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The dark side of ibuprofen in the treatment of patent ductus arteriosus: could paracetamol be the solution?

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Abstract

Introduction: Patent Ductus Arteriosus (PDA) persistence is associated, in prematures, to several complications. The optimal PDA management is still under debate, especially regarding the best therapeutic approach and the time to treat. The available drugs are not exempt from contraindications and side effects; ibuprofen itself, although representing the first-choice therapy, can show nephrotoxicity and other complications. Paracetamol seems a valid alternative to classic Non Steroidal Anti-inflammatory Drugs, with a lower toxicity.

Areas covered: Through an analysis of the published literature on ibuprofen and paracetamol effects in preterm neonates, this review compares the available treatments for PDA, analyzing the mechanisms underlining ibuprofen-associated nephrotoxicity and the eventual paracetamol-induced hepatic damage, also providing an update of what has been yet demonstrated and a clear description of the still open issues.

Expert Opinion: Paracetamol is an acceptable alternative in case of contraindication to ibuprofen; its toxicity, in this setting, is very low. Lower doses may be effective, with even fewer risks. In the future, paracetamol could represent an efficacious first-line therapy, although its safety, optimal dosage and global impact have to be fully clarified through long-term trials, also in the perspective of an individualized and person-based therapy taking into account the extraordinary individual variability.

Keywords: ibuprofen, paracetamol, PDA treatment, nephrotoxicity, hepatotoxicity

Highlights Box

- In preterm newborns, PDA persistence can lead to several complications and its management still remains a controversial topic, particularly regarding the moment and the modality of intervention
- The most common approach is a pharmacological treatment with ibuprofen when PDA is hemodynamically significant. In presence of drug contraindications or failure after repeated cycles, a surgical ligation can be evaluated
- Ibuprofen shows a good success rate in PDA closure, but its use has been associated with several side-effects included nephrotoxicity, being able to cause transient kidney injury
- Paracetamol, proposed as a possible alternative to classical NSAIDs in PDA management, has been demonstrated very promising, with comparable success rates and a good safety profile if used at the dose of 15 mg/kg every 6 hours for 3-7 days: a transient elevation in liver transaminases has been observed only in a few number of patients
- However, aspects such as real efficacy in extremely low birth weight (ELBW) newborns, the best route of administration and dosage, timing of the first dose, long-lasting effects, remain largely unexplored. Therefore, more studies are needed before to propose this medication as a first-line therapy

1. Introduction

The condition of Patent Ductus Arteriosus (PDA), mostly occurring in preterm newborns, is known to be related to a great number of potentially severe complications. The management of delayed or failed ductal closure still remains a controversial topic for clinicians, despite years of studies and clinical practice. Fields of debate are represented by timing and kind of intervention, which can vary from no treatment to a pharmacological and/or surgical approach [1-5].

Today, the most suitable strategy of treatment appears to be a pharmacological approach, performed with ibuprofen and directed only to the cases of hemodynamically significant PDA (hsPDA), even if it is well known that this drug shows some contraindications and various side-effects [1,6-8].

In the last years, some authors [9] linked paracetamol (acetaminophen) administration with PDA closure and the recent introduction of this medication in PDA management has been demonstrated as very promising, showing a comparable success rate and less side-effects compared to Non Steroidal Antiinflammatory Drugs (NSAIDs) [10-14].

However, even if paracetamol has a therapeutic advantage over NSAIDs, since it does not show a peripheral vasoconstrictive effect [15,16,], some aspects (efficacy in ELBW infants, the best route of administration, optimal dose, timing of the first dose) remain largely unexplored and information is lacking particularly as regards its long-lasting effects [17,18].

The aim of this paper is to compare benefits, efficacy and safety of ibuprofen and paracetamol, used for PDA treatment in the vulnerable category of preterm newborns, in order to improve the actual knowledge and to enable the clinicians to choose the safest management, considering that the ultimate goal should be represented by an individualized, effective, personalized therapy with the lowest associated side-effects.

2. Patent Ductus Arteriosus

2.1 Definition

During fetal life, Ductus Arteriosus (DA) is the physiological anatomic connection between pulmonary artery and aorta [19,20].

In full-term neonates, DA usually undergoes functional closure between 24 and 72 hours of life [1,2,7,21], promoted by several mechanisms, such as the reduction in ProstaglandinE2-related (PGE2) effects on DA smooth muscle relaxation [22-24]. The complete anatomical closure, through the evolution into a structure called *ligamentum arteriosum*, usually occurs in a few weeks [22,25].

In preterm neonates, the frequent failure or delay in DA closure is due to several factors (i.e. persisting high levels of PGE2) and PDA persistence can lead to several degrees of immediate and/or long-term complications [1,2,20].

Although deeply studied, many factors involved in PDA condition remain still unknown. Recently, the group of Kahvecioglu et al., demonstrated a possible additional role of platelet dysfunction, finding a higher collagen-ADP duration among the preterms with a “open PDA”, although this result has been detected on a small sample of newborns [26].

2.2 Prevalence

Recent published data showing PDA prevalence in accordance to gestational age (GA) at birth and/or days of postnatal life, evidenced a higher occurrence of this condition among neonates with a lower GA. In fact, on the 4th day of life PDA would persist in about 10% newborns presenting 30-37 weeks (wks) of GA, in 80% among 25-28 wks and in 90% of preterms born at 24 wks. From the 7th day of postnatal life, PDA percentage would decrease, respectively, to about 2%, 65%, and 87% in the mentioned groups [2].

Many authors reported that PDA can undergo spontaneous closure even in prematures [4,27,28], respectively in 73% of neonates with a GA > 28 wks and in 94% of newborns presenting a birth weight (BW) > 1000 g [2].

A randomized trial comparing prophylactic indomethacin to placebo evidenced that non intervention has not been associated to an impairment in clinical conditions and/or complications in 50% of infants with a BW between 500 and 999 g [2].

Data from a prospective study reported a spontaneous PDA closure during early postnatal life in 35% of ELBW neonates and in 70% of those with a GA > 28 wks [29].

In another report, 75% of newborns with GA < 27 wks affected by PDA at discharge moment underwent spontaneous ductal closure in the first year of life [7].

Less information can be found about PDA spontaneous closure in more immature newborns or in those in which PDA is associated with respiratory distress syndrome (RDS), due to the tendency of therapeutic closure in these delicate categories [2].

2.3 Clinical Features

Physiopathology of PDA includes the mechanisms of lung hyperflow, depending on the degree of left-right shunt volume through PDA and resulting in pulmonary congestion, edema and chronic lung function deterioration, and the occurrence of “diastolic steal” which reduces systemic circulation flow and impairs vital organ perfusion, leading to significant effects especially on brain, kidney and bowel [1,2,22].

