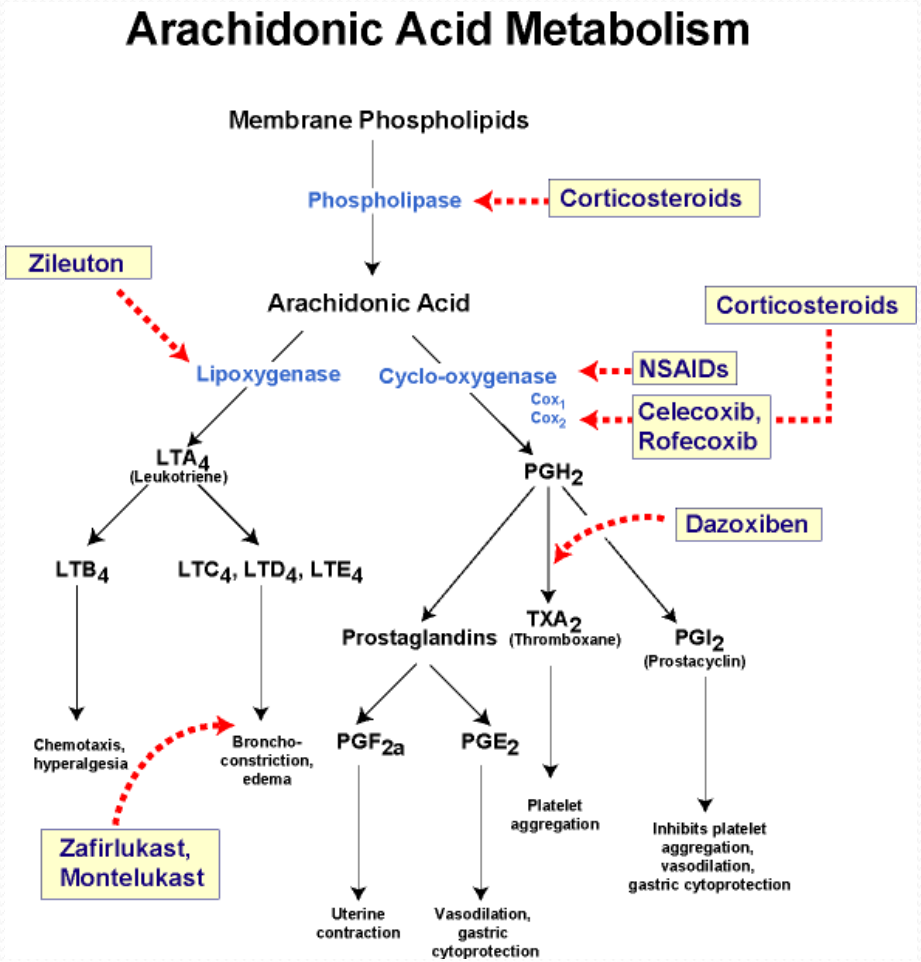
Acetaminophen for prevention or treatment of pain in newborns

Dr Tran Thi Le Uyen
Neonatal intensive care unit
Children 2 Hospital

- Introdution
- Background
- Objectives
- Search methods
- Selection criteria
- Data collection and analysis
- Main result
- Conclusion

Introdution about acetaminophen

- The primary mechanism of action is belived to be inhibition of cyclooxygenase (COX), with a predominant effect on COX-2. Inhibition of COX enzymes prevents the metabolism of arachidonic acid to prostaglandin H2, an unstable intermidiate byproduct which is converted to pro-inflamatory compounds. In the central nervous system, inhibition of COX enzymes reduces concerntrations of prostaglandin E2 which lowers the hypothalamic set-point to reduce fever and activation of descending inhibitory serotogernic pathways to produce analgesia.
- Acetaminophen does not possess significant anti-inflamatory properties nor alter platelet aggregation.



MODE OF ACTION

Tissue damage, release of pyrogens and phospholipids from cell membrane

Archidonic acid

NSAID block COX –1*and COX –2 in periphery and CNS

PG PG PG

Paracetamol blocks COX –2 and COX –3 ? in CNS

Fever and Pain

COX –1* is critical to maintain the integrity of platelets,renal function and gastric mucosa.

Background

Newborn infants have ability to experience pain. Newborns treated in NICU are exposed to numerous painful produces. Healthy newborns are exposed to pain if the birth process consists of asisted vaginal birth by vacuum extraction or by forceps and during blood sample for newborn screening tests.

