Endoscopic Retrograde Appendicitis Therapy for Acute Appendicitis: A Systematic Review and Meta-Analysis

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract: Background and study aim: 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 added advantage of preservation of appendix and simultaneous inspection of colon. We performed a systematic review and meta-analysis on ERAT in patients with AA.

Patients and methods: We conducted a comprehensive search of multiple electronic databases (from inception through Jan 2022) to identify the 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. The meta-analysis was performed using Der Simonian and Laird random effect model.

Results 7 studies reporting on 298 patients were included. Majority of the patient population were males (55.3%), with mean age of 31±12.39 years. The pooled technical success rate was 99.36% (95% CI 97.61-100, I2=0) and the pooled clinical success rate was 99.29% (95% CI 97.48-100, I2=0). The pooled adverse event rate was 0.19% (95% CI 0-1.55, I2=0). The most common adverse event was perforation with 0.19% (95% CI 0-1.55, I2=0). Recurrence rate was 6.01% (95% CI 2.9-9.93, I2=20.10). Average length of procedure was 41.1±7.16 min. Low heterogeneity was noted in our meta-analysis.

Conclusion: ERAT is a safe procedure with high clinical and technical success in patients with acute appendicitis. Further randomized controlled trials should be performed to assess utility of ERAT in acute appendicitis as compared to laparoscopic appendectomy.

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Conclusion:

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

Key words: Appendicitis; ERAT; Endoscopy; Meta-analysis

Acute Appendicitis (AA) is one of the most common surgical emergencies with a lifetime risk of 7% in the United states.[1] AA is usually caused secondary to obstruction of 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 be caused by tumors, infections, lymphoid hyperplasia or other causes. This obstruction leads to distension of appendix and manifests with clinical symptoms of generalized abdominal pain, right lower quadrant pain, fever, nausea, vomiting. Further distension leads to arteriolar thrombosis which results ischemia, gangrene and perforation.

The current standard of treatment for AA is laparoscopic appendectomy. New data suggests antibiotics, instead of surgery, could also be used for treatment of appendicitis, and was found to be non-inferior to laparoscopic surgery. However, these studies showed nearly 30% of patients treated with antibiotics had a repeat episode of appendicitis within 1 year. Negative appendectomy (defined as appendectomy performed on a pathologically normal appendix) rates range from 10-15% leading to increase in hospital costs and morbidity. 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.

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. The procedure consists of the passage of a colonoscope to the opening of the appendix for the 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 the 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 the success and adverse events of 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 of a third investigator (YN). This search was performed in accordance of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. [13] This study selection is outlined in Supplementary Figure 1 and PRISMA checklist is outlined in Supplementary Figure 2.

**Study Selection**

Inclusion criteria- All the studies evaluating the technical success, clinical success and adverse of events of ERAT in acute appendicitis 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 for cohort studies and Cochrane risk of bias tool for randomized control trial (RCT). [14,15] Details of these scales are provided in Supplementary Table 1 and Supplementary Figure 3.

Outcomes assessed

The primary outcomes assessed were the technical and clinical success of ERAT in AA. The secondary outcomes assessed were the overall adverse events and the adverse event subtypes.

Definitions

The technical success was defined as successful intubation of appendix and successful drainage of the appendiceal cavity with or without placement of stent.[10,11,16-19] The clinical success was defined as improvement in symptoms such as abdominal pain, nausea and fever.[10,11,17-20] Adverse events were related directly to the procedure such as bleeding and perforation.

Statistical analysis

The random effects model was used to calculate the 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 zero’s occurred in the incidence of an outcome of a study.[22] We utilized the Cochran Q statistical test and I² statistics to assess heterogeneity.[23,24] Low, moderate, substantial or considerable heterogeneity was classified by the values of <30%, 30% -
60%, 61% - 75%, and >75% respectively.[25] All analyses were performed using STATA v16.1 software (StataCorp, LLC College Station, TX)

RESULTS

Search results and population characteristics

From an initial group of 142 studies, 7 studies reported data regarding the use of ERAT in 298 patients with appendicitis. Studies with overlapping cohorts were identified and the most appropriate ones were included in final analysis. The majority of the patients were males (53.3% reported in 5 studies) and the mean age was 31±12.39 years (range 1-74) years.

Average procedure length was 41.1±7.16 min with an average hospital length of stay was 3.93±1.01 days. The 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 Figure 1.

Characteristics and quality of included studies

There were 6 single center studies, no population-based and one multi-center study included in our final analysis. Four studies included greater than 30 patients, 2 studies included greater than 20 patients, and one study greater than 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 scale for cohort studies and Cochrane-risk-of-bias tool for randomized controlled trial. 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 Figure 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). Figures 1 and 2 demonstrate the Forest Plots for technical and clinical successes of ERAT in appendicitis.

