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The Risk of Renal Injury in Infants Associated with Ibuprofen Use: A Systematic Review

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ABSTRACT

Background: More recently ibuprofen, was used for the indication of the patency of ductus arteriosus closure in preterm infants; this drug is associated similar side effects include cerebral, renal, and mesenteric circulation.

Methods: An electronic search was carried out using search terms such as "renal failure", "kidney failure", "renal injury", ibuprofen, "side effects", "adverse effect", complications. The search in MEDLINE and EMBASE through PubMed search engine resulted in 31 articles. These articles were screened for eligibility criteria included studies aimed to assess renal injury caused by ibuprofen use in infants.

Results: After exclusion of irrelevant duplicated and review studies, 12 studies were included in this review. Eight studies were randomized control, 3 retrospective evaluation and 1 retrospective cohort study. the effect of the treatment on the renal function there are two outcomes reported either reduction in serum creatinine or incidence of acute renal failure. Incidence of acute renal failure reported in 4 studies.

Conclusion: Although renal failure was more common in infants receiving Indomethacin compared to Ibuprofen, oral Ibuprofen was less toxic to the kidneys than intravenous and the serum creatinine levels after treatment did not differ, this is not significant.

Keywords: Ibuprofen, Kidney, Failure, Infants, Creatinine

INTRODUCTION

Ibuprofen is an over-the-counter non-steroidal anti-inflammatory drug (NSAID) most commonly used to treat pain and fever in children [(1)]. Like other NSAIDs, ibuprofen cause acute kidney injury (AKI) by decreasing renal plasma flow through its inhibition of prostaglandin synthesis, especially in hypovolemic patients. NSAIDs may also induce kidney damage by triggering acute interstitial nephritis (AIN) [(2)].

The placenta and the patency of the ductus arteriosus (PDA) determine normal fetal circulation. After separation of the placenta and initiation of breathing following birth, the closure of the ductus starts and circulation changes promptly [(3)]. However, in about a thirty percent of low birth weight ((LBW) < 2500 g) infants the PDA stays open, especially during first days of life. In preterm infants, the PDA often fails to close. The haemodynamic instability caused by the left to right shunt and associated run off has been shown to cause renal or gastrointestinal effects including spontaneous perforation and necrotizing enterocolitis (NEC), chronic lung disease and, if not managed, may lead to death. The presence of a PDA is associated with reduced middle cerebral artery blood flow velocity [(4)].

The surgical closure of the symptomatic PDA reduces duration of mechanical ventilation, improves haemodynamics and improves lung compliance. However, medical treatment is still considered the treatment of choice in the majority of cases because of the risks related to the surgery. In a recent large Canadian cohort (n = 3779) of very low birth weight (VLBW < 1500 g) infants, 28% required treatment for a PDA; 75% were treated with indomethacin alone, 8% with surgical ligation alone, and 17% required both indomethacin and surgical ligation. Infants with lower birth weight were more likely to be treated surgically [(5)].

Prostaglandins play a significant role in keeping the ductus arteriosus patent. PDA-related morbidity and mortality have been shown to be reduced with the use of indomethacin, which acts as an inhibitor of prostaglandin forming cyclo-oxygenase enzymes [(6)]. However, indomethacin use has been associated with transient or permanent derangement of renal function, NEC, gastrointestinal hemorrhage or perforation, alteration of platelet function and impairment of cerebral blood flow/cerebral blood flow velocity [(7)]. These negative effects of indomethacin are possibly related to mechanisms other than inhibition of prostaglandin synthesis. This review aimed to obtain the scientific evidence about the presence or absence of renal injury associated with use of ibuprofen in infants.

METHODS

An electronic search was carried out using search terms such as "renal failure", "kidney failure", "renal injury", ibuprofen, "side effects", "adverse effect", complications.. The data were collected for items such demographic characteristics of patients, sample

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size, condition for which ibuprofen was taken with dose and regimen, presence of other chronic diseases, other NSAIDs taken by the patients at the same period, and the extent of injury to kidney (reduced renal functions or acute or chronic renal failure). The data were extracted from included studies to the data extraction forms which designed specifically for this review.

