CLINICAL TRIAL PROTOCOL

In children undergoing laparoscopic appendicectomy for suspected acute appendicitis, does local anaesthetic sprayed onto the peritoneum, compared to saline, reduce post-operative pain: a randomized, double-blind, placebo-controlled, two-arm parallel group trial

STUDY NAME

SPRAYED **P**ERITONEAL **R**EGIONAL **A**NALGESIA IN APPENDICECTOM**Y**

(SPRAY)

REGISTRATION

Australian and New Zealand Clinical Trials Registry Number ACTRN12613001159741

Universal Trial Number (UTN)

U1111-1148-7094

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Scientific background and rationale

Appendicectomy for acute appendicitis is the most common emergency abdominal operation performed for children. At Starship Hospital, the operation is routinely performed laparoscopically because this approach is less painful; however, post-operative pain can still be severe.[1] [2] Data from two recent randomized controlled trials from our unit reveal 70-80% of children receive opiate analgesia after laparoscopic appendicectomy. The first trial demonstrated no benefit from warm humid gas versus room temperature dry gas for distending the abdomen during laparoscopic appendicectomy.[3] Our second trial (recently completed and as yet unpublished) demonstrated significantly reduced pain in the first 6 hours with an ultrasound guided rectus sheath nerve block (that is, reducing the pain at the umbilicus where the largest incision is made). However, pain was still quite severe after the nerve block had worn off.

A systematic review of the literature uncovered only three peritoneal local anaesthetic trials in paediatric laparoscopic surgery involving a total of 125 children.[4-6] Only one was a randomized prospective study, involving 30 children undergoing a variety of elective laparoscopic procedures.[4] This trial demonstrated significantly lower pain scores in the peritoneal local anaesthetic group; however, several methodological aspects of the study including its small size, no report of the randomization method, no blinding and no placebo group suggest further evidence is needed before peritoneal local anaesthetic can be considered efficacious in paediatric surgery.[4]

In adults, the benefits of peritoneal local anaesthetic have been well documented. Professor Hill's group at the University of Auckland South Auckland Clinical School have demonstrated in systematic reviews reduced pain after laparoscopic cholecystectomy and laparoscopic gastric procedures, and shown in a randomized controlled trial improved recovery after open colorectal surgery.[7-9] Evidence for peritoneal local anaesthetic in acute appendicitis, however, is lacking.

We hypothesise that a significant proportion of post-operative pain may be mediated by afferent nerve fibres in the parietal peritoneum. Furthermore, the vagus nerve may contribute to a poorly localised 'visceral' pain.[10] Vagal afferent nerve endings are located in the visceral peritoneum. Peritoneal inflammation from the inflamed appendix and from the surgical dissection may cause considerable pain through these two neural pathways.

Objectives

Our hypothesis is peritoneal local anaesthetic spray will reduce pain in children after acute laparoscopic appendicectomy.

The specific objectives of the trial are to:

1. Reduce pain in children after laparoscopic appendicectomy;

2. Reduce opiate requirements;

3. Reduce length of hospital stay.

Potential benefits

If successful in reducing pain, the technique is expected to improve patient care, satisfaction, and could potentially reduce hospital bed utilisation and costs. The research could enhance knowledge on how the peritoneum contributes to pain after surgery.

METHODS

Trial design

Randomized placebo controlled parallel arm trial with a 1:1 allocation ratio.

Participants

Inclusion Criteria

Children 8 years of age or older presenting to Starship Children's Hospital with a diagnosis of acute appendicitis and offered laparoscopic appendicectomy for suspected acute appendicitis.

Exclusion Criteria

- Developmental delay, neuro-muscular impairment, chronic pain, or psychiatric illness;
- Unable to speak and read English;
- Partially sighted or blind;
- Presence of any abdominal prostheses such as a gastrostomy or ventriculo-peritoneal shunt;
- Allergy to bupivacaine;
- Less than 20kg in weight;
- Consent not obtained from both the participating child and a parent or legal guardian.

Setting

The trial is set in Starship Children's Hospital, specifically children are recruited in the Children's Emergency Department or on inpatient wards, when they are clinically assessed for suspected appendicitis. The interventions occur in the Starship Hospital Operating Rooms. Data collection occurs in operating theatre, on the wards and at outpatient follow-up (whether phone or in clinic).

Interventions

Consent

1. Written consent is obtained from the participating child and an accompanying parent/ guardian.
2. Details of the study are explained by the operating surgical registrar, consultant or Principal Investigator. Prospective participants and their accompanying parent/ guardian receive information sheets about the trial. Adequate time is given for answering questions and discussion with other family/whānau members.
3. Consent is obtained as soon as possible (within 2 hours) in keeping with the acute nature of appendicitis and the need for early operative treatment.

