Less opioids after major abdominal surgery in young infants using wound catheter infusion with local anesthetics: a randomized controlled trial.

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In this prospective, double-blind, randomized controlled trial, we investigate the hypothesis that regional anesthesia provided by WCI with ropivacaine will reduce pain postoperatively (as measured with COMFORT behavior scale and Numeric Rating...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal stenosis and obstruction
Study type	Interventional

Summary

ID

NL-OMON47384

Source
ToetsingOnline

Brief title
Wound catheter infusion after abdominal surgery in baby's

Condition

- Gastrointestinal stenosis and obstruction
- Ureteric disorders
- Gastrointestinal therapeutic procedures

Synonym
abdominal surgery in infants (for example for atresia of duodenum or jejunum)

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Stichting Erasmus Fonds Pijngeneeskunde;Stichting Coolsingel

Intervention

Keyword: infants, locoregional anesthesia, ropivacaine, wound catheter

Outcome measures

Primary outcome

Primary Objective: Morphine sparing effect of WCI

The mean cumulative amount of morphine administered over 48 hours

postoperatively, in mcg/kg, will be compared in both groups (R group and

control group).

Secondary outcome

Secondary Objectives:

1. Efficacy of treatment of postoperative pain: To determine if WCI with

ropivacaine

provides adequate treatment of postoperative pain, COMFORT behaviour scale and

NRS Pain are measured, and these pain assessments are used to administer rescue

morphine doses IV.

Parameters:

* Number of patients needing extra morphine boluses (rescue), over 48 hours.

* Total amount of morphine administered postoperatively, until removal of the

wound catheter.

* AUC 24 hours COMFORT-B score and NRS, and percentage of high pain scores (NRS

* 4 and COMFORT * 17).

2. Safety of the use of WCI with ropivacaine: To investigate if WCI with local anesthetics is safe for the treatment of postoperative pain in children, the incidence of adverse events related to the wound catheter and the use of ropivacaine is registered

Parameters:

* Toxicity due to overdose or inadvertent intravascular injection of local anesthetic:

- hypotension
- arrhythmia
- convulsions

* The incidence of adverse effects related to the wound catheter:

- accidental luxation of the wound catheter
- infection (wound infection, sepsis)
- hematoma of the wound
- delayed healing of the wound
- wound dehiscence

* Plasma concentrations of ropivacaine (total and unbound) will be measured during the phase of continuous infusion in the wound, to determine if plasma levels do not exceed toxic thresholds.

3. Adverse events related to the use of opioids:

* Signs of respiratory depression:

- number of apnea episodes
- number of intubated and ventilated patients in each group, when admitted to the PICU

- time on the ventilator postoperatively

- number of reintubated patients during the study period

- number of patients receiving naloxone

- time until discharge from the PICU (if admitted to the PICU)

- time until discharge to the ward (if admitted to the recovery postoperatively)

* Gastro-intestinal:

- signs of intestinal obstruction and nausea and vomiting

- time to first feeding

* Hemodynamic:

- hypotension with the need for vaso- active medication or fluid boluses

- bradycardia (other than due to or directly related to the disease or operation)

4. Other variables:

* Surgical stress:

To classify the surgical stress of the different procedures, the Surgical Stress Score is computed by the surgeon at the end of surgery: the amount of blood loss (score range 0-3); site of surgery (score range 0-2); amount of superficial trauma (score range 1-3); extent of visceral trauma (score range 1-4); duration of surgery (score range 1-5); associated stress factors: hypothermia (score range 0-3) and infection (score range 0-3). The total scores are used to divide the procedures in minor, moderate or severe surgical stress.

* The Parents* Postoperative Pain Measure- Short Form:

One week after the operation, the parents are contacted to fill out a

questionnaire: the PPPM-SF, a validated questionnaire, which shows the postoperative recovery of a child after discharge from the hospital.[35]

Dutch translation:

Kinderen gedragen zich soms anders als ze herstellen na een operatie. Op de onderstaande lijst staat bepaald gedrag dat uw kind wel of niet heeft laten zien na de operatie. Geef voor elke punt aan of dit van toepassing is door ja of nee te antwoorden.

De volgende vragen gaan over het gedrag van uw kind na het ontslag uit het ziekenhuis.