**Secondary outcomes**

The calculated pooled rate of adverse events 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 adverse event. Table 2 describes the adverse events.

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

**Heterogeneity**

Based on Q statistics, and $I^2$ analysis for heterogeneity, no heterogeneity was noted in the analysis of technical, clinical success and total adverse events 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 endoscopic retrograde appendicitis therapy (ERAT) is an effective, minimally invasive procedure that can diagnose and treat acute uncomplicated appendicitis. This meta-analysis shows that ERAT has a high technical and clinical success rate with a low rate of recurrences and adverse events in patients with acute uncomplicated appendicitis.

Because the shape and size of the appendix varies greatly, it is often challenging to reliably diagnose acute appendicitis 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 acute appendicitis.[10,11,18] [19]

The technical success and clinical success of ERAT in our meta-analysis was 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), and open appendectomy (OA).[10,16,20] In two studies, the length of hospital stay postoperatively was shorter in the ERAT cohort as compared to antibiotic therapy alone and laparoscopic/open appendectomy.[10,16]
ERAT appears to be safe and carries low rate of adverse events. The overall adverse event rate in our meta-analysis was only 0.19%. 3 cases of perforation occurred in our meta-analysis. One patient required an emergency appendectomy after 48 hours when contrast leakage into the abdominal cavity was 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 from 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 of comparison of ERAT to antibiotics.

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 adverse event rates. In addition, it can be used as a tool to supplement the diagnosis of acute appendicitis. Further studies with randomized controlled trials should be performed for it to become an alternative to surgery.
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**Figure and Table Legend**

Supplementary Figure 1 Study selection process in accordance with preferred reporting items for systematic reviews and meta-analysis statement

Supplementary Figure 2 PRISMA checklist

Supplementary Table 1 Quality assessment of the cohort studies with NOS scale

Supplementary Figure 3 Cochrane risk of bias tool for RCT (Kang 2020)

Table 1 Characteristics of included studies

Figure 1 Pooled rates of technical success of ERAT

Figure 2 Pooled rates of clinical success of ERAT

Table 2 Adverse events and recurrence of ERAT
| Author     | Newcastle-Ottawa Scale | Selection | Comparability | Outcome |
|------------|------------------------|-----------|---------------|---------|
| Kong, 2021 | ***                    | *         | ***           |         |
| Ding, 2021 | ***                    | *         | ***           |         |
| Chen, 2019 | ***                    | *         | **            |         |
| Ye, 2018   | ***                    | *         | ***           |         |
| Li, 2016   | ***                    | *         | ***           |         |
| Liu, 2015  | ***                    | *         | ***           |         |

Supplementary Table 1 Quality assessment of the cohort studies with NOS scale
| Study | Year | Country | Type of study | Type of center | Type of publication | No. of patients | Mean age | Males | Females |
|-------|------|---------|---------------|----------------|---------------------|----------------|---------|-------|---------|
| Kong  | 2021 | China   | Prospective   | Single         | Manucript           | 14             | 32.9    | 5     | 9       |
| Ding  | 2021 | China   | Retrospective | Single         | Manucript           | 70             | 39.9    | 42    | 28      |
| Kang  | 2020 | China   | RCT           | Single         | Manucript           | 36             | 6.74    | 22    | 14      |
| Chen  | 2019 | China   | Prospective   | Single         | Abstract            | 101            | --      | --    | --      |
| Ye    | 2018 | China   | Prospective   | Single         | Manucript           | 22             | 39.5    | 9     | 13      |
| Li    | 2016 | China   | Prospective   | Single         | Manucript           | 21             | 36      | 9     | 12      |
| Liu   | 2015 | China   | Retrospective | Multi          | Manucript           | 34             | --      | --    | --      |

Table 1 Characteristics of included studies
| Study | Year | Total adverse events | Perforation | Bleeding | Obstruction | Infection | Recurrence |
|-------|------|----------------------|-------------|----------|-------------|-----------|------------|
| Kong  | 2021 | 0                    | 0           | 0        | 0           | 0         | 0          |
| Ding  | 2021 | 1                    | 1           | 1        | 0           | 0         | 0          | 2          |
| Kang  | 2020 | 0                    | 0           | 0        | 0           | 0         | 0          | 2          |
| Chen  | 2019 | 0                    | 0           | 0        | 0           | 0         | 0          | 13         |
| Ye    | 2018 | 0                    | 0           | 0        | 0           | 0         | 0          | 2          |
| Li    | 2016 | 1                    | 1           | 1        | 0           | 0         | 0          | 1          |
| Liu   | 2015 | 1                    | 1           | 1        | 0           | 0         | 0          | 2          |

