Comparison of oral ibuprofen and indomethacin on closure of patent ductus arteriosus in preterm infants

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مقارنة بين مفعول إعطاء الأيبوبروفين والإيندوميثاسين عن طريق الفم في إغلاق القناة الشريانية السالكة في الأطفال الخدَّج (المبتسرين)

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الخلاصة: على الرغم من استخدام كل من الأيبوبروفين والإيندوميثاسين داخل الوريد على نطاق واسع لغَلْق القناة الشريانية السالكة في الأطفال الخدَّج (المبتسرين)، إلا أن هذه التركيبات الدوائية الوريدية لا تتوافر في جمهورية إيران الإسلامية. ولقد أجريت هذه الدراسة لمعرفة الأثر العلاجي للمعالجة الفموية، فأعطي عشوائياً، 20 خديجاً الأيبوبروفين الفموي (X1 10 مغ/كغ، ثم X2 5 مع/كغ بفاصل زمني مدته 24 ساعة) أو الإيندوميثاسين (0.2X3 مع/كغ بفاصل زمني مدته 24 ساعة). ولقد شوهد الانغلاق التام للقناة في 7 من 10 في المجموعة التي أعطيت الإيندوميثاسين، و8 من 10 في المجموعة التي أعطيت الأيبوبروفين. ولم يكن الاختلاف اختلافاً يُعْتَدُّ به، كما لم يبلَّغ عن عَوْدة انفتاح القناة بعد إغلاقها، لا أثناء الإقامة في المستشفى ولا أثناءَ زيارات المتابعة التي تمت لاحقاً لكلٍّ من المجموعتين. ولم يلاحظ أي ارتفاع ملحوظ في مستويات نيتروجين اليوريا في الدم أو في كرياتينين المصل.

ABSTRACT Although intravenous indomethacin and ibuprofen are widely used for closure of patent ductus arteriosus in premature infants, these formulations are unavailable in the Islamic Republic of Iran. In this study of the therapeutic effects of oral treatments, 20 preterm infants were randomized to oral ibuprofen (1 × 10 mg/kg, then 2 × 5 mg/kg at 24-hour intervals) or oral indomethacin (3 × 0.2 mg/kg at 24-hour intervals). Complete ductal closure was seen in 7/10 of the indomethacin and 8/10 of the ibuprofen group. The difference was not significant. There was no reopening after the ductal closure during the hospital stay or in the follow-up visits in either group and no excessive increases in the blood urea nitrogen or serum creatinine levels were observed.

Comparaison des effets de l'ibuprofène et de l'indométacine par voie orale sur la fermeture du canal artériel persistant chez les prématurés

RÉSUMÉ Alors que l'indométacine et l'ibuprofène par voie intraveineuse sont très souvent utilisés pour la fermeture du canal artériel persistant chez les enfants nés avant terme, ces formulations ne sont pas disponibles en République islamique d'Iran. Dans cette étude sur les effets thérapeutiques des traitements oraux, 20 prématurés ont été randomisés pour recevoir de l'ibuprofène par voie orale (1 ×10 mg/kg, puis 2 × 5 mg/kg à intervalles de 24 heures) ou de l'indométacine par voie orale (3 × 0,2 mg/kg à intervalles de 24 heures). Une fermeture complète du canal a été observée chez 7 nouveau-nés sur 10 du groupe indométacine et chez 8 sur 10 du groupe ibuprofène. Cette différence n'est pas significative. Il n'y a pas eu ensuite de réouverture du canal artériel au cours de l'hospitalisation ou des visites de contrôle dans l'un ou l'autre groupe, ni d'augmentation excessive des taux d'azote uréique du sang ou de créatinine sérique.

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Introduction

Patent ductus arteriosus (PDA) is one of the most common clinical findings and most frequent source of complications in premature infants [*1*]. The presence of respiratory distress syndrome (RDS) is also associated with increased frequency of significant PDA [*2*]. The incidence of PDA in very-low-birth weight infants with RDS is about 40% on the 3rd day of life, leading to several undesirable consequences, including haemodynamic, pulmonary, cerebral, renal and gastrointestinal disturbances [*3*]. The treatment of PDA, particularly when accompanied by RDS, is therefore crucial in preterm infants.

