**Clinical Study Protocol**

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| **Title** | Does Peritoneal Lavage Influence the Rate of Complications in Paediatric Laparoscopic Appendicectomy? A Multisite Prospective Randomised Controlled Trial. |
| **Short Title** | SWAP- Suction vs Washout for Appendicectomy in the Paediatric populaton |
| **Protocol Number** | 4.1 |
| **Coordinating Principal Investigator/ Principal Investigator(s)** | Mr. Ramesh Nataraja  Mr. Maurizio Pacilli  Miss Samantha Leng |
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| **Location** | Monash Children’s Hospital (Monash Health) |

**Research Summary**

**Study Title**

Does Peritoneal Lavage Influence the Rate of Complications in Paediatric Laparoscopic Appendicectomy? A Multisite Prospective Randomised Controlled Trial.

**Study Design**

This study is a multicentre national prospective, randomised controlled trial that compares the use of peritoneal lavage (‘washout’) and suction only in paediatric complex appendicitis (≤16 years old) treated by a laparoscopic appendicectomy . The trial has been designed as per the recommendations of the CONSORT Statement.1

**Study Outcome Measures**

The primary outcome endpoints are the development of the post-operative complication of an intra-abdominal abscess (IAA). IAA will be defined as recurrent abdominal pain, pyrexia >38, raised inflammatory markers and ultrasound evidence of an intra-abdominal collection (>5cm in diameter).

Secondary outcomes will include the development of small bowel obstruction (SBO), length of stay (LoS), surgical wound infection (WI) and post-operative analgesia requirement.

**Study Protocol**

For this trial, we have defined complex appendicitis as the presence of an appendiceal perforation, intra-peritoneal faecolith, intra-operative mass or 4 quadrant purulent material.2

Eligible patients and their parent/guardian will be approached for enrolment prior to being taken to the operating theatre. If intra-operatively the surgeon determines them to have complex appendicitis they will be randomised intra-operatively to having peritoneal lavage (PL) or suction only (SO) using the SNOSE method.3 All patients will be recruited into the trial regardless of operative technique; laparoscopic (standard 2 x 5mm, 1 x 10mm port technique) or single incision appendicectomies. Open appendicectomies will be excluded from the trial due to the lack of a visualised PL.

Postoperatively patients will receive the standard care, including 5 days of intravenous antibiotics (broad spectrum according to institutional practice or IV ceftriaxone & metronidazole). Patients will be followed-up during their inpatient stay, and 4-6 weeks postoperatively during an outpatient clinic appointment by a research associate. If the patient is unable to attend their follow-up appointment, they will be contacted via telephone by a member of the research team.

**Study Population and Participant Groups**

Participants considered eligible for this study will be children 16 years of age and under who present to Monash Children’s Hospital or the other trial centres and are diagnosed as having complex appendicitis intra-operatively. Exclusion criteria will include any patient not willing to take part in the study, patients with non-perforated appendicitis and little or no peritoneal contamination, primary open appendicectomies and any appendectomy converted to an open procedure.

If consent has been obtained from the parent/ guardian, as well as the patient in the case of mature minors, randomisation to peritoneal lavage or suction only will be performed intra-operatively if complex appendicitis has been identified by the surgeon.

**Sample Size**

A power calculation has been based on the results of the recent systematic review and meta-analysis by Hajibandeh S et al. [Surg Innov. 2018 Apr;25(2):174-182]. This study demonstrated an overall incidence in postoperative IAA of 5.8% with irrigation and 2.6% with suction alone in complicated appendicitis. Therefore, we calculated that 1232 (616 in each group) patients are required to have an 80% chance (1-β=0.80) of detecting a statistically significant difference between the two groups (α = 0.05).

**Study Duration**

We anticipate that the study will commence in February 2020 and continue until February 2022. If the target sample size is reached prior to the estimated end-date an analysis will be conducted to determine whether further data should be collected before the study is ceased. The trial will undergo an interim analysis by an independent committee not involved in the trial when 616 (50%) of the patients have been recruited: the criteria for stopping the trial earlier is defined as a significant difference (p<0.01) between the two arms in post-operative IAA.