4. If a parent/guardian is not present during the consent process, consent can be discussed and obtained by telephone. Written consent should be obtained as soon as possible thereafter.
5. Study Consent Forms is kept in participants' clinical notes.
6. When consent is not obtained from an eligible child and/or respective parent/caregiver for any reason, the circumstances are documented by the Principal Investigator. This helps to ensure enrolled patients are representative of the entire study population and allows identification of problems arising during the recruitment process.

Pre-operative Management

The diagnostic work-up of each participant is at the discretion of surgical admitting team. Normal resuscitation practices are followed as clinically indicated. Pre-operative administration of antibiotics are standardised according to *Starship Children's Health Clinical Guidelines for Treatment of Suspected Appendicitis*. This algorithm outlines the appropriate use of antibiotics before, during and after surgical treatment for simple and complicated appendicitis. It is available on the Starship Hospital Clinical Guidelines page of the ADHB intranet.

Intra-operative Intervention

After inserting the laparoscopic ports and inspecting the abdominal cavity, the surgeon sprays 20ml of blinded study solution (either local anaesthetic or saline) onto the peritoneum of the right iliac fossa and pelvis. The surgeon will usually spray the peritoneum before dissecting out the appendix, but may elect to spray at the end before removing the ports, specifically when pus is present requiring peritoneal lavage.

Local anaesthetic and placebo preparation

After determining group allocation, the unblinded circulating theatre nurse together with the scrub nurse draw up in a 20ml syringe either (according to allocation) bupivacaine according to the dose schedule below, *or* 0.9% sodium chloride. They label the syringe 'Study Drug' and attach it to one lumen of a 5mm CoSeal DuploSpray MIS Applicator® Ref: 0600044 *(Micromedics, St. Paul, MN)*. The side luer of the DuploSpray® is occluded with a luer plug *(Double Ended Cap, CareFusion, San Diego, CA)* (blue coloured luer lock on the anaesthetic trolley). The DuploSpray® will fit down a 5mm port. Alternatively, the scrub nurse can connect the 'Study Drug' 20ml syringe to an 8 French Feeding Tube to go down a 3mm port.

As a rule, the team will use the DuploSpray® system because it gives a better spray effect. If not available, they can use the 8 Fr Feeding Tube, remembering this will require a 3mm suprapubic port (trying to put it down a 5mm port will result in an air leak).

Local anaesthetic dose

The volume of solution available for the nerve block will be calculated according to the patient's body weight, to maintain a maximum dose of bupivacaine at or below 2.5mg/kg.

- If **36kg or more**, draw up 20ml 0.25% bupivacaine;

- If **26kg or more**, but under 36kg, draw up 20ml 0.125% bupivacaine (dilute 10ml 0.25% with 10ml saline and mix well);
- If 25kg or less, it is crucial to use the figures in Table 1 to avoid overdose.

Table 1. Volume of local anaesthetic / study solution to be drawn up for the block.

WEIGHT (kg)	Total Study Solution (ml)	Bupivacaine concentration
36 or more	20	**0.25%**
26 - 35	20	*0.125%*
25	18	*0.125%*
24	16	*0.125%*
23	14	*0.125%*
22	12	*0.125%*
21	10	*0.125%*
20	8	*0.125%*

In addition to the peritoneal spray, the surgeon or anaesthetist will perform a rectus sheath nerve block with 20ml 0.25% bupivacaine with adrenaline, and the surgeon with infiltrate port sites with 6ml 0.25% bupivacaine with adrenaline, 2ml at each port site. The local infiltration will be subcutaneous at the umbilical port and infiltrated into the abdominal muscles under laparoscopic guidance for left iliac fossa and suprapubic ports. The total volume available for these blocks is stipulated in Table 1.
In summary, the scrub nurse will have 3 syringes on the sterile table:

1. 6ml bupivacaine in a 10ml syringe for local port site infiltration.
2. 10 ml bupivacaine for the rectus sheath nerve block.
3. 'STUDY DRUG' in a 20ml syringe for peritoneal spray.

Standardised Anaesthesia

Intraoperative analgesia is standardised to:
Morphine up to 0.3mg/kg;
Fentanyl 2mcg/kg titrated as required;
Paracetamol 15mg/kg, if paracetamol has not been given pre-operatively;
Parecoxib 1mg/kg up to a maximum of 40mg, if not contraindicated.
Standardised prophylactic antiemetic is ondansetron 0.15mg/kg and dexamethasone, if not contraindicated.
~~Steroid and/or non steroidal anti-inflammatory agents may be given at the discretion of the anaesthetist~~

Nerve block technique

1. Ultrasound preparation: Prepare the Sonosite® using the "Patient, Probe, Preset" approach. Chose a nerve or vascular preset. Adjust the depth so the posterior rectus sheath is half way between the top and the bottom of the screen. Optimise near and far gain. Note a point near the lateral edge of rectus at or slightly cranial to the level of the umbilicus.

