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Endoscopic retrograde appendicitis therapy for acute appendicitis: a systematic review and meta-analysis

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ABSTRACT

Background and study aims Endoscopic retrograde appendicitis therapy (ERAT) is an endoscopic procedure for management of patients with acute appendicitis (AA). In addition to being minimally invasive, it has the added advantages of preservation of appendix and simultaneous inspection of colon. We performed a systematic review and meta-analysis on ERAT in patients with AA.

Methods We conducted a comprehensive search of multiple electronic databases (from inception through January 2022) to identify studies reporting ERAT in AA. The primary outcome was to evaluate the overall clinical and technical success of ERAT. The secondary outcome was to study the total and individual adverse events (AEs). The meta-analysis was performed using Der Simonian and Laird random effect model.

Results Seven studies reporting on 298 patients were included. The majority of the patient population was male (55.3 %), with mean age of 31 ± 12.39 years. The pooled technical success rate was 99.36 % (95 % CI 97.61–100, I^2 = 0) and the pooled clinical success rate was 99.29 % (95 % CI 97.48–100, I^2 = 0). The pooled AE rate was 0.19 % (95 % CI 0–1.55, I^2 = 0). The most common AE was perforation with 0.19 % (95 % CI 0–1.55, I^2 = 0). The recurrence rate was 6.01 % (95 % CI 2.9–9.93, I^2 = 20.10). Average length of procedure was 41.1 ± 7.16 min. Low heterogeneity was noted in in our meta-analysis.

Conclusions ERAT is a safe procedure with high rates of clinical and technical success in patients with AA. Further randomized controlled trials should be performed to assess the utility of ERAT in AA as compared to laparoscopic appendectomy.

Introduction

Acute appendicitis (AA) is one of the most common surgical emergencies, with a lifetime risk of 7 % in the United states [1]. AA usually occurs secondary to obstruction of the appendiceal orifice. The obstruction itself is most commonly caused by a piece of impacted stool called a fecalith. However, obstruction of the appendix may also have other causes, such as tumors, infections, or lymphoid hyperplasia [2]. This obstruction leads to distension of the appendix and manifests with clinical symptoms of generalized abdominal pain, right lower quadrant pain, fever, nausea, and vomiting. Further distension leads to arteriolar thrombosis, which results in ischemia, gangrene and perforation [3].

The current standard of treatment for AA is laparoscopic appendectomy [4]. New data suggest that antibiotics instead of surgery could also be used for treatment of appendicitis, and they were found to be non-inferior to laparoscopic surgery [5, 6]. However, these studies showed that nearly 30 % of patients treated with antibiotics had a repeat episode of appendicitis within 1 year [7]. Negative appendectomy rates (defined as appendectomy performed on a pathologically normal appendix) range from 10 % to 15 %, leading to an increase in hospital costs and morbidity [8, 9]. The appendix is also now thought to play a role in immune function and to possibly maintain the colonic flora, favoring the potential benefit of avoiding an appendectomy [10, 11].

Endoscopic retrograde appendicitis therapy (ERAT) is an endoscopic procedure used for management of AA and is an alternative to laparoscopic appendectomy. This procedure was first reported by Liu et al in 2012 [12]. The procedure consists of passage of a colonoscope to the opening of the appendix for placement of a stent or drain in the infected appendix via the appendiceal orifice, relieving appendiceal obstruction. The benefits of performing ERAT over laparoscopic appendectomy are avoidance of surgical intervention, preservation of the appendix, as well as direct visualization of the colon, with subsequent or concurrent management of any abnormalities noted and possibly decreasing rates of negative appendectomy.

We present the first systematic review and meta-analysis to evaluate rates of success and adverse events (AEs) with ERAT in management of AA.

Methods

Search strategy

Multiple databases such as PubMed, EMBASE, CINAHL, Cochrane and Google Scholar (from inception to Jan 2022) were searched utilizing combinations of keywords such as: 'endoscopic', 'retrograde', 'appendicitis', 'appendiceal', 'therapy', 'treatment', 'endoscopy', 'endoscope' and 'acute'. Reference lists from articles, conference proceedings and prior reviews were also searched for additional articles. Two investigators (BD and AP) independently carried out the search with discrepancies being resolved with assistance from a third investigator (YN). This search was performed in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. [13] This study selection is outlined in **Supplementary Fig. 1** and PRISMA checklist is outlined in **Supplementary Fig. 2**.

