ID: LATE BREAKER
TITLE: PROPHYLACTIC IBUPROFEN IN PREMATURE INFANTS BELOW 1250GM AND 32 WEEKS MAY NOT PROTECT AGAINST INTRAVENTRICULAR HEMORRHAGE OR PATENT DUCTUS ARTERIOSUS CLOSURE AND MAY INCREASE O2 REQUIREMENT AT 28 DAYS OF LIFE.
AUTHORS:
AFFILIATIONS:

CONTENT:

Background
Patent ductus arteriosus (PDA) is a common diagnosis among extreme premature infants and associated with significant neonatal morbidities. Administration of prophylaxis cyclo-oxygenase (COX) inhibitors (eg, indomethacin or ibuprofen) to promote closure of the ductus arteriosus may decrease such morbidities. Prophylaxis cyclo-oxygenase (COX) is still controversial as potential side effect of therapy and long term benefits are not clear.

Objectives
To determine the effectiveness, safety and adverse effect of prophylactic ibuprofen in preterm (below 32 weeks) and/or very low birth weight infants (below 1250 gm).

Method and sample
This cross sectional trial at Al-Makassed Hospital NICU in Jerusalem city in which inborn preterm infants with gestational ages of < 32 weeks and birth weight below 1250 gm from January 2016 to December 2018, who received prophylactic ibuprofen within first 24 hours of life (10 mg/kg, followed by 5 mg/kg after 24 and 48 hours) compared with preterm infants of same characteristics who received nothing in that period. The decision to give ibuprofen was upon consultant opinion after discussion of the details of each case.

The primary outcome was Presence of patent ductus arteriosus (clinically symptomatic or diagnosed by echocardiography in response to clinical suspicion; secondary outcomes were mortality, bronchopulmonary dysplasia (defined as oxygen requirements at 36 corrected gestational age), severity of respiratory distress syndrome (defined as use of more than two doses of surfactant), Definitive sepsis (clinical symptoms and signs of sepsis and a positive bacterial blood culture in a specimen obtained by sterile technique), massive pulmonary hemorrhage, Intraventricular hemorrhage (IVH) (grade III or IV), oxygen requirements at 28 days’ postnatal age and Necrotizing enterocolitis (NEC) (stage 2 or 3).

Results
Forty four preterm infant were given prophylactic ibuprofen and 71 preterm with no intervention. PDA diagnosed in 14 patients (31.8%) of prophylactic ibuprofen group compared with 25 patients (35.2%) of no intervention group (control group) and P-value was 0.709. Analysis for secondary outcome showed No difference was identified for mortality (18 patient(40.9%) in prophylactic group compared with 22(31.0%) control group with P-value 0.278), severe intraventricular hemorrhage (IVH) (5 patient(11.4%) in prophylactic group compared with 10(14.1%) of control group with P-value 0.674), definitive sepsis (18 patient(40.9%) in prophylactic group compared with 18(25.4%) of control group with P-value 0.080), or NEC (6 patient(13.9%) in prophylactic group compared with 15(21.2%) of control group with P-value 0.597). There is an increased risk of pulmonary hemorrhage (12 patients (27.3%) in prophylactic group compared with 9(12.7%) of control group with P-value 0.049), and O2 requirement at 28 days (19 patients (43.2%) in prophylactic group compared with 11(15.5%) of control group with P-value 0.001.

Conclusion:
Prophylactic use of ibuprofen, compared to no intervention, did not result in decreasing the incidence of patent ductus arteriosus, mortality, and severe IVH with no significant increase of NEC or sepsis risks. There has been an increased risk of pulmonary hemorrhage, and O2 requirement at 28 days.

Recommendation:
Current evidence does not support the use of Prophylactic ibuprofen for prevention of PDA in premature infants below 1250 gm and 32 weeks or prevention of morbidities associated with it.
ORAL AMOXICILLIN/CLAVULANIC ACID IN NEAR TERM AND TERM NEWBORNS: DO WE REACH TARGET LEVELS?