* Zeurt of klaagt uw kind meer dan normaal? Ja/nee

* Speelt uw kind minder? Ja/nee

* Is uw kind niet bezig met wat hij of zij normaal doet? Ja/nee

* Is uw kind meer ongerust dan normaal? Ja/nee

* Is uw kind stiller dan normaal? Ja/nee

* Heeft uw kind minder energie dan normaal? Ja/nee

* Eet uw kind minder dan normaal? Ja/nee

* Raakt uw kind de pijnlijke plek (van het lichaam) steeds aan? Ja/nee

* Kreunt en kermt uw kind meer dan normaal? Ja/nee

* Is uw kind aanhankelijker dan normaal? Ja/nee

*

Study description

Background summary

Postoperative pain in infants
Treatment of pain in neonates and infants has much improved in the last decades, when it became clear that young children respond to tissue injury with specific behaviour and with autonomic and hormonal responses and signs of metabolic stress.[1, 2] Pain may lead to several unwanted consequences, such as discomfort and distress, but may also have long-term behavioural consequences.[3-6]
Worldwide, the standard analgesic drug after major surgery in neonates and infants is morphine, with or without paracetamol. However, young children are vulnerable to the side effects of opioids, especially respiratory depression, but also gastrointestinal dysfunction, delayed feeding and bladder retention. Morphine administration may also prolong the need for ventilatory support in infants.[7] Numerous experimental data have suggested long term neurobiological sequelae of early opioid exposure in the offspring.[5,8]

Regional anesthesia
Regional anesthesia (RA) provides profound analgesia with minimal physiological perturbations or side effects and is an effective alternative to systemic analgesics.[9-11] Only a few prospective randomized controlled trials comparing RA with systemic analgesics in children are available in the literature.[9-10] According to the Guidelines for Postoperative Pain Treatment (page 176), released in 2013 by the Dutch Society for Anesthesiology (Nederlandse Vereniging voor Anesthesiologie), there is a lack of scientific evidence on RA in children. More research is needed to show the advantage of RA over other treatment modalities for postoperative pain (oral, rectal, intravenously).[12]
There are several regional analgesia techniques for the treatment of postoperative pain after abdominal surgery, such as epidural catheters and regional blocks of the abdominal wall.[13,14] In adults, epidural analgesia has shown to be effective after abdominal surgery.[15] Pediatric epidural analgesia is however associated with risks, especially in children < 6 months of age, such as nerve root damage, dural puncture and accidental intrathecal administration of drugs.[11,16] Although the risks are considered small in experienced hands, a peripheral regional block is considered safer than a neuraxial block.[11,16,17]
Peripheral blocks of the abdominal wall provide analgesia restricted to the site of surgery, with a good safety record, especially when performed under ultrasound guidance.[14] However, as these abdominal wall blocks are single shot blocks, the analgesic effect is short-lived, and opioid use is not always reduced.[14,17] Therefore, pediatric anesthesiologists are still in search of regional anesthetic techniques, which can be performed safely in neonates and infants, and with a longer duration of effect.

Wound Catheter Infusion
The use of a subcutaneous wound catheter infusion (WCI) with local anesthetics

