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REVIEW

Ibuprofen and indomethacin for the closure of the patent ductus arteriosus

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The ductus arteriosus connects the pulmonary artery with the aorta and allows right ventricular blood to bypass the unexpanded lungs. In mature infants, the ductus arteriosus closes after birth. Patent ductus arteriosus occurs in 70% of preterm infants with a birth weight < 1,000 grams. Failure of the ductus arteriosus to close has been associated with intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, periventricular leukomalacia, renal failure, and persistent pulmonary hypertension. The drugs used to treat the patent ductus arteriosus are ibuprofen and indomethacin which are potent non-selective inhibitors of cyclo-oxygenase (COX) and therefore inhibit prostaglandin E2 synthesis. Prostaglandin E2 relaxes smooth muscle and tends to inhibit the closure of the patent ductus arteriosus. Intravenous ibuprofen and indomethacin inhibit prostaglandin E2 synthesis and thereby close the patent ductus arteriosus with similar efficacy. Indomethacin reduces the blood flow velocity in kidneys, intestine and brain. Ibuprofen has less effect on blood flow velocity in these organs. There is a significant increase in serum creatinine after indomethacin administration but not after ibuprofen and infants treated with ibuprofen have higher creatinine clearance. Oliguria (urine output < 1 ml/kg/h) occurs more frequently with indomethacin than with ibuprofen. Indomethacin requires furosemide for urine output more often than ibuprofen. Ibuprofen reduces the risk of necrotizing enterocolitis and transient renal insufficiency and it is the drug of choice for closing the patent ductus arteriosus. Ibuprofen and indomethacin may be administered orally. In conclusion, intravenous ibuprofen and indomethacin close the patent ductus arteriosus at the same rate, but indomethacin is more toxic than ibuprofen.

KEYWORDS: Ibuprofen, Indomethacin, Neonate, Patent-ductus-arteriosus.

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INTRODUCTION

The ductus arteriosus is a large fetal vessel connecting the pulmonary artery with the aorta and allowing right ventricular blood to bypass the unexpanded lungs. In mature infants, with the start of lung ventilation and the attendant rise in blood oxygen tension, the ductus arteriosus closes and the cardiovascular system acquires its final architecture. A persistent patent ductus arteriosus occurs in 70% of extremely low birth weight with a birth weight < 1000 g.

A persistent patent ductus arteriosus in preterm infants results in serious hemodynamic changes with consequent morbidities affecting the renal, respiratory, and gastrointestinal systems. Thus, treatment is mandatory and should be implemented as soon as possible, preferably in first 2 weeks of life. Two treatment options are available, namely (a) a conservative approach, consisting of a pharmacological treatment with the cyclo-oxygenase inhibitors Indomethacin or Ibuprofen or (b) an invasive approach, consisting of the surgical ligation of the ductus. Indomethacin and Ibuprofen are equally effective in closing the ductus, but differences exist between them. Indomethacin has a protective effect on the incidence of intraventricular hemorrhage, but reduces the blood flow to the kidneys and the brain. Ibuprofen is less toxic but has no effect on intraventricular hemorrhage. Efficacy of pharmacological treatment is influenced by timing of initiation

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of therapy: an early onset of treatment increases the chances of success.[1] At the time of writing, ibuprofen is becoming the first choice for ductal closure due to its higher association with cerebral, gastrointestinal and renal blood flow velocity, whereas ibuprofen does not exhibit this effect.[2] Renal failure is more common in infants receiving indomethacin compared to ibuprofen.[3]

Surgical treatment is the only option when pharmacological treatment fails to close the PDA in symptomatic infants.[1]

As noted, ibuprofen and indomethacin are potent non-selective cyclo-oxygenase (COX) inhibitors and therefore block the conversion of arachidonic acid to prostaglandins.[1] Prostaglandin E2 relaxes vascular smooth muscle, and as a consequence, tends to inhibit the closure of the patent ductus arteriosus; by the same token, it induces vasodilation of the afferent renal arterioles and thus sustains glomerular filtration. By inhibiting prostaglandin E2 synthesis, Ibuprofen and indomethacin favor the closure of the patent ductus arteriosus, but reduce glomerular filtration rate with a consequent decrease of urine output and an increase of serum creatinine concentration.

Indomethacin has been used to treat and to prevent patent ductus arteriosus in premature infants since 1976. However, concerns have always remained regarding safety because of its undesired effects on renal, gastrointestinal and cerebral blood flow. Ibuprofen has been more recently introduced to treat and prevent the condition with less serious side effects on these critical vascular circuits.