AUTHORS:

AFFILIATIONS:

CONTENT:

Background
Oral antibiotic use is scarce in neonates due to pharmacokinetic uncertainties in the first weeks of life. Amoxicillin/clavulanic acid covers most causative pathogens of early-onset neonatal sepsis, eg. group B streptococci (GBS) and E. coli. Efficacy of amoxicillin depends on time above MIC; for clavulanic acid, a target is currently lacking but its efficacy is thought to be dependent of the area under the curve (AUC). Amoxicillin/clavulanic acid has a good bio-availability in children and adults, but evidence in neonates is lacking. We evaluated the pharmacokinetics of oral amoxicillin/clavulanic acid in term newborns (0-28 days of age).

Methods
As part of a multicenter RCT evaluating neonatal intravenous-to-oral switch therapy in probable bacterial infection (1), we measured serum levels in patients allocated to the intervention group. They switched to amoxicillin/clavulanic acid suspension (25/6.25mg/kg tid), after 48 hours of intravenous penicillin/gentamicin. Two blood samples from different dosing intervals, were obtained and directly stored at -80°C. Initially, and to ensure that amoxicillin levels were attained as safety marker, levels in the second part of the timeframe (4-8h after administration) were collected. For the second batch, peak levels (1-2h after administration) were collected. Analysis was performed using Liquid Chromatography and Mass Spectrometry. For amoxicillin, an MIC of 8 mg/L for ≥50% of time was considered appropriate.

Results
Samples of 30 patients have been analysed (mean GA 40±1 ± 1.0 weeks; mean birthweight 3641 ± 429 grams). Patients switched to oral therapy on average after 2.5 days of intravenous therapy. Through levels (n=44) were collected 6.0±1.3h after antibiotic administration. Top levels (n=13) were collected on average 1.6±0.5h after administration (mean±S.D.). Amoxicillin levels were all above MIC of GBS (0.25 mg/L) and E. coli (8 mg/L); range: 5.4-72.9 mg/L for more than 50% of time.
Clavulanic acid levels were also detected in all patients but a great variance was observed. Trough level: 1.4mg/L (0.20-4.82); top level: 1.9 mg/L (0.39-6.79); median (range). AUC’s in individual patients were in range with reported AUC’s in literature.

Conclusions
Oral amoxicillin is well absorbed in newborns leading to adequate serum levels. Oral clavulanic acid is absorbed in term newborns, but a great variance is seen. AUC’s following oral administration are comparable to those of children and adults.

Trial Registration
This trial has been registered in Clinicaltrials.gov Trial number NCT03247920


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ID: 444
TITLE: THE STABILITY OF NORADRENALINE INFUSIONS IN THE NICU ENVIRONMENT
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CONTENT:

Hypotension is a common problem in preterm and unwell term infants, sometimes associated with sequelae such as renal/hepatic impairment, necrotising enterocolitis, and intraventricular haemorrhage. It can thus lead to adverse neurodevelopmental outcomes.

In UK NICUs, hypotension is increasingly managed with noradrenaline infusions. While available evidence suggests that such infusion solutions retain adequate drug concentrations for at least 24 hours, there have been no studies examining their stability in NICU environmental conditions.

This prospective drug stability study aims to establish whether the current practice of changing noradrenaline infusions every 24 hours is appropriate.

Noradrenaline infusions in different vehicles (glucose 5%, glucose 10%, sodium chloride 0.45% and sodium chloride 0.9%/glucose 5%) were subjected to a simulated NICU environment over 24 hours: incubators with/without humidification, ambient temperature, and conditions associated with the delivery of therapeutic hypothermia. Samples of the noradrenaline solutions were taken at the time of infusion commencement, after 30 minutes, 12 hours and 24 hours, and analysed with high-performance liquid chromatography. Furthermore, the impact of phototherapy on infusion stability was also examined.

A percentage loss of >7.5% was deemed significant. At room temperature and associated with therapeutic hypothermia, all infusion vehicles retained acceptable concentrations of noradrenaline. However, when exposed to an incubator, and particularly with humidity, significant changes were noted in all solutions. Noradrenaline concentrations were within limits at 24 hours in an incubator, ambient temperature and with therapeutic hypothermia only in sodium chloride 0.9%/glucose 5%; but not in a humidified incubator, where adequate concentration in this diluent was maintained only at 12 hours.