As a consequence, complications of a prolonged condition of PDA in preterms can include: severe respiratory distress syndrome (RDS), prolonged need for assisted ventilation, pulmonary hemorrhage, necrotizing enterocolitis (NEC), several degrees of renal function damage, intraventricular hemorrhage (IVH), periventricular leukomalacia (PLV), cerebral palsy, bronchopulmonary dysplasia (BDP) or death [1,19,25,30-35].

2.4 Standard (Classical) Treatment

Several strategies are available to achieve PDA closure, in order to prevent the mentioned complications. Up to now, the most reasonable strategy seems to be reserving the treatment only to hsPDA, which determines a more significant hemodynamic lung hyperflow and a higher risk of related complications [1, 7].

The correct definition of hsPDA can be performed according to echocardiographic criteria, taking into account the values of internal diameter of the duct size (generally > 1,5 mm), left atrium/aortic root ratio ($La/Ao \geq 1,4$) and the occurrence of left to right shunt in addition to diastolic reversal of blood flow in aorta [1, 36]. However, the cut-off of the mentioned parameters may show a great variability among different authors and centers, as recently reported [1].

The first-line approach is pharmacological. In fact, although the correct PDA management is still under debate up to now, with different approaches according to the considered Center [2,3], most evidence supports a pharmacological approach in case of hsPDA and ibuprofen results the drug of choice [1,6,7].

However, the available strategies vary from prophylaxis to early or delayed treatment, but prophylactic treatment is no longer recommended due to neonatal exposure to drug toxicity without relevant clinical benefits [19,25,37].

In case of drug contraindication or failure after several cycles, a surgical ligation can be evaluated and eventually performed [30].

Recently, some authors seem to sustain the feasibility of a conservative approach [4,27,28], but the published results are controversial, due to the heterogeneity of diagnostic parameters and the clinical management of these patients among the different hospitals involved in the studies [1].

In every case, some published studies demonstrated a lower rate of pharmacological treatment and/or ligation necessity in a PDA group treated with a conservative approach [38], the lack of difference in terms of BPD or mortality between treated and non treated preterms showing PDA [39] and no differences in severe morbidity incidence (BDP, IVH, PVL, NEC, ROP) among a conservative group weighing ≤ 1500 g [27]. Other authors described, in their retrospective multicentric study, an increasing trend of the conservative PDA approach in 134 Californian Hospitals [40].

Although performed on large cohorts of newborns, these mentioned studies supporting a conservative treatment for PDA present some limitations, such as the heterogeneity in the therapeutic approach and echocardiographic criteria to define hsPDA. Due to these reasons they could result hardly comparable to other trials.

2.4.1 Non steroidal antiinflammatory drugs: mechanism of action

Nowadays, the correct PDA management is still under debate, with different approaches according to the considered Center [2,3]. However, most evidence supports a pharmacological approach in case of hsPDA and ibuprofen results the drug of choice [1,6,7].

Prophylactic treatment is no longer recommended due to neonatal exposure to drug toxicity without relevant clinical benefits [19,25,37].

A condition of hsPDA should be attested through echocardiography, even if considered parameters show a great variability as regard the cut-off among different authors, as recently reported [1].

NSAIDs promote PDA closure preventing the conversion of arachidonic acid into prostaglandins via cyclooxygenase (COX) inhibition, acting on the two existing isoforms: COX-1, which is a constitutive enzyme present in most tissues, and COX-2, mostly inducible (its constitutive presence has been also detected in some tissues, including kidneys, and usually occurs later than COX-1, after glomerular vascularization). The preferential COX-2 selective inhibition showed by some NSAIDs seems to enhance their efficacy and renal safety [3,30,41,42]. As a result, prostaglandin (PG) levels reduction achieve DA muscular wall constriction. Thus, in association with other related events, such as platelet recruitment and activation, obstruction, fibrosis and anatomical ductal closure are promoted [4,9,41,43].

2.4.2 Intravenous indomethacin

Intravenous (iv) indomethacin has been the first nonselective COX inhibitor used for this purpose, presenting a PDA closure success rate of about 70–85% [44,45].

Unfortunately, its high vasoconstrictor power can lead to several side-effects even at low doses (0,2 mg/Kg), such as impairment in renal function including acute or chronic renal failure, oliguria, proteinuria, hyperkalemia, cerebral white matter damage, impairment in cerebral perfusion, NEC, gastro-intestinal perforation and hemorrhage (especially when coadministered with corticosteroids), and platelet dysfunction [3,20,21,46]. Glomerular filtration reduction is usually reversible within 48 hours after suspension, although oliguria can often persist until 2 weeks [21,42].

2.4.3 Intravenous and oral ibuprofen

Subsequently, another NSAID, ibuprofen, has been introduced, showing a success rate in PDA closure comparable with indomethacin [21,41], but lower renal and cerebral side-effects [42,47-51] (**Table 1**).

The reduced nephrotoxic effect is often correlated to a more rapid normalization of serum creatinine after treatment [21]. The lower vasoconstrictor effects and the less severe impairment in renal function and microcirculation observed with ibuprofen seem to be partly determined by a more

pronounced selective effect of indomethacin on COX-1, but also by other mechanisms not already known [52,53].

Ibuprofen can be intravenous (iv) or orally administered, at the therapeutic scheme of 10 mg/Kg/dose on the first day, followed by 5mg/Kg/dose/day on 2^o and 3^o days of therapy, eventually repeatable for 1–3 courses [54].

Despite the observed advantages, ibuprofen use has been associated with several side-effects in addition to nephrotoxicity, such as pulmonary hypertension, hyperbilirubinemia, NEC, intestinal perforation or platelet dysfunction [1,2,22,25], therefore during ibuprofen administration the patient must be strictly evaluated for hepato- and nephrotoxicity occurrence and the therapy must be stopped, or not started at all, if the following contraindications are present: active or recent intracerebral hemorrhage (<48 h), thrombocytopenia (<50,000/mm³), bleeding diathesis (INR > 1.5 and/or hematuria, blood in the stool, tracheal secretions or at the injection site), sepsis, NEC, intestinal perforation, pulmonary hemorrhage, hepatic damage with severe hyperbilirubinemia, renal dysfunction (oliguria <1ml/kg/h also after adequate hydration, serum creatinine >110–140 μ mol, and BUN > 14mmol/l), and hypersensitivity to the medication [1,35,55,56].