RESULTS

The search in MEDLINE and EMBASE through PubMed search engine resulted in 31 articles. These articles were screened for eligibility criteria included studies aimed to assess renal injury caused by ibuprofen use in infants. After exclusion of irrelevant duplicated and review studies, 12 studies were included in this review. We included 12 studies enrolling 1714 infants. Eight studies were randomized control, 3 retrospective evaluation and 1 retrospective cohort study conducted. Eight studies were randomized control, 3 retrospective evaluation and 1 retrospective cohort study. the effect of the treatment on the renal function there are two outcomes reported either reduction in serum creatinine or incidence of acute renal failure. Incidence of acute renal failure reported in 4 studies.

Table (1): The findings of included studies assessed renal injury caused by ibuprofen use in infants

Study	Sample size	Age of patients	Dose and regime	Other NSAIDs taken	Injury to kidney	Conclusion
(8)	124 received indomethacin and 70 received ibuprofen	Preterm infants (32 weeks or less)	3 doses of indomethacin at 12-hour intervals and the dose varied by age (< 48 hours of life, 0.2 mg/kg, 0.1 mg/kg, and 0.1 mg/kg)	Indomethacin	Acute renal dysfunction Indomethacin group 16.6% Ibuprofen group 14.2%	Ibuprofen is as effective as indomethacin in the treatment of symptomatic PDA in preterm infants.
(9)	78 neonates, immature (n=49) mature (n =29)	Mean ± S.D. in days In IV-INDO group =217 ± 23.5, in PI IBU group= 224 ± 28.1	Iv indomethacin 48 h after birth, 0.2 mg/kg mg/kg dose at 0.1 to 24 h intervals of	Indomethacin	Serum creatinine values were lowered in mature infant treated with ibuprofen (p = 0.032).	Adverse effects of oral ibuprofen were less severe than intravenous indomethacin.
(10)	732	Infants	Not-reported	Indomethacin	Renal Failure Indomethacin 10.8% Ibuprofen 4.6%	Renal failure was more common in infants receiving INDO compared to IBU
(11)	n=36 19 ibuprofen group and 17 controls	Weeks 28> and/or birth weight of <1,000 g	The intervention group received oral ibuprofen 10 mg/kg within 12–24 h after birth followed by 5 mg/kg at 24 and 48 h.	Not reported	In the intervention group two infants developed acute kidney failure 10%	PDA was observed in five (26 %) infants in the intervention group and ten (58 %) infants in the control group (p00.09).
(12)	100	Mean GA was 30.63.4 weeks	The first dose of IBU (10 mg/kg) is administered via nasogastric tube. Afterwards, two additional doses of OIBU of 5 mg/kg are given at 24-hour intervals	Not reported	Impairment of renal function (n=1) 1%	Clinically non-significant impairment of renal function
(13)	21	35 weeks OR less	Group I received 3 doses of IV indomethacin 0.2 mg/kg at	Indomethacin	Reduction in serum creatinine in ibuprofen group	Oral ibuprofen was less toxic to the kidneys and compatible with the GI tracts of our

			12-hour intervals, while intervention group received three daily doses of oral ibuprofen (20 mg/mL syrup)			population
(14)	102	Age 32 weeks or less, birth weight 1500 g	Intravenous or oral ibuprofen at an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 hours	Not-reported	The serum creatinine levels after treatment did not differ significantly between the groups	No significant renal impairment
(15)	70 infants	<29weeks	IV ibuprofen n (10-5-5mg/kg/day; n = 35). And high-dose intravenous regimen (20-10-10mg/kg/day; n = 35	Not-reported	Serum creatinine in standard dose= 0.94 ± 0.41, and in high dose= 1.20 ± 0.55	Renal function was similar in the two groups, as demonstrated by similar mean values of serum creatinine and similar urine output and rates of occurrence of serum creatinine levels and oliguria. >1.5mg/dl
(16)	64	< 32 weeks; birth weight < 1500 g; postnatal age between 48 and 96 hours	A dose of 10 mg/kg of either oral (group O) or intravenous (group I) ibuprofen.	Not-reported	No significant differences in serum creatinine between intervention and control groups	The adverse effects were fewer with oral ibuprofen in comparison to the intravenous route, but the differences were not statistically significant
(17)	36	30.9-31.5 weeks	3 oral doses of indomethacin (0.2mg／kg, at an interval of 24 hrs) or ibuprofen (at dose of 10me／kg, Followed at an interval of 24 hrs by two doses of 5m (g/kg)	Indomethacin	Serum creatinine was in ibuprofen group= 0.85±0.33 before and 1.02±0.38 after treatment	There were no significant differences in renal injury between studied groups
(18)	232	Gestational age 23–34 weeks	3 doses IV Indomethacin (0.2 mg/kg, at 12 h intervals) or ibuprofen (a first 10 mg/kg dose followed by two doses of 5 mg/kg at 24 h intervals)	Indomethacin	Patients treated with INDO showed a significant increase in serum creatinine (89±24 versus 82±20 mmol/l, *P*=0.03)	ibuprofen has fewer effects on renal function in terms of urine output and fluid retention, with much the same efficacy and safety in closing patent ductus arteriosus in preterm infants with respiratory distress syndrome
(19)	119 infants	Gestational age ⩽28 weeks	Either indometacin (0.2 mg/kg) or ibuprofen (10 mg/kg), starting at <24 hours of life, followed by half these first doses within 48 hours at 24-hour intervals if indicated by echocardiographic PDA flow pattern.	Indomethacin	Although not significantly different, more infants (9/59 (15.3%)) treated with indomethacin tended to develop oliguria (<1 ml/kg/h) more than ibuprofen group	Ibuprofen is as effective as indomethacin for the early-targeted PDA treatment in extremely premature infants, without increasing the incidence of complications