Guimaraes et al.[4] explored the use of ibuprofen and indomethacin in 45 Intensive Care Units of 19 European countries. Intravenous indomethacin was used in 32 neonatal intensive care units, intravenous ibuprofen is used in 16 and oral ibuprofen is used in 13 neonatal ICUs. There is a wide variation among the neonatal intensive care units regarding the use of ibuprofen and indomethacin in European neonatal intensive care units. Guidelines or recommendations are necessary to standardize treatment of patent ductus arteriosus in Europe in order to give all newborns identical health care opportunities.

BIBLIOGRAPHIC SEARCH

The bibliographic search was performed using PubMed database as search engine; May 2015 was the cutoff point. The following key words "ibuprofen, indomethacin, patent ductus" were used. In addition, the books Neonatal Formulary[5] and NEOFAX by Young and Mangum[7] were consulted. A previously published report covers this theme and here we will only discuss extensively reports that were not included in that previous review.[7]

RESULTS

Preliminary filtering

A total of 177 articles were retrieved. After excluding duplication, articles not in English and inappropriate articles a total of 32 were selected. Ten of these had been discussed in our 2014 review[7] and were likewise excluded.

Dosage and General aspects

Indomethacin is administered as an intravenous infusion of 0.2 mg/kg by syringe pump over at least 30 min to minimize adverse effects on cerebral, intestinal, and renal blood flow velocities. Supplementary doses of 0.2 mg/kg are usually administered at 12 to 24 hour intervals. Usually three doses are given per course, with a maximum of two courses. Ibuprofen is administered as an intravenous infusion of 10 mg/kg, usually infused over 15 min by a syringe pump; this should be followed by 5 mg/kg after 24 and 48 hours. Oral ibuprofen has been tested and found to be be equally effective. A second course of treatment may be effective when the first course is not.[5] Urine output must be monitored: if anuria or severe oliguria occurs, subsequent doses should be delayed.[6] We shall present and discuss studies in which Indomethacin and ibuprofen were administered to neonates in comparable conditions.

Pharmacological treatment vs placebo trials

Ibuprofen has also been proposed as a prophylactic agent: Ohlsson & Shah[8] determined the effectiveness and safety of prophylactic ibuprofen compared to placebo/no intervention in the prevention of patent ductus arteriosus in preterm infants. They conclude that prophylactic use of ibuprofen decreases the incidence of patent ductus arteriosus, decreases the need for rescue with cyclo-oxygenase inhibitors and the need for surgical closure. But they also note that in the control group, the patent ductus arteriosus closed spontaneously by day 3 in 58% of neonates. They conclude that this prophylactic strategy exposes infants to a drug that has cerebral, renal and gastrointestinal side effects without conferring any important short-term benefits. Jones et al.[9] reviewed the effects of indomethacin or ibuprofen compared with placebo on closure of patent ductus arteriosus in preterm infants < 37 weeks of gestation. Twenty trials were analyzed; Intravenous Indomethacin ibuprofen closed the patent ductus arteriosus more effectively than placebo. However, they also note that treatment with intravenous ibuprofen may increase the risk of chronic lung disease.

Indomethacin vs. Ibuprofen by intravenous administration

The majority of studies compared indomethacin and ibuprofen administered intravenously. The usual endpoint is closure of the ductus. Chan et al.[10] compared

the effectiveness and complications of intravenous ibuprofen versus indomethacin for closure of patent ductus arteriosus in 95 infants. Ibuprofen and indomethacin were equally effective for non-surgical closure of the patent ductus arteriosus in premature infants, with similar rates of failure (31% for ibuprofen, 33% for indomethacin). Intestinal complications (necrotizing enterocolitis or spontaneous intestinal perforation) and side effects occurred in less than 10% of cases, but were more frequent following indomethacin. Katakam et al.[11] analyzed safety and effectiveness of Indomethacin vs. ibuprofen for the treatment of patent ductus arteriosus. The rates of closure were similar, 62% for indomethacin vs. 58% for ibuprofen. The rate of complications (death, necrotizing enterocolitis or intestinal perforation) was 40% for indomethacin group and 32% for ibuprofen, with no difference between groups in terms of serum creatinine. Similar results were described by Sivanandan et al.[12] A total of 54 infants received indomethacin and 70 received ibuprofen. Closure was 68.5% in the indomethacin group vs. 60% in the ibuprofen group. No difference was observed between treatments in terms of acute renal dysfunction, necrotizing enterocolitis, spontaneous intestinal perforation or gastrointestinal bleeding. The proportion of infants treated with surgical ligation of patent ductus arteriosus was similar between the two groups. Fanos et al.[13] reported a retrospective analysis of clinical data in order to compare the efficacy and the renal tolerability of ibuprofen and indomethacin in infants with a gestational age ≤ 30 weeks for the treatment of patent ductus arteriosus. Ibuprofen resulted pharmacologically as efficient as indomethacin and could be an alternative in prematures. As regards renal tolerability, they confirm that both drugs affect at least transiently renal function. Indomethacin was more nephrotoxic compared to ibuprofen, because creatinine concentrations normalize more slowly in this group. The difference for this parameter barely attained significance.