- **Background**

Evolving evidence suggests that neonates/infants experience pain (Ohlsson 2000; Ohlsson 2007). This was documented as early as 1518, when Jörgen Ratgeb painted the circumcision of Jesus. The picture of crying Jesus shows the same facial expressions that were later depicted in an etching of the same event by Rembrandt in 1630 (Schwartz 1977; Ohlsson 2007). In 1872, Darwin commissioned photographs of infants experiencing pain and described the facial, vocal and bodily expressions of infants in pain (Darwin 1872; Ohlsson 2007). Similar observations form the basis for several validated neonatal pain scales in use today (Ohlsson 2007).

Over the centuries, little progress was made in the prevention and management of infant pain. The first controlled trial of an intervention for pain in infants was probably that conducted in the 1960s by Palmer, who found in a double-blind, controlled study involving 86 infants with teething pain that an active gel (choline salicylate) was more effective than placebo in reducing pain (Palmer 1962). Dorsal penile nerve block (DPNB) was introduced in 1978 for circumcision (Kirya 1978), and in 1983 in a double-blind investigation, Holve and co-workers demonstrated that circumcision following DPNB with an injection of lidocaine reduced the time spent crying and reduced the mean increase in heart rate compared with DPNB with saline or no DPNB (Holve 1983). In a trial that used random allocation for assignment of infants to study groups, Harpin and Rutter demonstrated that a mechanical heel lance was considerably less painful than a manual heel lance (Harpin 1983).

In 1987, Anand and co-workers reported the results of a small randomised controlled trial (Anand 1987a). Preterm infants undergoing ligation of a patent ductus arteriosus were given nitrous oxide and d-tubocurarine. Eight infants received additional fentanyl (10 µg/kg) IV to the anaesthetic regimen, and eight infants did not. Hormonal responses to the surgery were significantly greater in the non-fentanyl group. In contrast to the fentanyl group, the non-fentanyl group had circulatory and metabolic complications postoperatively (Anand 1987a).

Later the same year, Anand and Hickey published the very influential paper, "Pain and its effects in the human neonate and fetus", in *New England Journal of Medicine* (Anand 1987b). As of May 16, 2015, the paper had been quoted more than 700 times according to the Web of Science. Anand and Hickey provided evidence that fetuses that are mature enough to survive outside the womb with or without extensive life support have the anatomical, biochemical and physiological requisites in place to respond to painful stimuli (Anand 1987b). That same year, the American Academy of Pediatrics published a one-page opinion paper on "neonatal anesthesia" and stated, "The Committee on Fetus and Newborn, the Committee on Drugs, the Section on Anesthesiology, and the Section on Surgery believe that local or systemic pharmacological agents now available permit relatively safe administration of anesthesia or analgesia to neonates undergoing surgical procedures and that such administration is indicated according to the usual guidelines for the administration of anesthesia to high-risk, potentially unstable patients" (AAP 1987).

Infants treated in neonatal intensive care units (NICUs) are exposed to numerous painful procedures. Did increased awareness in 1987 about neonatal pain and its treatment change how healthcare workers approach pain management? Many surveys on pain management have been conducted, but changes in clinical practice have not occurred quickly. A survey of 30 Canadian level III NICUs in 1992 with a 87% response rate concluded that procedural and disease-related pain is frequently untreated (Fernandez 1994).

Between September 2005 and January 2006, data on all painful and stressful procedures and corresponding analgesic therapy from the first 14 days of admission were prospectively collected from 430 neonates admitted to 13 tertiary care centres in the Paris region of France (Carbajal 2008). The mean (standard deviation (SD)) postmenstrual age (PMA) of the infants and the length of the intensive care unit stay were 33.0 (4.6) weeks and 8.4 (4.6) days, respectively. Neonates experienced 60,969 first-attempt procedures, of which 42,413 (69.6%) were painful and 18,556 (30.4%) were stressful procedures. Neonates experienced a median of 115 (range 4 to 613) procedures during the study period and 16 (range 0 to 62) procedures per day of hospitalisation (Carbajal 2008). In order of frequency, the five most common painful procedures to which the neonates were exposed consisted of nasal aspiration, tracheal aspiration, heel lance, adhesive removal and gastric tube insertion. The five most frequently performed stressful procedures to which infants were exposed included nursing care, oral aspiration, washing of the neonate, blood pressure measurement and x-rays (Carbajal 2008).

