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Title: Appendicectomy is associated with a lower complication rate than antibiotics for suspected uncomplicated appendicitis: A meta-analysis of major post-intervention complications.

Running Title: Appendicectomy or antibiotics for suspected uncomplicated appendicitis.

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SUMMARY

Objectives: Recent literature has concluded antibiotic therapy results in fewer complications than appendicectomy for patients with uncomplicated appendicitis. This studies aim was to undertake a meta-analysis of major post-intervention outcomes in patients with suspected uncomplicated appendicitis treated with antibiotics or appendicectomy, and determine which treatment is associated with the lowest rate of major complications.

Methods: We analysed randomised trials of antibiotics vs. appendicectomy in adults with suspected uncomplicated appendicitis. The primary outcome measure was a composite of major complications, peritonitis and intra-abdominal abscess, occurring after appendicectomy or initiation of therapeutic antibiotics.

Results: The rate of major post-intervention complications was 0.8% (2/263) in the appendicectomy group and 10.1 % (27/268) in the antibiotic group. This difference was statistically significant by the random effects model: Risk Ratio 7.71, 95% C.I. 2.33 to 25.53, Risk Difference 0.09: 95% C.I. 0.05 to 0.13. The Number Needed to Harm (NNH) from antibiotic therapy is 10.7.

Conclusions: Suspected uncomplicated appendicitis has a lower rate of major post-intervention complications when managed with primary appendicectomy compared to antibiotic therapy.

KEYWORDS: Antimicrobial, Appendicectomy, Appendicitis

INTRODUCTION

The traditional management of appendicitis, both complicated (perforated) and uncomplicated, has been appendicectomy. The rationale is that appendicectomy is indicated for complicated appendicitis, it is difficult to distinguish between complicated and uncomplicated appendicitis, and appendicectomy is associated with limited morbidity.[1,2] The use of appendicectomy for suspected uncomplicated appendicitis has though been challenged in trials comparing antibiotics to surgery. A meta-analysis of these trials determined that the incidence of complications was less in patients treated with antibiotics than in those managed surgically.[3] Given the lifetime incidence of appendicitis is approximately 8%, a move from predominantly surgical management of appendicitis to antibiotic therapy has the potential to impact on many patients.[4] This impact might be direct, through outcomes associated with the condition itself, or indirect, through the generation and transmission of antibiotic resistance. In view of the potential impact of widespread antibiotic use for uncomplicated appendicitis we carried out a meta-analysis comparing major outcomes in patients with acute uncomplicated appendicitis managed with appendicectomy or antibiotics.

METHODS

Study selection: Randomised controlled trials comparing antibiotics vs appendicectomy as primary treatment for suspected uncomplicated appendicitis in adults were included in the meta-analysis. Three authors (VC, GF, AK) searched clinical trials within Medline, Embase and the Cochrane Library (February 2014, no date restrictions). Search terms included appendicitis, appendicectomy, appendectomy, antibiotic, placebo, drug therapy and a selection of antimicrobial names. Identified studies were entered into Review Manager version 5.2 software to facilitate completion of the meta-analysis. All studies were assessed in relation to the inclusion criteria (VC, GF, AK).

Outcome measure: We used a composite primary outcome measure of the major complications of peritonitis or abscess occurring after the primary intervention, namely appendicectomy or a therapeutic dose of antibiotic. Peritonitis was defined as a perforated or gangrenous appendix at the time of secondary appendicectomy, or where a CT scan confirmed a clinical diagnosis. Abscesses were counted when reported. Outcomes occurring at any time within the studies' one year follow up periods are included. Outcomes were analysed on an intention-to-treat basis. Surgical wound infections were not included as an outcome measure as they were not considered to be of equivalent severity as the major outcomes of peritonitis and intra-abdominal abscess.