**Trial Registration**

ANZCTR trial request number- 378378

**Background and Research Objectives**

Appendicitis is the most common abdominal pathology in children. Laparoscopic appendicectomy is becoming the standard treatment in most developed countries.4 Infections such as IAA or WI remains the most common post-operative complication; with reported rates between 2.5–36% 5 Currently at MCH we perform approximately 330 laparoscopic appendicectomies per 12 month period. Of these approximately one third will be perforated appendicitis with significant peritoneal pus. Based on the pilot RCT that was conducted at our centre there is a low incidence of IAA with only 1 occurring in the cohort.2 The LoS was the primary end point for this trial rather than the IAA incidence.

Peritoneal lavage is an intraoperative manoeuvre performed whereby following removal of contamination the peritoneal cavity is washed out with saline and then suction applied to remove the saline solution. At appendicectomy not all surgeons will perform peritoneal lavage.

Peritoneal irrigation has been advocated as a method to reduce post-operative complications. The evidence for peritoneal lavage is largely historical and based on adult practice6. It is proposed that lavage reduces intraperitoneal bacterial load,7 and furthermore that laparoscopy facilitates improved peritoneal lavage in peritonitis.8

However, the evidence is divided with some indicating that it may in fact increase the risk of post-operative infections. Advocates of this argument proposed that lavage may spread contamination throughout the peritoneal cavity9 with an increased risk of abscess formation.10 Studies assessing lavage with antibiotic solutions have shown no difference in outcomes.11,12

Currently throughout the world there is no consensus and both techniques are commonplace and accepted modes of practice.

Therefore, the aim of this study is to assess whether intraoperative peritoneal lavage in laparoscopic appendicectomy in children reduces post-operative complications, with the eventual goal of minimizing post-operative infection rate and hence morbidity associated with laparoscopic appendicectomies. As the initial RCT study at our institution had a low incidence of complications we are planning a larger study to answer this question conclusively.

We hypothesise that the rates of post-operative complications will be significantly decreased with the use of adequate peritoneal lavage (2000mls or more) as compared with suction only, wherein:

* The rate of intra-abdominal abscess formation will be significantly decreased
* The rate of small bowel obstruction will be significantly decreased
* The length of inpatient stay post-operatively will be significantly decreased
* The rate of surgical wound infection will be significantly decreased
* Post-operative analgesic requirement will be significantly decreased

**Methodology**

All patients aged 16 years old and under presenting to participating sites for appendicitis, and requiring a laparoscopic appendicectomy between February 2020 and February 2022 will be eligible to participate in the study. Exclusion criteria will include any patient not willing to take part in the study, patients with non-perforated appendicitis and little or no peritoneal contamination and any appendectomy converted to an open procedure.

We aim to enrol 1232 patients over a two-year period at the different trial centres. These patients will be recruited on presentation to the participating sites with symptoms of appendicitis that are planned for operative treatment with laparoscopic appendectomy. Patients and their parent/ guardian will be approached by a research associate or a member of their treating team and written consent will be obtained from the parent/ guardian (as well as from the patient if they are deemed by the treating clinician to be a mature minor). In theatre the surgeon will make a subjective decision as to whether the patient has complex appendicitis (where the appendix is perforated or there is widespread pus in the abdomen). At this point enrolment takes place. Routine appendicectomy is performed and then patients are randomised into 2 intervention groups. One group will receive thorough intra-abdominal peritoneal lavage and suction, and the second group will receive suction alone. The lavage group will receive a minimum of 2000mls of 0.9% saline lavage until the surgeon judges that the lavage fluid is clear. The suction group will be limited to a maximum of 100mls of fluid use if required by the surgeon.