When associated with phototherapy, significant concentration degradation was noted in all infusion vehicles.

Definitive recommendations for practice cannot be derived from the results due to inherent wide margins of error, but results suggest that noradrenaline infusion solutions are not stable in the NICU environment. The use of sodium chloride 0.9%/glucose 5% as a diluent may be an adequate strategy to overcome stability issues when phototherapy is not required, but further research in this area is needed.

IMAGES:
https://www.eiseverywhere.com/eselectv3/v3/events/351149/submission/files/download?fileID=aa546706ba8810756c5494fcd755aaf3-MjAxOS0wNSM1Y2UyNyY2Y2VvYmEy

Noradrenaline concentration over 24 hours in different vehicles/environments

COI: Lisa Kaiser, Dr Heike Rabe and Dr Bhavik Patel declare that there is no conflict of interest
ID: 575

TITLE: LARYNGEAL MASK AIRWAY VS ENDOTRACHEAL INTUBATION DURING NEONATAL ANAESTHESIA FOR EYE SURGERY

AUTHORS: Małgorzata Domagalska 1; Michal Gaca 2; Daniele Trevisanuto 3; Marta Szymankiewicz- Breborowicz 4; Izabela Miechowicz 5; Tomasz Szczapa 6

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CONTENT:

Endotracheal intubation and mechanical ventilation remains the most common approach for neonates undergoing anaesthesia during surgical procedures. However, it may be associated with transient reduction of oxygenation (in particular cerebral), tachycardia, hypertension, reflex apnea, and may increase the risk of prolonged ventilation. Hence, less invasive methods of ventilatory support are under investigation. According to the available literature ventilation of a neonate can be effectively carried out using a laryngeal mask airway (LMA) and may potentially reduce the number of anaesthesia associated complications eg. desaturation, laryngospasm, cough and apnea.

Neonates undergoing ophtalmologic procedures (laser photocoagulation, injection of ranibizumab and vitrectomy) were randomized in two airway management groups: a) endotracheal intubation (ET) and b) i-gel LMA. The following parameters were monitored: saturation and heart rate (SpO2, HR), % of leak, end-tidal CO2 (EtCO2), NIRS cerebral oxygenation (StO2) and selected haemodynamic parameters measured with electrical impedance velocimetry (EIV). Anaesthesia was performed with sevoflurane and infusion of remifentanil.

41 neonates were enrolled. There were no significant differences in corrected gestational age between groups (median 36.5 (range 30-58) vs 35 (range 33-44) weeks). LMA insertion time was shorter than the intubation time (median 6 (range 6-8) vs 8 (range 5-9),p<0.05). The leakage of anesthetic gases was significantly lower with LMA (median a) 17%(range 8-31%) vs b) 13%(range 3-15%),p<0.05). Complications were observed only in the group a) SpO220s (15% of cases). Patients in group a) had significantly greater fluctuations in SpO2 (SD 2.58 vs. 1.73,p<0.05), StO2 (SD 4.51 vs 2.75,p< 0.05), HR (SD 6.01 vs 4.74,p<0.05), cardiac output (SD 21.28 vs 14.87,p<0.05) and stroke volume (SD 20.67 vs 7.96;p<0.05). After the procedure LMAs were removed sooner than endotracheal tubes (median 3.25 (range 2.7-3.7) vs 180 (range 60-1800) minutes,p<0.05).

Anaesthesia during neonatal eye surgery performed with LMA seems safe and effective. Lesser leak of gases and fewer respiratory complications were observed with LMA compared with endotracheal intubation. The use of a LMA was associated with more stable cerebral StO2 and hemodynamic parameters. Application of LMA also seems to facilitate a sooner return to spontaneous breathing. These findings warrant further studies.

