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Clinical efficacy and safety of magnetic sphincter augmentation (MSA) and transoral incisionless fundoplication (TIF2) in refractory gastroesophageal reflux disease (GERD): a systematic review and meta-analysis

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ABSTRACT

Background and study aims Proton pump inhibitors (PPI) are effective medical therapy options for gastroesophageal reflux disease (GERD). However, 20 % to 40 % of patients report symptoms despite taking daily PPI. Transoral incisionless fundoplication (TIF2) and magnetic sphincter augmentation (MSA) are less invasive options for the treatment of refractory GERD and are increasingly gaining popularity.

Methods We conducted a comprehensive search of several databases to identify relevant studies. Our primary aim was to compare the efficacy of both interventions reported as improvement in Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) score, overall patient satisfaction, improvement in post-procedure regurgitation, and fraction of patients completely off PPI therapy at follow up.

Results Twenty-four studies with 1942 patients were included in the final analysis. Both MSA and TIF2 had comparable technical success and clinical success based on im-

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provement in GERD-HRQL scores i.e. 98.8% (CI 95.6,99.7) vs 98.5% (CI 95.7,99.5) and 80.4% (CI 66,89.6) vs 77.7% (CI 64.1,87.2), respectively. A significantly greater proportion of patients reported improvement in regurgitation, i.e. 91.1% (CI 83.8,95.3) vs 73.1% (CI 62.5,81.7) and were able to completely discontinue PPI therapy with MSA compared to TIF2 i.e. 91.3% (CI 81.5,96.2) vs 63.8% (CI 51.6,74.4). Patients' BMI and presence of a hiatal hernia did not have any effect on procedural outcomes.

Conclusion Both procedures performed at par when comparing clinical success in terms of improvement in GERD-HRQL scores. In terms of overall patient satisfaction, post procedure regurgitation and cumulative number of patients off PPI therapy, MSA outperforms TIF2.

Introduction

An estimated 9 million visits to the primary care physician are attributed to gastroesophageal reflux disease (GERD) and when severe, this condition can significantly impair a person's quality of life [1]. Treatment with proton pump inhibitor (PPI) therapy has been the mainstay of medical therapy for decades. Although most patients with acid reflux respond satisfactorily to PPI therapy, 20% to 42% may be considered "difficult to treat" [2–4]. While cheap and generally safe, there have been some concerns with PPI therapy, including increased infectious complications, nutritional deficiencies, as well as a potential risk of osteoporosis and dementia with long term use [5].

Patients who fail medical therapy or those who are referred to as having "refractory" GERD are often considered for anti-reflux surgery (which can be performed either via open or laparoscopic surgery or endoscopically). Surgical fundoplication is a highly efficacious procedure and remains the current gold standard in the surgical management of GERD [6]. Unlike PPI therapy, surgically manipulating the lower esophageal sphincter (LES) significantly reduces the number of reflux events, rather than merely reducing the acidity of the refluxate [7]. Traditional surgical fundoplication can at times result in complications such as postoperative dysphagia, recurrent heartburn and wrap disruption [8–10].

To help circumvent these complications, magnetic sphincter augmentation (MSA) with the LINX device (Torax Medical) was approved by the US Food and Drug Administration in 2012 for patients with mild to moderate GERD. This device is composed of a string of beads containing a sealed core of magnetic neodymium iron boride, which are interlinked with independent titanium wires. These magnets produce a very precise force of inward attraction (~40 g at full contraction, 7 g at full expansion), which augments the closure of the lower esophageal sphincter. The beads are interconnected by small mobile wires that allow the device to expand so as to permit the passage of a food bolus as well as physiologic functions like belching or vomiting [11].

Transoral Incisionless Fundoplication (TIF) was first introduced in 2007. The procedure involves tissue manipulation using an endoscopic suturing device called EsophyX (Endogastric Solutions, Redmond, Washington, United States). TIF attempts to restore competency to the LES, preventing reflux of gastric contents. Eligible candidates include those with intractable reflux symptoms, no or mild esophagitis with hiatal hernia <2 cm in length and abnormal acid reflux [12, 13].

While there have been several studies reporting clinical success and safety profile for both MSA and TIF, no randomized controlled trials have directly compared the two interventions. The goal of this study was to evaluate the clinical outcomes of these procedures, reported as improvement in cumulative GERD Health-Related Quality of Life (GERD-HRQL) scores, patient reported symptom improvement, and overall patient reported satisfaction as well as total number of patients off PPI therapy at maximum follow up, by meta-analysis methods.

Methods

Search strategy

The literature was searched by a medical librarian for studies that reported on the use of magnetic sphincter augmentation (MSA) and trans-oral fundoplication (TIF) in the treatment of gastroesophageal reflux disease (GERD). Searches were run in December 2019 in ClinicalTrials.gov, Ovid EBM Reviews, Ovid Embase (1974+), Ovid Medline (1946+including epub ahead of print, in-process & other non-indexed citations), Scopus (1970+) and Web of Science (1975+). Results were limited to English language. All results were exported to Endnote where 815 obvious duplicates were removed leaving 869 citations. The full search strategy is available in **Supplementary Appendix 1**. The MOOSE checklist was followed and is provided as **Supplementary Appendix 2** [14]. Reference lists of evaluated studies were examined to identify other studies of interest.

Study selection

In this meta-analysis, we included studies that evaluated the clinical outcomes of MSA and TIF in patients undergoing treatment for refractory GERD. Studies were included irrespective of inpatient/outpatient setting, study sample-size, follow-up time, and geography as long as they provided the clinical outcomes data needed for the analysis.

Our exclusion criteria were as follows: (1) studies that evaluated TIF1 procedure; (2) studies where TIF was performed with concurrent hiatal hernia repair [15–17]; (3) studies where MSA was performed with concurrent hiatal hernia repair [18–20]; (4) studies that did not report on the clinical outcomes of interest; (5) studies performed in the pediatric population (Age <18 years); and (6) studies not published in English language. In cases of multiple publications from a single research group reporting on the same patient, same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained. The retained studies

were selected by two authors (BPM, SC) based on the publication timing (most recent) and/ or the sample size of the study (largest). In situations where a consensus could not be reached, overlapping studies were included in the final analysis and any potential effects were assessed by sensitivity analysis of the pooled outcomes by leaving out one study at a time.

