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ANTIBIOTICS TREATMENT VERSUS SURGICAL TREATMENT FOR MANAGEMENT OF UNCOMPLICATED APPENDICITIS: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Background & Purpose: Till lately, the best treatment alternative considered for patients with acute appendicitis changed into surgical treatment. Now, six randomized researches show that non-operative management is a secure and possible therapeutic choice for sufferers with uncomplicated appendicitis. The Aim of this work is to provide cumulative data about the efficacy and safety of Antibiotics Treatment (AT) versus Surgical Treatment (ST) for management of uncomplicated appendicitis. ***Methods:*** A systematic search was performed of PubMed, Cochrane library Ovid, Scopus & Google scholar to identify general surgery RCTs, clinical trials, and comparative studies, which studied the outcome of AT group versus ST group of uncomplicated appendicitis patients. A meta-analysis was done using fixed and random-effect methods. The primary outcome of interest was success rate (treatment effectiveness). Secondary outcome was complications rate. We calculated efficacy (favorable outcome), for

each group through success rate. We also calculated safety (adverse outcome), for each group through complications rate (including recurrence). ***Results:*** A total of 6 studies were identified involving 1985 patients, with 1082 patients in AT group, and 903 patients in ST group. Regarding efficacy outcome measure, the fixed-effects model of the meta-analysis study showed highly significant decrease in success rate in AT group compared to ST group ($p < 0.01$). Regarding safety outcome measures, the random-effects model of the meta-analysis study showed significant decrease in complications rate in AT group compared to ST group ($p = 0.017$). ***Conclusion:*** To conclude, despite the fact that antibiotics may also prevent a few patients from appendectomies, surgical procedure represents the definitive, one-time simplest treatment with a known risk profile.

KEYWORDS: Antibiotics, Surgery, Uncomplicated Appendicitis.

INTRODUCTION

Acute appendicitis is inflammation of the vermiform appendix and stays the most common cause of the acute abdomen in teenagers. The mainstay of treatment in maximum facilities is an appendectomy, and, consequently, this is one of the most common operations carried out on the acute abdomen.[1]

Acute appendicitis is one of the most typical of surgical emergencies, and appendectomy has emerge as established as the gold standard of therapy. However, because the analysis of appendicitis in most nations is especially a clinically diagnostic one, based totally on history and exam, diagnostic uncertainty in patients with suspected appendicitis may additionally cause a delay in treatment or poor surgical explorations, including to the morbidity related to the circumstance.[2]

The analysis of appendicitis is supported by way of a records of abdominal pain that starts within the acute abdomen and migrates to the right lower quadrant, tenderness to palpation on physical examination of that region, nausea or vomiting, slight leukocytosis, and occasional-grade fever, however these capabilities are erratically gift, and fewer than 50% of sufferers might also have a majority of these functions.[3]

Nowadays, computed tomography (CT) has allowed for the extra correct analysis of appendicitis, and antibiotics which are extra powerful have end up to be had for the treatment of intraabdominal infection.[4]

Appendectomy has been the standard treatment for acute appendicitis for over a century. more than 300 000 appendectomies are finished annually within the United States.[5] Urgent appendectomy has been the mainstay of treatment for appendicitis for the reason that late 1800s, with a main improve made in the 1990s, whilst the use of the laparoscopic technique was suggested in place of the more traditional method regarding incision inside the right lower quadrant ("open" technique).[3]

Meanwhile, non-operative management with antibiotics has been set up for the treatment of complicated appendicitis, simple diverticulitis, neonatal enterocolitis, salpingitis, and cholecystitis. Till lately, the best treatment alternative considered for patients with acute appendicitis changed into surgical treatment. Now, six randomized researches show that non-operative management is a secure and possible therapeutic choice for sufferers with uncomplicated appendicitis. Moreover, it is apparent that two thirds of sufferers can be spared an appendectomy.[6]

Only 20% of sufferers present with complicated appendicitis, and non-operative management with antibiotics and supportive treatment has been explored as a therapeutic option for sufferers with early uncomplicated appendicitis, with decision in most of them. Antibiotic treatment became regularly taken into consideration as a bridge to surgical treatment in sufferers with suspected appendicitis however no clear indications for appendicectomy such as signs and symptoms of perforation or peritonitis. But, the habitual use of antibiotics in patients with uncomplicated acute appendicitis was no longer properly supported, as a result of inherent pitfalls within the fine and layout of individual researches.[7]

Early operation as a way to avoid accelerated morbidity, including abscess and perforation or mortality due to complicated appendicitis, is the usual. The Therapeutic approach also embraces the effort to lower the number of bad appendectomies. some authors have said that thanks to progressed diagnostic tools, the range of poor appendectomies may be reduced without influencing the perforation rate, provided intensive surveillance is executed inside the case of diagnostic uncertainty. No matter the diagnostic possibilities, but, the frequency of appendectomy remains a whole lot better than the incidence of appendicitis.[8]

AIM OF THE STUDY: The Aim of this work is to provide cumulative data about the efficacy and safety of Antibiotics Treatment (AT) versus Surgical Treatment (ST) for management of uncomplicated appendicitis.