Randomization will be using a random sequence in opaque envelopes. Allocation concealment will be ensured as a third party will disclose to the operating surgeon which group each patient will be allocated to (theatre nurse). 3

Post operatively all patients will receive 5 days intravenous broad spectrum antibiotics. This will be dictated by institutional practice or ceftriaxone and metronidazole in possible. If after 5 days there is clinical concern antibiotics can be continued as per current clinical practice. During this inpatient stay patients will be assessed for the primary outcome (formation of intra-abdominal abscess), as well as secondary outcomes (development of small bowel obstruction, length of stay, surgical wound infection and post-operative analgesia requirement). Follow-up will also occur 4-6 weeks post-operatively during an outpatient clinic appointment or by telephone. Data collection will be performed prospectively and by direct patient review or phone call follow up at 6 weeks. All data collected will use patient UR number, will be anonymous and stored on a password protected spreadsheet.

**Statistical Methods**

Results will be analysed after data extraction with dedicated statistical software. Data will be expressed as mean ± SD, median (range), interquartile range (IQR), count number, or percentages, as indicated. The D’Agostino and Pearson normality test will be used to evaluate the normal distribution of continuous variables. Unpaired Student’s t, Mann–Whitney U, Chi-squares, or Fischer’s exact test will be used where appropriate to identify differences between the two groups for continuous or categorical variables. Multiple regression analysis will be used to identify factors leading to IAA formation post-operatively. Sub analysis will be performed to look for difference in incidence of IAA according to the type of the antibiotic therapy.

**Informed Consent Process**

Eligible patients, children 16 years of age and under who are to receive laparoscopic appendicectomy as treatment for appendicitis, will be recruited on presentation to the participating sites with symptoms of appendicitis that are planned for operative treatment with laparoscopic appendectomy. Patients and their parent/ guardian will be approached by a research associate or a member of their treating team and written consent will be obtained from the parent/ guardian (as well as from the patient if they are deemed by the treating clinician to be a mature minor). In all cases, the exact nature and aims of the study, potential risks and follow-up requirements of the study will be explained prior to the surgery before consent is sought.

At the time consent is obtained, all of the following information will be provided in written form to the patient and their parent/ guardian and can be discussed with the research associate:

* Aims and relevant outcomes of the study
* The principal investigators in the study, sites involved, and the primary site at which the research is being conducted (Monash Children’s Hospital)
* Eligibility criteria, including all inclusion and exclusion criteria
* An explanation of what participation in the study will involve and require from the patient, both as an inpatient and during the follow-up process
* Discussion that participation in the study is entirely voluntary and that participation will in no way impact upon the patient’s quality of care
* Discussion of the potential benefits and risks of participation (detailed below)
* Discussion that participation in the study can be withdrawn at any time if desired, both by the patient and/ or their parent/ guardian with no impact on the patient’s operative or post-operative care
* Explanation of the way in which participants’ results will be obtained and retained in a confidential fashion
* Explanation that any identifying information collected will be kept confidential and only de-identified results will be published for public access
* Contact information for the research team and Monash Health HREC to discuss any queries or complaints

**Benefits and Risks to Participants**

Upon commencement of this study there is no clear evidence to support either benefits or risks that are likely to affect participants. Current trials have only included a total of 353 paediatric patients, and have not reached a definitive consensus as to whether either technique (peritoneal lavage, or suction only) is superior.10 Should our hypothesis be supported, however, the expectation is that the participants randomised to the peritoneal lavage arm of the study will have fewer postoperative complications of complex appendicitis and hence decreased morbidity. This may include lower rates of intra-abdominal abscess formation, small bowel obstruction and surgical wound infection. These patients may also have a shorter inpatient admission post-operatively, and have less pain (and hence require less analgesia) during this admission.

The predominant risk associated with participation in the study is that peritoneal lavage, conversely to our hypothesis, causes more harm than suction alone. If this is the case, participants may be at higher risk of the identified primary and secondary outcomes. This will mean that the patients return to the baseline level of risk for the common adverse complications of laparoscopic appendicectomies for complex appendicitis as they would should they have chosen not to participate in the study.

**Conflicts of Interest**

There are no conflicts of interest to declare by the principal investigators of this study.

**References**

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