Data abstraction and quality assessment

Data on study-related outcomes from the individual studies were abstracted independently onto a standardized form by at least four authors (BPM, SRK, SC, MB). Authors (SC, LLK, LKJ and SA) cross-verified the collected data for possible errors and two authors (BPM, SC) did the quality scoring independently.

The Newcastle-Ottawa scale for cohort studies was used to assess the quality of studies [21]. This quality score consisted of eight questions, the details of which are provided in **Supplementary Table 1**.

Outcomes assessed

The outcomes assessed were as follows:

1. Pooled rates of clinical success as determined by > 50 % improvement in cumulative GERD-HRQL score
2. Pooled rate of clinical success as determined by patient satisfaction (per Alimentary Satisfaction (AS) score [22] or reported as "Dissatisfied, Neutral, Satisfied" [23–25] at follow-up
3. Pooled rate of clinical success as determined by percentage of patients

reporting improvement in regurgitation at follow up as determined by Reflux Disease Questionnaire (RDQ) [26–28], Foregut Symptom Questionnaire (FSQ) [29, 30], Regurgitation Score [23, 24, 31]

1. Pooled rate of number of patients completely off PPI therapy at follow up
2. Pooled rates of technical success of MSA and TIF2
3. Pooled rate of post-procedural dysphagia
4. Meta-regression analysis to assess effect of BMI on outcomes of in both study
5. cohorts
6. Meta-regression analysis to assess the effect of presence of pre-procedure

hiatal hernia on clinical success in both study cohorts

Assessment methodology and definitions

The collected data were matched between the groups (MSA, TIF2) before statistical analysis. Comparison analysis was performed by sub-group analysis between the pooled outcomes of MSA and TIF2. This model of comparison is comparable to a retrospective case-control study with matched groups and should be considered non-causal [32].

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird using the random-effects model [33]. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis [34].

We assessed heterogeneity between study-specific estimates by using Cochran Q statistical test for heterogeneity, 95 % prediction interval (PI), which deals with the dispersion of the effects, and the I^2 statistics. [35, 36] In this, values of < 30 %, 30 % to 60 %, 61 % to 75 %, and > 75 % were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.

Publication bias was ascertained, qualitatively, by visual inspection of funnel plot and quantitatively, by the Egger test [37]. When publication bias was present, further statistics using the fail-Safe N test and Duval and Tweedie's 'Trim and Fill' test was used to ascertain the impact of the bias [38]. Three levels of impact were reported based on the concordance between the reported results and the actual estimate if there were no bias. The impact was reported as minimal if both versions were estimated to be same, modest if effect size changed substantially but the final finding would still remain the same, and severe if basic final conclusion of the analysis is threatened by the bias [39]. $P < 0.05$ was used a-priori to define significance between the groups compared.

When possible, meta-regression analysis was carried out to study the effects of clinical variables on pooled outcomes. Single variable analysis was done assuming other variables to be constant using a random-effects model. A Knapp-Hartung 2-tailed $P < 0.05$ was considered statistically significant.

All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, New Jersey, United States).

Results

Search results and population characteristics

From an initial pool of 1684 studies, 869 records were screened and 64 full-length articles were assessed. A total of 24 studies (1942 patients) were included in the analysis. 1074 patients (566 males, 508 females) underwent treatment with MSA (9 studies) and 868 patients (379 males, 489 females) underwent treatment with TIF2 (15 studies).

The schematic diagram demonstrating our study selection is illustrated in **Supplementary Fig. 1**. Baseline population characteristics were comparable between the MSA and TIF2 cohorts. The mean and/or median age ranged from 44 to 63 years in the MSA cohort and 36 to 68 years in the TIF2 cohort. The mean duration of GERD pre-treatment ranged from 5 to 14.2 years in the MSA cohort and 5 to 11.2 years in the TIF2 cohort. A total of 389 patients in the MSA cohort and 462 patients in the TIF2 cohort had hiatal hernias. In the TIF2 group, 158 patients had a Hill Grade III/IV hiatal hernia. Further details along with the population characteristics are described in ▶ **Table 1a**, ▶ **Table 1b** and ▶ **Table 2**.

▶ **Table 1a** Study details – Patient characteristics

	Design, Period, Center, Country	Device	Age	Total (N)	N @ F/u	M/F	GERD Duration (Years)	BID PPI duration (Years)	Barrett's (N)		Hiatal Hernia	GEJ Hill Grade				BMI (kg/m2)	MSA – No# Beads/ TIF – Fasteners	Esophagitis (Pre-MSA)			
									Pre-Procedure	Post-Procedure		I	II	III	IV			Grade A	Grade B	Grade C	Grade D
MSA/LINX (9 Studies)																					
Asti, 2016	Prospective, Mar 2007 and Jul 2014, Single center, Italy.	LINX	44 ± 20	135	135 (1y), 118 (2y), 94 (3y), 59 (4y)	44/91	5.0 (7.0)	4.0 (5.5)	6	–	–	–	–	–	–	23.94 ± 4.54	NR	–	–	–	–
Bell, 2019	Prospective, RCT, Jul 2015 to Feb 2017, Multicenter, USA.	LINX	46 (21–76)	50 (Total), 47 (MSA Procedure)	47	31/19	–	–	–	–	29	–	–	–	–	28 ± 4.3	NR	10	9	–	–
Ganz, 2016	Prospective, Jan 2009 to Sep 2009 (Data From 2013), Multicenter, USA and Netherlands.	LINX	53 (18 – 75)	100	85	52/48	10 (1–40)	5 (<1–20)	–	0	–	–	–	–	–	28 (20 – 35)	NR	20	40	–	–
Louie, 2019	Prospective, Mar 2013 to Aug 2015, Multicenter, USA.	LINX	48.5 (19.7–71.6)	200	182	102/98	11.9 (0.5–50.0)	8.5 (0.5–30.0)	–	–	–	–	–	–	–	27.4 (18–39)	NR	36	11	2	1
Reynolds, 2016	Retrospective, Jan 2010 to Jun 2013, Multicenter, USA.	NR	53	52	48	33/20	–	–	16	–	35	–	–	–	–	26	NR	–	50	–	–
Riegler, 2015	Prospective, As of July 2013, Multicenter, Austria, Germany, Italy, UK.	LINX	46.6 ± 13.9	202	202	125/77	8.7 ± 7.8	6.3 ± 5.4	2	–	174	–	–	–	–	25.7 ± 3.8	NR	65	19	1	1

