Evaluation of the safety of NSAIDs in ELBW infants: a retrospective cohort study

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Background

- Extremely low birth weight (ELBW) infants are at risk of complications from underdeveloped organ systems
- Intraventricular hemorrhage (IVH) is a common ELBW morbidity and prophylaxis with indomethacin has been shown to decrease frequency of severe IVH
- ELBW infants are at increased risk of symptomatic patent ductus arteriosus (PDA) which is treated with non-steroidal anti-inflammatory drugs (NSAIDs), indomethacin and ibuprofen
- Some ELBW infants receive indomethacin to prevent severe IVH and additional NSAID therapy for treatment of symptomatic PDA
- In ELBW infants, NSAIDs have been associated with increased risk of adverse drug events (ADEs) including spontaneous intestinal perforation, necrotizing enterocolitis (NEC), acute kidney injury (AKI), and bleeding
- Studies evaluating the safety of NSAIDs for IVH prophylaxis and PDA are limited to one treatment course

Objectives

- Describe and compare the rate of ADEs in ELBW infants receiving a single course versus multiple courses of NSAIDs

Methods

Retrospective cohort study

- Collected in reverse chronological order (Apr 2012 – Jul 2018)

Inclusion criteria

- ELBW infants (< 28 weeks gestational age, birth weight < 1000 grams)
- Received at least 1 dose of NSAID in the first 4 weeks of life

Definitions

- NEC: clinical suspicion with antibiotic treatment and nothing by mouth for ≥ 5 days, or confirmed by pathology or imaging
- AKI: urine output < 0.6 mL/kg/hour for ≥ 12 hours during NSAID therapy and for 5 days after, or serum creatinine > 150 µmol/L or increase of > 100 % from baseline during NSAID therapy and for 7 days after
- IVH: any new or interval progression of IVH
- Platelet dysfunction: platelets < 50 x 10^9/L or required a platelet transfusion
- Clinically significant bleed: bleeding that required a transfusion or a bolus of intravenous fluids, was documented as significant or active, or grade III or IV IVH

Statistics

- Descriptive statistics with a population proportion = 0.5, confidence level = 95%, and absolute precision = 0.07 required a sample size of 196
- Chi-squared test used for statistical analysis

Results

Table 1: Patient and NSAID characteristics

Number of NSAID courses		All (N=198)	Single (n=137)	Multiple (n=61)
Patient characteristics				
Median gestational age [weeks (range)]		25^{+2} (22^{+6} to 27^{+6})	25^{+3} (22^{+6} to 27^{+6})	25^{+0} (22^{+6} to 27^{+4})
Median birth weight [grams (range)]		747 (335 to 997)	750 (335 to 997)	743 (510 to 995)
Male sex [n (%)]		106 (54)	75 (55)	31 (51)
Multiple gestation baby [n (%)]		70 (35)	40 (29)	30 (49)
Death at postnatal age ≤ 28 days [n (%)]		18 (9)	16 (12)	2 (3)
PDA [n (%)]	Absent Asymptomatic Symptomatic	53 (27) 28 (14) 117 (59)	52 (38) 23 (17) 62 (45)	1 (2) 5 (8) 55 (90)
Median postnatal age when first exposed to NSAID [days (range)]		1 (0 to 27)	1 (0 to 27)	1 (0 to 18)
NSAID indication [n (%)]	IVH prophylaxis PDA treatment Both	82 (41) 87 (44) 29 (15)	81 (59) 56 (41) 0 (0)	1 (2) 31 (51) 29 (48)
Concomitant medications [n (%)]	Nephrotoxic medication Vasopressor or inotrope Corticosteroid	166 (84) 50 (25) 16 (8)	115 (84) 35 (26) 11 (8)	51 (84) 15 (25) 5 (8)
NSAID characteristics				
Indomethacin mean total dose [mg/kg (SD)]		0.5 (0.3)	0.3 (0.1)	0.8 (0.3)
Ibuprofen mean total dose [mg/kg (SD)]		24.8 (9.2)	19.5 (3.5)	27.9 (10.2)
Number of NSAIDs courses	Two Three	–	–	57 4