2.4.4 Prophylaxis

In prophylaxis, although this practice is no longer used, ibuprofen is not recommended and indomethacin is preferred, due to its effect on the reduction of intraventricular hemorrhage incidence [19,55,57].

2.4.5 New routes and dosage

New regimens for ibuprofen administration have also been evaluated, such as the use of higher doses (20-10-10mg/Kg/dose), which showed an improved closure rate, even if, according to some authors, the potential associated adverse effects must be still accurately investigated [25,55].

The very recent systematic review published by Mitra and colleagues [58] reinforces the possibility to perform hsPDA closure using a higher dose of oral ibuprofen with shorter intervals among the doses (administration of 15-20 mg/Kg followed by 10-7,5 mg/Kg every 12 or 24 hours), reporting some data that demonstrate the association of this regimen to a higher closure rate instead of iv standard dose ibuprofen or indomethacin [58-60] and how this more rapid PDA closure seems associated to a lower rate of NEC [58,61].

In addition, an alternative rectal route of administration has been recently proposed in a trial, where this modality resulted as effective as the oral route in very low birth weight (VLBW) neonates treated for hsPDA [62]. These data suggest the need to perform additional trials to fully understand the whole implications of the available and new proposed therapies.

2.4.6 Surgical ligation

the surgical approach to PDA should be evaluated after the inefficacy of two or more courses of medical treatments, if there are drug contraindications and the patient presents severe consequences of a large hsPDA or need ventilator and oxygen support [21,25,40,63-65].

PDA ligation has been associated with several adverse effects, such as vocal cord dysfunction, impaired neurological outcome, risk of BDP, retinopathy of premature (ROP), chylothorax and diaphragmatic paralysis, bleeding, pneumothorax, cardiorespiratory failure, acute and severe hemodynamic side-effects and worsening in neurodevelopmental outcomes [1,7,18,25,40,41].

According to the published literature, early prophylactic ligation must be avoided [28,54,66].

2.5 Paracetamol as a new approach

Paracetamol is the last drug introduced in PDA management, proposed as a possible alternative because of the potential side-effects of classical NSAIDs [9,12]. Usually, it is administered through i.v or oral route at the standard dose of 15 mg/Kg/dose/6 hours, for 3-7 days [9].

The exact mechanism of action of paracetamol remains uncertain, but probably it acts at the peroxidase segment of the prostaglandin synthetase enzyme to inhibit prostaglandin synthesis and peroxidase is activated at 10-fold lower peroxide concentrations compared to COX [15]. Therefore, paracetamol can work well also in hypoxic conditions, where a COX-inhibitor, such as ibuprofen, results ineffective.

During the administration, it is suitable to monitor treated newborns for eventual occurrence of hepatotoxicity, alimentionation disturbances, abdominal distension and nephrotoxicity too (even if this side-effects has never been observed) [55]. Moreover, several trials are needed to evaluate its real safety and associated long-term outcomes (even up to 18-24 months of postnatal life), especially in terms of neurocognitive impact [1,6,10,11,20,30,41,67].

2.5.1 Oral versus intravenous therapy

Different case series available in the literature explored two different modalities of administration (oral and iv) of paracetamol, given when classical NSAIDs were contraindicated/ineffective or alone as first choice.

Chronologically, the first author that hypothesized a role for paracetamol in the closure of PDA in preterm infants was Cathy Hammerman in 2011. Five preterm newborns (26-29 wks of gestation, 720-1210 body weight), with a hemodynamically significant PDA previously resistant to two courses of ibuprofen or with contraindications to this medication (hyperbilirubinemia, severe thrombocytopenia), were treated with oral paracetamol, 15 mg/kg every 6 hours for at least 2-3 days. In all treated neonates, a complete ductal closure or a significant ductal constriction was achieved within 2 days of treatment [9].

During the period 2013-2014, other 12 case series comprising in total 104 neonates (GA 23-36 wks) explored the effects of enteral [68-74] or iv [12,17,74-77] paracetamol in patients who either failed or who had contraindications to ibuprofen for PDA closure. The most frequently administered dose was 15 mg/kg every 6 hours, but in some situations lower doses (7.5 or 10 mg/kg) were used [76,77]. Paracetamol was mostly administered for 3 days, up to 7 days if ECHO showed patency. Clinical success occurred in 78 of 104 patients (75%), while 26 neonates required surgical ligation.

More recently, other authors published some small case series in order to explore the effects of paracetamol on PDA closure in presence of contraindications or side-effects to ibuprofen.

In a first article, 13 preterm infants (mean GA 29 wks) received iv paracetamol initially at a dose of 15 mg/kg every 6 hours, that was decreased to 10 mg/kg every 8 hours after elevation of transaminases levels observed in a patient. In 10 neonates (76.9%) PDA closed within 4 days [78].

Eleven preterm neonates (GA between 23 and 30.3 wks) were treated with iv paracetamol 15 mg/kg every 6 hours for three days in presence of contraindications to ibuprofen. Successful ductal closure was achieved in 10 out of 11 neonates (90.9%) [79].

In presence of severe thrombocytopenia and other contraindications to the use of ibuprofen, 3 preterm infants were treated with iv paracetamol 15 mg/kg every 6 hours. The first neonate (28-week GA) started treatment on the 14th day of life and PDA closed after 5 doses; the second infant (32-week GA) received paracetamol when a large PDA was diagnosed on the fifth day of life and after 48 hours the ductus closed; the third neonate (31-week GA) started paracetamol on the third day of life and PDA closure was achieved after 48 hours [80].

A study analysed in comparison the efficacy of oral vs iv paracetamol in 18 VLBW infants (GA \leq 30 wks) unresponsive to ibuprofen or where this drug was contraindicated (IVH, oliguria), reporting a higher PDA cumulative closure rate when the drug was administered orally (88% vs 70%) even if the difference was not statistically significant [81].

In 2 other small case series, paracetamol was administered as first-line therapy to favour PDA closure. Some authors investigated the efficacy of oral paracetamol 15 mg/kg every 6 hours in 6 preterm infants (mean GA 28.5 wks). The first dose was given within the first 7 days of life and the treatment duration was 3 days, eventually extended to 6 days (second cycle). Successful closure of PDA was observed in 5/6 neonates (83.3%) [13].

Other authors treated 10 preterm infants (GA 30-36 wks) with oral paracetamol 15 mg/kg every 6 h in their first 10 days of life. Ductal closure was observed in 7/10 neonates (70%) mostly after one cycle of therapy: the success rate was greater in patients weighing more than 1 kg [82].

2.5.2 Early versus late therapy

Apart from these case series, some studies examined the effects of early iv paracetamol treatment given prophylactically with the aim to reduce the incidence of PDA in preterm newborns.