▶ **Table 1a** (Continuation)

	Design, Period, Center, Country	Device	Age	Total (N)	N @ F/u	M/F	GERD Duration (Years)	BID PPI duration (Years)	Barrett's (N)		Hiatal Hernia	GEJ Hill Grade				BMI (kg/m2)	MSA – No# Beads/ TIF – Fasteners	Esophagitis (Pre-MSA)			
									Pre-Procedure	Post-Procedure		I	II	III	IV			Grade A	Grade B	Grade C	Grade D
Schwameis, 2018	Retrospective, Mar 2012 to Sep OR Nov 2017, Single center, Austria.	LINX	45 (IQR 38–58)	68	62	46/22	–	–	–	–	52	–	–	–	–	25 (IQR 22–29)	15 (12–16)	–	–	–	–
Smith, 2014	Prospective, Oct 2011 and Jun 2013, Single center, USA.	LINX	53.7 (18–86)	66	65	28/38	–	–	3	–	44	–	–	–	–	26.0 (17.6–34.1)	NR	–	–	–	–
Warren, 2016	Retrospective, Apr 2007 to Dec 2014, Multicenter, USA.	LINX	54 (42–64)	201	169	105/96	–	–	18	–	55	7	19	42	32	32	NR	18	13	4	2
TIF (15 Studies)																					
Raza, 2018	Retrospective, Nov 2016 to May 2018, Single Center, USA.	EsophyX	51 (25–69)	34	34	14/20	–	–	–	–	NR	–	–	–	–	–	NA	–	–	–	–
Toomey, 2014	Prospective – Case-controlled study, 2010 to 2013, Single center, USA.	EsophyX	68 (61 ± 14.7)	20	20	7/13.	11 (13 ± 14.0)	–	–	–	3	–	–	–	–	25 (25 ± 2.3)	NA	–	–	–	–
Hunter, 2015	Prospective – RCT, Jun 2011 to Sep 2013, Multicenter, USA.	EsophyX2	52 (22 – 74)	87	87	47/40	10 (0.6 – 37)	9 (1 – 30)	–	–	60	4	57	25	–	27.1 (20.3 – 35.5)	23 (13–37)	10	7	–	–
Rinsma, 2014	Prospective, 2008 to 2012, Single center, Netherlands.	EsophyX2	41 (23–66)	15	15	11/4.	>6 m	–	–	–	9	1	7	5	2	26.2 ± 1.1	–	3	4	1	–

▶ **Table 1a** (Continuation)

	Design, Period, Center, Country	Device	Age	Total (N)	N @ F/u	M/F	GERD Duration (Years)	BID PPI duration (Years)	Barrett's (N)		Hiatal Hernia	GEJ Hill Grade				BMI (kg/m2)	MSA – No# Beads/ TIF – Fasteners	Esophagitis (Pre-MSA)			
									Pre-Procedure	Post-Procedure		I	II	III	IV			Grade A	Grade B	Grade C	Grade D
Wilson, 2014	Prospective, Jan 2010 to Feb 2011, Multicenter, USA.	EsophyX2	53 (18 – 75)	100	96	35/65	9 (1 – 35)	9 (1 – 15)	–	–	75	5	65	12	0	18.0 to 35.1	12 to 20	–	–	–	–
Bell, 2014	Prospective, Jan 2010 to Apr 2011, Multicenter, USA.	EsophyX2	53.1 (13.4)	127	100	41/86	10 (+/-6.9)	8.3 (+/-5.9)	6	NR	83	8	82	15	0	26.8 ± 4.3	20 (11–27)	18	45	6	0
Barnes, 2011	Retrospective, Nov 2008 to Dec 2009, Multicenter, USA.	EsophyX2	60 (21–87)	124	110	29/81	9 (1–35)	8 (1–25)	4	0	70	0	89	21	0	27.5 (19.0–47.9)	12–20	42	20	2	0
Ebright, 2017	Retrospective, Feb 2009 to Apr 2012, single center, USA	EsophyX2	48 (22–84)	80	41	41/39	NR	NR	–	–	23	1	9	18	8	–	–	–	–	–	–
Hakansson, 2015	Prospective RCT, Jan 2011 to Jan 2013, Multicenter, Sweden, Belgium, France.	EsophyX	41 (21–67)	22	21	8/14.	10 (2–25)	6 (2–20)	–	–	17	0	4	11	–	26.6 (18.6–33.9)	21 (16–36)	5	1	–	–
Hoppo, 2010	Prospective, Apr 2008 to Jul 2009, Multicenter, USA and Australia.	EsophyX	48.2 (26–81)	19	19	11/8	–	–	–	–	4	–	–	–	–	24.6 (19.6–29.4)	–	–	–	–	–
Petersen, 2012	Prospective, Mar 2009 to Aug 2010, Single center, USA.	EsophyX	47 (19 – 62)	22	19	6/17.	–	–	2	–	3	0 (Preoperative), 20 (Postoperative)	13 (Preoperative), 2 (Postoperative)	7 (Preoperative), 0 (Postoperative)	3 (Preoperative), 0 (Postoperative)	29 (20 – 43)	–	–	–	–	–

▶ **Table 1a** (Continuation)