Study selection

All studies evaluating the technical success, clinical success and AEs of ERAT in AA irrespective of age were included in our final analysis. The following exclusion criteria were used: (1) sample size < 10 patients; and (2) studies not in English language. This study was not registered. In case of cohort overlap, the most comprehensive study was included after discussion with three authors (BD, AP, YN).

Data abstraction and quality assessment

Two authors (BD and YN) independently reviewed each study for quality assessment using the Newcastle-Ottawa scale (NOS) for cohort studies and Cochrane risk-of-bias tool for randomized control trials (RCTs) [14, 15]. Details of these scales are provided in **Supplementary Table 1** and **Supplementary Fig. 3**.

Outcomes assessed

The primary outcomes assessed were technical and clinical success of ERAT in AA.The secondary outcomes assessed were overall rates of AEs and AE subtypes.

Definitions

Technical success was defined as successful intubation of the appendix and successful drainage of the appendiceal cavity with or without placement of a stent [10, 11, 16–19]. Clinical success was defined as improvement in symptoms such as abdominal pain, nausea, and fever [10, 11, 17–20]. AEs were related directly to the procedure, such as bleeding and perforation.

Statistical analysis

A random effects model was used to calculate pooled estimates for each outcome of interest as suggested by the meta-analysis techniques by DerSimonian and Laird [21]. Forest plots were used for presentation of our results. A continuity correction of 0.5 would be added prior to statistical analysis if zeros occurred in incidence of an outcome of a study [22]. We utilized the Cochran Q statistical test and I^2statistics to assess heterogeneity [23, 24]. Low, moderate, substantial or considerable heterogeneity was classified by values < 30 %, 30 % to 60 %, 61 % to 75 %, and > 75 %, respectively [25]. All analyses were performed using STATA v16.1 software (StataCorp, LLC College Station, Texas, United States).

Results

Search results and population characteristics

From an initial group of 142 studies, seven studies reported data regarding use of ERAT in 298 patients with appendicitis. Studies with overlapping cohorts were identified and the most appropriate ones were included in the final analysis. The majority of patients were males (53.3 % reported in 5 studies) and their mean age was 31 ± 12.39 years (range 1–74).

▶ **Table 1** Characteristics of included studies.

Study	Year	Country	Type of study	Type of center	Type of publication	No. patients	Mean age	Male	Female
Kong	2021	China	Prospective	Single	Manuscript	14	32.9	5	9
Ding	2021	China	Retrospective	Single	Manuscript	70	39.9	42	28
Kang	2020	China	RCT	Single	Manuscript	36	6.74	22	14
Chen	2019	China	Prospective	Single	Abstract	101	–	–	–
Ye	2018	China	Prospective	Single	Manuscript	22	39.5	9	13
Li	2016	China	Prospective	Single	Manuscript	21	36	9	12
Liu	2015	China	Retrospective	Multi	Manuscript	34	–	–	–

Average procedure length was 41.1 ± 7.16 minutes with an average hospital length of stay of 3.93 ± 1.01 days. Average duration of follow up was 14.07 ± 8.75 months. ▶ **Table 1** describes the characteristics of the included studies. A schematic diagram of the study selection process is illustrated in **Supplementary Fig. 1**.

Characteristics and quality of included studies

There were six single-center studies, no population-based, and one multicenter study included in our final analysis. Four studies included > 30 patients, two studies included > 20 patients, and one study includes > 10 patients. Six studies were published in manuscript form and one study was published in abstract form.

Quality assessment was performed with the help of the NOS for cohort studies and Cochrane risk-of-bias tool for RCTs. All seven studies were of good quality and no poor quality studies were found. Details of quality assessment can be seen in **Supplementary Table 1** and **Supplementary Fig. 3**.

Meta-analysis outcomes

Primary outcomes

The rate of technical success was 99.36 % (95 % CI: 97.61 %, 100.00 %; I^2 = 0.0 %; PI: 0.97,1.00) and the calculated pooled rate of clinical success was 99.29 % (95 % CI: 97.48 %, 100.00 %; I^2 = 0.00 %; PI: 0.97,1.00). ▶ **Fig. 1** and ▶ **Fig. 2** show the Forest Plots for technical and clinical success of ERAT in appendicitis.