In an observational, prospective study conducted between February 2009 and August 2009 in the level III NICU of Sophia Children's Hospital in Rotterdam, The Netherlands, bedside data were collected on all procedures that infants underwent during the first 14 days of admission (Roofthooft 2014). A procedure was defined as any medical, nursing, surgical, diagnostic or therapeutic intervention provided to a patient. Study authors did not distinguish between painful and stressful procedures. Invasive or painful procedures were defined as interventions that cause mucosal or skin injury from removal or introduction of foreign material (Roofthooft 2014). A total of 21,076 procedures were performed during 1730 patient-days (mean 12.2 days) in the 175 neonates studied. The mean number of painful procedures per neonate per day was 11.4 (SD 5.7) - significantly fewer than the 14.3 (SD 4.0) painful procedures reported in a similar study in the unit in 2001. Use of analgesics was 36.6% compared with 60.3% in 2001. Sixty-three per cent of all peripheral arterial line insertions failed versus 37.5% in 2001, and 38% of intravenous cannula insertions failed versus 30.9% in 2001. Study authors concluded that the mean number of painful procedures per NICU patient per day had declined over time (Roofthooft 2014).

To our knowledge, no surveys have been performed to determine how commonly newborns are exposed to clinically painful conditions such as, for example, birth trauma, congenital anomalies (myelomeningoceles, hydrocephalus, open cutaneous lesions), necrotising enterocolitis and burns.

Why it is important to do this review

Infants may be exposed to prolonged and repeated pain during lengthy hospitalisation in neonatal intensive care units (Grunau 1998). The low tactile threshold in preterm infants when they are in the neonatal intensive care unit, while their physiological systems are unstable and immature, potentially renders them more vulnerable to the effects of repeated invasive procedures (Grunau 2006). Animal and human studies have documented how neonatal pain is associated with short-term and long-term adverse consequences (Fitzgerald 2009; Hall 2012). Growing evidence suggests that not only do these early events induce acute changes, but permanent structural and functional changes may result (Porter 1999). Early procedural pain in very preterm infants may contribute to impaired growth and brain development (Brummelte 2012; Vinall 2012). Enhanced survival of extremely low-birth-weight infants makes them more susceptible to the effects of pain and stress because of increased exposure (Hall 2012). "Effective pain management in infants requires a specialist approach - analgesic protocols that have been designed for older children cannot simply be scaled down for central nervous system pain pathways and analgesic targets that are in a state of developmental transition" (Fitzgerald 2009).

The most common non-pharmacological techniques used to treat pain include non-nutritive sucking with or without sucrose, kangaroo care, swaddling and massage therapy (Hall 2012). Drugs used to treat neonatal pain include opiates, benzodiazepines, barbiturates, ketamine, propofol, acetaminophen and local and topical anaesthetics (Hall 2012).

In the prospective study conducted in 13 intensive care units in Paris, France, of 42,413 painful procedures, 2.1% were performed with pharmacological therapy alone; 18.2% with non-pharmacological interventions alone; 20.8% with pharmacological, non-pharmacological or both types of therapy; 79.2% without specific analgesia; and 34.2% while the neonate was receiving concurrent analgesic or anaesthetic infusions for other reasons. Study authors concluded, "During neonatal intensive care in the Paris region, large numbers of painful and stressful procedures were performed, the majority of which were not accompanied by analgesia" (Carbajal 2008).

A similar prospective study was conducted in 14 Canadian neonatal intensive care units between February and October 2007 (Johnston 2011a). Infants (n = 582) were followed for one week for all invasive procedures. A total of 3508 tissue-damaging (mean = 5.8, SD = 15) and 14,085 non-tissue-damaging (mean = 25.6, SD = 15) procedures were recorded. Half of the procedures (46% tissue-damaging and 57% non-tissue-damaging) had no analgesic interventions (Johnston 2011a). Study authors noted that parental presence had a positive influence on comfort strategies, and they offered encouragement and support to parents to remain with their infant during procedures (Johnston 2011a). Non-pharmacological interventions for procedural pain in neonates include sensory stimulation approaches, oral sweet solutions and maternal interventions (Johnston 2011).

