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Endoscopic treatment in pediatric patients with recurrent and H-type tracheoesophageal fistulas – A systematic review and meta-analysis☆

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ABSTRACT

Objectives: Endoscopic treatments for managing recurrent tracheoesophageal fistula (rTEF) and H-type TEF are being utilized lately; however, the preferred technique is yet to be determined. We aimed to systematically review existing publications on endoscopic treatment of rTEF and H-type TEF to analyze their success and complication rates.

Methods: PRISMA guidelines were followed. MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials were comprehensively searched in accordance to a priori developed protocol, from 1975 until 2020. English, Spanish and German papers were included. Studies were independently screened and analyzed by two reviewers.

Results: 84 full texts were assessed for eligibility out of 581 screened studies, of these, 39 studies with 127 patients were eligible for inclusion (115 rTEF and 12 H-type TEF). All included studies were cases reports or case series. Overall success rate was 45% with sealant injection, 87% with de-epithelialization and 80% with sealant injection and de-epithelialization combined. The mean number of required treatments for success was 1.9 (range 1–6). Mixed effect model meta-analysis of case series with $n > 1$ showed that sealant injection had a significantly lower success rate of 50% (95% CI 1–99%, I^2 72%) compared to de-epithelialization 90% (95% CI 72–99%, I^2 27%), $p = 0.007$ and the combination of both techniques 87% (95% CI 68–99%, I^2 11%), $p = 0.02$. Nine patients (7%) had transient respiratory distress. No mortalities reported.

Conclusion: Endoscopic treatment for rTEF and H-type fistula is a minimally invasive technique with favorable outcome and considerably less morbidity compared to open surgery, suggesting it as a safe and effective first line treatment option. Repeated endoscopic treatment attempts can be expected to obtain complete closure. De-epithelization techniques with or without combined tissue adhesive injection had significantly better results than sealant injection techniques alone.

1. Introduction

Esophageal atresia with tracheoesophageal fistula (TEF) is a relatively rare congenital malformation reported in 1 in 2400–4500 live births [1]. Five types have been described by Gross [2], the most common being proximal esophageal atresia and distal TEF (88.5% of cases). TEF without esophageal atresia or "H"type TEF is considerably rarer, comprising only about 4% of cases. The majority of such anomalies undergo repair in early infancy. H-type fistula, however, may be diagnosed later in life due to its presentation with non-specific symptoms such as chronic or recurrent cough, choking related to feeding, and recurrent pneumonia.

Abbreviations: TEF, Tracheoesophageal fistula.

☆ There are no prior publications or submissions with any overlapping information, including studies and patients.

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Generally, the classic treatment of all types is through an open thoracic or cervical approach surgery. Open surgery has a fairly good outcome, although with a long term risk of respiratory and gastrointestinal complications [1].

The recurrence rate of TEF after initial repair has been reported between 5 and 10% [3] of cases, most often within 2–18 months after the repair [1].

Recurrent tracheoesophageal fistulas (rTEF) is a challenging situation from diagnostic and treatment perspectives, often requiring multiple investigations and repair procedures [4]. Revision open repair is a technically challenging surgery with associated high morbidity and mortality rates [5–7]. This has led investigators to seek less invasive interventions. Various endoscopic techniques have been described for the treatment of rTEF over the years, with variable published success rates. The disparity in the selection of cases and techniques has led to a lack of clear data or consensus regarding the effectiveness of an endoscopic approach, appropriate patient selection criteria, and the most effective technique. Recurrent tracheoesophageal fistulas and congenital H-type fistulas share similar clinical presentation and management options, hence both entities are commonly included in series describing endoscopic treatment. However, both are relatively rare disorders, thus, a consolidation of reported cases is needed to analyze the efficacy of such treatment approaches.

The objective of this systematic review was to identify and review cases of patients with endoscopic treatment of rTEF or H-type TEF published to date, aiming to analyze their success and complication rates.

2. Methods

2.1. Search strategy

The systematic review protocol, including search strategy and inclusion/exclusion criteria for studies, was developed a priori. A comprehensive search strategy in MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials was conducted from inception until December 2020 in accordance to PRISMA guidelines [8].

The search terms used for tracheoesophageal fistula were: tracheoesophageal* fistula* or esophagotracheal* fistula* or esophag* trache* fistula* or esophagotracheal* fistula* or esophago tracheo bronchial fistula* or oesophageal* fistula* or oesophageal* fistula* or trache* esophag fistula* or trache* oesophageal* fistula*. The study population was specified using search terms: child* or pediatr* or paediatr* or juvenile* or adolescent* or teen* or youth or boy or boys or girl* or infant* or newborn* or neonat* or toddler* or preschool* or pre-school* or school age* or elementary or high school* or secondary school* or grade school* or preteen* or pre-teen* or prepubescence* or pre-pubescens* or middle school* or schoolchild*. The search terms used for endoscopic treatment were: endoscopy* or bronchoscopy* or bronchial telescope* or esophagoscopy* or oesophagoscopy* or tracheoscopes*.

2.2. Criteria for inclusion

The eligible studies were randomized controlled trials, observational studies (cohort studies, case control studies), case series and case reports of pediatric patients diagnosed with rTEF or H-type fistula and undergoing endoscopic treatment. Conference abstracts were also included if they met inclusion criteria. These records were then limited to the English, Spanish and German languages.

The initial eligibility of studies was based on the title and abstract content and was assessed independently and in duplicate by two authors (C.G.L. and K.L.). Any disagreement between the two reviewers was adjudicated by a third author (N.K.C). Only studies with a congenital TEF in the pediatric population treated via endoscopic techniques were included. Other non-congenital TEF etiologies (e.g. traumatic, caustic agents) were excluded. Studies using only esophagoscopy were also excluded. However, the studies where esophagoscopy was used combined with a bronchoscopy were included.