A number of studies carried out in the last decade have demonstrated the effectiveness of intravenous indomethacin and ibuprofen for closure of PDA, and these are now widely used as treatments [*1–7*]. However, the intravenous form of these drugs is unavailable in the Islamic Republic of Iran, and a comparative study was therefore conducted to evaluate the therapeutic effects of oral administration of indomethacin capsules or ibuprofen suspension on closure of PDA in preterm infants.

Methods

This study was conducted in the neonatal intensive care unit of the Nemazee hospital, Shiraz, Islamic Republic of Iran over a 6-month period in 2001.

All eligible premature infants of less than 37 weeks gestation who were admitted to the hospital during their first 10 days of life with clinical PDA confirmed by Doppler echocardiography were enrolled in the study. They were randomized into ibuprofen or indomethacin groups. As soon as the diagnosis was made for the 1st eligible baby, he/she was enrolled to the ibuprofen group and then the next eligible baby was assigned to the indomethacin group, and so on. The randomized distribution sequence was continued until the statistically recommended sample size was achieved.

The non-eligible infants were those with major congenital malformations, congenital heart defects, persistent pulmonary hypertension, intraventricular haemorrhage, blood urea nitrogen (BUN) concentration > 14 mmol/L, hyperbilirubinaemia in the level of exchange transfusion [*3*], bleeding tendency, evidence of necrotizing enterocolitis (NEC), platelet count < 50 000 /mm^3, oliguria < 1 mL/kg/hr, and serum creatinine concentration > 1.8 mg/dL [*8*].

For the indomethacin group, the powder content of a 25 mg indomethacin capsule (Hakim Pharmaceutical Company, Tl-67-HM-026) was freshly prepared by dissolving in 25 mL distilled water. This was given orally as 0.2 mg/kg for 3 doses at 24-hour intervals [*8*]. For the ibuprofen group, an ibuprofen oral suspension containing 100 mg in 5 mL (Hakim Pharmaceutical Company, 75-HM-30) was given as an initial dose of 10 mg/kg, followed by 2 further doses of 5 mg/kg at 24-hour intervals [*8*]. Administration of the 2nd or 3rd doses of each drug was dependent on achievement of ductal closure after the initial doses.

Apart from the regular daily care and clinical examinations, a 2nd and 3rd Doppler echocardiographic evaluation was performed for all neonates shortly after receiving the last doses of the drugs and 1 week later to visualize the state of the ductus and the shunting through it.

The 2 groups were evaluated and compared for sex, gestational age, vital signs and age at starting treatment, ductal closure, serum bilirubin level, renal function, thrombocyte count and evidence of NEC.

The Fisher exact test was used for data analysis.

The Board of the Department of Paediatrics and the Committee for Research Proposals approved the study design, and informed consent for participation in the study was obtained from all the parents.

Results

In a period of about 6 months from May to October 2001, 63 neonates were admitted to the neonatal intensive care unit, 45 of whom were premature. A total of 7 preterm infants did not develop PDA. From the remaining 38 eligible infants, 18 were excluded during the study (5 died on the 2nd or 3rd day of life due to asphyxia and intraventricular haemorrhage, 8 had bleeding tendency following fulminant septicaemia, 2 had elevated BUN and renal dysfunction, and 3 developed right-to-left shunting with severe pulmonary hypertension). Therefore, 20 preterm infants with symptomatic PDA confirmed by Doppler echocardiography entered the study and were randomized into ibuprofen and indomethacin groups

The characteristics of both groups are shown in Table 1. No significant differences were found between the 2 groups in terms of birth weight, gestational age, sex, related maternal conditions, required trend of other treatments and some of the predictable complications of prematurity.

Of the 20 neonates, 14 who had hyperbilirubinaemia before the onset of treatment received phototherapy; none of them needed exchange transfusion during or after therapy. The mean airway pressure and mean fraction of inspired oxygen (FIO_2) concentration following PDA treatment were not different between the groups.