Table 2 Adverse events and recurrence of ERAT
### Technical Successes

| Study     | ES (95% CI)         | %   | Technical success | No. of patients |
|-----------|---------------------|-----|-------------------|-----------------|
| Liu (2015)| 0.9706 (0.8506, 0.9948) | 11.44 | 33                | 34              |
| Li (2019) | 1.0000 (0.8454, 1.0000)  | 7.13 | 21                | 21              |
| Ye (2018) | 1.0000 (0.8513, 1.0000)  | 7.46 | 22                | 22              |
| Chen (2019)| 0.9804 (0.9026, 0.9845) | 33.67 | 97                | 101             |
| Kang (2020)| 1.0000 (0.9030, 1.0000)  | 12.11 | 36                | 36              |
| Ding (2021)| 1.0000 (0.9460, 1.0000)  | 23.38 | 70                | 70              |
| Kong (2021)| 1.0000 (0.7847, 1.0000)  | 4.81 | 14                | 14              |
| Overall (I^2 = 0.00%, p = 0.52) | 0.9939 (0.9761, 1.0000) | 100.00 |                  |                 |

with estimated predictive interval: (0.97, 1.00)
Databases from their inception through Jan 2022

Total no. of articles found on search in Pubmed, Embase and others (n=142)

Titles and abstracts screened (n=72)

Excluded (n=33)
- Duplicates
- Case reports
- Review articles

Abstracts were reviewed (n=39)

Excluded (n=32)
- Incomplete data
- Cohort overlap

Full text screened for eligibility (n=7)

Studies for systematic review (n=7)
| Section and Topic | Item # | Checklist item | Location where item is reported |
|------------------|--------|----------------|---------------------------------|
| **TITLE**        | 1      | Identify the report as a systematic review. | 1                               |
| **ABSTRACT**     | 2      | See the PRISMA 2020 for Abstracts checklist. | 1-2                             |
| **INTRODUCTION** | 3      | Describe the rationale for the review in the context of existing knowledge. | 3                               |
| **OBJECTIVES**   | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 4                               |
| **METHODS**      | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 4                               |
|                  | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the data when each source was last searched or consulted. | 4                               |
|                  | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 4                               |
|                  | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each record retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 4, 5                            |
|                  | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 4                               |
|                  | 10     | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 5                               |
|                  | 11     | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 5                               |
|                  | 12     | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 4, 5                            |
|                  | 13a    | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 4                               |
|                  | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 5                               |
|                  | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 5                               |
|                  | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent ofstatistical heterogeneity, and software package(s) used. | 5, 6                            |
|                  | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | 6                               |
|                  | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 7                               |
|                  | 14     | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 6, 8                            |
|                  | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 8                               |
| **RESULTS**      | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 6                               |
|                  | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | 6                               |
|                  | 17     | Cite each included study and present its characteristics. | 6                               |
|                  | 18     | Present assessments of risk of bias for each included study. | 6                               |
|                  | 19     | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credibility interval), ideally using structured tables or plots. | Figure 1.2, Table 2, Supp fig 3 |
|                  | 20a    | Describe the synthesis, succinctly summarise the characteristics and risk of bias among contributing studies. | Figure 1.2                      |
|                  | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credibility interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Table 2, Supp fig 3             |
|                  | 20c    | Present results of all investigations of possible causes of heterogeneity among study results. | 6                               |
|                  | 20d    | Present results of all sensitivity analyses conducted to assess robustness of the synthesized results. | 6                               |
|                  | 21     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 6                               |
|                  | 22     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 7                               |
| **DISCUSSION**   | 23a    | Provide a general interpretation of the results in the context of other evidence. | 8                               |
|                  | 23b    | Discuss any limitations of the evidence included in the review. | 9, 10                           |
|                  | 23c    | Discuss any limitations of the review process used. | 9, 10                           |
| **OTHER INFORMATION** | 24a | Provide registration information for the review, including name and registration number, or state that the review was not registered. | 4                               |
|                  | 24b    | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 4                               |
|                  | 24c    | Describe and explain any amendments to information provided at registration or in the protocol. | NA                             |
| **SUPPORT**      | 25     | Describe sources of financial or non-financial support for the review and the role of the funders or sponsors in the review. | Title page                     |
| **COMPETING INTERESTS** | 26   | Declare any competing interests of review authors. | Title page                     |
| **AVAILABILITY OF DATA, CODE AND OTHER MATERIALS** | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | NA                             |