is a relatively new technique, which has shown to produce effective postoperative analgesia in adults.[18-20] WCI was associated with low pain scores comparable to epidural analgesia, decreased morphine consumption, increased patient satisfaction, normal postoperative recovery and was not associated with any adverse effects regarding to wound healing.[18,20] An interesting aspect of WCI and postoperative wound healing is that local anesthetics seem to have an antimicrobial effect, inhibit local inflammatory response to injury and reduce the release of inflammatory mediators.[21,22]
In children, WCI has been described after iliac crest bone harvesting, abdominal surgery, sternotomy, thoracotomy, and orthopaedic surgery.[23-29] However, most of these studies included older children (> 3 years of age). These studies show that WCI provides good postoperative analgesia, and is safe to use in children. In one study, the lower requirement for IV morphine was associated with earlier return of bowel function.[28] In a retrospective study WCI led to a decreased rate and duration of postoperative urinary catheter placement.[29] A reduction in opioid requirements could not always be demonstrated.
So far, few studies have been published on the use of WCI in children < 1 year old. One RCT published in 2013 investigated the efficacy of WCI after abdominal surgery in children (6 months * 13 years old).[27] Thirty-three children undergoing elective minor abdominal surgery were included. Patients were randomized to receive bupivacaine or saline via WCI. All patients received paracetamol. In case of pain, a bolus morphine was administered IV (0.05 mg/kg). Primary outcome was the number of postoperative rescue morphine doses. Mean age of the children included in this study was 3.4 years in the bupivacaine group (n=17) and 2.8 years in the saline group (n=16). On the first postoperative day, patients in the bupivacaine group had significantly less need for morphine compared to the saline group with a mean of 1.3 (SD 1.3) and 3.1 (SD 2.5) respectively (p< 0.05). No plasma bupivacaine concentrations were measured. In this study, children < 9 kg received a lower dose of bupivacaine (0.2 mg/kg/h) than children > 9 kg (0.4 mg/kg/h). No separate analysis of morphine rescue doses was performed for the group < 9 kg, and the number of patients included in this weight group is unknown. Also, they could not demonstrate an opioid sparing effect of WCI in children < 6.3 kg. This group was given the lowest dose of WCI, and may have been under dosed.
Another RCT published in 2009 was performed in 72 children after sternotomy for open heart surgery.[28] The treatment group (n=35) received levobupivacaine 0.25% or bupivacaine 0.25% via WCI, the control group (n=37) saline. Children aged > 3 months and < 17 years and weight > 5 kg were included. An elastomeric bulb device filled with local anesthetic or saline was attached to the wound catheter, and a continuous infusion of 0.5-5.0 ml/h was used, depending on the weight of the patient. Rescue analgesia was IV morphine 0.05 mg/kg. Patients of > 5 years old were given PCA morphine IV as rescue. Total morphine requirements over the first 24 hours were significantly lower in the treatment group than in the control group (p=0.007), but not on postoperative days two and three. Levobupivacaine plasma levels remained below the toxic threshold (4 mcg/ml) throughout the study period. However, the relationship between weight of the

child, dose of local anesthetic administered and level of local anesthetic measured in the plasma was not investigated.
A group from the Karolinska University in Stockholm, Sweden published 2 studies on the use of WCI in neonates after thoracotomy for ligation of ductus Botalli, and plasma concentrations of local anesthetics (levobupivacaine) during WCI in these patients. The WCI technique was associated with low pain scores, apparently normal postoperative recovery and was not associated with any adverse effects with regard to wound healing.[30] The levels of total and unbound plasma concentrations of levobupivacaine remained within acceptable safety limits during 72 hours in these studies.[30,31]

Ropivacaine * rationale for drug choice
Most studies regarding WCI in children have been performed with bupivacaine as local anesthetic.[24-28]
However, levobupivacaine and ropivacaine are associated with a lower risk for serious systemic toxicity compared with bupivacaine, and should therefore preferably be used in children.[32]
Amide local anesthetics (such as (levo)bupivacaine and ropivacaine) bind to serum AGP (a1-acid glycoprotein). AGP concentrations are very low at birth and progressively increase during the first year of life. This is why neonates and young infants have a much higher free fraction of local anesthetics than adults.[33] Also, CYP1A2 activity, which metabolizes ropivacaine, is immature before the age of 4-7 years.[33] Neonates and infants are therefore more prone to develop toxicity.
Ropivacaine appears to be the least toxic of the available long-acting local anesthetics, but is less potent than levobupivacaine and bupivacaine.[32] In the ErasmusMC-Sophia, there is much experience with the use of ropivacaine in children, as this is the local anesthetic of choice for continuous infusions in epidural and locoregional catheters in children.

Conclusion
Further investigations are needed to determine the analgesic and opioid sparing effect of WCI in children < 1 year of age. The technique seems promising, however few data are available on the efficacy of WCI for treatment of postoperative pain in neonates and infants, the group of children who would benefit especially from the opioid sparing effect.
Since the data on the use of ropivacaine for WCI in children are sparse, investigations are needed to determine the adequate dose to establish analgesia and an opioid sparing effect, including measurements of plasma concentrations to determine whether the dose used is safe for infants and neonates.

Study objective

In this prospective, double-blind, randomized controlled trial, we investigate the hypothesis that regional anesthesia provided by WCI with ropivacaine will

reduce pain postoperatively (as measured with COMFORT behavior scale and Numeric Rating Scale Pain scores) and lead to a morphine-sparing effect of at least 30% after major abdominal surgery in infants < 1 year of age.
In this investigation also plasma ropivacaine levels will be measured, during the phase of continuous infusion via the wound catheter, to determine if levels of ropivacaine remain below toxic thresholds.