2. *Nerve block:* Insert the Sonoplex needle guided by an in-plane ultrasound image, and advance the tip stepwise using the sequence "advance-visualise" to the junction of the posterior rectus sheath with the rectus muscle. Aim for a point 1-2cm medial to the lateral edge of the rectus sheath. Aspirate (to avoid vascular placement) and inject 1-2ml. An hypo-echogenic lentiform swelling will confirm correct needle tip position. If the needle is too superficial (within muscle) or too deep (under posterior rectus sheath) readjust and repeat. Half of the solution is injected at this point. The process is repeated on the contralateral side.

Standardised Surgery

Laparoscopic access is by three ports, generally a 5mm umbilical Hasson port, 5mm left iliac fossa and 3mm suprapubic. The 5mm umbilical port may need to be enlarged to remove the appendix. Some surgeons may chose to place a 5mm suprapubic port, especially in larger children in whom the longer 5mm instruments may be required.

The rectus sheath nerve block is performed prior to placing the umbilical port. The block may be placed by either the surgeon (after prep and drape) or the anaesthetist (prior to prep and drape). See section above.

Local anaesthetic (2ml 0.25% bupivacaine with 1:400,000 adrenaline) is infiltrated at each site prior to incision. At the umbilical site, local is infiltrated subcutaneously only. At the 5mm port sites local is instilled mainly into fascia and muscle under laparoscopic guidance.

Other technical aspects of the appendicectomy are at the surgeon's discretion. Generally, after inspecting the abdominal cavity, identifying the appendix and taking appropriate laparoscopic photos, the mesoappendix is carefully sealed with a 5mm bipolar diathermy forceps and divided, or sealed and divided with the monopolar hook diathermy, and the appendix base is ligated with two 0 PDS Endoloops®. The appendix is removed via the umbilical port, usually in a bag or the finger of a sterile non-latex glove, to avoid contamination. Wounds are closed with absorbable sutures.

Post-operative Pain Management

1. Paracetamol

Oral paracetamol 20mg/kg 6 hourly for 24 hours (maximum single dose 1000mg; maximum 24 hour dose is the lesser of 90mg/kg, or 4000mg).

Substitute with intravenous paracetamol 15mg/kg 6 hourly for 24 hours if not able to tolerate oral intake (maximum single dose 1000mg; maximum 24 hours dose is the lesser of 60mg/kg, or 4000mg).

2. Tramadol

Oral, 1-2mg/kg, Q4-6hourly PRN: Maximum dose 800mg/24h.

3. Morphine

As per IV protocol. The Starship Children's Health Clinical Guideline for Morphine Administration is available on the ADHB Intranet.

4. Antiemetic

Ondansetron IV PRN

5. PCA

Patients who require more than 5 titrations of morphine within a 25 minute period may be provided with a patient controlled analgesia pump devices (PCA). Morphine or fentanyl are used for PCAs at the discretion of the Acute Pain Service.

***NB Pain team**, please record 6 hour, 12 hour and 24 hour opiate doses for PCA patients.*

Post-operative Care

- Vital signs and pain (LOLIPOPS) recordings at 0, 2, 4 ,6, 8 hours then 4 hourly
- Anti-emetic medications as required
- Eating and drinking as soon as able to tolerate
- Early mobilisation

Discharged Criteria

- Afebrile
- Tolerating adequate oral intake
- Mobilising independently
- Free of nausea and vomiting
- Oral analgesia for pain relief

Outcomes

Intra-operative findings to be noted

1. Macroscopic state of the appendix
    a. Normal
    b. Early acute
    c. Suppurative
    d. Gangrenous
    e. Perforated

        NB. definition of 'perforated' is a visible hole in the appendix at laparoscopy, or a fecolith in the abdomen.
2. Sites of pus
    a. Right iliac fossa
    b. Pelvis
    c. Left iliac fossa
    d. Right upper quadrant
    e. Generalised
3. Other pathology (e.g. Meckel's diverticulitis; torted ovarian cyst)

Post-Operative Pain Scores

Record pain scores using the LOLIPOPS pain chart in the Post-Anaesthetic Care Unit (PACU) and at 0, 2, 4, 6, 8, 12, 16, 20 and 24 hours post-operatively ('0' defined as the time the patient entered PACU). *The 0, 2 hour, 4 hour and 6 hour post-op pain scores should be performed* (sleeping children may need to be briefly woken to perform these). After that (i.e. for the 8, 12, 16, 20 & 24 hours scores) the normal LOLIPOP instructions may be followed for sleeping children, i.e. do not awake but perform a pain score as soon as possible after waking (rather than simply waiting until the next 4-hour observations are due).