2.3. Critical appraisal

Quality assessment of the included case series was conducted using the Joanna Briggs Institute (JBI) Critical Appraisal tool [9], a 10 questions checklist designed for assessing the quality of a case series in systematic reviews. 'Yes' answer received a score of +1. 'No' and 'Unclear' answers were assigned a score of 0. A question that is not applicable for all the included case series ('Not applicable' answer), will be omitted from the potential total score of 10. Two reviewers assessed the quality of the case series (C.G.L. and A.T.) independently. Discrepancies in scoring were discussed until agreement was achieved or adjudicated by a third author (N·K·C).

2.4. Data extraction and analysis

Eligible study full texts were reviewed for data extraction. Outcome measures were developed a priori, and included the number of patients, age at the time of treatment, technique(s) used, number of interventions, outcome, and complications. A summary statistic was performed on all included studies to describe the means of age at the time of rTEF endoscopic repair, number of treatments needed for success (in successful cases) and follow up duration in months. Closure success rates were also summarized as a percentage of total patients in all case reports and case series.

Following published guidelines, a proportional meta-analysis using case series only was performed [10]. TEF closure success rates were pooled for each technique with 95% confidence intervals using a random-effects model with Freeman-Tukey double arcsine transformation. Heterogeneity was assessed visually with forest plots and using the I^2 statistic. A mixed-effects model was used to compare the closure rates of the techniques. $P < 0.05$ was considered statistically significant. All statistical analysis was performed using the metafor package in R (version 4.2.1).

3. Results

Initial searches identified a total of 581 studies after removal of duplicates (Fig. 1). Following review of the studies titles and abstracts, 84 studies were considered potentially relevant to the study, and full-text articles were obtained. Forty-five studies were excluded for the following reasons: age, non-endoscopic intervention, or another diagnosis. 39 studies met the inclusion criteria and were thus included in this systematic review (See online supplement A). The eligible articles were published between the years 1975 and 2019. All included studies were case reports or case series. They included 127 patients, with a mean age at endoscopic repair of 21.9 months, range 0.13–168 months. Twelve patients had congenital H-type TEF, and 115 presented with rTEF (Table 1).

3.1. Endoscopic treatment techniques

All patients underwent endoscopic treatments via bronchoscopy. Some studies also employed esophagoscopy at the same time. Different endoscopic techniques were described. For further analysis, they were classified into three categories [11]:

I.- Injection of a sealant into the fistula tract or submucosa of the tracheal side of the fistula. The most commonly used were fibrin glue, butylcyanoacrylate (Histoacryl ™), and hyaluronic acid gel. 4 case series eligible for meta-analysis, 7 case reports.

II.- De-epithelization of the fistula tract. This was achieved with electrocautery, mechanical brush, trichloroacetic acid (TCA), silver nitrate, Nd:YAG laser, diathermy coagulation, or laser diode. 7 case series eligible for meta-analysis, 2 case reports.

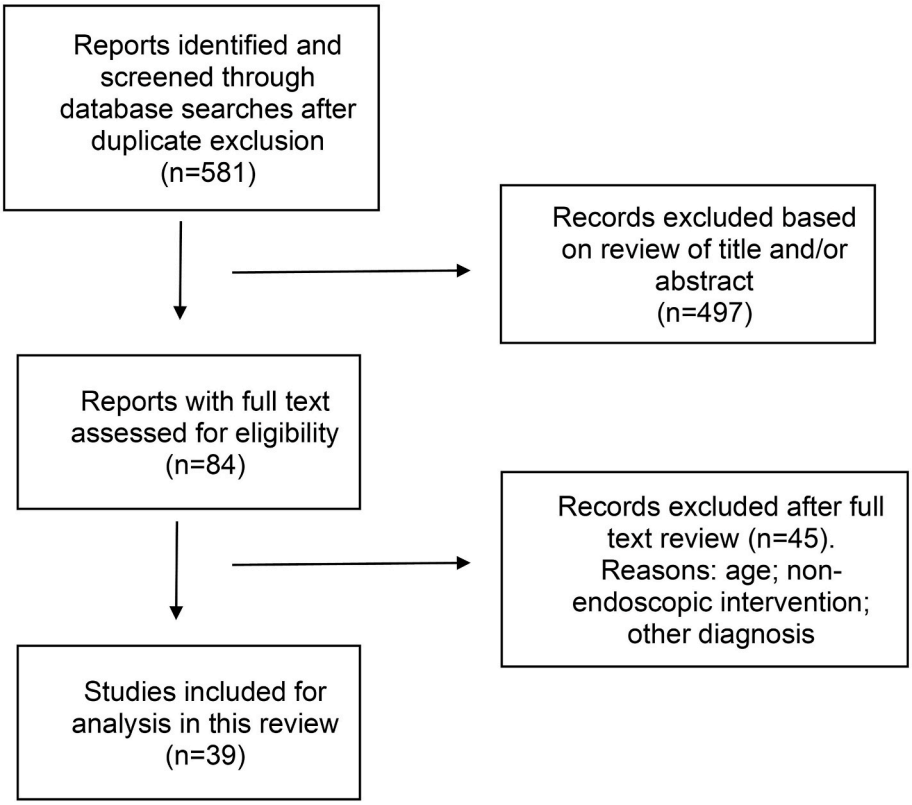

Fig. 1. Flow diagram of systematic review selection criteria.