In a first study, 102 neonates, born < 32 wks of gestation and admitted to the NICU of Oulu University Hospital from January 2008 to December 2011, received iv paracetamol (loading dose 20 mg/kg followed by 7.5 mg/kg every 6 hours) within the first 72 hours of life to alleviate pain and discomfort and were studied retrospectively in comparison with a control group comprising 88 neonates, with the aim to evaluate if early paracetamol therapy could have influenced the development of PDA. In the group of neonates treated early with paracetamol, the incidence of PDA was lower compared to control group (14.7% vs 30.7%, $p=0.008$). Surgical ligation was required in three paracetamol-exposed neonates (2.9%) and in seven control infants (8%). Paracetamol treatment was associated with a lower relative risk for PDA [83].

Another study, a controlled double-blinded phase I-II trial, compared iv paracetamol (loading dose 20 mg/kg given prophylactically within 24 h from birth as 15 min-infusion, followed by 7.5 mg/kg every 6 h for 4 days) with placebo in 48 preterm infant with a GA < 31 wks. Ductus closure was observed faster (within 3 days) and in a higher number of patients (19/23 vs 16/25, $p=0.016$) in the paracetamol group. GA influenced the ductal closure, with a better response after 27 wks of gestation [84].

Instead, other authors examined the efficacy of a late therapy with iv paracetamol.

In a retrospective review, iv paracetamol (15 mg/kg every 6 hours for 3-6 days) was given to 36 neonates admitted to two hospital Units in Dublin (Ireland), where a conservative, non-pharmacological approach to PDA is applied. Paracetamol was administered at a median postnatal age of 27 days. An immediate PDA closure was observed in 9 neonates (25%), while there was no response in 4 neonates (11%) all undergoing subsequently surgical ligation. In the other 23 infants (64%), PDA constricted at the end of the treatment leading to a complete closure prior to discharge in all but one patient. In a few number of neonates ibuprofen was previously administered without any effect on PDA closure [85].

The only study that reported the non efficacy of paracetamol in PDA closure was a prospective observational cohort study involving 33 neonates with a GA <28 wks admitted to the Erasmus-Sophia Children's Hospital in Rotterdam (the Netherlands) between December 2012 and September 2014. Iv paracetamol was started at a median postnatal age of 14 days, at the dose of 15 mg/kg every 6 hours for 3-7 days: 13 patients received paracetamol because of existing contraindications to ibuprofen, 8 after an incomplete unsuccessful therapy with ibuprofen, 12 after two cycles of ibuprofen. Ductal closure was achieved in only 6/33 patients (18%) who received paracetamol as first-line therapy [35].

The efficacy of iv paracetamol given as early or late therapy was assessed in a population of 48 preterm infants (GA 23-32 wks) admitted to NICU of University of Padua (Italy) between January 2013 and August 2014. The group treated with paracetamol given early as "first-line" treatment (30/48 patients) was compared with another group where the medication was administered later in case of ibuprofen failure ("rescue" group 18/48 patients). The cumulative efficacy of iv paracetamol (15 mg/kg every 6 hours for 3 days) was confirmed with both treatments: PDA closure rates were

respectively 56.7% and 61.1% after two cycles, 63.3% and 77.8% after three cycles. In total, medical treatment failed in 11 out of 48 neonates (22.9%). GA emerged as an independent predictor of PDA closure in the “first-line” group, with a higher efficacy of treatment in patients ≥ 28 wks of gestation. Instead, clinical risk index score resulted as independent predictor for PDA closure failure in the “rescue” group [56].

2.5.3 Paracetamol versus ibuprofen

Data referred to RCTs where paracetamol was compared to ibuprofen as first-line therapy are relatively limited and shown in **Table 2** [10,14,30,52,86].

A total of 704 preterm newborns have been included: randomly, 361 neonates were treated with paracetamol orally or intravenously while 343 received oral or iv ibuprofen.

One hundred and sixty preterm neonates ($GA \leq 34$ wks), admitted to the Department of Neonatology of the First Hospital of Jilin University (Changchun, China) between May 2012 and March 2013, received either oral paracetamol 15 mg/kg every 6 hours for three days or oral ibuprofen (initial dose of 10 mg/kg followed by 5 mg/kg after 24 and 48 hours). A second cycle of therapy was required in 25% and 31% of cases respectively after paracetamol and ibuprofen treatment. Successful ductal closure was achieved in 65/80 infants treated with paracetamol (81.2%) and in 63/80 patients receiving ibuprofen (78.8%). The mean number of days required to close the ductus was shorter in the paracetamol group (3.22 ± 0.14 vs 3.71 ± 0.16 days) [10].

In the Neonatal Intensive Care Unit of Zekai Tahir Burak Maternity Teaching Hospital of Ankara (Turkey), 90 preterm infants ($GA \leq 30$ wks, postnatal age 48 to 96 hours) were enrolled between February and December 2012 to receive either oral paracetamol 15 mg/kg every 6 hours for three days or oral ibuprofen (initial dose of 10 mg/kg followed by 5 mg/kg after 24 and 48 hours). Ten neonates died before completed treatment. No statistically significant difference has been observed in closure rate after the first course: 72.5% in paracetamol group, 77.5% in ibuprofen group. The reopening rate was higher in the paracetamol group, but not statistically different (24.1% vs 16.1%). Only 2 patients in the paracetamol group and 3 in the ibuprofen group required surgical ligation [14].

A total of 87 preterm newborns ($GA < 37$ wks), admitted to the Neonatal Ward of the Xuzhou Hospital of Medical College of Southeast University (China) between October 2012 and June 2015, were enrolled in the study and randomly received orally either paracetamol (15 mg/kg every 6 hours for three days) or ibuprofen (10 mg/kg as initial dose followed by 5 mg/kg after 24 and 48 hours). The ductal closure rate resulted similar among the two groups: 70.5% with paracetamol and 76.7% with ibuprofen [86].

A randomized clinical trial was performed in the Neonatal Intensive Care Unit of Afzalipour Medical Center (Kerman, Iran) between July and November 2014. Among 160 preterm neonates initially enrolled in the study ($GA < 37$ wks, postnatal age less or equal to 14 days) and randomly assigned at a 1:1 ratio to oral paracetamol (15 mg/kg every 6 h for 3 days) or oral ibuprofen (initial dose 20 mg/kg followed by 10 mg/kg after 24 and 48 hours), 31 patients were excluded or died before completed treatment. After the first course of treatment, PDA completely closed in 82.1% neonates in the paracetamol group compared to 75.8% of the ibuprofen group. Twelve patients receiving oral paracetamol and 15 treated with oral ibuprofen required a second course of therapy, with a ductal closure rate of 50% and 73.3% respectively. In total, closure rates after the two courses of treatment were 91% for paracetamol and 90.3% for ibuprofen [30].