In view of such results, ibuprofen has been proposed as the preferential alternative vs. indomethacin in treating patent ductus arteriosus. However, Hammerman et al.[14] contend that short and long-term safety concerns regarding ibuprofen remain. In this study, their objective was to show that treating a persistent ductus with continuous indomethacin vs. ibuprofen results in similar effects on urine output, renal function, and blood flow velocities in the renal, superior mesenteric, and anterior cerebral arteries. Sixty four prematures with PDA were randomly and prospectively assigned to either treatment. Closure rates, serum creatinine, oliguria, estimated glomerular filtration rate, and fractional excretion of sodium were similar in both groups.

Thomas et al.[15] performed a meta-analysis of intravenous ibuprofen versus intravenous indomethacin for closure of patent ductus arteriosus. Data from the nine relevant trials (n = 566), showed no significant difference in the efficacy of ibuprofen and indomethacin in patent ductus closure ($p = 0.70$). However, five trials (n = 443) provided serum creatinine concentration data that revealed a significantly lower increase favoring ibuprofen ($p < 0.001$), and urine output data that showed a significantly lower decrease favoring ibuprofen ($p < 0.001$). In two trials (n = 188) the proportion of infants who required postnatal oxygen therapy at 28 days (defined as chronic lung disease) was significantly higher with ibuprofen (52/94; 55.3%) than with indomethacin (38/94; 40.4%, $p < 0.05$). No statistically significant differences were found in mortality, intraventricular hemorrhage, necrotizing enterocolitis, surgical ligation, sepsis, retinopathy of prematurity, periventricular leukomalacia, length of hospital stay, gastrointestinal bleeding, reopening of patent ductus arteriosus, back-up treatment, surfactant therapy, or days on a ventilator. Ibuprofen and indomethacin have similar efficacy in patent ductus arteriosus closure, but preterm infants treated with ibuprofen experience lower serum creatinine values, higher urine output, and less undesirable organ blood flow and adverse vasoconstrictive adverse effects.

Van Overmeire et al.[16] compared ibuprofen and indomethacin with regard to efficacy and safety for the early treatment of patent ductus arteriosus in 148 preterm infants with a gestational age of 24 to 32 weeks who had respiratory distress syndrome and patent ductus arteriosus. The infants were randomly assigned to receive 3 doses of indomethacin or ibuprofen. The rate of ductal closure was similar with the two treatments: ductal closure occurred in 49 of 74 infants given indomethacin (66%), and in 52 of 74 given ibuprofen (70%) $p = 0.41$. The numbers of infants who needed a second pharmacologic treatment or surgical ligation did not differ significantly between the two groups. Oliguria occurred in 5 (6.7%) infants treated with ibuprofen and in 14 (18.9%) infants treated with indomethacin ($p = 0.03$).[17] There were no significant differences with respect to other side effects and complications. Ibuprofen therapy on the third day of life is as efficacious as indomethacin for the treatment of patent ductus arteriosus in preterm infants with respiratory distress syndrome and is significantly less likely to induce oliguria.

Intravenous Indomethacin vs. oral Ibuprofen

A number of research projects has compared the effects of oral ibuprofen vs. intravenous indomethacin. The discussion centers around the concepts of efficacy and cost. Loomba & Nijhawan[17] performed a systematic review of the literature comparing oral ibuprofen vs. intravenous indomethacin for closure of the patent ductus arteriosus in premature infants. Oral ibuprofen was as effective as intravenous indomethacin. When comparing both drugs, the only difference noted between the ibuprofen and indomethacin was that ibuprofen was associated with a lesser increase in serum creatinine after treatment.