Estimating the effectiveness of antibiotic therapy for perforated appendicitis: In the appendicectomy group perforated appendicitis was assessed at primary appendicectomy. The rate of perforations in the appendicectomy group was used, given patients had been randomised, to estimate the pre-intervention rate of complicated appendicitis in the antibiotic group. The post-intervention rate of perforations was defined by findings at secondary appendicectomy. The estimate of the effectiveness of antibiotic therapy for perforated appendicitis was the difference between these two values.

Data collection and Statistical analysis: Data were extracted by two authors (AK and RPH). Statistical analysis was completed using R statistical software version 3.0.0 including the meta package version 2.3.0.[5,6] The primary outcome measure was compared using the Mantel-Haenszel method. Risk Ratio and Risk Difference were calculated using Random Effects models to allow for heterogeneity between studies. Heterogeneity between study protocols was present e.g. choice of antibiotic prophylaxis. Publication bias was assessed with a funnel plot of the Risk Ratio and Risk Difference.

RESULTS

We identified three relevant studies of antibiotic therapy vs. appendicectomy for the management of suspected uncomplicated appendicitis, Table 1.[1,7, 8] A PRISMA flow diagram documenting the selection of studies is included, Figure 1. The rate of major post-intervention clinical complications was 0.8% (2/263) in the appendicectomy group, lower than the 10.1% (27/268) rate in the antibiotic group (Table 2). This difference was statistically significant by the Random Effects model analysis with regard both Risk Ratio (RR) (RR 7.71: 95% C.I.2.3 to 25.5) and Risk Difference (RD 0.09: 95% C.I. 0.05 to 0.13) (Figure 2 and 3).

The Number Needed to Harm (NNH) based on the Risk Difference is 10.7. That is, for every 10.7 patients treated with antibiotics for suspected uncomplicated appendicitis one additional patient will develop peritonitis or an abscess.

In the antibiotic group there was no significant difference in the estimated pre-intervention rate of perforated appendices (10.6%) and the post-intervention documented rate of perforated appendixes, < 1 month 6% (p=0.06), 0-12 months 9.3% (p=0.67) (Table 3). The Risk Ratio in the antibiotic group at 1 month was 0.56 (0.3 to 1.1), and the Risk Difference 0.047 (-0.04 to 0.091). The Risk Ratio in the antibiotic group including entire follow up periods (0-12 months) was 0.88 (0.51 to 1.5), and the Risk Difference 0.013 (-0.04 to 0.066). No publication bias was identified.

DISCUSSION

We conclude that suspected uncomplicated acute appendicitis treated with appendicectomy carries a lower rate of major post-intervention complications than an antibiotic treatment strategy.

This studies conclusion contrasts to the findings of a recent met-analysis by Varadhan *et al* which compared the same treatments for the same condition as this meta-analysis, namely antibiotics and surgery for suspected uncomplicated appendicitis.[3] Varadhan concluded that antibiotics are safe as primary treatment for patients with uncomplicated appendicitis. We reviewed the methods of Varadhan *et al*, to explain these opposing conclusions, and concluded their combined primary outcome measure, and application of inclusion criteria, had limitations. Combined outcome measures should be clinically significant and of comparable severity; in appendicitis significant outcomes include peritonitis, abscess formation, perforation, surgical wound infection and death. Peritonitis and abscess are relatively common and allow statistically valid comparisons to be made between treatment strategies. However, in their meta-analysis Varadhan *et al* included a resected perforated appendix in surgically managed patients and surgical wound infection as outcome measures. We consider these were included inappropriately. Firstly, in patients treated by appendicectomy, perforation is a pre-intervention outcome which cannot be influenced by the intervention. Secondly, with respect to surgical wound infection, despite this being an important post-operative outcome, it is not of a comparable severity as peritonitis or abscess to justify inclusion as part of a combined primary outcome measure. Also, peri-operative antibiotic prophylaxis was not reported in two of the four studies in the Varadhan *et al* meta-analysis (and confirmed as not given by personnel communication with Dr Styrud).[7,8] The surgical wound infection rate in patients undergoing primary appendicectomy was 2.8% (8/286) in the Varadhan selected studies in which antibiotic prophylaxis was reported as administered,[1,9] compared with 11.8% (17/144) in the studies which did not report the use of antibiotic prophylaxis. Antibiotic therapy is now accepted clinical practice, with studies reporting wound infection is reduced by antibiotic prophylaxis from 15% to 5%.[10] Not using prophylaxis had the potential to bias results against the surgical treatment. The only study with antibiotic prophylaxis reported that was included in our analysis (Vons *et al*) showed no difference in wound infection rates (2/120 in the antibiotic group vs. 1/119 in the surgery group).[1] These data preclude including surgical wound infection as a secondary outcome measure in our meta-analysis. With respect to the application of inclusion criteria, we included three studies in our analysis of suspected uncomplicated appendicitis, compared to four studies included by Varadhan *et al* who studied uncomplicated appendicitis. We excluded the study by Hansson *et al* as they included patients "irrespective of the risk of perforation", i.e. they made no attempt to exclude patients with complicated appendicitis.[10] We therefore believe the methodological limitations of Varadhan *et al's* meta-analysis limit the clinical applicability of their conclusions.