COI: None declared
ID: 889

TITLE: VANCOMYCIN RENAL ELIMINATION CLEARANCE IS MUCH MORE REDUCED IN PRETERM NEONATES TREATED WITH INDOMETHACIN (-55%) COMPARED TO IBUPROFEN (-16%) TO CLOSE A SYMPTOMATIC PATENT DUCTUS ARTERIOSUS

AUTHORS: Siziana Cristea 1; Karel Allegaert 2,3; Almicar Falcao 4; Fatima Falcao 5,6; Ricardo Silva 5; Anne Smits 3,7; Catherijne Knibbe 1,8; Elke Krekels 1

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CONTENT:

Ibuprofen and indomethacin are NSAIDs commonly used to induce ductus arteriosus closure in preterm neonates. Our group previously reported that ibuprofen decreased vancomycin clearance by 16%. In this study we quantified the impact of indomethacin co-administration on vancomycin clearance by extending our vancomycin population pharmacokinetic model with a dataset containing vancomycin concentrations measured in preterm neonates co-medicated with indomethacin.

The modeling dataset includes concentration-time data of vancomycin administrated alone or in combination with either ibuprofen or indomethacin collected in the neonatal intensive care units of UZ Leuven (Leuven, Belgium) and São Francisco Xavier Hospital (Lisbon, Portugal). The derived vancomycin pharmacokinetic model was subsequently used to propose dose adjustments that yield effective vancomycin exposure (i.e., AUC0-24h between 300-550 mg·h/L, with a probability below 0.1 of sub-therapeutic exposure) in preterm neonates with patent ductus arteriosus.

We found indomethacin co-administration to reduce vancomycin clearance by 55%. Model simulations showed that the most recent vancomycin dosing regimen which was based on an externally validated model, requires a 20% and 60% decrease of the loading and maintenance dose of vancomycin, respectively, when aiming for optimized exposure in the neonatal population.

By analyzing vancomycin data from preterm neonates co-medicated with indomethacin we found a substantial decrease in vancomycin clearance of 55% versus a previously reported 16% for ibuprofen. This decrease in clearance impacts vancomycin dosing and we anticipate that other drugs eliminated by glomerular filtration are likely to be affected to a similar extent as vancomycin.

COI: none
ID: 992

**TITLE:** METHADONE AS TREATMENT FOR NEONATAL REPETITIVE PROCEDURAL PAIN IN A RAT MODEL: ATTENUATION OF ACUTE AND LONG-TERM EFFECTS

**AUTHORS:** NJ van den Hoogen, PhD; T de Geus, MSc; J Patijn, MD, PhD; D Tibboel, MD, PhD; EAJ Joosten, PhD

**AFFILIATIONS:** University of Maastricht

**CONTENT:**

Repetitive pain during early postnatal life affects the postnatal development of the spinal pain transmission network, leading to increased pain sensitivity to re-injury of the same dermatome in adulthood. At the same time, optimal analgesia during the neonatal period including the prevention of long-term changes in nociception is still challenging. The aim of the present study was to identify whether methadone analgesia during neonatal repetitive procedural pain can prevent acute and long-term hypersensitivity in the rat.

Male and female Sprague-Dawley rat pups underwent 4 needle pricks per day into the left hind-paw from day of birth (postnatal day 0 (P0)) until P7. Methadone (NP+M, 1 mg/kg) was administered before the first needle prick on each day from P0-P7. Sex-matched littermates received saline before the first needle prick (Needle prick; NP). A second control group of sex-matched littermates received saline and a tactile stimulus instead of needle pricks (Tactile control; TC). When adult, animals underwent a paw incision in the ipsilateral hind-paw as a model of acute post-operative pain. Mechanical sensitivity was assessed using Von Frey filaments. Mechanical sensitivity was tested daily from P0-P7; weekly from 3-8 weeks, and until 7 days post-incision; 50% withdrawal thresholds were calculated.

During the neonatal period, NP animals showed significant mechanical hypersensitivity due to the needle pricks as compared to TC animals. Methadone treatment reversed the acute hypersensitivity. After re-injury of the ipsilateral paw in adulthood, NP animals showed increased hypersensitivity on post-operative day 5 compared to TC. NP+M animals showed no differences compared to tactile control.

The results in this study suggest that early treatment with methadone during neonatal repetitive procedural pain may attenuate both acute and long-term mechanical hypersensitivity.

**COI:** none declare