Other authors [52] compared the efficacy and safety of paracetamol (15 mg/Kg iv infusion over 30', followed by 15 mg/Kg/6 h for 3 days), ibuprofen (10 mg/Kg iv infusion followed by 5 mg/Kg/day for 2 days) and indomethacin (0.2 mg/Kg iv infusion over 30', three doses every 12 h) in 300 preterm neonates (mean GA 26 wks, mean BW 1.1 kg, postnatal age < 14 days) with a hemodynamically significant PDA admitted to the Neonatal intensive care Unit of Tanta University Hospital (Egypt). No difference has been observed between the three drugs as regards efficacy in

PDA closure (80% in paracetamol group, 77% in the ibuprofen group, 81% in the indomethacin group). The cumulative closure rate increased after the second treatment cycle (88% in paracetamol group vs 83% ibuprofen and 87% indomethacin) and also the number of neonates undergoing surgical ligation was similar.

Recently, a randomized multicentre controlled study involving 5 Italian NICUs and 110 neonates (25-31 wks of GA) with PDA, exploring the efficacy and safety of iv paracetamol in comparison to iv ibuprofen, has been approved and actually is on course (Clinicaltrials.gov NCT 02422966; Eudract n. 2013-003883-30) [67].

The most recent prospective RCT comparing oral paracetamol and ibuprofen, in 60 preterm newborn showing GA \leq 34 wks, has been performed by El-Farrash et al. [36]. After a diagnosis of hsPDA, they were assigned into two groups and treated with one or two courses of the same drug. Paracetamol and ibuprofen showed a comparable efficacy in ductal closure and in the rate of surgical treatment. In these data, both drugs were well tolerated, without signs of liver and renal toxicity, or complications such as gastrointestinal bleeding, NEC, IVH, BDP. In addition, paracetamol resulted more effective in improving echocardiographic parameters after the second cycle of administration; all these findings, even if reported in a small sample of patients, suggest that paracetamol could represent a valid and safe first-line option in hsPDA treatment [36].

3. Side-effects: focus on nephrotoxicity and hepatotoxicity

3.1 Ibuprofen and nephrotoxicity

Anatomical and functional maturation of kidneys usually occurs in the first phases of life, mainly depending on cardiac output, vascular resistances and blood pressure. Preterm's kidneys immaturity at birth is related to lower GA and BW, especially in terms of glomerular filtration and tubular development [87-89].

For these reasons, preterm's kidney shows a reduced glomerular filtration rate (GFR), which closely depends on a delicate equilibrium between vasoconstriction and vasodilation of renal vessels, and results highly susceptible to endogenous and exogenous stress, especially when occurring in newborns with lower GA and overlap to conditions of hypoxia, hypotension, hypovolemia and/or vasoactive or nephrotoxic drugs [87] or other conditions frequently reported in NICU, such as RDS, sepsis, hyperbilirubinaemia, diselectrolytemia [21], which increase the susceptibility to damage of neonatal kidney. Moreover, the immature renal function also leads to a lower excretory and detoxifying role after drug administration. These mechanisms predispose preterms to renal function impairment, especially Acute Kidney Injury (AKI) [87,90], frequently occurring in NICU. It has been demonstrated that AKI contributes to an immediate morbidity and mortality and/or long-term increase in renal susceptibility in such critical populations [1,91-95].

At birth, serum creatinine depends on maternal values and does not represent an instrument to evaluate renal function [87,96-98]. Subsequently, many authors demonstrated that creatinine values increase after 36-96 hours of life, directly depending on GA (a higher increase is showed at lower GA, especially in neonates with GA < 27 wks), and then gradually decrease [21,96]. Such transient increase in serum creatinine results higher in preterm newborns if compared to full term newborns and also shows a slower normalization in such population, due to a delay in glomerular function progression [96,99,100] and to a greater creatinine reabsorption rate by immature tubular structures [96,101].

The authors agree that a role can be also played by the drug-related nephrotoxicity (especially induced by antibiotics and NSIADs administration in these categories of newborns), which could result a confounding factor in the collection of these data and even an adjunctive mechanism impairing more vulnerable glomerules. Therefore, another mechanism probably involved in this damage may be related to the high number of drugs administered to preterm newborns [87], so that these trends in creatinine values must be considered during evaluation of drug nephrotoxicity.

However, renal toxicity can be more likely attributed to drugs if occurring few hours after their administration and results generally reversible after the suspension [3].

At birth, serum creatinine depends on maternal values and do not represent an instrument to evaluate renal function [87,96-98]. Subsequently, creatinine values increase after 36-96 hours of life and then gradually decrease [21,96].

Gallini and other authors demonstrated that in neonates with lower GA (especially < 27 wks), there is a higher increase in serum creatinine (compared to full term newborns) which also shows a slower decrease, due to a delay in glomerular function progression [96,99,100] and to a greater creatinine reabsorption rate by immature tubular structures [96,101]. Another mechanism probably involved in this damage may be related to the high number of drugs administered to preterm newborns [87]. In preterms, these trends in creatinine values must be considered during evaluation of drug nephrotoxicity.

It has been widely demonstrated as both maternal NSAIDs assumption during pregnancy [42,87,102-104] and ibuprofen administration to newborns should be relevant determinants of renal function impairment, underlying the multifactorial origin of renal damage in preterms [87,103]. NSAIDs administration during pregnancy is also associated to the constriction of DA, with negative consequences [42].

It is well known that early postnatal exposure to nephrotoxic drugs can interfere with nephron generation and tubular maturation, even if the exact correlation with long-term consequences and renal function impairments is not exactly known. Some authors correlate these events to cases of chronic kidney damage (CKD) [91,92,105,106], suggesting the need of a strict monitoring after drug administration and long-term follow up in newborns who developed AKI [91,107].

Newborns show high PG circulating levels, whose action consists in vasodilation of afferent arteriolar vessels, protection of renal blood flow, regulation of glomerular filtration rate (including water and electrolytes homeostasis) and action against postnatal systemic vasoconstriction and resistances increase. For these reasons, PG contrast catecholamines, angiotensin II, vasopressin and endothelin vasoconstrictor effect. PG receptors can be found along the nephron and interact with PGD₂, PGE₂, PGF₂ α , PGI₂ and TXA₂ [42].

