v 15 ± 2 days: $p=0.03$)
Su B H et al, 1999 Taiwan	93 ventilated infants <1500g with hsPDA on Doppler & clinical signs. Randomisation to 2 groups: <ul style="list-style-type: none"> Protocol group: 1st course (0.2, then 0.1 or 0.2, then 0.1 or 0.2 mg/Kg). If PDA open on Doppler, 2nd course (0.2mg/kg x 3 mg/kg) & Doppler 24 hrly 'til closure. Echo group Doppler prior to 1st course, then 24 hrly after 1st dose. Further doses only if pulsatile or growing flow pattern on 24 hr Doppler. 	Total number of doses of Indo. Need for ligation after 2nd course or if Indo contraindicated. (Protocol group – ligation if PDA symptomatic after 2nd course. Echo group – ligation if no 'closing' or 'closed' pattern after 6 doses).	Doses of Indo: Protocol = 3.2, Echo = 1.6 ($p<0.01$). Using PDA flow pattern analysis as a guide to Indo treatment allows the use of significantly fewer doses. Ligation rates: Protocol = 5 (10.9%) Echo = 5 (10.6%).
Clyman R et al, 1985 USA	123 premature infants weighing <2500g at birth who required Indo (0.2, 0.1, 0.1mg/kg) for treatment of PDA.	Clinical & Doppler evidence of PDA after 1st and 2nd courses.	87% of infants had no clinical or echo evidence of PDA after 1st course. Duct reopened in 23% of those initially closed by Indo. Incidence of reopening inversely related to birth weight, <1000g 33% reopened, >1500g 8%. 76% who had 2nd course closed their duct again.
Tammela O et al, 1999 Finland	Infants <33 weeks with hsPDA & L to R shunt on Doppler. Treatment with Indo decided by attending neonatologist. 2 groups: Short course (n=31) – 3 doses (0.2, 0.1, 0.1 mg/kg) at 12 hr intervals. Long course (n= 30) – 7 doses (0.1 mg/kg) at 24 hr intervals. Echo in all if signs of PDA then repeated on 3rd, 9th, 14th days after 1st dose, also if non-closure or reopening suspected clinically.	Echo presence or absence of clinically & hsPDA on 9th day. Complete closure rate, reopening rates.	Primary responders: Short 94%, Long 67% $p=0.011$. PDA reopened needing treatment: Short 19%, Long 7%, NS. Sustained closure after 1st course: Short 74%, Long 60% NS. Indo repeated: 29% both groups. After closure confirmed by Doppler, 50% re-openers responded to 2nd course Indo.
Rajadurai and Yo, 1991	103 ventilated preterm neonates (24-36 wk), who survived to day 3. 1st course (3-6 doses) given between 3-7 days of age, if large L-R shunt on Doppler but before cardiovascular compromise. Serial echo performed & further courses considered if large L-R shunt persisted/ recurred. Ligation if duct remained after > 1 course of Indo or course incomplete due to complications.	Response of duct to Indo (success, constriction, failure, recurrence) using Doppler. Complications from Indo therapy.	1st course closure in 61%, constriction in 19%, failure in 19%. 7 (5 non-responders & 2 re-openers) had 2nd course: 2 (28%) successful closure. Treatment failure, ligation & major complications exclusively at <28 wk. Success with Indo: 61% at 24-28 wks, 100% at 29-36 wks ($p<0.025$). Recurrence: 11% at 24-28 wks, 6% at 29-36 wks. >1 course of Indo: 33% at 24-28 wks, 6% at 29-36 wks. Ligation: 22% at 24-28 wks, 0% at 29-36 wks.
Quinn D et al, 2002 USA	341 babies < 27 weeks treated with Indo. 28 died. 30 had no response. 69 had partial duct closure with 1st course of Indo (0.2, 0.1, 0.1 mg/Kg). Ducts in 214 babies closed permanently.	Echo closure by further doses of Indo or ligation.	1 death. 51/68 (75%) reopened duct symptomatically. 48/68 (71%) eventually ligated. Only 2 factors related independently with ductal closure: the longer course of Indo (6 days v 3 days), and higher gestation.

TABLE 1 Summary of results from the six papers studied.