	Design, Period, Center, Country	Device	Age	Total (N)	N @ F/u	M/F	GERD Duration (Years)	BID PPI duration (Years)	Barrett's (N)		Hiatal Hernia	GEJ Hill Grade				BMI (kg/m2)	MSA – No# Beads/ TIF – Fasteners	Esophagitis (Pre-MSA)			
									Pre-Procedure	Post-Procedure		I	II	III	IV			Grade A	Grade B	Grade C	Grade D
Stefanidis, 2017	Prospective, Dec 2008 to Feb 2012, Single center, Greece.	EsophyX	36 (23–55)	45	44	29/16	5 (1–24)	3 (1–20)			45					26.2 (18.3–34.9)	12–18	14	19	–	–
Testoni, 2019	Retrospective, Jan 2007 to Dec 2012, Single center, Italy.	EsophyX	45 ± 16	50	45 (2 & 3y), 34 (5y), 24 (7y), 12 (10y)	35/15	–	–	–	–	28	3	34	12	1	22 ± 3	12 ± 4	10/11	1/11	–	–
Trad, 2018	Prospective, Randomized, Aug 2012, Multicenter, USA.	EsophyX2	51.5 (10.3)	63	44	27/33	11.2 (9.8)	8.6 (6.5)	1	–	NR	5	32	–	–	28.5 (3.7)	21 ± 4	–	–	–	–
Witteman, 2015	Prospective – RCT, 2008 to 2011, Multicenter, Netherlands and USA.	EsophyX2	42.4 ± 13.3	60	53 (6 m); 45 (12 m)	38/22	4.5 (0.05–18.95)	–	–	–	42	3	29	15	3	26 ± 3.7	18 (7–26)	10	9	–	–

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; GEJ, gastroesophageal junction; BMI, body mass index; MSA, magnetic sphincter augmentation; LOS, length of stay; AE, adverse event; GERD-HRQL, Gastroesophageal Reflux Disease-Health Related Quality of Life; RCT, randomized clinical trial; NR, not reported; NA, not applicable

▶ **Table 1b** Study details – Outcomes

	Clinical Success	Technical Success	Clinical Success	Clinical Success	Post-Procedure Off PPI	Operative Time (mins) (range)	Maximum Follow Up (months)	Length of Stay (Days)	Adverse Events	Post procedure dysphagia
	GERD-HRQL		Patient Satisfaction	No regurgitation						
MSA/LINX (9 Studies)										
Asti, 2016	59/135	135/135	NR	NR	NR	42 ± 34	44	2	0	NR
Bell, 2019	38/47	47/47	NR	37/47 (RDQ)	43/47	NR	6	NR	1	15
Ganz, 2016	70/84	100/100	70/84	NR	74/85 (3y)	36 (7 – 125)	60	1	0	4
Louie, 2019	169/200	200/200	NR	112/123 (FSQ)	159/182	NR	12	1	0	30
Reynolds, 2016	NR	52/52	43/52	NR	41/48	66 ± 23	12	0.7 ± 0.4	0	22
Riegler, 2015	NR	NR	NR	111/117 (FSQ)	165/202	NR	12	NR	1	14
Schwameis, 2018	62/62	68/68	59/62 (AS)	44/46	54/62	27 (11–55)	13 (4.2–45)	1	0	2
Smith, 2014	NR	66/66	60/65	NR	54/65	NR	5.8 (1 – 18.6)	0.75	0	4
Warren, 2016	169/201	201/201	NR	NR	150/169	60	12	0.54	1	1
TIF (15 Studies)										
Raza, 2018	34/34	34/34	NR	NR	NR	42.7±8.3	NR	1	0	None
Toomey, 2014	NR	NR	13/20	NR	NR	71 ± 18.4	NR	1 ± 1.1	0	NR
Hunter, 2015	NR	NR	NR	58/87 (RDQ)	NR	49 (21–119)	6	1	5	2
Rinsma, 2014	NR	NR	12/15	NR	10/15	NR	6	NR	0	0
Wilson, 2014	62/85	100/100	82/96	46/58 (Regurgitation Score)	74/96	NR	12	1	1	2
Bell, 2014	63/96	127/127	63/102 (Diss/Satis/Neutral)	62/88 (Regurgitation Score)	69/98	46 (18 – 90)	24	1–2	0	0
Barnes, 2011	88/110	123/124	79/110 (Diss/Satis/Neutral)	81/94 (Regurgitation Score)	102/110	45 (21–122)	7 (5–17)	1	Epigastric pain 62n (50 % of patients), left shoulder pain 19n (15 %), sore throat 5n (4 %), nausea 1n (1 %), pneumonia 1n (1.24 %)	0
Ebright, 2017	NR	80/80	NR	NR	15/39	75 (36–180)	24 (6–68)	1 (± 1.4)	6 degraded wrap, 5 urinary retention, 1fever, 1ieus, 1 aspiration pneumonia	NR
Hakansson, 2015	NR	22/22	NR	NR	13/22	69 (34–133)	6	1	4 dysphagia, 4 bloating, 2 flatulence, 10 post op pain, 1 vomiting	4
Hoppo, 2010	14/19	19/19	8/19 (Good/Poor)	9/19 (Symptom)	5/19	98.3 (50–193)	10.8 (4–19)	1 (1–3)	10 heartburn , regurgitation 10, dysphagia 1, and atypical symptoms 3	1

▲ Table 1b (Continuation)

	Clinical Success	Technical Success	Clinical Success	Clinical Success	Post-Procedure Off PPI	Operative Time (mins) (range)	Maximum Follow Up (months)	Length of Stay (Days)	Adverse Events	Post procedure dysphagia
	GERD-HRQL		Patient Satisfaction	No regurgitation						
Petersen, 2012	NR	20/22	NR	10/17 (Symptom)	8/19	–	6.7	1 (0–2)	3 nausea, 4 bloating	3
Stefanidis, 2017	44/44	44/45	39/44 (Satis/Diss)	NR	32/44	60 (45–100)	59 (36–75)	3 (2–5)	1 pneumothorax, 1 hematemesis, epigastric pain 39, pharynx irritation 22	NR
Testoni, 2019	12/12	49/51	NR	NR	5/12	69 ± 19 (Data from 2015)	120	NR	1 pneumothorax	NR
Trad, 2018	31/44	63/63	NR	37/43 (RDQ)	12/19	38 (20–68)	60	NR	0	NR
Witteman, 2015	20/37	60/60	NR	NR	28/37	33.4 (17–75)	6	NR	Pneumoperitoneum (1), Pneumonia (3), Epigastric Pain (1)	NR

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; GEJ, gastroesophageal junction; BMI, body mass index; MSA, magnetic sphincter augmentation; LOS, length of stay; AE, adverse event; GERD-HRQL, Gastroesophageal Reflux Disease-Health Related Quality of Life; RCT, randomized clinical trial; NR, not reported; NA, not applicable

Characteristics and quality of included studies

In the MSA cohort, six studies [26, 29, 30, 40–42] were prospective and three [22, 43, 44] were retrospective, whereas in the TIF2 cohort, 11 studies were prospective [23, 25, 27, 28, 31, 45–50] and four were retrospective [24, 51–53]. There were no TIF or MSA studies based on population data. Based on the New-Castle Ottawa scoring system, all nine MSA studies [22, 26,29,30,40–44] were considered to be of high quality, 12 TIF studies were of high quality, and three TIF studies [46, 49,51] were of medium quality. There were no low-quality studies.