METHODS

This review was carried out using the standard methods mentioned within the Cochrane handbook and in accordance with the (PRISMA) statement guidelines.[9]

Identification of Studies

- An initial search carried out throughout the PubMed, Cochrane library Ovid, Scopus & Google scholar using the following keywords: Antibiotics, Surgery, Uncomplicated Appendicitis.
- We will consider published, full text studies in English only. Moreover, no attempts were made to locate any unpublished studies nor non-English studies.

Criteria of Accepted Studies

- **Types of Studies**

The review will be restricted to RCTs, clinical trials, and comparative studies, either prospective or retrospective, which studied the outcome of AT group versus ST group of uncomplicated appendicitis patients.

- **Types of Participants**

Participants will be uncomplicated appendicitis patients.

- **Types of outcome Measures**

1. Success rate "complication-free treatment success" (1ry outcome)
2. Complications rate (2ry outcome)

Inclusion Criteria

- ✓ English literature.
- ✓ Journal articles.
- ✓ Between 2009 until 2016.
- ✓ Describing uncomplicated appendicitis treated by either AT group or ST group.
- ✓ Human studies.

Exclusion Criteria

- ✓ Articles describing acute complicated appendicitis.
- ✓ Irrelevance to our study.

METHODS OF THE REVIEW

■ Locating Studies

Abstracts of articles identified using the above search strategy will be viewed, and articles that appear of fulfill the inclusion criteria will be retrieved in full, when there is a doubt, a second reviewer will assess the article and consensus will be reached.

■ Data Extraction

Using the following keywords: Antibiotics, Surgery, Uncomplicated Appendicitis, data will be independently extracted by two reviewers and cross-checked.

Statistical Analysis

Statistical analysis done using MedCalc ver. 18.11.3 (MedCalc, Ostend, Belgium). Data were pooled and odds ratios (ORs) as well as standard mean differences (SMD), were calculated with their 95 per cent confidence intervals (CI). A meta-analysis was performed to calculate direct estimates of each treatment, technique or outcome. According to heterogeneity across trials using the I^2-statistics; a fixed-effect model ($P \geq 0.1$) or random-effects model ($P < 0.1$) was used.

Study Selection

We found 143 records; 103 were excluded based on title and abstract review; 40 articles are searched for eligibility by full text review; 19 articles cannot be accessed or obtain full text; 10 studies were reviews and case reports; the desired treatment not used in 5 studies leaving 6 studies that met all inclusion criteria (Fig. 1).

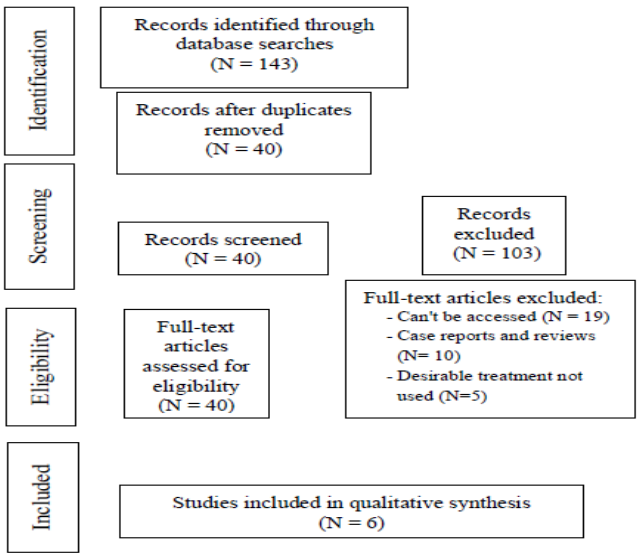

Figure 1: Flow Chart for Study Selection.

RESULTS

Descriptive analysis of all studies included (Tables 1, 2)

Table 1: Patients and Study Characteristics.

N	Author	Number of patients			Antibiotic used	Follow up time (average months)
		Total	AT group	ST group		
1	*Turhan et al., 2009*	290	107	183	Ampicillin + gentamicin + metronidazole	12
2	*Vons et al., 2011*	239	120	119	Amoxicillin clavulanic acid	12
3	*Hansson et al., 2012*	553	442	111	Piperacillin tazobactam	14
4	*Park et al., 2014*	278	119	159	Second-generation cephalosporin + metronidazole	12
5	*Salminen et al., 2015*	530	257	273	Ertapenem + levofloxacin	21
6	*Minneci et al., 2016*	95	37	58	Piperacillin tazobactam + ciprofloxacin + metronidazole	12

#Studies were arranged according to publication year.

