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[Intervention Review]

Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants

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ABSTRACT

Background

In preterm newborns, the ductus arteriosus frequently fails to close and the infants require medical or surgical closure of the patent ductus arteriosus (PDA). A PDA can be treated surgically; or medically with one of two prostaglandin inhibitors, indomethacin or ibuprofen. Case reports suggest that paracetamol may be an alternative for the closure of a PDA. An association between prenatal or postnatal exposure to paracetamol and later development of autism or autism spectrum disorder has been reported.

Objectives

To determine the effectiveness and safety of intravenous or oral paracetamol compared with placebo or no intervention, intravenous indomethacin, intravenous or oral ibuprofen, or with other cyclo-oxygenase inhibitors for treatment of an echocardiographically diagnosed PDA in preterm or low birth weight infants.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 10), MEDLINE via PubMed (1966 to 6 November 2017), Embase (1980 to 6 November 2017), and CINAHL (1982 to 6 November 2017). We searched clinical trial databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials (RCT) and quasi-randomised trials.

Selection criteria

We included RCTs in which paracetamol was compared to no intervention, placebo or other agents used for closure of PDA irrespective of dose, duration and mode of administration in preterm (≤ 34 weeks' postmenstrual age) infants. We both reviewed the search results and made a final selection of potentially eligible articles by discussion. We included studies of both prophylactic and therapeutic use of paracetamol.

Data collection and analysis

We performed data collection and analyses in accordance with the methods of the Cochrane Neonatal Review Group. We used the GRADE approach to assess the quality of evidence for the following outcomes when data were available: failure of ductal closure after the first course of treatment; neurodevelopmental impairment; all-cause mortality during initial hospital stay (death); gastrointestinal bleed or stools positive for occult blood; and serum levels of creatinine after treatment (µmol/L).

Main results

We included eight studies that reported on 916 infants. One of these studies compared paracetamol to both ibuprofen and indomethacin. Five studies compared treatment of PDA with paracetamol versus ibuprofen and enrolled 559 infants. There was no significant difference between paracetamol and ibuprofen for failure of ductal closure after the first course of drug administration (typical risk ratio (RR) 0.95, 95% confidence interval (CI) 0.75 to 1.21; typical risk difference (RD) −0.02, 95% CI −0.09 to 0.09); I^2 = 0% for RR and RD; moderate quality of evidence. Four studies (n = 537) reported on gastrointestinal bleed which was lower in the paracetamol group versus the ibuprofen group (typical RR 0.28, 95% CI 0.12 to 0.69; typical RD −0.06, 95% CI −0.09 to −0.02); I^2 = 0% for RR and RD; number needed to treat for an additional beneficial outcome (NNTB) 17 (95% CI 11 to 50); moderate quality of evidence. The serum levels of creatinine were lower in the paracetamol group compared with the ibuprofen group in four studies (moderate quality of evidence), as were serum bilirubin levels following treatment in two studies (n = 290). Platelet counts and daily urine output were higher in the paracetamol group compared with the ibuprofen group. One study reported on long-term follow-up to 18 to 24 months of age following treatment with paracetamol versus ibuprofen. There were no significant differences in the neurological outcomes at 18 to 24 months (n = 61); (low quality of evidence).

Two studies compared prophylactic administration of paracetamol for a PDA with placebo or no intervention in 80 infants. Paracetamol resulted in a lower rate of failure of ductal closure after 4 to 5 days of treatment compared to placebo or no intervention which was of borderline significance for typical RR 0.49 (95% CI 0.24 to 1.00; P = 0.05); but significant for typical RD −0.21 (95% CI −0.41 to −0.02); I^2 = 0 % for RR and RD; NNTB 5 (95% CI 2 to 50); (low quality of evidence).

Two studies (n = 277) compared paracetamol with indomethacin. There was no significant difference in the failure to close a PDA (typical RR 0.96, 95% CI 0.55 to 1.65; I^2 = 11%; typical RD −0.01, 95% CI −0.09 to 0.08; I^2 = 17%) (low quality of evidence). Serum creatinine levels were significantly lower in the paracetamol group compared with the indomethacin group and platelet counts and daily urine output were significantly higher in the paracetamol group.