Figure 1: ADEs in the single course group compared to the multiple courses group

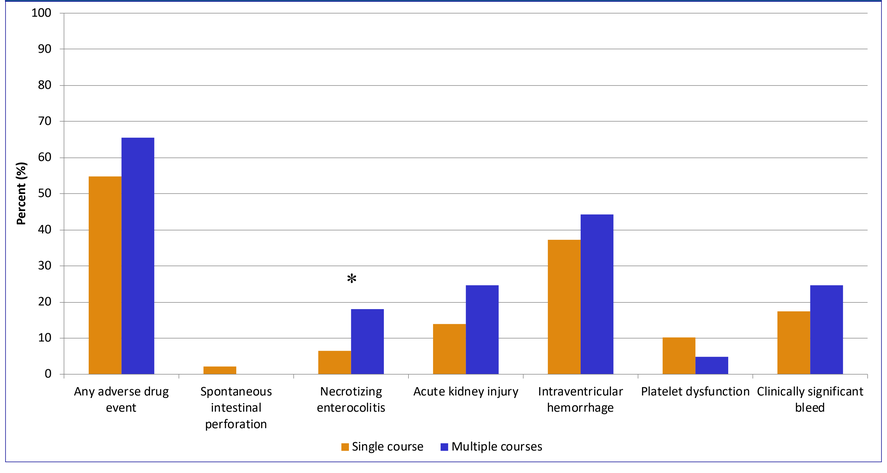
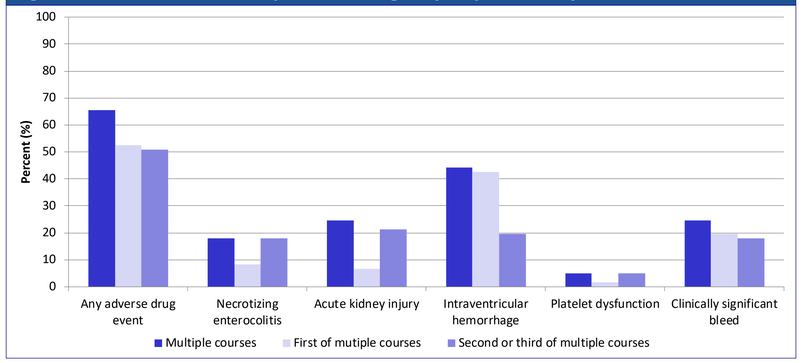


Table 2: ADE outcomes

Number of NSAID courses	Single (n=137)	Multiple (n=61)	p-value
Any adverse drug event [n (%)]	75 (55)	40 (66)	0.154
Spontaneous intestinal perforation [n (%)]	3 (2)	0 (0)	0.244
Necrotizing enterocolitis [n (%)]	9 (7)	11 (18)	0.013*
Acute kidney injury [n (%)]	19 (14)	15 (25)	0.065
Intraventricular hemorrhage [n (%)]	51 (37)	27 (44)	0.350
Platelet dysfunction [n (%)]	14 (10)	3 (5)	0.219
Clinically significant bleed [n (%)]	24 (18)	15 (25)	0.248
Number of patients who experienced more than 1 ADE [n (%)]	35 (26)	21 (34)	0.200
Mean number of ADEs per patient (SD)	0.9 (1.0)	1.3 (1.4)	–

Figure 2: ADEs in the multiple courses group separated by the NSAID course



Limitations

- Selection bias possible as infants are more likely to receive multiple courses of NSAIDs if they did not experience ADEs with the first course
- Results are possibly confounded by the fact that infants were older when they received their 2nd or 3rd course of NSAID and were at lower risk of complications of prematurity which overlap with the ADEs associated with NSAID therapy

Conclusions

- ELBW infants who received multiple courses of NSAIDs experienced more ADEs than infants who received a single course, however this was not statistically significant
- Significantly more NEC occurred in infants who received multiple courses of NSAIDs