III.- Combination of both techniques I and II: De-epithelization and injection of a sealant. 10 case series eligible for meta-analysis, 5 case reports.

Studies describing a different treatment technique that did not fit into the above mentioned 3 categories were included in the overall endoscopic techniques table, but were excluded from the analysis comparing the 3 common endoscopic techniques mentioned above; for example Wang et al. described the use of tracheal stents [12], others have described applying gastroendoscopic clip following de-epithelization [13,14] or biosynthetic mesh (Surgisis®) [15]. Studies that used more that one of the three techniques in sequential endoscopic treatments on a single patient were also excluded from the comparisons [14,16]. Papers including 2 different techniques applied consistently to a selected group of patients with clear separable results for both techniques were included in the comparison analysis accordingly [17,18]. However, if outcomes were not clearly separable for each specific technique, the study was not included in the comparative analysis [19].

3.2. Success rate

The outcomes and details of all included studies are summarized in Table 1. The overall success rate of r/H-type TEF closure for the 127 patients treated endoscopically was 69% (88/127), and 29% (34/116) after the first or a single endoscopic attempt. The mean number of treatments required for success was 1.9 (171 treatments for 88 successful subjects, range 1–6 interventions). Follow-up periods included in the studies had a mean of 26.8 months. Table 2.1–2.3 (appendix B) outlines the data separately according to each of the techniques used. Summary statistic of all patients included showed success rate after single intervention was lower than 50% in all the techniques, with final overall success rate of 45% in the sealant injection group, 87% in the de-epithelization group and 80% in the combination of both group (Fig. 2). Quantitative analysis of the pooled success rate of case series with $n > 1$ using random effect model revealed that sealant injection had a statistically significant lower overall success rate of 50% (95% CI 1–99%, I^2 72%) compared to de-epithelialization and the combination of both techniques with 90% (95% CI 72–99%, I^2 27%), $p = 0.007$, and 87% (95% CI 68–99%, I^2 11%) $p = 0.02$ respectively. Differences between de-epithelialization and combined techniques were non-significant ($p = 0.56$) (Fig. 3).

3.3. Complications

9 of 127 (7%) patients reported temporary post-operative complications. Four patients experienced significant respiratory distress. Three patients suffered bronchospasm; one patient evolved with bacterial pneumonia, and one patient presented with lung atelectasis, presumably due to aspiration of a glue plug. No mortality was reported.

3.4. Critical appraisal

21 out of the 39 included papers were case reports for which the quality rating was not applicable. The remaining 18 studies were small case series, where statistical analysis was not applicable, hence the statistical analysis question was omitted, resulting in a potential maximum score for the JBI critical appraisal tool of 9 instead of 10. One third of the cases series (6/18) had a score of 9/9. Three case series scored 8/9 and another three papers scored 7/9. The remaining 6 case series scored 6/9 or lower (Table 1).

4. Discussion

Recurrence of TEF after a primary surgical repair has been reported within the range of 5–10% [3], and even up to 20% in some series. H-type fistulas compose only a small portion of all congenital TEF, though it shares similar clinical presentation and treatment strategy with rTEF; hence, both were included in this review. Historically, a repeat of the open surgical intervention was the only treatment option

Table 1
Included studies with patient's characteristics, technique used, reported success and complications rate.

First author, year	Pt (s)	Mean age at repair in mo (range)	Mean number of treatments required for success	Diagnosis	Technique	Follow up - mo (successful patients)	Successful single treatments n (%)	Overall closure success (%)	Complications	JBI critical appraisal score for case series
Acker 2013	1	3	3	rTEF	Deepithelization by cauterization + fibrin glue injection	4 months	0 (0%)	1 (100%)		n/a
Atabek 2011	1	72	1	rTEF	Fibrin glue injection	n/d	0 (0%)	0 (0%)		n/a
Bhatnagar 1999	5	33 (1–156)	2 (1–4)	3 rTEF, 2 H-TEF	Electrocautery 3 Pt, Nd:YAG Laser 2 Pt	3 months	2/5 (40%)	3/5 (60%)	3 Pt – Respiratory distress (electrocautery was used). 1 Pt needed a tracheostomy. 2 Pt needed intubation for 48hrs	9
Briganti 2011	5	7.8 (1–18)	2.5 (2–3)	rTEF	Deepithelization with a brush and/or biopsy forceps + submucosal injection of dextranomer/ hyaluronic acid copolymer (Deflux)	n/d	0 (0%)	2/5 (40%)		9
Fallon 2018	1	144	1	rTEF	Deepithelization with bugbee electrocautery	7 months	1 (100%)	1 (100%)		n/a
Farra 2010	1	0.6	1	rTEF	Fibrin glue injection	21 months	1 (100%)	1 (100%)		n/a
Gutierrez 1994	1	0.5	1	rTEF	Fibrin glue injection	3 months	1 (100%)	1 (100%)		n/a
Gutierrez San Roman 2006	7	0.55 (0.46–0.66)	1.5 (1–3)	rTEF	Fibrin glue injection 3 Pt. Deepithelization by cauterization + fibrin glue injection 4 Pt	7.1 years (2–11)	3/7 (43%)	6/7 (86%)		7
Hoelzer 1999	1	72	1	rTEF	Fibrin glue injection	4 years	1 (100%)	1 (100%)		n/a
Hosseini 2011	3	na (2–8)	1	rTEF	Deepithelization with bugbee electrocautery + tissue glue injection	6 months	3/3 (100%)	3/3 (100%)		2
Janek 2019	2	9 (0.5–18)	1.5 (1–2)	H-TEF	Deepithelization with bugbee electrocautery + hyaluronic acid gel injection	19 (16–22) months	1/2 (50%)	2/2 (100%)		n/a
Keckler 2008	1	12	3	rTEF	Deepithelization with brush + biosynthetic mesh (Surgisis™) was rolled like a cigar and was introduced into the fistula tract (+ fibrin glue was injected only in the first attempt)	36 months	0 (0%)	1 (100%)	1 Pt – Respiratory distress two days after first intervention. No evidence of the fibrin glue migration on emergent bronchoscopy. Extubated later.	n/a
Khurana 2004	6	13 (0.5–54)	2.2 (1–3)	rTEF	Endoscopic diathermy coagulation ± fibrin glue (only in one patient)	53 (16–96) months	1/6 (17%)	5/6 (83%)		9
Kilic 1999	1	6	2	rTEF	Deepithelization with bugbee electrocautery + Fibrin glue injection	n/d	0 (0%)	1 (100%)		n/a
Lara 2019	11	n/d	1.3	11 rTEF and 1 H-TEF	Deepithelization with brush + TCA	12 months (2–36)	n/d	10/11 (91%)	2 Pts Bronchospasm	5
Lelonge 2016	14	20.2 (3–156)	1.8	14 rTEF	TCA application	41 months (8–72)	6/14 (43%)	14/14 (100%)	1 Pt Bacterial pneumonia 1 Pt bronchospasm	8
Linke 2002	1	0.13	3	H-TEF	NdYag-laser		0/1 (0%)	0/1 (0%)		n/a
Lopes 2003	1	11	2	rTEF	1st procedure: Fibrin glue injection. 2nd procedure: Ebucrilate injection (Histoacrylate®) via bronchoscope and	3 years	0 (0%)	1 (100%)	1 Pt – lung atelectasis, presumably due to aspiration of a glue plug	n/a