Table 2: Summary of Efficacy and Safety Outcome Measures in All Studies.

N	Author	Efficacy outcome		Safety outcome	
		Success rate		Complications rate	
		AT group	ST group	AT group	ST group
1	*Turhan et al., 2009*	87	183	0	34
2	*Vons et al., 2011*	76	119	12	21
3	*Hansson et al., 2012*	304	109	55	45
4	*Park et al., 2014*	96	159	4	11
5	*Salminen et al., 2015*	187	272	7	4
6	*Minneci et al., 2016*	33	58	1	8

The included studies published between 2009 and 2016.

The total number of patients in all the included studies was 1985 patients, with 1082 patients in AT group, and 903 patients in ST group, while their average follow up time was (14 months).

Regarding antibiotics used, 2 studies used Ampicillin and Amoxicillin, 3 studies used Metronidazole, 2 studies used Piperacillin tazobactam, 2 studies used levofloxacin and ciprofloxacin, and 1 study used Second- generation cephalosporin and Ertapenem.

Meta-Analysis of Outcome Measures

Data were divided into two groups:

1) AT group
2) ST group

Meta-analysis study was done on 6 studies which described and compared the 2 different treatments for appendicitis; with overall number of patients (N=1985).

(A) Efficacy

Patients who achieved favorable outcomes were pooled to evaluate efficacy by:

Efficacy of a specific technique was measured by

✓ **Odds Ratio (OR)**

- For success rate.

Regarding efficacy outcome measure,

We found 6 studies reported success rate with total number of patients (N=1985).

I^2 (inconsistency) was 0% with non-significant Q test for heterogeneity (p = 0.723), so fixed-effects model was chosen to assess efficacy; with overall OR= 0.018 (95% CI 0.007 to 0.044).

The fixed-effects model of the meta-analysis study showed highly significant decrease in success rate in AT group compared to ST group (p < 0.01).

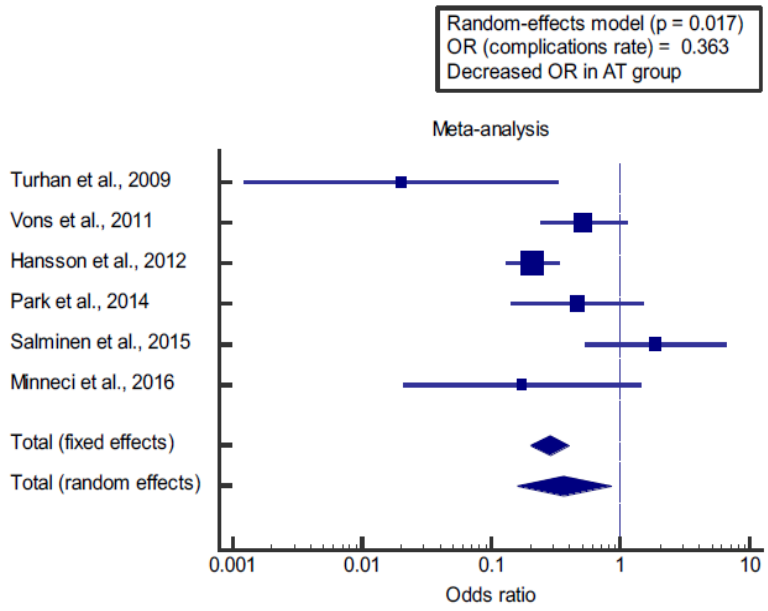

Figure 2: Forest plot of (success rate) on AT group vs ST group – Odds ratio.

(B) Safety

Patients who reached serious adverse events (SAEs) – were pooled to evaluate safety by:

Safety of a specific technique was measured by

✓ **Odds Ratio (OR)**

- For complications rate.

Regarding safety outcome measure,

We found 6 studies reported complications rate with total number of patients (N=1985).

I^2 (inconsistency) was 71% with highly significant Q test for heterogeneity (p = 0.0039), so random-effects model was chosen to assess efficacy; with overall OR= 0.363 (95% CI 0.158 to 0.837).

The random-effects model of the meta-analysis study showed significant decrease in complications rate in AT group compared to ST group (p = 0.017).