Surveys of procedural pain in neonates and associated analgesic interventions have been conducted in many countries, including Australia (Foster 2013), Canada (Johnston 2011a), France (Carbajal 2008), The Netherlands (Roofthooft 2014), Japan (Ozawa 2013), Korea (Jeong 2013), Italy (Lago 2013) and Sweden (Gradin 2011). Although adherence to national or international pain guidelines has increased, infant pain remains undertreated.

Paracetamol offers an advantage over other pain-reducing interventions in that it can be administered via nasogastric tube, intravenously or rectally. In a review of health policy and health economics related to neonatal pain, Lee was not able to identify any studies that examined quality of life adjustment strictly as a function of pain (Lee 2007).

Controversy continues regarding the safety and long-term impact of many interventions aimed at reducing stress or pain (or both) in neonates (McPherson 2014). These interventions include sucrose, anaesthetics and pharmacological agents (benzodiazepines and opioids) (McPherson 2014).

The possible link between perinatal exposure to paracetamol and autism has recently been raised and needs to be explored further (Bauer 2013).

Researchers and healthcare providers working with neonates have an obligation to reduce painful stimuli and interventions and to identify effective pain-reducing pharmacological and non-pharmacological agents. Paracetamol may be one such agent. By performing this review, we hope to ascertain which types of pain are amenable to treatment with paracetamol.

Objectives

- To determine the efficacy and safety of acetaminophen for the prevention or treatment of procedural/postoperative pain or pain associated with clinaical conditions in neonates.
- To review the effects of various doses and routes of administration (enteral, intraveinous, rectal) of acetaminophen for the prevention or treatment of pain in neonates.

Methods

- Type of studies:

  They included randomised and quasi-randomised controlled trials of acetaminophen for prevention or treatment of pain in neonates.

- Type of participants:

  Term or preterm neonates who underwent one or more of the following painful procedures during their hospital stay or as out-patients: heel lance, venipuncture, lumbar puncture, bladder tap, insertion of nasogastric tubes, insertion of endotracheal tubes, insertion of venous or arterial catheter or chest drain or surgery.

  Neonates have a clinical condition that is painful such as a long bone fracture, necrotising enterocolitis or open skin lesions..

  Included newborn infants born at term up to postatal age of 30 days, or preterm infants if they were enrolled up to 30 days beyond the expected day of birth.

Method

- Type of interventions:

  Aacetaminophen at any dose, administered intravenously, orally, rectally, compared with placebo (no intervention or another pain reducing intervention : non pharmacological or a pharmacological agent) for the prevention or treatment of pain. They included studies that report on single administration of acetaminophen or multiple doses over a prolonged period during iniatal hospital stay. Analysis of repeat administration of acetaminophen would focus on potential adverse effects.

Method

- Types of outcome measures:

  - Primary outcomes:

    + Pain scores as measured by a validated tool (cry duration, proportion of time crying, facial actions)

    + Physiological events: heart rate, respiratory rate, saturation of peripheral oxygen in the blood, transcutaneous oxygen and carbon dioxide.

    + Biochemical measures: urine, plasma or salivary cortisol levels.

    + Validated composite pain scores.

    + Combination of these.

Method

- Secondary outcomes:
  + Shorterm outcomes:

    All-cause mortality during initial hospiatal stay

    Neonatal mortality

    Plasma, salivary or urinary cortisol levels

    Duration of ventilatior support (days)

    Duration of need for supplementary oxygen (days)

    Intraventricular haemorrhage

    Severe IVH

Spontaneous intestinal perforation

Gastrointestinal bleed

Retinalpathy of prematurity (ROP)

Decreased urine output during treatment

Peak serum levels of creatinin after treatment

AST/ALT levels > 100 UI/ml

Peak serum ALT followig treatment

Peak serum billirubin following treatment

Liver failure

Duration of hospitalisation

Parent satisfaction with care provided in NICU

+ Longterm outcomes:

  Infant mortality

  Neurodevelopmental outcome

  Altered reactions to stimuli following NICU discharge

  Autism spectrum disorder in childhood

  Other side effects reported by authors.