(*continued on next page*)

Table 1 (*continued*)

First author, year	Pt (s)	Mean age at repair in mo (range)	Mean number of treatments required for success	Diagnosis	Technique	Follow up - mo (successful patients)	Successful single treatments n (%)	Overall closure success (%)	Complications	JBI critical appraisal score for case series
					polidocanol injection via esophagoscopy					
McGahren 2001	1	3	3	rTEF	Deepithelization by cauterization + fibrin glue injection	3.5 years	0 (0%)	1 (100%)		n/a
Meier 2007	3	39 (5–108)	2 (1–3)	rTEF	Deepithelization with a brush + fibrin glue injection	4 (3–5) years	1/3 (33%)	2/3 (66%)		8
Nazir 2017	3	6 (3–9)	2.3 (1–3)	rTEF	Deepithelization with bugbee electrocautery + Fibrin glue injection	3 years	1/3 (33%)	3/3 (100%)		9
Piastra 2013	2	6.5 (2–11)		rTEF	1 Px Laser diode + histoacryl gum injection; 1Px Submucosal infiltrations of Permacol™ (fibrous sheet of acellular crosslinked porcine dermal collagen)		0 (0%)	0/2 (0%)		n/a
Propst 2014	1	1	4	rTEF	Bugbee electrocautery ± Tisseel injection (one procedure)		0 (0%)	0 (0%)		n/a
Rakoczy 2010	1	n/d	3	rTEF	1st and 2nd procedure: deepithelization with bugbee electrocautery + Fibrin glue injection. 3rd attempt: KTP laser	1.5 years	0 (0%)	1 (100%)		n/a
Rangecroft 1984	2	60 (1 patient nd)	5.5 (5–6)	rTEF	Diathermy coagulation	1 year	0/2 (0%)	2/2 (100%)		n/a
Schmittenbecher 1992	3	1	1	H-TEF	Nd:YAG laser	3 months	2/3 (66.7%)	2/3 (66%)		6
Sung 2008	3	57.6 (1–156)	3.3 (3–4)	rTEF	Chemocauterization using 50% trichloroacetic acid.	7.6 (5–9)	0 (0%)	3/3 (100%)		8
Valiyev 2019	9	18 (4–70)		rTEF	4 patients laser cauterization and fibrin glue injection, 4 patients TCA application), 1 patient both	28 (3–70) months	1/9 (11%)	1/9 (11%)		4
Wang 2016	2	16 (3–29)	2	rTEF	Tracheal stents		0 (0%)	0 (0%)		7
Wiseman 1995	2	12 (6–18)	2.5 (1–4)	rTEF	Deepithelializatio using a bronchial biopsy brush + fibrin glue injection	6 months	1/2 (50%)	1/2 (50%)		n/a
Witte 2019	1	168		rTEF	Deepithelializatio using a bugbee + argon plasma endoscopically + Ovesco clip endoscopically		0/1 (0%)	0/1 (0%)		n/a
Richter 2008	4	11.5 (3–20)	1.25 (1–2)	rTEF	Deepithelization with bugbee electrocautery + Fibrin glue injection + added aprotinin and thrombin.	19.5 months (range, 4–38months)	3/4 (75%)	4/4 (100%)		9
Tzifa 2006	8	10,6 (0,3–60)	1,5 (1–2)	2 H-TEF and 6 rTEF	De-epithelialization (suction or electrocautery) and histoacryl glue + lipiodol injection	54 (3–132) months	4/8 (50%)	7/8 (88%)		9
Linder 2006	5	68 (12–156)	4,3 (4–5)	rTEF	Deepithelization with silver nitrate + glue.	3 years (2–4)	0 (0%)	3/5 (60%)		7
Van Niekerk 2012	1	6	1	rTEF	De-epithelization with brush + Permacol (porcine dermal biological mesh)+ Duraseal	2 years	1 (100%)	1 (100%)		n/a
Pompino 1979	2	4	5	rTEF	Histoacryl injection	10 (8–12) months	0/2 (0%)	2/2 (100%)		n/a
Gdanietz K. 1975	1	9	1	rTEF	Histoacryl injection	n/d	1 (100%)	1 (100%)		n/a