Our analysis of the efficacy of antibiotic therapy for perforated appendicitis showed that over the one year follow up period there was no reduction in the rate of perforation: 10.6% in patients treated by appendicectomy vs. 9.3% in patients treated with antibiotics. The increased rate of post-intervention complications in patients treated with antibiotics may therefore have resulted from the fact that it was not, at study entry, possible to identify and exclude patients with perforated appendicitis. The studies used different methods to identify and exclude patients with complicated appendicitis, including clinical examination, CT scan or an ultrasound scan, but no method was entirely successful. This resulted in a number of patients with complicated appendicitis being allocated to treatment with antibiotics alone. For as long as there is no reliable method of differentiating uncomplicated from complicated appendicitis, studies into the management of patients with suspected uncomplicated appendicitis will unwittingly enrol patients with complicated appendicitis, some of whom will be treated with antibiotic therapy. This approach is likely to delay the diagnosis of complicated appendicitis, potentially increasing morbidity.[11,12]

A limitation of this meta-analysis is the exclusion of surgical wound infections. This was unavoidable and due to the lack of administration of antibiotic prophylaxis in included studies. The results of this meta-analysis are therefore restricted in application to the major complications of peritonitis or abscess. The study by Vons *et al* which reported the use of antibiotic prophylaxis did not show any difference in surgical wound infections between antibiotic and surgically treated patients making it unlikely that this omission will impact on the clinical applicability of this meta-analysis. Another possible limitation is the applicability of these finding to hospitals who routinely offer CT (computerised tomography) scans to patients before appendicectomy. CT scans may detect stercoliths (faecal stones), and Vons *et al* reported a stercolith was a risk factors for complications in antibiotic treated patients. Vons did though report a numerically higher rate of complications in antibiotic treated patients, even with stercolith cases removed. Centres using CT scans before appendicectomy to identify stercoliths may be able to reduce the complication rate in antibiotic treated patients by excluding these patients from an antibiotic management strategy.

In summary, the conclusion of our meta-analysis is that the rate of post-intervention complications in suspected uncomplicated appendicitis was lower in patients who were managed with appendicectomy than in patients managed with antibiotic therapy. On a background of increasing antibiotic resistance, appendicectomy remains the most appropriate treatment of choice for patients with appendicitis.

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Figure 1: PRISMA flow diagram

Figure 2: Risk Ratio forest plot of major post-intervention complications (peritonitis or abscess) in appendicectomy vs. antibiotics for treating suspected uncomplicated appendicitis. RR=Risk Ratio, W =Weight.

Figure 3: Risk Difference forest plot of major post-intervention complications (peritonitis or abscess) in appendicectomy vs. antibiotics for treating suspected uncomplicated appendicitis. RR=Risk Ratio, W =Weight.