Complete ductal closure was seen in 15 babies: 7/10 in the indomethacin group and 8/10 in the ibuprofen group. The difference was not significant ($P = 0.5$). There was no reopening during the hospital stay or in the follow-up visits in either group.

Table 1 **Pretreatment characteristics of neonates with patent ductus arteriosus in the indomethacin and ibuprofen treatment groups**

Neonate characteristic	Indomethacin (*n* = 10)	Ibuprofen (*n* = 10)
Mean (SD) birth weight (g)	1720 (630)	1860 (402)
Mean (SD) gestational age (weeks)	33.2 (3.1)	31.3 (4.4)
Sex (No. of males)	6	7
Maternal premature rupture of membranes (%)	70	50
Maternal pre-eclampsia (%)	33	35
Maternal betamethasone treatment (%)	80	75
Mean (SD) airway pressure at 24 hr (cm H_2O)	8.1 (2.1)	7.5 (2.1)
Mean (SD) fraction of inspired oxygen at 24 hr (%)	55 (23)	59 (35)
Surfactant therapy (No.)	7	8
Mean (range) age at onset of therapy (days)	6.4 (5–8)	5.5 (4–7)
Respiratory distress syndrome (No.)	9	10
Hyperbilirubinaemia (No)	7	7

n = ***number of neonates; SD = standard deviation.***
No significant differences between groups (P > 0.5).

There were no significant differences in the levels of serum creatinine before and after treatment with oral ibuprofen or indomethacin (mean differences were 0.35 and 0.45 mg/dL respectively). No neonate in either group developed cardiac insufficiency and none of them demonstrated drug side-effects such as excessive increase in BUN level (> 14 mmol/L), NEC, gastrointestinal disorders, thrombocytopaenia (< 50 000 mm^3) or bleeding tendency.

All 5 preterm infants who required surgical ligation of the ductus had weight < 1270 g and gestational age < 30 weeks. Two of them (1 in each group) had severe respiratory distress and pulmonary hypertension. Respiratory distress was defined as respiratory rate more than 60 breaths/minute. These 2 neonates (1 in each group) had respiratory rate of > 80 breaths/minute and both had proven echocardiographic evidence of pulmonary hypertension. The other 3 neonates (2 in the ibuprofen and 1 in the indomethacin group) who needed high oxygen therapy (100%) had large PDA and cardiac insufficiency.

Discussion

Intravenous indomethacin, and also since 1993 intravenous ibuprofen [*4*], have been proven effect and are the conventionally used drugs to treat haemodynamically significant PDA in preterm infants [*5*]. Although both are cyclo-oxygenase blockers, they have different effects on regional circulation [*5*]. Indomethacin may cause significant reductions in cerebral and gastrointestinal blood flow [*9*], and may be associated with altered platelet function and gastrointestinal perforation or haemorrhage [*3*]. Ibuprofen closes the ductus with enhancement of cerebral blood flow autoregulation, with no intestinal haemodynamic derangement [*3,10*] or increased incidence of intracranial haemorrhage [*5*]. However, in the present study no neonate in either group developed signs of bleeding or gastrointestinal disorders. Compared with indomethacin, ibuprofen is believed to be less likely to induce NEC [*7*]. Data indicate that there is an increased risk of NEC and bowel perforation in premature infants with PDA receiving indomethacin due to a significant reduction in mesenteric blood flow velocity [*11*]. No signs suggestive of NEC were observed among the neonates of either group in our study.

By comparison, ibuprofen has fewer effects on renal function in terms of urine output and fluid retention [*5*]. Ibuprofen-treated patients have higher urine output and creatinine clearance, with lower BUN values, in contrast to indomethacin-treated infants [*2,3*] who show a significant number of oliguric patients, increases in serum creatinine and a tendency for lower fractional excretion of sodium [*5*]. However, no significant differences in the levels of serum creatinine before and after treatment with oral ibuprofen or indomethacin were observed in our study, and no neonate in either group demonstrated an excessive increase in BUN level.

The efficacy of ibuprofen is comparable to indomethacin for closure of PDA in many clinical trials [*5–7,9–11*] and while concern remains regarding the safety of indomethacin, intravenous ibuprofen has been used without significant adverse effects [*3,4,12–14*].