(*continued on next page*)

Table 1 (*continued*)

First author, year	Pt (s)	Mean age at repair in mo (range)	Mean number of treatments required for success	Diagnosis	Technique	Follow up - mo (successful patients)	Successful single treatments n (%)	Overall closure success (%)	Complications	JBI critical appraisal score for case series
Waag 1979	2		1,5 (1–2)	1 rTEF and 1 H-TEF	Histoacryl injection		0 (0%)	1/2 (50%)		n/a
Montedonico 1999	8	n/d		rTEF	Histoacryl or fibrin glue injection		0 (0%)	0 (0%)		6
Overall	127	21.9 (0.13–168)	1.9			26.8	34/116 (29%)	88/127 (69,3%)		

Pt: Patient; rTEF: recurrent tracheoesophageal fistula; H-TEF: H type tracheoesophageal fistula; n/d: no data; TCA: trichloroacetic acid, JBI Joanna Briggs Institute, n/a non-applicable.

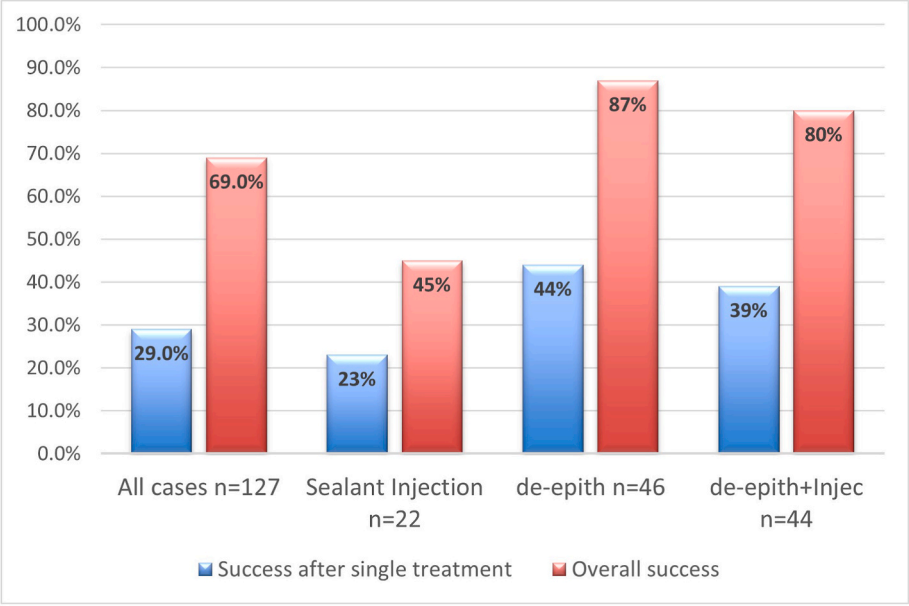

Fig. 2. Summary statistics, including all case reports and case series, for success rate of endoscopic treatment for recurrent TEF or H-type TEF. De-epith: de-epithelization; de-epith + Inject: de-epithelization + sealant injection.

for rTEF. Depending on the level of the fistula, it can be cannulated via bronchoscopy to assist its identification during dissection and ligation, often via transcervical or thoracotomy access. Some authors recommend adding an interposition tissue (e.g. pericardium, pleura) between the sutured ends of the esophagus and trachea [11]. A revision open surgical repair entails the risk of high morbidity, complications, and further recurrence [7]. Endoscopic techniques for treating rTEF were originally described by Gdanietz and Krause in 1975 [20]. Since then, endoscopic treatment has gained more interest given its potential for a lower risk profile.

Through this review, the available data on endoscopic techniques and outcomes have been collected and analyzed. Combining all endoscopic techniques for the 127 included patients, the success rate of fistula closure after a single intervention was only 29%, but this improved to almost 70% after an average of 1.9 intervention attempts. In a previous systematic review, Aworanti et al. compared 108 patients who underwent open techniques for the management of rTEF versus 57 patients treated endoscopically, up until 2014 [11]. They found a re-fistulation rate of 21% after open surgery, with an average of 1.1 procedures required to achieve treatment success. Re-fistulation rate after endoscopic treatment was 63%, with an average of 2.1 treatments required to achieve successful fistula closure. The overall success rate for open repair was 93.5% compared to 84% in patients managed endoscopically. In our review, a wider search strategy was employed and included English, Spanish and German languages as well.

Only nine patients treated endoscopically (7%) were reported to have temporary respiratory compromise. No mortality cases were reported. In Aworanti's paper, 16% of the patients treated with open surgery reported major leak complications. In addition, they reported four deaths (3.7%), three perioperatively and one died 10 months later, with a second rTEF found at autopsy. According to our data, the low risk profile of endoscopic treatment, combined with an acceptable success rate approaching 70%, makes this a reasonable option to consider as a first line treatment for rTEF or H-type TEF.

Over the years, different endoscopic techniques to treat rTEF and H-type TEF have been described. However, controversy still exists as to which technique is superior. The heterogeneity of the techniques used, the patients included in various studies, together with the lack of controlled comparative studies, increases the challenge of comparing the different methods.