Follow-up

10-day recovery questionnaires

Patients will complete a 10 question report, adapted from the PedsQL™ Pediatric Quality of Life Inventory, 10 days after their operation. At the same time they will be asked a general satisfaction question on perceived quality of care, and this will be scored on a 10cm linear analogue scale. Participants will be given these at enrolment, and the investigator will ring families at 10 days to gather the results.

6-week follow-up

At 6 weeks post-operatively an investigator will phone parents / families to enquire about:

- Any complications
- Date returned to "all normal activities"
- Date returned to sport
- Date returned to school
- Overall satisfaction with recovery
- Number of GP or A&E visits
- Any readmission to hospital

Summary of Study Outcome Measures

1. Pain scores:
    a. Global pain severity scores;
    b. Pain severity by location scores, using the Lolipops tool;
2. Morphine equivalent daily doses (MEDD):
    a. Intraoperative MEDD;
    b. 0-6 hour post-operative MEDD;
    c. 6-12 hour post-operative MEDD;
    d. 12-24 hour post-operative MEDD;
3. The proportion of children who received opiates;
4. Length of hospital stay, total and post-operative;

5. Revised Quality of Life recovery score at 10 days post-operatively;
6. Global satisfaction post-operatively;
7. Complications or readmission rates in the first 30 days;
8. Post-operative nausea and vomiting.

Sample size

The projected sample size was calculated using G*Power version 3.1.3[15] using data from the global pain scores at 3-6 hours post-operatively in the intervention arm of the recently completed SNAP trial. We considered a 30% reduction in the mean pain scores from 4.39 to 3.07 to be clinically significant, set the standard deviation 2.646, assumed equal variance, and used a t-test. At alpha error probability 0.05 and 1-beta error probability 0.9, G*Power calculated the total sample size = 174 (87 in each group).

Randomisation

Sequence generation

The allocation sequence is generated using an open source computer-based on-line random number generator, http://www.random.org. All numbers from 1 to 209 (to give 20% redundancy) are generated in random sequence and arranged in 2 columns. Columns are labelled 'A' and 'B'; 'A' and 'B' are randomly assigned to represent intervention and placebo groups.
Randomization is not restricted or stratified.

Allocation concealment mechanism

The 'code' defining columns 'A' or 'B' to intervention or placebo groups is placed in a sealed opaque envelope labelled 'Code'.
Sheets of paper indicating the allocation - 'Local Anaesthetic' or 'Saline', and the allocation number - are placed into sealed opaque sequentially numbered envelopes. These envelopes are placed in a box and kept in the operating room accessible by theatre nursing staff.

Implementation

A research assistant generates the random number sequence, assigns random number columns to groups, seals the code in the 'Code' envelope, and places allocations into the 209 sequentially numbered allocation envelopes.
Surgical registrars and surgeons enrol patients.
Theatre nurses assign participants to interventions. Once recruited and consented, the unblinded circulating nurse opens the allocation envelope and prepares the study solution. The unblinded scrub nurse draws up the study solution. Prior to participants entering the room, these two unblinded nurses draw up either (according to allocation) bupivacaine with adrenaline (according to the dose schedule), or 0.9% sodium chloride, into a 20ml syringe, taking care to do this out of view of other theatre personnel. The syringe is labelled 'STUDY DRUG' and subsequently handed to the operator without

divulging allocation. The volume of study solution will be determined from Table 1. A copy of Table 1 will be placed on the wall in the acute operating room for easy reference.

Blinding

Patients, families, investigators, surgeons, anaesthetists, theatre personnel (except the unblinded circulating nurse and scrub nurse), ward nursing staff and pain team responsible for the intra- and post-operative care of participants are all blinded to group allocation.

Blinded investigators will collect data. The principle investigator will perform statistical analysis blinded to group allocations and will prepare data spreadsheets labelled with the coded study group allocations. Allocations will subsequently be revealed at the completion of data analysis.

The interventions are similar, leading to little risk of being able to break blinding through observation intraoperatively or post-operatively. The write-up of the report of the study will commence prior to revealing group allocations (introduction and methods) in an effort to avoid publication bias.

Statistical methods

Appropriate statistical analysis will be performed for comparison of groups. Pain scores involve repeated measures over time for each participant, so we *a priori* plan to use a general linear mixed model to analyse pain score data. We *a priori* plan subgroup analysis of the non-perforated / uncomplicated appendicitis group.

Data Collection and Storage

The Principal Investigator is responsible for ensuring all sections of the Investigator's Checklist are completed.

Study data will be stored securely at Auckland District Health Board for the duration of study and for 10 years from the time the youngest participant turns 16 years of age.

Registration

The SPRAY trial has been registered with the Australian and New Zealand Clinical Trials Register, allocation number ACTRN12613001159741, web address http://www.ANZCTR.org.au/ACTRN12613001159741.aspx.

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