Meta-analysis outcomes

Clinical success (measure of improvement in GERD HRQL score)

The pooled rate of clinical success with MSA was 80.4 % (95 % CI: 66–89.6) and with TIF2 was 77.7 % (95 % CI 64.1–87.2). The rates were not statistically significantly different (▶ **Fig. 1**). The pooled rate of clinical success with MSA in ≤ 12 months follow-up (3 studies) was 83.3 % (95 % CI 65.3–93); I2 = 0 and in > 12 months follow-up was 75.9 % (95 % CI 50.8–90.5). The pooled rate of clinical success with TIF2 in ≤ 12 months (4 studies) was 71.2 % (95 % CI 57.3–82); I2 = 67 and in > 12 months (4 studies) was 76.1 % (95 % CI 59.6–87.3); I2 = 70. The rates were comparable.

Clinical success (Overall patient satisfaction reported at follow up)

The pooled rate of clinical success with MSA was 86.3 % (95 % CI 74.8–93.1) and with TIF2 was 72.5 % (95 % CI 61.6–81.3). The rates were not statistically significantly different (▶ **Fig. 2**).

Clinical success (Improvement in post procedure regurgitation symptoms at follow up)

The pooled rate of clinical success with MSA was 91.1 % (95 % CI 83.8–95.3) and with TIF2 was 73.1 % (95 % CI 62.5–81.7). The difference between the cohorts was statistically significant (P = 0.002) (▶ **Fig. 3**).

Patients off PPI

The pooled proportion of patients off PPI therapy with MSA was 86.5 % (95 % CI 80.4–91) and with TIF2 was 64.4 % (95 % CI 55–72.8). Based on sub-group comparison MSA seemed to be significantly superior to TIF2 (P = 0.001) (▶ **Fig. 4**).

Technical success

The pooled rate of technical success for MSA was 98.8 % (95 % CI 95.6–99.7) and for TIF2 was 98.5 % (95 % CI 95.7–99.5) (**Supplementary Fig. 2**).

Post-procedure dysphagia

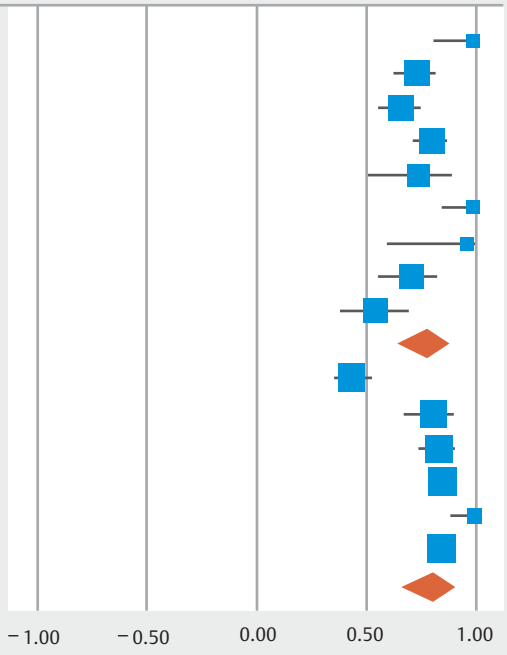
The pooled rate of dysphagia with MSA was 9.1 % (95 % CI 4.2–18.8) and with TIF was 3.6 % (95 % CI 1.4–8.8). Although greater, the P value was non-significant (P = 0.05) (**Supplementary Fig. 3**).

▶ **Table 2** Study details: pre-procedure and post-procedure patient scores.

	GERD-HRQL (Max f/u)		DeMeester score (Max f/u)		GERSS score		RSI score	
	Pre-procedure	**Post-procedure**	**Pre-procedure**	**Post-procedure**	**Pre-procedure**	**Post-procedure**	**Pre-procedure**	**Post-procedure**
MSA/LINX (9 Studies)								
Asti, 2016	21.00 (9.00)	0 (4)	31.4 (25.3)	–	–	–	–	–
Bell, 2019	23.5 ± 10.1 {On PPI} // 31.6 ± 10.4 {Off PPI}	6	40.3 (28.1–53.0) (47)	–	–	–	–	–
Ganz, 2016	–	–	36.6 (16.3 – 83.8)	13.5 (1y)	–	–	–	–
Louie, 2019	26.0 ± 6.5	4.0 ± 9.7	33.4 [8.7, 113.0]	12.0 [0.2, 59.7]	–	–	–	–
Reynolds, 2016	17	4 ± 6	–	–	–	–	–	–
Riegler, 2015	20	3	–	–	–	–	–	–
Schwameis, 2018	24 (16–30)	3 (IQR 0–6)	–	–	–	–	–	–
Smith, 2014	26	6	32.3 (1.4 – 67)	–	–	–	–	–
Warren, 2016	21 (15–25)	3	34 (21–51)	–	–	–	–	–
TIF (15 Studies)								
Raza, 2018	31.8±11.4	3.2±2.8	–	–	–	–	–	–
Toomey, 2014	–	–	35 (63 ± 60.6)	—	–	–	–	–
Hunter, 2015	25 (0 – 41) {On PPI} // 29 (347) {Off PPI}	–	33.6	23.9	22 (3 – 54) {On PPI} // 30 (5 – 60) {Off PPI}	–	–	–
Rinsma, 2014	27.5 ± 1.8	13.2 ± 2.4	–	–	–	–	–	–
Wilson, 2014	26 (0 – 47)	15 (0 – 44)	–	–	26 (2–60)	4 (0–54)	20 (0–41)	5 (0–44)
Bell, 2014	26 (10–47)	6 (0–36)	34.4 (32.4)	17.2 (10.8) [24m]	35 (19–60)	5 (0–48)	24 (14–41)	6 (0–3)
Barnes, 2011	28 (0–45)	2 (0–35)	-	-	46 (8–60)	0 (0–12)	29 (3–45)	4 (0–30)
Ebright, 2017	22	10	-	-	–	–	–	–
Hakansson, 2015	–	–	-	–	–	–	–	–
Hoppo, 2010	–	–	–	–	–	–	–	–
Petersen, 2012	–	–	32.5 (14.2– 99.1)	19.3 (0.3 – 76.9)	–	–	–	–
Stefanidis, 2017	27 (2–45)	4 (0–26)	–	–	–	–	–	–
Testoni, 2019	20 ± 13 (ON PPI), 46 ± 19 (OFF PPI)	9.5 ± 6.1	22 ± 12 (Data from 2015)	19 ± 20 (24 m) (Data from 2015)	–	–	–	–
Trad, 2018	27 (4–48)	4 (0–33)	–	–	–	–	22.2	6.3
Witteman, 2015	27.1 (8.4)	10.3 (7.8) (12m]	–	–	–	–	–	–