The reported endoscopic techniques could be classified into three types as previously discussed. Tissue adhesive injection to obliterate the fistula was described back in 1975 [20]. Butylcyanoacrylate (Histoacryl™) and fibrin glue (Tisseel™)) were among the various agents described [11] (Table 2, appendix B). Based on our results, this technique showed the lowest efficacy rate, achieving only 23% success on a first attempt and 45% success when repeated (see Fig. 2). Smaller studies did show better results with this technique (Richter [7] 78%, and Lal [4]

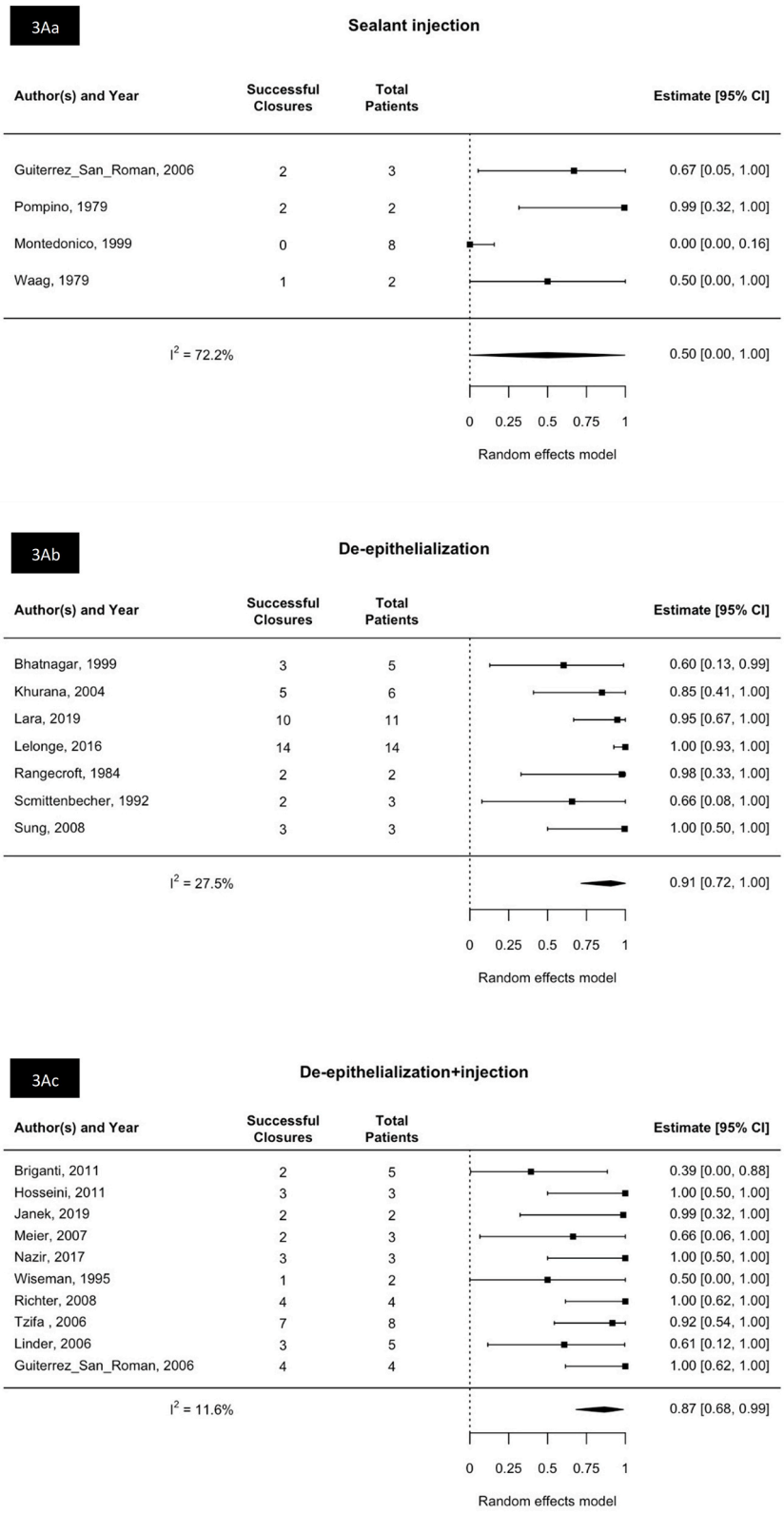

Fig. 3. Success rate of endoscopic treatment for r-TEF or H-type TEF - analysis of case series with n > 1.3A: Forest plots of overall TEF closure rates using sealant injection (3Aa), de-epithelialization (3Ab) and combination of both (3Ac) with 95% CI. 3B: Comparison of the pooled overall and after single intervention success rates of the three techniques. Overall success rate of de-epith technique (90%, 95% CI 72–99%, I^2 27%) and the combination of de-epith-injec technique (87%, 95% CI 68–99%, I^2 11%) were significantly higher than injection of tissue sealant technique (50%, 95% CI 1–99%, I^2 72%), $p = 0.007$ and $p = 0.02$ respectively. Differences between de-epith and de-epith-injec were not significant ($p = 0.56$). rTEF: recurrent tracheoesophageal fistula; H-TEF: H-type tracheoesophageal fistula; de-epith: de-epithelialization; de-epith-injec: de-epithelialization and sealant injection; CI: confidence interval, heterogeneity: I^2.