DISCUSSION

The infants included in these studies were preterm ranged from 23- 38.5 gestational weeks with birth weight of 1000-1500 g with patent ductus arteriosus. Regarding the treatment, either by Ibuprofen or Indomethacin. Six studies compared Indomethacin with Ibuprofen, 3 of them compared oral Indomethacin to oral Ibuprofen [10, 17, 19], the other 3 studied compared intravenous Indomethacin with intravenous Ibuprofen [8, 9, 18]. Two studies compared between intravenous Ibuprofen and oral Ibuprofen [14, 16].

One study compared standard dose to a high dose of Ibuprofen [15].One examined the effect of repeated doses of oral Ibuprofen[12]. Two studies examined the effect of oral Ibuprofen [11, 13]. Concerning the dose, all the infants receive either 3 doses of intravenous or oral Ibuprofen at an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 hours or three doses of IV Indomethacin 0.2 mg/kg at12-hour intervals, except in a study of **Dani *et al***.[15] where high-dose intravenous regimen (20-10-10mg/kg/day) was adminstred.

Regarding the main outcome, the effect of the treatment on the renal function there are two outcomes reported either reduction in serum creatinine or incidence of acute renal failure. Incidence of acute renal failure reported in 4 studies [10] where Indomethacin group was 10.8% compared to 4.6% in Ibuprofen group, while Indomethacin group was 16.6% versus 14.2% in Ibuprofen group in study of [8]. Incidence of renal failure in the intervention group who were received Ibuprofen two infants developed acute renal failure (10%) in a study conducted by **Kanmaz *et al***. [11], renal failure occurred in 1% as found by **Olgun *et al*.[12]**.

Serum creatinine values were lowered in mature infant treated with ibuprofen (P= 0.032 [9], serum creatinine was 1.2 mg/dL in Indomethacin group versus 0.6 mg/dL in the Ibuprofen group [13]. Serum creatinine before oral Ibuprofen was 0.63 ± 0.23, after 0.53 ± 0.25 compared to before IV Ibuprofen 0.8 ± 0.3 after 0.86 ± 0.4 mg/dL[14]. Standard dose serum creatinine was 0.94 ± 0.41compared to high dose 1.20 ± 0.55 mg/dL [15]. The change in creatinine concentrations in oral Ibuprofen group versus IV Ibuprofen group was 5.7 ± 1.2 mg/dL versus 10.9 ± 1.2 mg/dL [16], while serum creatinine by Ibuprofen was 0.85±0.33 versus 1.02±0.38 mg/dL in Indomethacin [17]. Patients treated with Indomethacin showed a significant increase in serum creatinine (89±24 versus 82±20 mmol/l) in Ibuprofen [18] and finally (15.3%) of infants treated with Indomethacin tended to develop oliguria (<1 ml/kg/h) than those treated with ibuprofen (6.7%) in [19].

CONCLUSION

Although renal failure was more common in infants receiving Indomethacin compared to Ibuprofen, oral Ibuprofen was less toxic to the kidneys than intravenous and the serum creatinine levels after treatment did not differ, this is not significant.

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