Authors' conclusions

Moderate-quality evidence according to GRADE suggests that paracetamol is as effective as ibuprofen; low-quality evidence suggests paracetamol to be more effective than placebo or no intervention; and low-quality evidence suggests paracetamol as effective as indomethacin in closing a PDA. There was no difference in neurodevelopmental outcome in children exposed to paracetamol compared to ibuprofen; however the quality of evidence is low and comes from only one study. In view of concerns raised regarding neurodevelopmental outcomes following prenatal and postnatal exposure to paracetamol, long-term follow-up to at least 18 to 24 months' postnatal age must be incorporated in any studies of paracetamol in the newborn population. At least 19 ongoing trials have been registered. Such trials are required before any recommendations for the possible routine use of paracetamol in the newborn population can be made.

PLAIN LANGUAGE SUMMARY

Paracetamol (acetaminophen) for patent ductus arteriosus (a blood vessel necessary for fetal survival) in preterm and low birth weight infants

Review question: How effective and safe are paracetamol, which has weak anti-inflammatory properties, compared with placebo (a substance with no active therapeutic effect), or no intervention, or nonsteroidal anti-inflammatory drugs (indomethacin and ibuprofen), for closure of a PDA in preterm/low birth weight infants?

Background: A common complication for preterm (premature) or small babies is a patent ductus arteriosus (PDA). Blood circulation to the (as yet) non-functioning lungs is unnecessary before birth (the fetal blood supply is oxygenated via the placenta). The PDA is a temporary fetal blood vessel that connects the pulmonary artery (the vessel that, after birth, takes blood depleted of oxygen from the heart to the lungs) to the aorta (the vessel that takes freshly oxygenated blood, returned from the lungs to the heart by the pulmonary vein, away from the heart and on the beginning of its journey round the body). In other words the PDA 'short-circuits' the fetal circulation of blood through the lungs.. It is necessary to sustain life in the womb, but it should close after birth. Sometimes it remains open because of the baby's immature stage of development. A PDA can lead to life-threatening complications. The usual treatment for PDA has been indomethacin or ibuprofen which inhibit the production of prostaglandins and promotes the closure of the PDA. Recently paracetamol (acetaminophen), a commonly used drug to treat fever or pain in infants, children and adults, has been suggested as an alternative to ibuprofen, with potentially fewer side effects. A number of case reports and case series have suggested that paracetamol may be an alternative for the closure of a PDA. Exactly how paracetamol works to close the PDA is not known, but probably involves inhibition of prostaglandin synthesis. Prostaglandins are chemical compounds which are made throughout the body (i.e. not in any one particular organ), particularly wherever soft tissues are damaged, and their production (synthesis) plays a key role in healing processes. They are known to play an important role in keeping the ductus arteriosus open (patent), so lowering their production would encourage closure of the ductus arteriosus.

Study characteristics: We identified a total of eight studies that enrolled 916 preterm infants and compared the effectiveness and safety of paracetamol versus ibuprofen, indomethacin or placebo in the treatment of a PDA in early life.

Key results: When the results of the included studies were combined, the success rate for paracetamol to close a PDA was higher than that of placebo and similar to that of ibuprofen and indomethacin. Paracetamol appears to have fewer adverse effects on kidney and liver

functions. In one small study that followed children to 18 to 24 months of age there was no difference in neurodevelopmental impairment. The evidence is up to date as of November 2017.

Conclusions: Paracetamol appears to be a promising alternative to indomethacin and ibuprofen for the closure of a PDA with possibly fewer adverse effects.

Additional studies testing this intervention and including longer-term follow-up are needed before paracetamol can be recommended as standard treatment for a PDA in preterm infants. Several studies are ongoing that will eventually provide additional information. Because of reports of a possible association between prenatal paracetamol and the development of autism or autism spectrum disorder in childhood and language delay in girls, long-term follow-up to at least 18 to 24 months' postnatal age must be incorporated in any studies of paracetamol in the newborn population.

Quality of evidence: Although the healthcare providers were not always 'blinded' (unaware of which drug the infants received) we judged the quality of the evidence to be moderate.