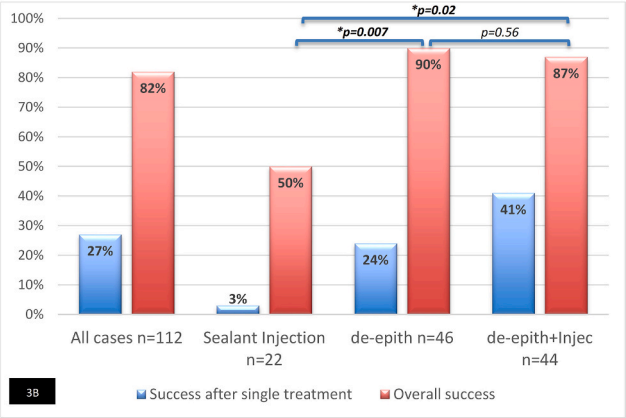

Fig. 3. (*continued*).

67%), however, these findings should be interpreted with caution due to the small numbers and the potential for reporting or publication bias.

De-epithelization of the fistulous tract can be achieved using different methods; thermal (electrocautery or laser), chemical (trichloroacetic acid, sliver nitrate), or traumatic (mechanical abrasion) (Table 2, appendix B), all seeking to ablate the fistula's tract epithelial lining, which may lead to its closure by the natural healing process with scarring. In our review, the de-epithelization techniques had the highest overall success rate (Figs. 2 and 3), however still showed a relatively low success rate after a single procedure. This highlights the frequent need for repeated endoscopic procedures regardless of the technique used to optimize outcome. Providing the caregivers with this information is of paramount importance in establishing realistic expectations of the treatment course.

The combination of both techniques, de-epithelialization of the fistulous tract with an injection of adhesives, was the third category that was analyzed separately. This is the most widely published technique, used in 15 studies included in this review. The combinations were diverse, with electrocautery and tissue glue injection being the most common. Tzifa [6] published the largest series to date, with eight patients presenting with either rTEF or H-Type fistula, using a combination of electrocautery and Histoacryl™ injection. They achieved definitive fistula closure in 7 of the 8 patients described. Combined techniques have been described to have the highest success in earlier smaller publications; Richter [7] reported 93%, and Lal [4] reported 82% overall success using this technique. Our data regarding combined techniques showed a non-significant, slightly lower efficacy compared to de-epithelization alone when quantitative analysis was performed on case series (87% vs 90%, respectively, $p = 0.56$, Fig. 3B).

The lower success rate of sealant injection compared to the other techniques, albeit being the first endoscopic technique described in the literature, might be related to the fact that a biological adhesive such as fibrin glue is completely absorbed during wound healing without causing foreign body reaction of extensive fibrosis [21]. We theorize that once the adhesive agent is broken down, if the fistulous tract had not adequately scarred closed, it may re-canalize.

We presume that on some occasions, by the act of its injection into the fistula tract, some form of trauma is applied to the epithelium, which might cause local inflammation and scarring leading to success in fistula closure. The sealant can provide a temporary fistula seal until the final scarring achieves a long-lasting closure. One of the major concerns regarding sealant injection is a risk of migration down the fistula with possible aspiration and respiratory distress, as demonstrated in some reports (see Table 1). Given the similar results found in our review of combining sealant injection with de-epithelization versus de-epithelialization alone, one may consider avoiding this injection to mitigate respiratory risks, particularly when the fistula location is distal and closer to the carina.

The main limitations of this review was that studies included were either case reports or small case series, with the inherent risk of publication or reporting bias, as such studies tend to more commonly report positive outcomes and experiences. This highlights the rarity of this condition but should still be considered as low level of evidence. Furthermore, the articles included in this study are heterogeneous concerning the patients, techniques used, and duration of follow-up. Additionally, there is a variation in surgeons' expertise in the different methods that is difficult to assess objectively and may affect the procedure outcome. In a similar manner, heterogeneity is also expected regarding the location, diameter, and length of the fistula. Due to the rarity of this condition, designing and performing a randomized trial is unlikely to be feasible. However, multicenter prospective data collection can address some of the questions highlighted in this review as to which endoscopic technique has a clear advantage over the others and whether it is possible to establish criteria for favoring endoscopic versus open approach in each case.

5. Conclusion

Endoscopic treatment for rTEF and H-type fistulae is a minimally invasive technique with a favorable outcome and considerably less morbidity compared to open surgery. Given the existing literature, we believe it is a safe and effective first line option. A need for repeated endoscopic treatment attempts should be expected to obtain complete closure with an average approaching 2 procedures to achieve success. An open surgical repair might be reserved as a rescue option in case of failure after multiple endoscopic attempts. The available data suggests that de-epithelization techniques with or without combined adhesive injections have significantly better results compared to adhesive injection technique alone. There was no apparent added value to adding sealant injection to de-epithelization alone.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijporl.2023.111541.

References

[1] T. Kovesi, S. Rubin, Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula, Chest 126 (2004) 915–925, https://doi.org/10.1378/chest.126.3.915.

[2] R.E. Gross, The Surgery of Infancy and Childhood, W. B. Saunders Co, Philadelphia, 1954.

[3] S.W. Bruch, R.B. Hirschl, A.G. Coran, The diagnosis and management of recurrent tracheoesophageal fistulas, J. Pediatr. Surg. 45 (2010) 337–340, https://doi.org/10.1016/j.jpedsurg.2009.10.070.

[4] D. Lal, K. Oldham, Recurrent tracheoesophageal fistula, Eur. J. Pediatr. Surg. 23 (2013) 214–218, https://doi.org/10.1055/s-0033-1347913.

[5] J.D. Meier, C.G. Sulman, P.S. Almond, L.D. Holinger, Endoscopic management of recurrent congenital tracheoesophageal fistula: a review of techniques and results, Int. J. Pediatr. Otorhinolaryngol. 71 (2007) 691–697, https://doi.org/10.1016/j.ijporl.2007.02.022.