Study design

Single center, prospective, randomized, double blind, placebo controlled study where children < 1 year of age undergoing major abdominal surgery will be randomized for the treatment with WCI with a bolus dose and continuous infusion with ropivacaine 0.2% (R group) or with placebo (saline) (Control).
At the end of surgery, following closure of the muscle layers, the surgeon will place a multi-hole wound catheter superficial to the muscle fascia under direct vision (On Q® Soaker Catheter, Halyard*) in all patients. The subcutaneous tissue is closed where after the skin is sutured.
Both groups will receive a bolus via the catheter: ropivacaine 2 mg/kg in the R group, saline (NaCl 0.9%) in the same amount in the control group. Both groups will receive a bolus intravenously: morphine 0.1 mg/kg in the control group, and the same amount in ml/kg saline in the R group. A continuous infusion via the wound catheter will be started in both groups: ropivacaine 0.2 mg/kg/h in the R group, and saline in the control group.
Both groups will receive intermittent administration of paracetamol IV (as primary analgesic) and titrated morphine IV in case of documented pain (rescue therapy).

Intervention

Wound catheter placement and medication
At the end of surgery, following closure of the muscle layers and subcutaneous tissue, the surgeon will place a multi-hole wound catheter superficial to the muscle fascia under direct vision (On Q® Soaker Catheter, Halyard) and tunneled from a separate stab incision approximately 3 cm lateral to the wound. Hereafter the skin is sutured. The catheter is fixated to the skin with a plaster (Steri Strip* and Tegaderm*) and is connected to a syringe in a perfusor pump, which is filled with either ropivacaine 0.2% or saline (placebo). Before end of anesthesia, all children will receive a bolus dose via the wound catheter: ropivacaine 2 mg/kg (R group) or the same amount in ml/kg of saline (saline) in the control group. WCI is started postoperatively: ropivacaine 0.2 mg/kg/h (R group) or saline (control group) in the same amount. At the end of surgery, the control group will receive a bolus dose of morphine 100 mcg/kg IV, because this is standard of care after major surgery in the Erasmus MC-Sophia (local pain protocol). Group R receives placebo (saline) in the same amount as IV bolus dose. All patients receive a first dose of paracetamol 20 mg/kg IV at the end of surgery. Paracetamol IV is continued as

standard analgesic, also according to local pain protocol.
Postoperatively, all children < 3 months of age (or 60 weeks PC age in premature children) are admitted to the PICU or the recovery ward (> 3 months of age, or > 60 weeks PC age). At the PICU or recovery ward, postoperative pain is assessed in all children using the COMFORT behavior scale and NRS pain. Based on these validated pain assessments, patients receive rescue morphine doses, when needed, according to an algorithm. (Appendix 1)
Children will be followed up for 72 hours postoperatively, after which the catheter will be removed.

Treatment of postoperative pain in both groups
All patients receive paracetamol IV postoperatively, according to a protocol published by our group.[34]
Additional IV morphine is administered whenever the NRS is equal to or greater than 4 and COMFORT > 16, which indicates pain. (Appendix 1) Doses of additional morphine are administered every 10 minutes whenever needed, with a maximum of 3 times per hour. Ten minutes after each extra dose of morphine, pain is re-assessed. If there is no improvement in the scores three additional (rescue) doses, an additional dose of morphine 100 mcg/kg IV is administered and continuous morphine infusion is started. This can be increased in total 2 times if the child still needs extra doses of morphine.

Plasma concentrations of ropivacaine
To determine if plasma ropivacaine levels do not exceed toxic levels, blood samples will be taken from an indwelling arterial line, or at the same time a regular blood sample is taken by heel prick, concomitant with blood sampling for clinical purposes (in case there is no arterial line). Patients will not suffer extra heel pricks for only study purposes. With respect to the ethical requirement that not more than 3% of the total blood volume (80-100 ml/kg) can be drawn from a patient, sampling will be restricted to maximum three samples per day (0.5 ml each) (maximum six samples over the whole study period (48 hours)). Weight of the patients will vary between approximately 3 and 10 kilograms, hence, in a 3 kg baby 6 x 0.5 ml = 3 ml is max 2% of TBV .