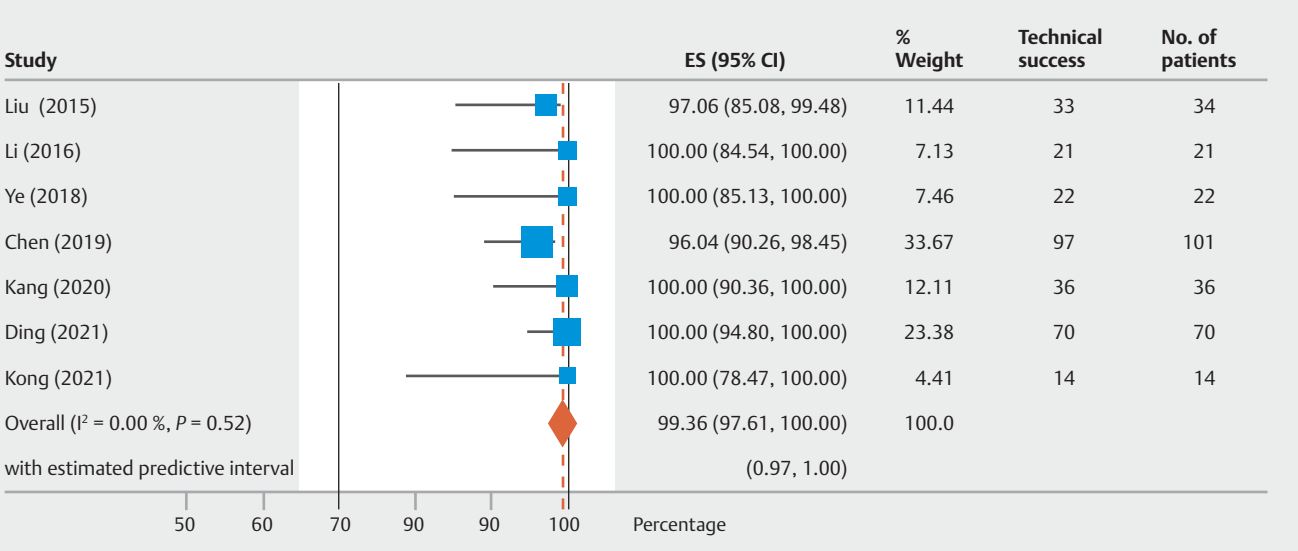
Secondary outcomes

The calculated pooled rate of AEs was 0.19 % (95 % CI: 0.00 %, 1.55 %; I^2 = 0.00 %; PI = 0.00,0.02) with perforation at 0.19 % (95 % CI: 0.00 %, 1.55 %; I^2 = 0.00 %; PI = 0.00, 0.02) being the most common AE. ▶ **Table 2** describes AEs.

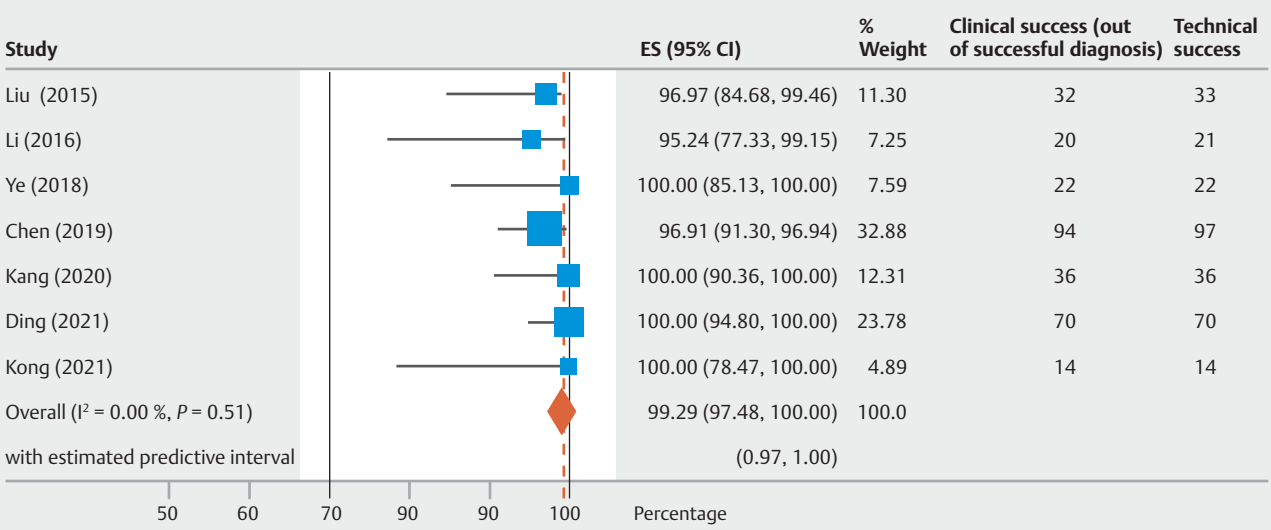
Validation of meta-analysis results

Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its



▶ **Fig. 1** Pooled rates of technical success of ERAT.