PIPP score (Premature Infant Pain Profile)

- The Premature Infant Pain Profile (PIPP) is a behavioral measure of pain for premature infants. It was developed at the Universities of Toronto and McGill in Canada.
- Indicators: (1) gestational age (2) behavioral state before painful stimulus (3) change in heart rate during painful stimulus (4) change in oxygen saturation during painful stimulus (5) brow bulge during painful stimulus (6) eye squeeze during painful stimulus (7) nasolabial furrow during painful stimulus
- Scoring instructions: (1) Score gestational age before examining infant. (2) Score the behavioral state before the potentially painful event by observing the infant for 15 seconds . (3) Record the baseline heart rate and oxygen saturation. (4) Observe the infant for 30 seconds immediately following the painful event. Score physiologic and facial changes seen during this time and record immediately

Neonatal Infant Pain Scale (NIPS) Ages Birth - One Year

- The Neonatal Infant Pain Scale (NIPS) is a behavioral scale and can be utilized with both full-term and pre-term infants. The tool was adapted from the CHEOPS scale and uses the behaviors that nurses have described as being indicative of infant pain or distress. It is composed of six (6) indicators: facial expression, cry, breathing patterns, arms, legs, state of arousal.

Result of the search

- Searches identified 8 studies for inclusion(Shah 1998; van Lingen 2001; Bonetto 2008; Badiee 2009; Manjunatha 2009; Ceelie 2013; Seifi 2013; Tinner 2013) and one ongoing study (NCT01938261).
- All studies applied paracetamol for the treatment of pain. No studies for the prevention of pain were identified.

- The study by Badiee 2009 was a single-centre study conducted at Alzahra University Hospital, Isfahan, Iran, during the period of April 2007 to August 2007.
Objective: to evaluate whether high-dose paracetamol (40 mg/kg orally) relieves pain in preterm infants.

  Population: 72 preterm neonates (≤ 34 weeks PMA, age ≥ 24 hours, no feeding for at least 30 minutes, Apgar scores > 3 at 5 minutes). 36 infants in each group.

  Intervention: Treatment group received oral paracetamol 40 mg/kg, and placebo group received sterile water 90 minutes before heel lance.

  Outcomes: PIPP and crying time during the first 3 minutes of the procedure. Differences in SpO_2 and heart rate between baseline and heel lancing period.

  Notes: Dr Badiee informed us on January 5, 2015, that the paracetamol solution looked similar to sterile water.

- The study by Bonetto 2008 was a single-centre study conducted at Sanatorium Allende, Córdoba, Argentina, during November and December 2007.
Objective: to assess whether administration of oral glucose, paracetamol or EMLA, given individually, can reduce the pain caused in newborns by heel lance, in an outpatient setting.

  Population: newborns of 36 weeks PMA or more, more than 24 hours old and less than 30 days old, who needed blood tests for neonatal screening.

  Intervention: oral glucose (n = 19) or oral paracetamol (20 mg/kg; 2 drops/kg) (n =19) or EMLA to the heel (n =19) and oral placebo (2 drops/kg distilled water) and placebo to the heel (n = 19).

  Outcomes: maximum NIPS and PIPP scores from the start of the heel lance to 3 minutes after the heel lance procedure.

- The study by Ceelie 2013 was a single-centre study conducted at a level III paediatric intensive care unit in Rotterdam, The Netherlands, between March 2008 and July 2010.
Objective: to determine whether intravenous paracetamol (acetaminophen) would significantly (30%) reduce morphine requirements in neonates and infants after major surgery.

  Population: 71 neonates or infants younger than 1 year undergoing major thoracic (noncardiac) or abdominal surgery.

  Intervention: All participants received a loading dose of morphine 30 minutes before the end of surgery, followed by continuous morphine or intermittent intravenous paracetamol up to 48 hours post surgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the guidance of the validated pain assessment instruments.

  Outcomes: Primary outcome was cumulative morphine dose (study and rescue dose). Secondary outcomes were pain scores and morphine-related adverse effects.

  Notes: We obtained unpublished information from Dr Saskia N de Wildt, one of the study authors, for the 41 infants who were ≤ 30 days of age at enrolment.

- The study by Manjunatha 2009 was a single-centre study conducted at Wishaw General Hospital, Lanarkshire, UK, between 2003 and 2005 .
Objective: to ascertain if and to what extent neonates experience pain and discomfort during ROP screening and to compare the effect of paracetamol, oral morphine or placebo on markers of pain in preterm infants.

  Population: infants who satisfied the criteria for ROP screening (≤ 31 weeks of gestation, or ≤ 1.5 kg birth weight).