In our study ductal closure was achieved in 70% the indomethacin group and 80% the ibuprofen group. These results are comparable with other recent studies. Ductal closure has been reported to be achieved in 66% to 93% of cases after indomethacin treatment [*2,3,5–7,9,10*] and in 62% to 90% of neonates treated with ibuprofen [*1–3,5,6,9–13*]. Therefore, if they were equally effective, oral ibuprofen for PDA

closure would have several important advantages over the intravenous route for the same purpose [*1,2*].

Conclusion

The intravenous types of indomethacin and ibuprofen are not available in the Islamic Republic of Iran. Our study suggests that oral preparations of these drugs may have a similar efficacy to the intravenous preparations for ductal closure in preterm infants in developing countries where supplies of intravenous drugs are unavailable. Considering the reported side-effects of indomethacin, oral ibuprofen suspension should be regarded as a safer alternative. However, drug serum levels were not measured in this study, and in view of the small study sample, larger comparative studies are warranted.

References

1. Lemons JA et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 Through December 1996. ***Pediatrics***, 2001, 107:E1.
2. Hammoud MS et al. Incidence and risk factors associated with the patency of ductus arteriosus in preterm infants with respiratory distress syndrome in Kuwait. ***Saudi medical journal***, 2003, 24(9): 982–5.
3. Clyman RI. Medical treatment of patent ductus arteriosus in premature infants. In: Long WA, ed. ***Fetal and neonatal cardiology***. Philadelphia: WB Saunders, 1990:682–-90.
4. Varvarigou A et al. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. ***Journal of the American Medical Association***, 1996, 275(7):539–44.
5. Lago P et al. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial. ***European journal of pediatrics***, 2002, 161(4):202–7.
6. Supapannachart S, Limrungsikul A, Khowsathit P. Oral ibuprofen and indomethacin for treatment of patent ductus arteriosus in premature infants: a randomized trial at Ramathibodi Hospital. ***Journal of the Medical Association of Thailand***, 2002, 85(Suppl. 4):S1252–8.
7. Chotigeat U, Jirapapa K, Layangkool T. A comparison of oral ibuprofen and intravenous indomethacin for closure of patent ductus arteriosus in preterm infants. ***Journal of the Medical Association of Thailand***, 2003, 86(Suppl. 3):S563–9.
8. Behrman RE, Kliegman RM, Jensen HB. ***Nelson textbook of pediatrics***, 17th ed. Philadelphia, Saunders, 2004: 580.
9. Patel J et al. Randomized double-blind controlled trial comparing the effects of ibuprofen with indomethacin on cerebral hemodynamics in preterm infants with patent ductus arteriosus. ***Pediatric research***, 2000, 47(1):36–42.
10. Mosca F et al. Comparative evaluation of the effects of indomethacin and ibuprofen on cerebral perfusion and oxygenation in preterm infants with patent ductus arteriosus. ***Journal of pediatrics***, 1997, 131(4):549–54.
11. Pezzati M et al. Effects of indomethacin and ibuprofen on mesentric and renal blood flow in preterm infants with patent ductus arteriosus. ***Journal of pediatrics***, 1999, 135(6):733–8.

12. De Carolis MP et al. Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants. ***European journal of pediatrics***, 2000, 159(5):364–8.

13. Dani C et al. Prophylaxis of patent ductus arteriosus with ibuprofen in preterm infants. ***Acta paediatrica***, 2000, 89(11):1369–74.

14. Gournay V et al. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. ***Lancet***, 2002, 359(9316):1486–8.

Maternal, newborn health and poverty
Paper No. 1: The effect of maternal–newborn ill-health on households: economic vulnerability and social implications

Pregnancy and childbirth are wonderful and life-changing events. They can also bring potential for illness and suffering. Women from economically developing societies are especially vulnerable during these periods. The overall objective of this paper is to undertake a review of the evidence base on economic vulnerability and social implications in relation to maternal and newborn ill-health, and to highlight the major gaps in this evidence base.

The paper can be downloaded at: http://www.who.int/reproductive-health/universal_coverage/issue1/index.htm.