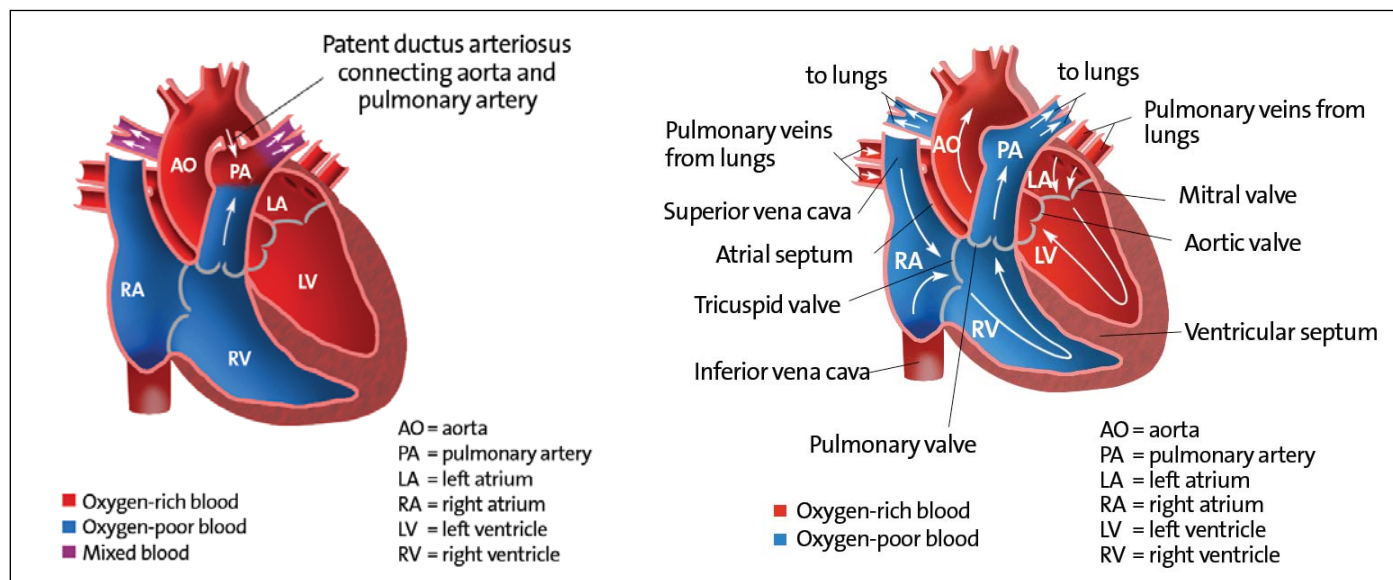


FIGURE 1 A patent ductus arteriosus (PDA) heart (left) and a normal heart.

did not close with the first course, and 25 (23%) reopened following initial closure with a first course. The incidence of reopening was inversely related to birth weight; <1000g – 33% reopened, >1500g – 8% reopened. Twenty four per cent of those who received a second course did not close their ducts, but no further data is given.

Tammela et al, 1999

In this study, Tammela et al⁴ compared closure rates between 31 infants (<33 weeks' gestation) who received a short course of indomethacin (3 doses of 0.2, 0.1, 0.1 mg/kg at 12 hourly intervals) and 30 who received a long course (7 doses of 0.1 mg/kg at 24 hourly intervals). Echocardiography was performed in all infants prior to starting indomethacin. Subsequent echos were performed on days 3, 9, and 14 after the first dose. Primary closure rates were 94% for the short course, 67% for the long course ($p=0.011$), but sustained closure rates were not significantly different (74% v 60%). Twenty nine percent of babies in each group had a further course of indomethacin, and overall 11/61 babies (18%) went on to have their ducts ligated.

Rajadurai and Yu, 1991

The authors looked at 36 ventilated preterm babies⁵. The results are displayed in **TABLE 2**. After a first course of indomethacin there was closure in 22 babies (61%), constriction in seven (19%) and failure in seven (19%) – five non-responders and two with complications. Reopening was seen on three occasions (12%). In four (57%) of seven babies who had a second course their ducts did not close. Four babies had ducts ligated. As the table shows, treatment failure and the need for a second course, and then ligation in some infants occurred significantly more frequently in babies of <28 weeks' gestation.

Quinn et al, 2002

The study reviewed 313 babies <27 weeks' gestation who had been treated with indomethacin for a PDA⁶. Two hundred and fourteen infants (68%) had clinically closed PDA, 30 (10%) were deemed non-responders and required ligation, and the remaining 69 (22%), one of whom later died, formed the cohort of babies with partial closure. Fifty one (75%) of 68 babies developed new symptoms and 48

(15% of the original cohort) were ligated. Quinn et al found that two factors were related independently with ductal closure – a longer course of indomethacin (6 v 3 days) and a higher gestation.

Comments and conclusion

There are no RCTs that specifically address the question of predictive factors for efficacy of a second course of indomethacin for PDA (**FIGURE 1**). In the studies reported, ligation was performed only after unsuccessful medical treatment – however defined. Reported ligation rates after two courses of indomethacin ranged from 0-71%^{1, 2, 4-6} with rates of 56%¹ at <28 weeks' gestation and 71%⁶ at <27 weeks' gestation.

Better prediction of the response to a second course of indomethacin can be achieved by considering gestation⁵, birth weight³, postnatal age⁷ and Doppler evidence of persistent ductal flow¹. Of these factors, the Doppler flow offered 100% sensitivity for persistence of a hsPDA when present after the first course, but 39% (the false negative rate) of those with no Doppler flow developed a hsPDA and needed ligation¹.