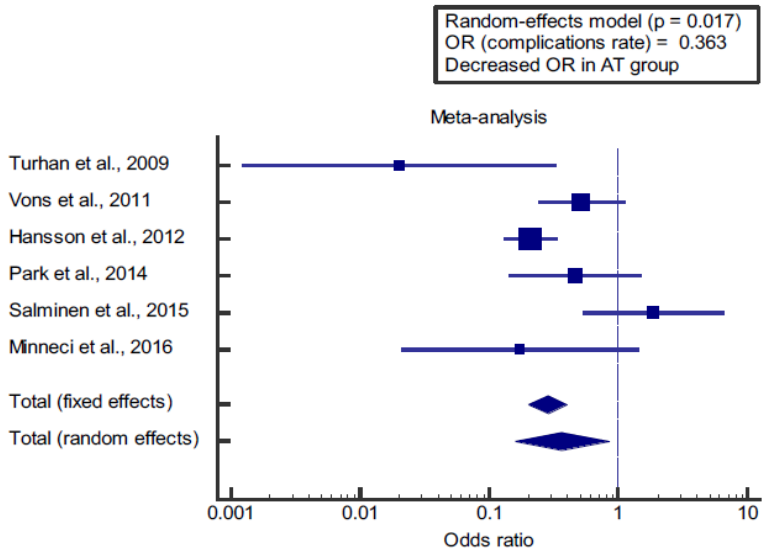

Figure 3: Forest Plot of (Complications Rate) on AT Group vs ST group – Odds ratio.

DISCUSSION

The Aim of this work is to provide cumulative data about the efficacy and safety of Antibiotics Treatment (AT) versus Surgical Treatment (ST) for management of uncomplicated appendicitis.

The total number of patients in all the included studies was 1985 patients, with 1082 patients in AT group, and 903 patients in ST group, while their average follow up time was (14 months).

Regarding antibiotics used, 2 studies used Ampicillin and Amoxicillin, 3 studies used

Metronidazole, 2 studies used Piperacillin tazobactam, 2 studies used levofloxacin and ciprofloxacin, and 1 study used Second- generation cephalosporin and Ertapenem.

Regarding efficacy outcome measure; We found 6 studies reported success rate with total number of patients (N=1985).

The fixed-effects model of the meta-analysis study showed highly significant decrease in success rate in AT group compared to ST group ($p < 0.01$) which came in agreement with ***Harnoss et al. 2017***[10] and disagreement with ***Varadhan, Neal, and Lobo 2012***[7] and ***Lee et al. 2018***[11] and ***Huang et al. 2017***[12]

Harnoss et al. 2017[10] reported that common postoperative complications were similar (RR 0.95) while the rate of unfavorable events (RR 3.18) and the prevalence of complicated appendicitis (RR 2.52) have been significantly higher in the antibiotic treatment group.

Varadhan, Neal, and Lobo 2012[7] reported that A secondary evaluation, apart from the study with crossover of patients between the two interventions after randomization, confirmed a significant relative risk reduction of 39% for antibiotic therapy (risk ratio 0.61; P=0.02). Of the 65 (20%) patients who had appendicectomy after readmission, nine had perforated appendicitis and four had gangrenous appendicitis. No significant differences have been visible for treatment efficacy, duration of stay, or risk of growing complicated appendicitis.

Lee et al. 2018[11] reported that, the results were equal between groups, except (non-operative Management) NOM had less days of pain medication.

Huang et al. 2017[12] reported that Nonoperative treatment was successful in 152 of 168 patients (90.5%), with a Mantel-Haenszel constant-outcomes risk ratio of 8.92 ($P > 0.05$).

Regarding safety outcome measure; We found 6 studies reported complications rate with total number of patients (N=1985).

The random-effects model of the meta-analysis study showed significant decrease in complications rate in AT group compared to ST group ($p = 0.017$) which came in agreement with ***Rollins et al. 2016***[13] and with ***Salminen et al. 2018***[14] and disagreement with ***Kirby et al. 2015***.[15]

Rollins et al. 2016[13] reported that there was a 39 % risk reduction in general complication rates in the ones handled with antibiotics as compared with those undergoing appendicectomy (RR 0.61, p = 0.002).

Salminen et al. 2018[14] reported that At five years, the general complication rate (surgical site infections, incisional hernias, abdominal pain, and obstructive symptoms) was 24.4% (n = 60/246) within the appendectomy organization and 6.5% (n = 16/246) in antibiotic group (P < .001).

Kirby et al. 2015[15] reported that, the rate of fundamental post-intervention complications changed into 0.8% (2/263) in the appendicectomy group and 10.1% (27/268) in the antibiotic group. This difference became statistically significant by the random effects version: risk Ratio 7.71, risk difference 0.09.

CONCLUSION

To conclude, despite the fact that antibiotics may also prevent a few patients from appendectomies, surgical procedure represents the definitive, one-time simplest treatment with a known risk profile.

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Conflict of interest

None.

Authorship

All the listed authors contributed significantly to conception and design of study, acquisition, analysis and interpretation of data and drafting of manuscript, to justify authorship.

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