Study burden and risks

Worldwide, the standard analgesic drug after major surgery in neonates and infants is morphine. However, young children are vulnerable to the side effects of opioids, especially respiratory depression. Morphine administration may also prolong the need for ventilator support in infants.
The use of a subcutaneous wound catheter infusion (WCI) with local anesthetics is a relatively new technique, which produces effective postoperative analgesia and is safe to use in adults and older children. WCI was associated with low pain scores and decreased morphine consumption. However, most of these studies included older children (> 3 years of age).
The WCI technique would provide postoperative analgesia without respiratory depression associated with opioids, which would be a great advantage in young

children. Therefore we would like to conduct this study in children < 1 year of age, who would benefit especially from the possible morphine-sparing effect. Eligible children will be children < 1 year of age already undergoing major abdominal surgery, elective or semi-urgent. These children will receive the standard perioperative care, this will not be changed because of the investigation.
All children will receive a woundcatheter during closure of the wound. The child is still under anesthesia, at the end of the operation. This will be no extra burden to the child. Ropivacaine (a local anesthetic) will be administered via the woundcatheter, subcutaneously: first a bolus dose, and then a continuous infusion in a lower dose. After a few days the woundcatheter will be removed. This is a painless procedure, and therefore not a burden to the child.
We exclude all children with an allergy to local anesthetics, contra-indications for regional anesthesia techniques (such as infection of the site of the wound) and also children with renal or hepatic dysfunction, as this may cause a higher risk of local anesthetic toxicity or toxicity from paracetamol or morphine administration.
Research on the woundcatheter in older children has shown that its use is safe: sometimes leakage of the local anesthetic from the wound is described, or redness of the skin around the wound. No increase of woundinfections or delayed wound healing has been shown.

Ropivacaine is a local anesthetic, which is the local anesthetic of choice in het Sophia Children's Hospital. It is registered for the use in young children: from the age of 0 months for the use as epidural infusion, ans in children > 1 year of age for use for peripheral nerve blockade. Risks of the administration of ropivacaine are accidental injection of the drug directly into a bloodvessel, which could lead to cardiotoxic reactions (arrhythmia). This can be prevented by aspiration of the catheter first, to see if blood is aspirated. Also, an overdose of the drug can lead to toxicity (arrhythmias, epileptic insults). As ropivacaine is not a registered drug for continuous wound infiltration in children < 1 year of age, we decided to stay on the safe side of dosage and use the recommended (en registered) dose advice for ropivacaine in epidural infusions in children < 6 months of age, which is 0.2 mg/kg/h for 72 hours.
To determine if plasma ropivacaine levels do not exceed toxic levels, blood samples will be taken from an indwelling arterial line, or at the same time a regular blood sample is taken by heel prick, concomitant with blood sampling for clinical purposes (in case there is no arterial line). Patients will not suffer extra heel pricks for only study purposes. Also a DSMB is established, who will examine the results, including plasma concentrations of ropivacaine per patient, after 10 and 30 patients have been included in the study. We thereby hope to have taken sufficient measures to reduce the overall risks for the children participating in this investigation.

A potential ethical concern of the study is that this is a placebo controlled

study investigating a new RA technique for the treatment of postoperative pain, and special care must be taken that no child included in the study is undertreated when having postoperative pain. We therefore have an extensive postoperative pain protocol, which is our current protocol in the pediatric intensive care unit, to guarantee that no child will suffer from severe postoperative pain during this trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:;- Informed consent;- Children < 1 year of age;- Minimal post-conceptual age of 35 weeks;- Minimal body weight of 1500 grams;- Abdominal (open) surgery

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:;- Withdrawal of informed consent;- Child with neurological disease, renal or hepatic dysfunction;- Chronic (more than one day) opioid or psychotropic drug (e.g. antiepileptics, benzodiazepines, antidepressants) exposure pre- or postnatal, in neonates (maximum 28 old) presenting for surgery, or < 1 month ago.;- Opioid exposure <24 hours before surgery;- Receiving ECMO therapy;- Known allergy / intolerance for paracetamol or morphine;- Contra-indications for regional analgesia techniques:;o Allergy to local anesthetics;o Local or general infection (sepsis)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-12-2017
Enrollment:	60
Type:	Actual

Medical products/devices used

Generic name:	Woundcatheter
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Ropivacaine

Generic name:	ropivacaine hydrochloride
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-04-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 20504
Source: Nationaal Trial Register

Title:

In other registers

Register	ID
EudraCT	EUCTR2015-002209-12-NL
CCMO	NL59689.078.17
OMON	NL-OMON20504