Persistent Doppler evidence of blood flow through a PDA following first course is a significant predictor of failure of a second course¹. If there is persistent Doppler flow through the duct after the first course then surgical ligation is a better option than a second course in neonates <28 weeks' gestation, but a second course in older infants appears to have a greater than 50% chance of closure.

In view of the low success rate of second

	24-28 weeks n = 18	29-36 weeks n = 18	Significance of difference
Overall success with indomethacin	11 (61%)	18 (100%)	39% (95% CI 13, 61%)
Closure	8 (44%)	14 (78%)	33% (2, 57%)
Needing >1 course	6 (33%)	1 (6%)	28% (1, 51%)
Ligation rates	4 (22%)	0	22% (0.2, 45%)

TABLE 2 Results of the study by Rajadurai et al⁵.

courses of indomethacin, greater attention needs to be given to optimising first courses of the drug⁸⁻¹⁰.

When indomethacin fails to close a duct, there is considerable variation in practice across the world. We could not find national British or American guidelines. Practice may depend as much on the distance to a major surgical centre as on specific protocols¹¹.

Surgical ligation is usually reserved for PDAs refractory to medical management. Conservative management of PDA in preterms is associated with a high frequency of bronchopulmonary dysplasia¹². In Western Australia geographical isolation from the nearest cardiac surgical centre meant that ligation was not an option until recently. There, in critically ill infants ≤ 28 weeks' gestation, the risk of death was 4.02 (95% CI 1.12, 14.51) times higher in those with (an unligated) persistent PDA compared to those without a hsPDA (4%), but not with those whose PDA closed after medical treatment (OR = 1.13). They concluded that a RCT of surgical ligation of ductus after medical treatment has failed, is

needed to compare the risks and outcome of surgical ligation of PDA versus conservative management¹¹.

Acknowledgement

A shortened version of this article was previously published on the BestBets website: www.bestBETs.org/cgi-bin/bets.pl?record=01319

References

1. Keller R.L., Clyman R.I. Persistent Doppler flow predicts lack of response to multiple courses of indomethacin in premature infants with recurrent patent ductus arteriosus. *Paediatrics* 2003; **112**: 583-87.
2. Su B.H., Peng C.T., Tsai C.H. Echocardiographic flow pattern of patent ductus arteriosus: A guide to indomethacin treatment in premature infants. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**: F197-F200.
3. Clyman R., Campbell D., Hymann M., Mauray F. Persistent responsiveness of the neonatal ductus arteriosus in immature lambs: A possible cause for reopening of patent ductus arteriosus after indomethacin-induced closure. *Circulation* 1985; **71**: 141-45.
4. Tammela O., Ojala R., Iivainen T. et al. Short versus prolonged therapy for patent ductus arteriosus in preterm infants. *J Pediatr* 1999; **134**: 552-57.
5. Rajadurai V., Yu V. Intravenous indomethacin therapy in preterm neonates with patent ductus arteriosus. *J Paediatr Child Health* 1991; **27**: 370-75.
6. Quinn D., Cooper B., Clyman R.I. Factors associated with permanent closure of the ductus arteriosus: A role for prolonged indomethacin therapy. *Pediatrics* 2002; **110**: e10.
7. Firth J., Pickering D. Timing of Indomethacin therapy in persistent ductus [letter]. *Lancet* 1980; July: 144.
8. Herrera C., Holberton J., Davis P. Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. *Cochrane Database of Systematic Reviews* 2007. Issue 2. Art. No.: CD003480. DOI: 10.1002/14651858.CD003480.pub3.
9. Cooke L., Steer P., Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. *Cochrane Database of Systemic Reviews* 2003. Issue 1, Art. No.: CD003745. DOI:10.1002/14651858.CD003745.
10. Fowle P.W., Davis P.G. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane Database of Systemic Reviews* 2002. Issue 3. Art. No.: CD000174. DOI:10.1002/14651858.CD000174.
11. Brooks J.M., Travadi J.N., Patole S.K., Doherty D.A., Simmer K. Is surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: 235-39.
12. Lelong Tissier M.C., Benoit A., Denham M. et al. Conservative management of patent ductus arteriosus in preterm infants. *Intensive Care Med* 1979; **5**: 33-36.

Make No Mistake...

Baxa Exacta-Med® Oral/Enteral Dispensers will increase your confidence in patient safety by reducing the possibility of wrong route delivery of oral liquid medication.

Individually wrapped and sterile, their precision design makes them highly accurate. Their purple plungers, clear labelling and unique tip immediately distinguish them from intravenous syringes, ensuring compliance with the NPSA guidelines on the design of oral/enteral syringes.

So make no mistake. Choose Baxa Exacta-Med Oral/Enteral Dispensers for your patients.

**Take the Safer Route –
Choose Purple.**



...the safer choice is PURPLE

Baxa

Baxa Ltd Radius Court, Eastern Road, Bracknell, Berkshire, RG12 2UP, UK

Tel: 01344 392902 Fax: 01344 392903 Email: choosepurple@baxa.co.uk Web: www.baxa.com/choosepurple