NSAIDs-induced PG synthesis reduction, whose role results highly relevant for kidney maturation in the first phases of life and is responsible for the impairment of renal perfusion and glomerular filtration, constitutes the substrate for nephrotoxicity related to this drugs administration, frequently leading to reversible oliguria [3,21,91,102,108,109] or even chronic renal failure, clinically relevant proteinuria, acute interstitial nephritis, fluid metabolism alterations and hyperkalemia [42]. In addition, PG also result involved in kidney pre- and post-natal maturation processes, especially in preterms, therefore this category results highly vulnerable to PG reduction. This is also evidenced by increased levels of urinary PGE₂ and PGI₂ (or prostacyclin) compared with full-term neonates or after a month of postnatal life [3,108,109].

Urinary PGE₂ has also been found to be a biomarker of nephrotoxicity, decreasing after PDA treatment with ibuprofen. This reduction correlated with the severity of side-effects [3,108].

Low levels of urinary PGE₂ allow to detect neonates more susceptible to nephrotoxic damage after ibuprofen administration [3], suggesting to avoid ibuprofen administration in those newborns showing PGE₂ urinary levels lower than 35 pg/ml. Moreover, the authors affirm that in neonates with rapid decrease in PGE₂ urinary levels during treatment, ibuprofen should be interrupted and neonates with PGE₂ levels lower than 5 pg/ml during or after ibuprofen administration result highly susceptible to significant renal injury [3].

Other markers of nephrotoxicity could be represented by urinary isoprostanes, whose reduction after ibuprofen administration seems to suggest a protective role of this drug against oxidative stress [3,110]. Cystatin-C (Cys-C) and Neutrophil Gelatinase-Associated Lipocalin (NGAL), whose excretion seems to increase during AKI [111] even if more trials are needed to demonstrate their role in a potential renal damage after a few days of NSAIDs treatment.

Up to now, it is not possible to define the exact rate of neonatal nephrotoxic drug associated AKI and its contribution on the development of CKD, due to the lack of studies on a great number of patients but also because of the absence of a systematic follow-up after neonatal AKI [91]. In a randomized clinical trial, after rectal ibuprofen administration an increase in Cys-C serum levels has been reported, suggesting nephrotoxicity [62].

Moreover, although some authors allow the use of high doses of ibuprofen to achieve ductal closure [112], other studies recommend the administration of low doses because of the detection of a higher nephrotoxicity, through a more relevant increase in Cys-C levels and also due to its inhibitory effect on hepatic glucuronidation of bilirubin and its high albumin binding affinity, which may potentially increase bilirubin encephalopathy risk [1,113-115].

In addition, a higher nephrotoxicity related to high dose ibuprofen regimen has been evidenced through a more relevant increase in Cystatin-C levels [25,115].

Another evidence of a promising role of Cys-C as AKI marker has been reported by Gokmen et al. [45], evaluating its increase after oral or iv ibuprofen administration. Firstly, patients receiving oral ibuprofen showed an initial lower Cys-C concentration (mean 1450 ng/mL) which increased 10% to a mean of 1600 ng/mL; this represents a statistically significant increase, however not inducing a clinically significant effect. Secondly, patients receiving iv ibuprofen showed an initial higher Cys-C concentration (mean 1570 ng/mL) presenting also the same mean (1600 ng/mL) as the oral ibuprofen receiving after treatment (therefore not showing an increased level of Cys-C after the assumption of ibuprofen). These represent small and clinically insignificant change with no real indication of AKI, even if the possible involvement of Cys-C in monitoring renal function should be deeper investigated [45].

A metabolomic olistic approach seems able to predict at birth, through a non invasive collected sample, the future condition of PDA. H-NMR analysis of the first urine sample, in preliminary data reported by some authors [116,117], allowed to define also differences in the individual response to ibuprofen treatment, finding different metabolic profiles between patients responding to therapy compared with non-responders neonates. These findings, evaluated on small groups of preterms, seem to be very promising and should be further investigated with more trials.

The same ibuprofen dose is actually administered to newborns of different GA and postnatal ages: this could result a pharmacokinetic and pharmacodynamic paradox. Ibuprofen metabolism is determined by several factors, for example, by the presence of two different enantiomers (S- and R-ibuprofen with half-lives of 25 and 10 hours, resp.) and by several genetic polymorphisms that may influence clinical and side-effects. Individuals carrying such polymorphisms can result extensive or poor metabolizers [22].

Genetic variants of cytochrome P450 isoenzymes, such as CYP2C8 and CYP2C9, can improve enzyme activity and modify NSAIDs metabolism. For example, individuals carrying CYP2C8*3 (rs11572080; rs10509681), CYP2C9*2 (rs1799853), or CYP2C9*3 (rs1057910) polymorphisms result more susceptible to gastrointestinal bleeding after NSAIDs administration [118].

Durrmeyer et al. did not find different responses in preterms showing CYP2C8 or 2C9 after ibuprofen administration for hsPDA. However, in this study a higher GA and non Caucasian ethnicity could have influenced drug response [119].

P450 polymorphisms have also been found to influence the pharmacokinetics of S-ibuprofen and R-ibuprofen, through CYP2C9*2 and CYP2C9*3 genetic variants [120]. In addition, individuals carrying CYP2C8*3, CYP2C9*2, and CYP2C9*3 alleles showed a reduced enantiomers metabolism [121] and fewer side-effects in individuals showing CYP2C8*3 variants, due to a higher clearance of R-ibuprofen [122,123].

The possible role of these genetic determinants for ibuprofen responses should be deeply investigated and fully clarified through several trials.

3.2 Paracetamol and hepatotoxicity

Paracetamol is a safe drug at appropriate doses and the potential hepatotoxicity is closely linked to its metabolism.

In the adult, the majority of paracetamol is conjugated with glucuronic acid and to a lesser extent with sulphate or cysteine [124]. Moreover, a fraction ranging from 5% to 15% is oxidized by some cytochrome P450 isoenzymes resulting in the formation of highly reactive compound, N-acetyl-p-benzoquinoneimine (NAPQI), toxic for hepatic cells [125]. At therapeutic doses, glutathione quickly combines with this intermediate and the complex is then converted to non-toxic cysteine or mercaptate conjugates, eliminated in the urine [126]. When maximum rates of glucuronidation and sulfation are reached and the availability of glutathione is insufficient to metabolize NAPQI, the free NAPQI binds covalently to hepatic proteins of the cysteine group triggering hepatotoxicity and cell death [127].