Similar results were described by Yang et al.,[18] comparing 26 low weight birth babies who received intravenous indomethacin with 22 preterm infants who received oral ibuprofen.[14] The overall rate of ductal closure was 88.5% indomethacin and 81.8% with ibuprofen. Lee et al.[19] compared the effects and complications of ductus arteriosus closure intravenous indomethacin (n = 85) vs oral ibuprofen (n = 52) in neonates weighing < 1500 grams. The closure rate was similar, but oral ibuprofen was associated with significantly fewer cases of necrotizing enterocolitis and had significantly lower rates of elevated creatinine levels. Heo et al.[20] compared intravenous indomethacin and oral ibuprofen with regard to efficacy and safety for treatment of patent ductus arteriosus in 49 immature and 29 mature infants. Ductal closure in immature infants treated with indomethacin was 74.1% and 92.9% ($p < 0.05$) with ibuprofen. Ductal closure in mature infants treated with intravenous indomethacin was 66.7% and in infants treated with oral ibuprofen was 92.9 ($p < 0.05$). Platelet counts were increased in immature infants treated with ibuprofen ($p = 0.027$). Hyponatremia occurred in immature infants treated with ibuprofen ($p = 0.002$) and in mature infants ($p = 0.001$ for both groups). Serum creatinine values were lower in immature infants treated with ibuprofen ($p = 0.032$). Administration of furosemide for urine output was more frequent in the mature infants than in the immature infants. Oral ibuprofen was as effective as intravenous indomethacin in closing the patent ductus arteriosus. Adverse effects of oral ibuprofen were less severe than intravenous indomethacin. Thus, oral ibuprofen could be used as an alternative agent for the treatment of patent ductus arteriosus in extremely low birth weight infants.

Oral indomethacin vs Oral ibuprofen

To the best of our knowledge only two studies compared oral indomethacin and oral ibuprofen. Pourarian et al.[21] compared oral ibuprofen and oral indomethacin for the closure of patent ductus arteriosus. 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, as shown by Yadav et al.[22] Fifty infants received ibuprofen and 33 indomethacin. Overall closure of the patent ductus arteriosus was 60% and 65.7% in the ibuprofen and indomethacin groups, respectively. Closure rate was significantly higher when the drugs were administered within 8 days of birth (83.3% for indomethacin, 75% for ibuprofen).

DISCUSSION

Intravenous ibuprofen and indomethacin close the patent ductus arteriosus in similar proportions in preterm infants. The rate of ductal closure depends on postnatal age. When this is < 8 days the rate of ductal closure is higher than in neonates with postnatal age > 28 days.[22] In mature infants, the ductal closure rate is 66.7% when treated with intravenous indomethacin and 92.9% when treated with oral ibuprofen ($p < 0.05$).[20] Both ibuprofen and indomethacin close the patent ductus arteriosus more effectively than placebo.[9] The rate of surgical ligation is not different after intravenous ibuprofen and indomethacin administration.[12] The overall rate of ductal closure is similar in infants treated with intravenous indomethacin and oral ibuprofen.[17-19] Intravenous indomethacin is associated with higher side effects than oral ibuprofen.[18,19] Intravenous ibuprofen is associated with approximately 30% greater risk of chronic lung disease than intravenous indomethacin.[9] Oral ibuprofen appears to be as effective as intravenous ibuprofen and intravenous indomethacin for closing the patent ductus arteriosus.[17]

The oral administration of ibuprofen is associated with a lesser increase in serum creatinine than the intravenous administration of indomethacin.[17] Indomethacin reduces the blood flow velocity in kidneys, intestine, and brain, ibuprofen has not this effect.[1,14] In infants who received 2 or more courses, the decrease in urine output and the increase in serum creatinine concentration were not different between ibuprofen and indomethacin.[14] Ibuprofen reduces the transient renal insufficieny.[23] Cerebral blood flow velocity falls significantly after intravenous administration of indomethacin but not after intravenous administration of ibuprofen.[24] In some infants, indomethacin reduces oxidized cytochrome oxidase concentration.[24] Oral ibuprofen is associated with significantly fewer cases of necrotizing enterocolitis and has significantly lower creatinine levels than intravenous indomethacin.[19] Oral ibuprofen reduces the risk of necrotizing enterocolitis and transient renal insufficiency and this drug appears to be the drug of choice for closing the patent ductus arteriosus in preterm infants.[23] The continuous slow intravenous administration of indomethacin does not affect the serum concentration of creatinine and the renal, intestinal and cerebral blood flow velocities. These parameters are similar to those obtained with intravenous administration of ibuprofen.[14]