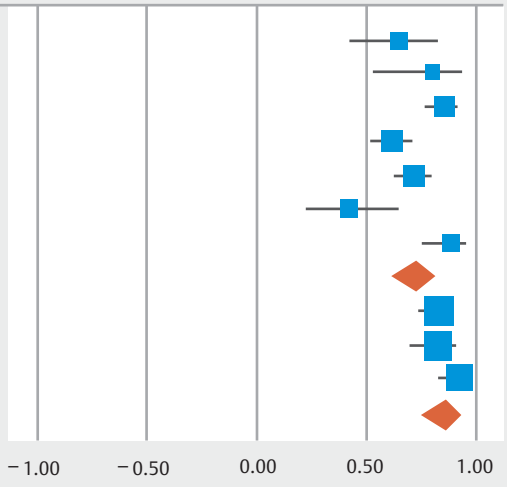
GERD-HRQL, Gastroesophageal Reflux Disease-Health Related Quality of Life; GERSS, Gastroesophageal Reflux Symptom Score; RSI, Reflux Symptom Index; PPI, proton pump inhibitor.

Group by Sub-group	Study name	Statistics for each study			Event rate and 95% CI
		Event rate	Lower limit	Upper limit	
aTIF2	Raza, 2018	0.986	0.809	0.999	
aTIF2	Wilson, 2014	0.729	0.626	0.813	
aTIF2	Bell, 2014	0.656	0.556	0.744	
aTIF2	Barnes, 2011	0.800	0.715	0.865	
aTIF2	Hoppo, 2010	0.737	0.502	0.886	
aTIF2	Stefanidis, 2017	0.989	0.846	0.999	
aTIF2	Testoni, 2019	0.962	0.597	0.998	
aTIF2	Trad, 2018	0.705	0.555	0.820	
aTIF2	Witteman, 2015	0.541	0.381	0.692	
aTIF2		0.777	0.641	0.872	
bMSA	Asti, 2016	0.437	0.356	0.522	
bMSA	Bell, 2019	0.809	0.671	0.897	
bMSA	Ganz, 2016	0.833	0.738	0.899	
bMSA	Louie, 2018	0.845	0.788	0.889	
bMSA	Schwameis, 2018	0.992	0.885	1.000	
bMSA	Warren, 2016	0.841	0.784	0.885	
bMSA		0.804	0.660	0.896	



▶ **Fig. 1** Forest plot of clinical success (GERD-HRQL).

Group by Sub-group	Study name	Statistics for each study			Event rate and 95% CI
		Event rate	Lower limit	Upper limit	
aTIF2	Toomey, 2014	0.650	0.426	0.823	
aTIF2	Rinsma, 2014	0.800	0.530	0.934	
aTIF2	Wilson, 2014	0.854	0.769	0.912	
aTIF2	Bell, 2014	0.618	0.520	0.707	
aTIF2	Barnes, 2011	0.718	0.627	0.794	
aTIF2	Hoppo, 2010	0.421	0.226	0.644	
aTIF2	Stefanidis, 2017	0.886	0.755	0.952	
aTIF2		0.725	0.616	0.813	
bMSA	Ganz, 2016	0.833	0.738	0.899	
bMSA	Reynolds, 2016	0.827	0.700	0.907	
bMSA	Smith, 2014	0.923	0.828	0.968	
bMSA		0.863	0.748	0.931	



▶ **Fig. 2** Forest plot of clinical success (patient satisfaction).

Meta-regression analysis

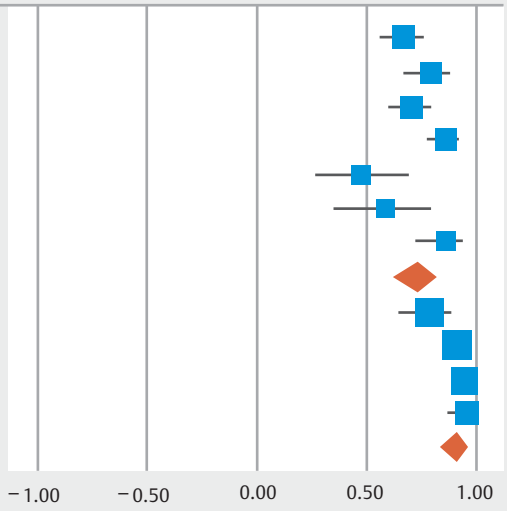
Patient variables that were amenable to meta-regression analysis were as follows: Patient BMI and presence of hiatal hernia. BMI did not have any statistically significant effect on outcomes of TIF2 ($P = 0.7$) or MSA ($P = 0.1$). Also, the presence of hiatal hernia did not affect clinical success in either of the two study cohorts (**Supplementary Fig. 4**).