  Intervention: Infants were randomly assigned to one of three groups and were given placebo (n = 6), paracetamol (20 mg/kg) (n = 6) or oral morphine sulphate (200 µg/kg) (n = 6), one hour before the eye examination.

  Outcomes: PIPP.

  Notes: Dr Manjunatha and Ms Hazel Fisher (Senior Pharmacist) volunteered, "The 3 solutions looked identical (clear, colourless solutions). The diluent for all 3 solutions was hydroxybenzoate, with the placebo being made up with preserved water".

- The study by Seifi 2013 was a single-centre study conducted in a tertiary level neonatal intensive care unit at Al Zahra Hospital, Tabriz, Iran, from October 2011 to October 2012.
  Objective: to compare the efficacy of sucrose and acetaminophen in pain control during eye examination in preterm infants.

  Population: preterm infants < 32 weeks PMA.

  Intervention: Group A (n = 41) received oral acetaminophen 15 mg/kg 30 minutes before eye examination and 0.2 mL sterile water during initiation of eye examination. Group B (n = 40) received 0.2 mL sucrose (25%) during initiation of eye examination. Group C (n = 39) received 0.2 mL sterile water as placebo during initiation of eye examination.

  Outcomes: PIPP during first 45 seconds and last 45 seconds of eye examination.

- The study by Shah 1998 was a single-centre study conducted at the level III NICU at Women's College Hospital in Toronto, Ontario, Canada.
  Objective: to evaluate the effectiveness of paracetamol in decreasing pain caused by heel lance.

  Population: seventy-five term neonates undergoing heel lance.

  Intervention: 60 to 90 minutes before the procedure, neonates received paracetamol orally at a dose of 20 mg/kg (n = 38) or an equal volume of placebo (n = 37).

  Outcomes: per cent facial action (brow bulge, eye squeeze and nasolabial fold) (range 0 to 300%) and per cent of time spent crying (range 0 to 100%). Pain assessments were made from videotapes by a research assistant blinded to treatment allocation.

- The study by Tinner 2013 was a multi-centre study conducted at the University Hospitals of Basel, Bern, and Zürich, Switzerland.
  Objective: to assess the efficacy of paracetamol (acetaminophen) for neonatal pain relief.

  Population: term and near-term infants (n = 123) delivered by forceps or vacuum.

  Intervention: Infants were randomly assigned to receive two suppositories with paracetamol (60/80/100 mg in infants < 3000 grams/3000 to 4000 grams/> 4000 grams birth weight) (n = 62) or placebo at two hours and eight hours of life (n = 61).

  Outcomes: Pain and discomfort during the first 24 hours were assessed by the Echelle de Douleur et d'Inconfort du Nouveau ne (neonatal pain and discomfort scale) score. The response to the subsequent heel prick for metabolic screening at days 2 to 3 of life was assessed by the Bernese Pain Scale for Neonates (BPSN).

  The study by van Lingen 2001 was conducted at two level II hospitals in The Netherlands during a 15 month period.
  Objective: to evaluate whether paracetamol (20 mg/kg rectally) relieves pain in infants delivered by vacuum extraction, and if it improves the clinical condition.

  Population: infants born by vacuum extraction with birth weight > 2500 grams, gestational age > 36 weeks, Apgar score at 5 minutes ≥ 7 and absence of congenital anomalies of the newborn.

  Intervention: Sixty-one infants were given paracetamol suppositories rectally. The dose of paracetamol used was as close to 20 mg/kg as available strengths of suppository (50 mg for birth weight 2500 to 2749 grams, 60 mg for birth weight 2750 to 3249 grams, 70 mg for birth weight 3250 to 3749 grams and 80 mg for birth weight 3750 grams) would allow. At 6, 12 and 18 hours thereafter, they received another suppository from the same batch. Paracetamol was suspended in Witepof sol H-15 as a fatty suppository base. In the placebo group, 61 infants received a rectal suppository with only a Witepsol H-15 base.

  Outcomes: a modified five-point facies scale at 1, 7, 13 and 19 hours after the first suppository had been given.

Result

- All studies applied paracetamol for the treatment of pain. We identified no studies on paracetamol for the prevention of pain
- Only short-term outcomes were reported.