For ibuprofen and indomethacin, the number of treatment courses is inversely correlated with birth weight and gestational age. Analysis of the first course revealed a significant increase in serum creatinine and decrease in urine output with both drugs, with a more pronounced effects of indomethacin.[25] Compared with ibuprofen, indomethacin treatment is associated with significantly higher mean serum creatinine levels and a higher percentage of infants with serum creatinine > 1.2 mg/dl and hyponatremia < 120 mmol/l. Treatment with ibuprofen is safer, decreasing the risk of renal failure, and hyponatremia.[26]

There are conflicting results about the ductal closure rate by oral indomethacin and oral ibuprofen. Fakhrae et al.[27] found that the patent ductus arteriosus is closed in all preterm infants (100%) treated with oral ibuprofen and

83% infants treated with oral indomethacin ($p < 0.05$). Yadav et al.[22] and Pourarian et al.[21] state that oral ibuprofen and oral indomethacin close the patent ductus arteriosus at similar rates.

Indomethacin has a protective effect on the incidence of intraventricular hemorrhage but reduces the blood flow in kidneys intestine and brain. Ibuprofen has less renal, mesenteric, and cerebral vasoconstrictive effects and ibuprofen has been proposed as a preferential alternative to close the patent ductus arteriosus.[14] Intravenous indomethacin causes a significant decrease in urinary antidiuretic hormone excretion, along with a significant reduction in urinary sodium, fractional excretion of sodium, and urinary osmolality. Ibuprofen treatment does not modify urinary antidiuretic hormone excretion, the urinary sodium and the fractional excretion of sodium.[28]

In conclusion, intravenous ibuprofen and indomethacin have similar efficacy in closing the patent ductus arteriosus in preterm infants. However, ibuprofen has less renal side effects than indomethacin. Oral ibuprofen could be used as an alternative to intravenous ibuprofen. Oliguria occurs in higher frequency in infants treated with indomethacin than in infants treated with ibuprofen. Furosemide is administered at a higher frequency after indomethacin than ibuprofen. Indomethacin reduces the cerebral, renal, intestinal and blood flow velocity whereas ibuprofen does not have this effects. Indomethacin is more toxic than ibuprofen in preterm infants and ibuprofen is the choice drug to close the patent ductus arteriosus. The slow continuous intravenous administration of indomethacin does not have side effects and behaves similarly to ibuprofen. The number of treatment courses of ibuprofen and indomethacin is inversely correlated with birth weight and gestational age.

CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

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IBUPROFEN, INDOMETACINA E FECHAMENTO DO CANAL ARTERIAL

O canal arterial conecta a artéria pulmonar com a aorta e permite que o sangue oriundo do ventrículo direito evite passar pelos pulmões fetais não expandidos. Em recém-nascidos maduros, o canal arterial se fecha após o nascimento. A persistência do canal arterial ocorre em 70% dos recém-nascidos prematuros com peso de nascimento < 1.000 gramas. O não fechamento do canal arterial associa-se a hemorragia intraventricular, enterocolite necrosante, displasia bronco-pulmonar, leucomalacia periventricular, insuficiência renal e hipertensão pulmonar persistente. Os medicamentos utilizados para tratar a persistência do canal arterial são o ibuprofeno e a indometacina. Ambos são potentes inibidores não seletivos da ciclo-oxigenase e inibem a síntese de prostaglandina E2. Esta relaxa a musculature vascular lisa e tende a inibir o fechamento do canal arterial. O ibuprofeno e a indometacina inibem a síntese de prostaglandina E2 e favorecem o fechamento do canal arterial. A indometacina reduz a velocidade do fluxo sanguíneo renal, intestinal e cerebral. O Ibuprofeno tem efeito menor sobre a velocidade do fluxo de sangue nesses órgãos. Há um aumento significativo da creatinina sérica após a administração de indometacina, mas não após o ibuprofeno; por isso, recém-nascidos tratados com ibuprofeno têm maior depuração da creatinina. A oligúria ocorre mais frequentemente com a indometacina vs. ibuprofeno. A indometacina requer furosemida para a produção de urina mais frequentemente do que o ibuprofeno. O ibuprofeno reduz o risco de enterocolite necrotizante e de insuficiência renal transitória e é a droga de escolha para o fechamento do canal arterial patente. O ibuprofeno e a indometacina podem ser ministrados por via oral. Em conclusão, o ibuprofeno e a indometacina fecham o canal arterial patente com a mesma velocidade, mas a indometacina é mais tóxica.

PALAVRAS-CHAVE: ibuprofeno, indometacina, recém-nascido, canal arterial patente.

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