▶ **Fig. 2** Pooled rates of clinical success of ERAT Figure 1 Pooled rates of technical success of ERAT.

▶ **Table 2** Adverse events and recurrence of ERAT.

Study	Year	Total adverse events	Perforation	Bleeding	Obstruction	Infection	Recurrence
Kong	2021	0	0	0	0	0	0
Ding	2021	1	1	0	0	0	2
Kang	2020	0	0	0	0	0	2
Chen	2019	0	0	0	0	0	13
Ye	2018	0	0	0	0	0	2
Li	2016	1	1	0	0	0	1
Liu	2015	1	1	0	0	0	2

ERAT, endoscopic retrograde appendicitis therapy.

effect on the main summary estimate. Based on this analysis, no single study significantly affected the outcome or heterogeneity.

Heterogeneity

Based on Q statistics, and I^2 analysis for heterogeneity, no heterogeneity was noted in the analysis of technical and clinical success or total AEs of ERAT.

Publication bias

Assessment of publication bias was difficult due to the small size of the majority of included studies, as these were single-arm studies with dichotomous outcomes.

Discussion

Our study demonstrates that ERAT is an effective, minimally invasive procedure that can be used to diagnose and treat acute uncomplicated appendicitis. This meta-analysis shows that ERAT has high technical and clinical success rates with a low rate of recurrences and AEs in patients with acute uncomplicated appendicitis.

Because the shape and size of the appendix varies greatly, it is often challenging to reliably diagnose AA with CT and abdominal ultrasound, resulting in high negative appendectomy rates [8, 17, 19, 26–29]. Several studies have demonstrated that endoscopy combined with appendiceal cavity imaging obtained with ultrasound or x-ray can accurately diagnose AA [10, 11, 18, 19].

The technical and clinical success rates for ERAT in our meta-analysis were 99.36 % and 99.29 %, respectively. In a recent study, ERAT was directly compared to antibiotic therapy alone in children with acute uncomplicated appendicitis [10]. ERAT was found to have a higher clinical success rate of 100 % in comparison to 80.9 % in the antibiotics-only cohort. ERAT also led to immediate relief of abdominal pain faster than antibiotic therapy alone, laparoscopic appendectomy (LA), or open appendectomy (OA) [10, 16, 20]. In two studies, length of hospital stay postoperatively was shorter in the ERAT cohort as compar-

ed to antibiotic therapy alone and laparoscopic/open appendectomy [10, 16].

ERAT appears to be safe and carries a low rate of AEs. The overall AE rate in our meta-analysis was only 0.19 %. Three cases of perforation occurred in our meta-analysis. One patient required an emergency appendectomy after 48 hours when contrast leakage into the abdominal cavity occurred during a second ERAT [11]. The second patient was managed successfully with a plastic stent without surgical intervention following appendicolith removal using an extraction basket [17]. The third case of perforation was thought to be caused by a guidewire injury and was managed conservatively with antibiotics [16]. The recurrence rate of appendicitis following ERAT was low, with an overall rate of 6.01 %. The appendix is also now thought to play a role in immune function and to possibly maintain the colonic flora, favoring the potential benefit of avoiding an appendectomy [10, 11].

This meta-analysis has several limitations. Several studies had small sample sizes and all the studies originated in one country. Due to this limitation, studies with patients from all age groups and different ERAT techniques were included. In addition, most of the studies were undertaken at single centers with advanced endoscopists and the results may not be generalizable. Data regarding head-to-head comparisons with laparoscopic/open appendectomy were not available. Only one study reported data from a comparison of ERAT to antibiotics.

Conclusions

In conclusion, ERAT appears to be a minimally invasive treatment option for management of acute uncomplicated appendicitis with high technical and clinical success and low AE rates. In addition, it can be used as a tool to supplement diagnosis of AA. Further studies with RCTs should be performed before it is adopted as an alternative to surgery.

Competing interests

The authors declare that they have no conflict of interest.

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