Validation of meta-analysis results

Sensitivity analysis

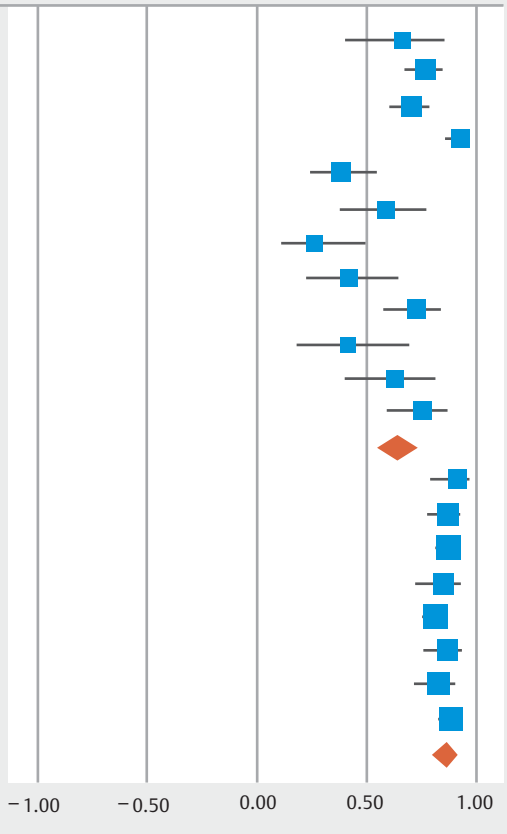
To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. In this analysis, no single study significantly affected the outcome or the heterogeneity.

Group by Sub-group	Study name	Statistics for each study Event rate	Lower limit	Upper limit
aTIF2	Hunter, 2015	0.667	0.562	0.757
aTIF2	Wilson, 2014	0.793	0.670	0.879
aTIF2	Bell, 2014	0.705	0.601	0.790
aTIF2	Barnes, 2011	0.862	0.776	0.918
aTIF2	Hoppo, 2010	0.474	0.268	0.689
aTIF2	Petersen, 2012	0.588	0.352	0.790
aTIF2	Trad, 2018	0.860	0.722	0.936
aTIF2		0.731	0.625	0.817
bMSA	Bell, 2019	0.787	0.648	0.882
bMSA	Louie, 2018	0.911	0.846	0.950
bMSA	Riegler, 2015	0.949	0.891	0.977
bMSA	Schwameis, 2018	0.956	0.872	0.986
bMSA		0.911	0.838	0.953



▶ **Fig. 3** Forest plot of clinical success (regurgitation).

Group by Sub-group	Study name	Statistics for each study Event rate	Lower limit	Upper limit
aTIF2	Rinsma, 2014	0.667	0.406	0.854
aTIF2	Wilson, 2014	0.771	0.676	0.844
aTIF2	Bell, 2014	0.704	0.607	0.786
aTIF2	Barnes, 2011	0.927	0.861	0.963
aTIF2	Ebright, 2017	0.385	0.247	0.544
aTIF2	Hakansson, 2015	0.591	0.382	0.772
aTIF2	Hoppo, 2010	0.263	0.114	0.498
aTIF2	Petersen, 2012	0.421	0.226	0.644
aTIF2	Stefanidis, 2017	0.727	0.579	0.838
aTIF2	Testoni, 2019	0.417	0.185	0.692
aTIF2	Trad, 2018	0.632	0.403	0.813
aTIF2	Witteman, 2015	0.757	0.595	0.868
aTIF2		0.644	0.550	0.728
bMSA	Bell, 2019	0.915	0.794	0.968
bMSA	Ganz, 2016	0.871	0.781	0.927
bMSA	Louie, 2018	0.874	0.817	0.915
bMSA	Reynolds, 2016	0.854	0.724	0.929
bMSA	Riegler, 2015	0.817	0.757	0.864
bMSA	Schwameis, 2018	0.871	0.763	0.934
bMSA	Smith, 2014	0.831	0.720	0.904
bMSA	Warren, 2016	0.888	0.830	0.927
bMSA		0.865	0.804	0.910



▶ **Fig. 4** Forest plot of patients off PPI therapy at follow-up.

▶ **Table 3** Pooled rates of outcomes with CI and PI.

	Pooled rates (95 % confidence interval) I2 heterogeneity %	
	MSA	**TIF2**
Clinical success (GERD HRQL)	80.4 % (66–89.6); 6 studies (P = 0.8) I2 = 94; PI: 23 to 98 ≤ 12 months (3 studies) 83.3 % (65.3–93); I2 = 0 > 12 months (3 studies) 75.9 % (50.8–90.5); I2 = 95	77.7 % (64.1–87.2) 9 studies I2 = 68; PI: 48 to 95 ≤ 12 months (4 studies) 71.2 % (57.3–82); I2 = 67 > 12 months (4 studies) 76.1 % (59.6–87.3); I2 = 70
Clinical success (patient satisfaction)	86.3 % (74.8–93.1); 3 studies (P = 0.06) I2 = 2; PI: 61 to 96	72.5 % (61.6–81.3) 7 studies I2 = 75; PI: 41 to 92
Clinical success (no regurgitation)	91.1 % (83.8–95.3); 4 studies (P = 0.002) I2 = 68; PI: 56 to 99	73.1 % (62.5–81.7); 7 studies I2 = 68; PI: 44 to 91
Patients off PPI at follow-up	86.5 % (80.4–91) 8 studies (P = 0.001) I2 = 0; PI: 78 to 92	64.4 % (55–72.8) 12 studies I2 = 80; PI: 28 to 91
Technical success	98.8 % (95.6–99.7); 11 studies (P = 0.5) I2 = 81; PI: 38 to 99	98.5 % (95.7–99.5); 8 studies I2 = 0; PI: 90 to 99
Postoperative dysphagia	9.1 % (4.2–18.8) 8 studies (P = 0.05) I2 = 89; PI: 1 to 50	3.6 % (1.4–8.8) 9 studies I2 = 58; PI: 1 to 34

MSA, magnetic sphincter augmentation; TIF, trans-oral fundoplication; GERD, gastroesophageal reflux disease; HRQL, health related quality of life; PI, 95 % prediction intervals; PPI, proton pump inhibitor.