Result

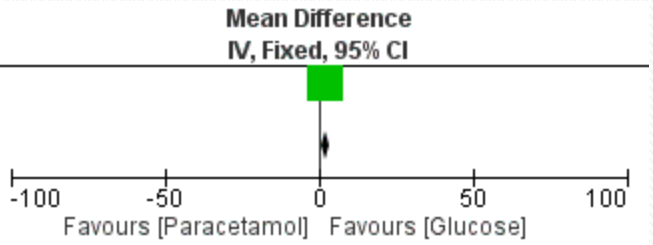
1. Heel lance:

There are 4 comparisions paracetamol oral vs sterile water, glucose oral, EMLA cream, cherry elixir

No evidence showed a reduction in pain associated with heel lance with the use of paracetamol compared with placebo (water or cherry elixir). Glucose appears to be more effective in reducing heel lance-associated pain than paracetamol.

	Paracetamol			Glucose				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Bonetto 2008	9.53	2.3	19	7.32	2.4	19	100.0%	2.21 [0.72, 3.70]
Total (95% CI)			**19**			**19**	**100.0%**	**2.21 [0.72, 3.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.90 (P = 0.004)



2. ***Assisted vaginal birth (vacuum extraction or forceps) - paracetamol suppositories vs placebo suppositories***

Paracetamol does not reduce pain associated with assisted vaginal birth (vacuum extraction or forceps) and may increase the pain response to a subsequent heel lance two to three days later.

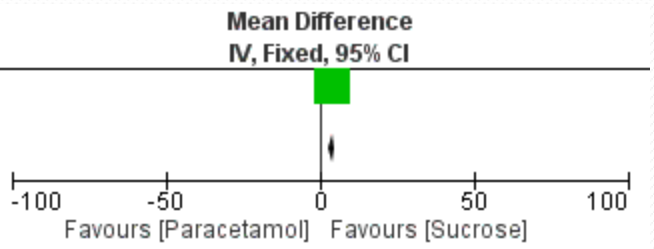
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Modified facies scores (possible score 0 to 4) 0, 1 or 2 at 1, 7, 13 and 19 hours	1	119	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.20]
2 Modified facies scores (possible score 0 to 4) 3 or 4 at 1, 7, 13 and 19 hours	1	119	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.66, 1.96]
3 EDIN score at 2 hours of age	1	123	Mean Difference (IV, Fixed, 95% CI)	1.0 [0.60, 1.40]
4 EDIN score at 4 hours of age	1	123	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.22, 0.22]
5 Difference in acute BPSN pain scores before and after heel lance at 2 to 3 days of life (by nurses)	1	123	Mean Difference (IV, Fixed, 95% CI)	2.0 [1.56, 2.44]
6 Difference in acute BPSN pain scores before and after heel lance at 2 to 3 days of life (by video)	1	123	Mean Difference (IV, Fixed, 95% CI)	2.0 [1.47, 2.53]
7 Infants who cried following	1	123	Risk Ratio (M	1.28 [0.95

3. Eye examination:

Paracetamol compared with water does not reduce pain associated with eye examinations performed to ascertain the presence of retinopathy of prematurity (ROP); on the contrary, Premature Infant Pain Profile (PIPP) scores were higher during eye examination for the paracetamol group than for the sucrose group.

	Paracetamol			Sucrose (24%)				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Seifi 2013	12.9	2.4	41	9	2.1	40	100.0%	3.90 [2.92, 4.88]
Total (95% CI)			**41**			**40**	**100.0%**	**3.90 [2.92, 4.88]**

Heterogeneity: Not applicable
Test for overall effect: Z = 7.79 (P < 0.00001)



4. Postoperative care - paracetamol vs morphine

Regular use of paracetamol may reduce the total amount of morphine required during the first 48 hours following major thoracic or abdominal surgery. However, one study that included infants up to postnatal age 10 months did not find that rectal paracetamol reduced morphine consumption after major surgery (van der Marel 2007).

Conclusion

- **Implications for practice**

  Given the lack of evidence of efficacy and the potential for adverse effects, paracetamol cannot currently be recommended for pain associated with heel lance, eye examinations or assisted vaginal birth. The effectiveness of paracetamol for other painful procedures/conditions in newborn infants has not been studied in randomised controlled trials. The findings of our review provide insufficient evidence to establish the role of paracetamol in reducing the effects of painful procedures in neonates.

- **Implications for research**

  Paracetamol may reduce the total amount of morphine required during the first 48 hours following major thoracic or abdominal surgery. Further trials are required to ascertain this possible beneficial effect of paracetamol for pain management in neonates.

Thank you!