In both preterm and **term** neonates, sulphate conjugation is the dominant metabolic pathway (glucuronide/sulphate ratios range from 0.12 in preterm neonates of 28-32 wks to 0.28 in those at 32-36 wks postconception and to 0.34 ± 0.08 in term neonates compared to 1.8 ± 0.32 in adults) [126,128], while the activity of CYP2E1, the major enzyme producing NAPQI, is not quantified, but is thought to be reduced [129]. These differences in the metabolic pathways, together with an increased ability to synthesize glutathione [130] partially protect neonates from paracetamol hepatotoxicity in an overdose situation. Moreover, a specific antidote, N-acetyl-cysteine, is available and serves as a glutathione precursor or substitute [131].

Serious hepatotoxicity or death after acute paracetamol overdose has rarely been reported in neonates [132]. Usually, reported cases of hepatotoxicity in neonates derive from transplacentally-acquired paracetamol, in some situations normalized after transfusions [133,134] or N-acetyl-cysteine administration [135-141] but sometimes leading to fetal death [137,142].

Other cases reported in the literature are due to therapeutic errors following parenteral administration of paracetamol as analgesic [143-146].

Nephrotoxicity and hepatotoxicity can be seen together after paracetamol overdose [131]. However, renal impairment after acute paracetamol overdose may also occur in the absence of hepatotoxicity [147,148] and has been attributed to the local formation of NAPQI that causes tubular necrosis [149], although other mechanisms have been suggested, including a role of prostaglandin synthetase and N-deacetylase enzymes [150].

The safety of using paracetamol for PDA closure at doses twice the standard recommended doses in preterm newborns <10 days of life (7.5 mg/kg every 6 h) may arouse concern, since some authors [151,152] reported hepatotoxicity in term neonates after three days of excessive paracetamol intake. In our analysis of the literature, data from the examined case series and uncontrolled trials confirm a good safety profile for paracetamol used at the dose of 15 mg/kg every 6 h for 3-7 days to close PDA in preterm neonates, at least in the short term period, since no severe adverse events have been reported. In particular, as shown in **Table 2** no signs of hepatotoxicity and no significant change in transaminases serum levels have been observed in RCTs including 361 patients treated with paracetamol [10,14,30,52,86], being the most of available data focused on the aspect of the efficacy of the medication. Only a transient increase in liver enzymes, correlated to high doses of the medication, has been observed in a small group of 7 neonates (**Table 3**) [72,75,76,78,80]. In these cases, drug withdrawal of the medication, without any treatment with N-acetyl-cysteine, was sufficient to normalize transaminases.

In detail, among the case series examined elevations in liver enzymes have been reported by some authors.

Alan et al. [75] reported elevated liver transaminases in two out of three preterm neonates (GA 26 and 33 wks) treated with iv paracetamol (15 mg/kg every 6 hours) for PDA.

Other authors [72] showed no elevation in AST or ALT enzymes and reported only gamma-glutamyl transferase levels mildly and transiently elevated in 3/7 preterm infants (GA 26-30 wks) treated with oral paracetamol 15 mg/kg every 6 hours for 3 days (160, 208, 244 U/L respectively).

Among 7 neonates treated with iv paracetamol for PDA, one preterm newborn (GA 29 wks, postnatal age 3 days) after the first 4 doses presented a transient significant elevation in transaminase levels compared to pretreatment values (AST 43 vs 260 U/L, ALT 11 vs 180 U/L). Treatment was stopped and transaminase levels decreased to normal values during the following five days without any treatment with N-acetyl-cysteine [76]. In another work, an extension of the previous paper, the same authors reported that the initial dose of iv paracetamol (15 mg/kg every 6 hours) given to 13 newborns (comprised the 7 neonates previously cited) was reduced to 10 mg/kg every 8 hours when a neonate developed hepatotoxicity. Subsequently, treated patients did not exhibit liver enzyme abnormalities [78].

Some authors reported the results of using iv paracetamol (15 mg/kg every 6 hours) to treat PDA in 3 preterm infants, underlying a transient hypertransaminasemia (GOT 2624 U/L, GPT 365 U/L) observed in one preterm infant (GA 31 wks) that normalized within 72 hours [80].

In all RCTs examined, paracetamol showed less side-effects on renal function (urine output, serum creatinine and BUN), in some cases statistically significant, compared to ibuprofen.[10,14,30,52,86].

4. Long-term safety of paracetamol

As regards safety, the available information is limited to a short period and reveals a good tolerability of paracetamol used in preterm neonates at doses higher than those licensed.

Instead, long-term effects still require a deep evaluation. In particular, a possible correlation between prenatal exposure to paracetamol (particularly with a longer duration use) and risk of ADHD [153,154], autism [154,155] and asthma [156] development has been hypothesized and needs a deep evaluation through specific large randomized trials. Therefore, a cautious approach has to be suggested, given the non optimal quality of the studies and the limited number of neonates treated.

It also would result very important to define the exact impact of PDA pharmacological treatment on the patients' neurocognitive development; in this perspective, there are few studies evaluating a long-term follow-up after paracetamol administration and this could still result a limitation to consider this drug a first-line therapy. The recent data of Oncel et al. [157] would suggest that a follow-up at 18 and 24 months evaluating ex preterm infants (≤ 30 wks) previously treated with paracetamol to achieve ductal closure would not present significant differences in their neurological outcomes if compared with patients treated with ibuprofen [157].

However these data should be confirmed on large samples of patients.

5. Conclusions

Paracetamol effectiveness and safety in PDA treatment of preterm newborns have been pointed out by several authors within the last years, so that this drug seems to represent a very interesting and highly promising alternative to the first line therapy in such patients showing contraindications to ibuprofen, which is currently the drug of choice and shows an effectiveness ranging about 8% and 85%.

Paracetamol seems to have similar rates of successful PDA closure; however, many authors agree on the necessity to perform more studies, such as multicenter prospective RCTs evaluating ibuprofen vs paracetamol, to fully define short- and long-term consequences of paracetamol before to propose it as the first-line therapy.

As specified in a systematic review comprising studies published between 2013 and 2014 (2 RCT and 14 uncontrolled studies) [158] and also by other authors [1], effectiveness of paracetamol for the treatment of PDA in preterm neonates results comparable with that of ibuprofen after three to seven days of treatment. However, our analysis of data suggests that the effectiveness of paracetamol may vary depending on some clinical characteristics of the neonates (a significant

improvement in efficacy was observed in the first days of life and in subjects > 28 wks) and the modalities of drug administration (oral route resulted more efficacious) [150, 151].

Other considerations regard the dose. The lowest effective dose of paracetamol for PDA closure has yet to be established: some authors suggest that probably half of the dose used for PDA closure could be equally effective [76-78,83].