Heterogeneity

We assessed dispersion of the calculated rates using the confidence interval (CI) and I^2 percentage values. The CI gives an idea of the range of the dispersion and I^2 tells us what proportion of the dispersion is true vs chance [36]. The PIs are reported with the pooled rates in ▶ **Table 3**. Overall, considerable heterogeneity was noted in the analysis.

Publication bias

Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was evidence of publication bias (**Supplementary Fig. 4**, Eggers 2-tailed $P = 0.01$). Further statistical analysis using the fail-Safe N test and Duval and Tweedie's Trim and Fill test revealed that the reported pooled results would not be significantly affected by the unpublished studies.

Discussion

Magnetic sphincter augmentation (MSA) and trans-oral incisionless fundoplication (TIF2) demonstrate comparable efficacy when comparing improvement in cumulative GERD-HRQL scores at follow-up. When comparing outcomes in terms of, post procedure regurgitation and percentage of patients off PPI therapy at follow up, MSA significantly outperforms TIF2. To the best of our knowledge, this study is the first quantitative review presenting a comparison between MSA and TIF2 in the treatment of refractory GERD.

The Gastroesophageal Reflux Disease-Health Related Quality-of-Life (GERD-HRQL) scale is a disease-specific instrument, developed to help overcome the variability in evaluating response to treatments for GERD and has been validated as the only significant predictor of patient satisfaction. A total score is computed for the heartburn symptoms questions based on a scale of 0 to 5, where 0 = no symptoms and 5 = incapacitation to do daily activities. A reduction of the score by 50 % or greater is considered to indicate a successful intervention [54]. In our analysis, based on improvement in GERD-HRQL at longest follow up, pooled clinical success was 80.4 % with MSA and 77.7 % with TIF2 ($P = 0.8$).

In recent years, there has been a growing body of literature raising concerns about long term PPI use [5]. We found that the pooled percentage of patients who were able to completely stop PPI therapy after MSA was 91.3 % compared to only 63.8 % after undergoing TIF2 ($P = 0.001$). Given the variability in outcome reporting in the literature, we also factored in overall patient satisfaction that was comparable, and improvement in post-operative regurgitation as measures of clinical success, which was better with MSA.

TIF is associated with fewer postoperative adverse effects such as gas bloating and dysphagia when compared with surgical fundoplication [55]. Dysphagia is thought to be prominent post MSA implantation but generally resolves within a few weeks [41]. We compared post procedure dysphagia between the two study cohorts and demonstrated a non-significant greater rate with MSA (9.1 % vs 3.6 %; $P = 0.05$). Follow up period

ranged from 5.8 to 60 months in the MSA cohort, and 6 to 120 months in the TIF2 cohort.

With regards to adverse events, LINX device was removed in 24 patients, most commonly due to postoperative GERD, chest pain and dysphagia. In the TIF2 cohort, postoperative epigastric pain was the most common adverse event, reported in 114 patients (0.1 %). Pneumothorax in two patients, pneumoperitoneum in 1 patient and postoperative pneumonia was reported in four patients. Ebright et al [52] reported six patients with a degraded wrap, five with urinary retention and one each with postoperative fever, ileus, and aspiration. Overall, there were 229 adverse events reported in the TIF2 cohort of patients.

In 2017, Huang et al, conducted a systematic review and meta-analysis of five randomized trials and 13 prospective studies and found that PPI use after TIF increased over time (albeit at a reduced dose) and the overall patient satisfaction rate was 69 % at 6-month follow-up [2]. This study included results from the first and second (current) generation of TIF devices. While the first-generation device (TIF1) was commercially introduced in 2007, it was not until 2009 that the second generation of the device, TIF2, was made available. Our study included only those patients who underwent the TIF2 procedure.

In 2019, Guidozzi et al [56] conducted a systematic review and meta-analysis comparing MSA to laparoscopic fundoplication and concluded that the former achieves good GERD symptomatic control similar to that of fundoplication, with 3.3 % of patients requiring device removal. Our study is the first in literature to compare MSA and TIF2 based on similar patient reported outcomes.

The strengths of this review are as follows: systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, inclusion of good quality studies with detailed extraction of data and rigorous evaluation of study quality. We calculated not only pooled subjective outcomes based on patient reported clinical symptoms but also objective outcomes i. e. percentage of patients successfully able to stop PPI therapy. We utilized meta-regression analysis to evaluate the effect of pre procedural BMI and presence of hiatal hernia on clinical outcomes. Finally, we excluded all TIF2 and MSA studies where patients underwent concurrent hiatal hernia (HH) repair. This is important because patients undergoing HH repair surgery have improved GERD-HRQL scores and can have post procedural side effects such as dysphagia [57].

There are limitations to this study as well, most of which are inherent to any meta-analysis. Our analysis had studies that were retrospective in nature contributing to selection bias. We compared outcomes based on improvement in GERD-HRQL score and used ≥ 50 % improvement in score as a measure of clinical success. While this was the most consistently reported outcome in the included studies, it is possible that studies reporting < 50 % improvement in GERD-HRQL score for either MSA or TIF2 were missed. While we were able to quantify the proportion of patients who discontinued PPI therapy at follow up, we were unable to objectively study this data in terms of post procedural pH testing data.

Manometry and impedance data were not consistently reported in all studies. Although we report meta-regression analysis, it is important to note that meta-regression analysis is considered a weak statistic in the analysis of patient variables on pooled outcomes. Our analysis has the limitation of non-causal comparison and heterogeneity. Nevertheless, this study is the best available data in literature thus far with respect to the clinical outcomes of MSA and TIF2 in patients with refractory GERD.

Conclusion

In conclusion, MSA and TIF2 appear to have similar efficacy based on post procedure GERD-HRQL scores however MSA seems to significantly outperform TIF2 in terms of patient reported outcomes with long term follow up. Overall, 91.3 % of patients were able to stop PPI therapy after MSA as compared to 63.8 % after TIF2. Future well-conducted trials with adequate follow-up time are warranted to establish or refute our findings.

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Competing interests

Dr. Adler is a consultant for Boston Scientific.

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