[6] K.T. Tzifa, E.L. Maxwell, P. Chait, A.L. James, V. Forte, S.H. Ein, J. Friedburg, Endoscopic treatment of congenital H-Type and recurrent tracheoesophageal fistula with electrocautery and histoacryl glue, Int. J. Pediatr. Otorhinolaryngol. 70 (2006) 925–930, https://doi.org/10.1016/j.ijporl.2005.10.017.

[7] G.T. Richter, F. Ryckman, R.L. Brown, M.J. Rutter, Endoscopic management of recurrent tracheoesophageal fistula, J. Pediatr. Surg. 43 (2008) 238–245, https://doi.org/10.1016/j.jpedsurg.2007.08.062.

[8] D. Moher, L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle, L.A. Stewart, M. Estarli, E.S.A. Barrera, R. Martínez-Rodríguez, E. Baladia, S. D. Agüero, S. Camacho, K. Buhring, A. Herrero-López, D.M. Gil-González, D. G. Altman, A. Booth, A.W. Chan, S. Chang, T. Clifford, K. Dickersin, M. Egger, P. C. Gøtzsche, J.M. Grimshaw, T. Groves, M. Helfand, J. Higgins, T. Lasserson, J. Lau, K. Lohr, J. McGowan, C. Mulrow, M. Norton, M. Page, M. Sampson, H. Schünemann, I. Simera, W. Summerskill, J. Tetzlaff, T.A. Trikalinos, D. Tovey, L. Turner, E. Whitlock, Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement, Rev. Esp. Nutr. Humana y Diet. 20 (2016) 148–160, https://doi.org/10.1186/2046-4053-4-1/TABLES/4.

[9] Z. Munn, T.H. Barker, S. Moola, C. Tufanaru, C. Stern, A. McArthur, M. Stephenson, E. Aromataris, Methodological quality of case series studies: an introduction to the JBI critical appraisal tool, JBI Evid. Synth. 18 (2020), https://doi.org/10.11124/JBISRIR-D-19-00099.

[10] M.H. Murad, S. Sultan, S. Haffar, F. Bazerbachi, Methodological quality and synthesis of case series and case reports, Evid. Base Med. 23 (2018) 60–63, https://doi.org/10.1136/bmjebm-2017-110853.

[11] O. Aworanti, S. Awadalla, Management of recurrent tracheoesophageal fistulas: a systematic review, Eur. J. Pediatr. Surg. 24 (2014) 365–375, https://doi.org/10.1055/s-0034-1370780.

[12] L. Wang, L. Zhang, H. Liang, M. Gao, D. Li, M. Li, F. Meng, Use of tracheal stents in the treatment of pediatric tracheoesophageal fistula: a report of three cases, J. Biomater. Tissue Eng. 6 (2016) 826–831, https://doi.org/10.1166/jbt.2016.1509.

[13] S.R. Witte, R.M. Juza, M.C. Santos, P.W. Dillon, E.M. Pauli, The combined bronchoscopic and endoscopic management of a recurrent tracheo-esophageal fistula, in: SAGES 2019, Annu. Meet., Baltimore, 2019.

[14] E.J. Propst, S.C. Ling, A. Daneman, J.C. Langer, Endoscopic clip for closure of persistent Tracheoesophageal fistula in an infant, Laryngoscope 124 (2014) 2182–2185, https://doi.org/10.1002/lary.24650.

[15] S.J. Keckler, S.D. St Peter, C.M. Calkins, G.W. Holcomb, Occlusion of a recurrent tracheoesophageal fistula with surgisis, J. Laparoendosc. Adv. Surg. Tech. 18 (2008) 465–468, https://doi.org/10.1089/lap.2007.0136.

[16] G. Rakoczy, B. Brown, D. Barman, T. Howell, A. Shabani, B. Khalil, Z. Sheehan, KTP laser: an important tool in refractory recurrent tracheo-esophageal fistula in children, Int. J. Pediatr. Otorhinolaryngol. 74 (2010) 326–327, https://doi.org/10.1016/j.ijporl.2009.12.009.

[17] C. Gutiérrez San Román, J.E. Barrios, J. Lluna, V. Ibañez, E. Hernández, L. Ayuso, E. Valdes, A. Roca, A. Marco, C. García-Sala, Long-term assessment of the treatment of recurrent tracheoesophageal fistula with fibrin glue associated with diathermy, J. Pediatr. Surg. 41 (2006) 1870–1873, https://doi.org/10.1016/j.jpedsurg.2006.06.014.

[18] M. Piastra, V. Briganti, E. Luca, M. De Carolis, P. Domenico, G. Conti, E. Stival, A. Tempera, A. Calisti, P. Serio, Recurrent tracheoesophageal fistula and respiratory failure: the role of early airway endoscopic approach, Eur. J. Pediatr. Surg. 23 (2013) 153–156, https://doi.org/10.1055/s-0032-1315805.

[19] N. Valiyev, K.K. Cerit, M.Y. Erdas, A.P. Ergenekon, G. Kiyan, DOZ047.91: bronchoscopic treatment of recurrent tracheoesophageal fistula: is it an effective option? Dis. Esophagus 32 (2019) https://doi.org/10.1093/dote/doz047.91 doz047.91.

[20] K. Gdanietz, I. Krause, Plastic adhesives for closing oesophago tracheal fistulae in children, Zentralblatt für Kinderchir 17 (1975) 137–138.

[21] M. Brennan, Fibrin glue, Blood Rev. 5 (1991) 240–244, https://doi.org/10.1016/0268-960X(91)90015-5.