If the results about paracetamol efficacy and safety will be confirmed, even regarding long-term outcomes, it is possible that in the future it may become the drug of choice for medical management of PDA.

6. Expert Opinion

In this paper, we provide a complete description of PDA-related issues in the vulnerable category of preterm newborns and update the actual knowledge about the available strategies of treatment.

An accurate analysis of the published literature allowed the authors of this review to analyze in detail the mechanisms that underlie ibuprofen-associated nephrotoxicity and the potential hepatotoxicity induced by paracetamol, which represents a valid and promising alternative to classic NSAIDs as emerged by many studies and in the future could represent the first-line therapy for PDA.

However, paracetamol data derive mostly from uncontrolled studies and from only 5 RCTs of non optimal quality which may introduce a potential bias. Therefore, due to the lack of well designed large RCTs about proper paracetamol dosing or long-term safety, important data still have to be provided before safely changing the actual standard care for PDA into paracetamol.

The ideal study would be a multicenter prospective randomized controlled trial comparing ibuprofen and paracetamol, investigating both the efficacy but also the potential short- and long-term side effects.

Since many years, our research group has been interested in the field of PDA treatment, NSAID-associated nephrotoxicity and paracetamol-safety evaluation. Therefore, in our opinion and to the best of our knowledge, the dark side of PDA treatment and the weakness in the management of this disease is represented by the impossibility to define, up to now, the optimal strategy of management, despite several years of studies, research and worldwide clinical practice, due to the absence of a univocal standardized approach in terms of diagnosis, timing and modality of intervention or no intervention.

Although some evidence results in agreement with a conservative approach, this mostly derives from poorly standardized multicentric studies, so that, according to us, it is very hazardous to decide for not treatment routinely.

On the other side, no one among the available pharmacological approaches can be defined as absolutely safe and a close clinical observation during drug administration must be recommended, to detect precociously possible signs of toxicity. PDA surgical ligation itself frequently shows a very negative impact on newborn's health and should be considered as a last instance intervention.

In the near future, it is desirable that "omics" technologies, such as metabolomics, may become routinely and easily used to clarify and predict at birth the possibility of a successive PDA persistence.

As discussed above, preliminary data on small group of preterms would recognize to metabolomics the ability to provide determinant information in a non invasive way, i.e. through the analysis of an urine sample. As a consequence, some specific and individualized mediators could be detected and provide information concerning both PDA persistence and also drug's response. If these correlations will be confirmed, such data could aid the therapeutic management, to avoid the exposure to drug-related toxicity for a great number of newborns who would undergo spontaneous closure. Moreover, this innovative technique could also provide additional information and monitoring of therapy response of each potentially treated subject [1,116,117].

The success of each pharmacotherapy and the biggest challenge to achieve would be the possibility to administer to each patient the exact individualized and efficacious dose, showing the highest safety and less toxicity as possible. In this personalized, patient-based, tailored medicine, pharmacokinetic and metabolomics are a very promising and interesting field of research, due to the prominent influence of each neonate's biochemical state on the great variety of individual differences.

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Table 1 – Ibuprofen treatment of PDA: what is already known.

	Ibuprofen
Advantages	<ul style="list-style-type: none">- Efficacy in PDA closure (70-85%)- Lower nephrotoxicity than indomethacin
Disadvantages	<ul style="list-style-type: none">- Toxicity- Contraindications: active or recent intracerebral hemorrhage (<48 h), thrombocytopenia (<50,000/mm³), bleeding diathesis (meaning INR > 1.5 and/or hematuria, blood in the stool, tracheal secretions or at the injection site), sepsis, NEC, intestinal perforation, pulmonary hemorrhage, hepatic damage with severe hyperbilirubinemia, renal dysfunction (oliguria <1ml/kg/h also after adequate hydration, serum creatinine >110–140 µmol, and BUN> 14mmol/l), hypersensitivity to ibuprofen
Dose	<ul style="list-style-type: none">- 10 mg/Kg/dose/day followed by 5 mg/Kg/dose/day on 2° and 3° days of therapy
Administration route Number of admitted courses	<ul style="list-style-type: none">- Intravenous or oral administration- 1-3 courses

Table 2 – Efficacy and safety of paracetamol, in comparison with ibuprofen, in preterm neonates with PDA (first-line therapy): results from RCTs. PARA = paracetamol; IBU = ibuprofen; INDO = indomethacin; wks = weeks.

Reference	Country	N. patients (G.A.)	Dosage (mg/kg)	Duration	Route of administration	Outcome
Dang et al 2013 ^[10]	China	160 (<34 wks)	PARA: 15 every 6 h IBU: 10-5-5 every 24 h	3 days (two course regimen)	Oral	Cumulative closure rate: 81.2% (PARA), 78.8% (IBU) No hepatotoxicity
Oncel et al 2014 ^[14]	Turkey	90 (<30 wks)	PARA: 15 every 6 h IBU: 10-5-5 every 24 h	3 days (two course regimen)	Oral	Closure rate (1st course): 72.5% (PARA), 77.5% (IBU) No hepatotoxicity
Yang et al 2016 ^[86]	China	87 (<37 wks)	PARA: 15 every 6 h IBU: 10-5-5 every 24 h	3 days	Oral	Closure rate: 70.5% (PARA), 76.7% (IBU) No hepatotoxicity
Bagheri et al 2016 ^[30]	Iran	129 (<37 wks)	PARA: 15 every 6 h IBU: 20-10-10 every 24 h	3 days (two course regimen)	Oral	Closure rate (1st course): 82.1% (PARA), 75.8% (IBU) No hepatotoxicity
El-Mashad et al 2017 ^[52]	Egypt	300 (<28 wks)	PARA: 15 every 6 h IBU: 10-5-5 every 24 h INDO: 0.2 every 12 h	3 days (two course regimen)	IV	Cumulative closure rate: 88% (PARA), 83% (IBU), 87% INDO No hepatotoxicity

Table 3 – Case series reporting transient elevation in liver enzymes after paracetamol administration in 7 neonates with PDA.

Reference	N° patients studied	Gestational age (weeks)	N° patients presenting alterations in liver enzymes	Outcome
Alan et al 2013 ^[75]	3	26-33	2	Recovery
Tekgündüz et al 2013 ^[76]	7	28-31	1*	Recovery
Kessel et al 2014 ^[72]	7	26-30	3	Recovery
Tekgündüz et al 2015* ^[78]	13	24-31	1*	Recovery
Tofè-Valera et al 2016 ^[80]	3	≤32	1	Recovery

* This study includes data previously reported by the same authors in 2013, therefore the neonate presenting alterations in liver enzymes and cited in both studies is the same