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Dr. Bing Hu, MD
Editor-in-Chief
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7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Dear Dr. Hu,

Thank you very much for your consideration of publication our manuscript entitled '**Magnetic sphincter augmentation (MSA): Optimal patient selection and referral care pathways**'. The comments provided by the reviewers were very helpful and we feel that our manuscript has been significantly strengthened based on our implementation of their suggestions. On the following pages, please find the description of the comments and our detailed response for each comment.

Please do not hesitate to contact us if you have questions or require any additional information.

We look forward to hearing from you.

Sincerely,

F. Paul Buckley III, MD
Associate Professor of Surgery
Director- Heartburn & Esophageal Disorders Center
Department of Surgery & Perioperative Care
Dell Medical School | The University of Texas at Austin
o: 512-495-5329 | clinic: 512 324-4373
E-mail: tripp.buckley@austin.utexas.edu

Reviewer #1 (03667297) – Accept (High Priority)

Well written manuscript. I wanted to know about the cost-effectiveness and longevity of the MSA.

Thank you for your kind remarks. Yes, we agree that the cost-effectiveness and longevity are important considerations for MSA. We have included the following paragraph regarding the cost-effectiveness:

"In regards to the economic consequences associated with MSA, a meta-analysis by Chen and colleagues (2017) showed that MSA had a significantly shorter operative time (MSA and fundoplication: RR = -18.80 minutes, 95% CI: -24.57 to -13.04, and p=0.001) and length of stay (RR = -14.21 hours, 95% CI: -24.18 to -4.23, and p=0.005) compared to fundoplication. A retrospective analysis of 1-year outcomes of patients undergoing MSA and LNF by Reynolds and colleagues (2016) showed that LNF and MSA were comparable in overall hospital charges ($48,491 vs. $50,111, p = 0.506). The charge for the MSA device was offset by lower charges in pharmacy/drug use, laboratory/tests/radiology, OR services, anesthesia, and room and board. There were significant differences in OR time (66 min MSA vs. 82 min LNF, p < 0.01) and LOS (17 h MSA vs. 38 h LNF, p < 0.01)."

We have included the following paragraph regarding the longevity of MSA:

"More than 75% of MSA patients experienced complete cessation of PPI use at up to 5 years[30,32-34,41,45,48,49]. The 5-year reoperation rate with MSA has been shown to range from 6.8%-7.0%[30,33]."

Reviewer #2 (03479350) – Major Revision

The authors have reported on the optimal patient selection and referral care pathways about magnetic sphincter augmentation (MSA). Although this manuscript is interesting and well written, the readers may roughly require the information, such as the indication, therapeutic strategies, side effect, and therapeutic outcomes, of MSA.

Thank you for your careful and insightful review of our manuscript. We agree with your comments regarding the indication, therapeutic strategies, side effects, and therapeutic outcomes and have described how we have addressed each comment in the following sections you outlined below.

Furthermore, there were several concerns which should be addressed by the authors.

1. **The title of this article and study aim suggest the description regarding the proper clinical indication and management of MSA. However, this review only has described the general management of GERD, without a minute discussion for MSA.**

The authors should address more clearly regarding the efficacy of MSA compared to drug medication and other surgical methods such as LNF.

Thank you for pointing out this lapse. We have added the following paragraphs to incorporate the indication and additional information about efficacy relative to drug medication and other surgical methods:

Indication:

"The LINX Reflux Management System is a laparoscopic, fundic-sparing anti-reflux procedure indicated for patients diagnosed with GERD as defined by abnormal pH testing, and who are seeking an alternative to continuous acid suppression therapy (i.e. proton pump inhibitors or equivalent) in the management of their GERD. LINX is contraindicated in patients with suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials."

Additional content on efficacy:

"Sixty-seven percent of patients undergoing LNF (54/87) reported new symptoms (i.e., excessive gas, abdominal bloating, dysphagia) after surgery[28]. LNF is associated with up to 15% reoperation rates and a cumulative surgery failure rate of up to 27.1%[26,29]."

"More than 75% of MSA patients experienced complete cessation of PPI use at up to 5 years[30,32-34,41,45,48,49]. The 5-year reoperation rate with MSA has been shown to range from 6.8%-7.0%[30,33]."

2. The descriptions in the Introduction and Findings (Target Population and Referral Pathways for MSA) are partly duplicate. The authors should revise them easier and simpler. Given that the authors review focusing on MSA, the present status of MSA should be described.

We feel that the sections differ because they 'Target Population and Referral Pathways for MSA' section puts the information about GERD treatment options in context relative to how the patients are currently managed in the clinical care system. In the Introduction, the content was derived from clinical studies evaluating the efficacy, effectiveness, and safety of the various interventions. The Target Population and Referral Pathways section presents the interactions that patients have with providers and the healthcare system in the 'real-world' setting more broadly. We do not see the duplication, but if you could be more specific or if the Editors feel that the information is redundant we would be happy to re-visit this comment and adjust the manuscript accordingly.

3. Although the authors mentioned three primary means of treating GERD in the introduction, lifestyle changes were not described in detail. The authors should describe lifestyle changes roughly.

Yes, thank you. We have added the following paragraph:

"Lifestyle interventions should be included as part of the therapy for GERD[15]. Counseling is often helpful to provide information regarding weight loss, head of bed elevation, tobacco and alcohol cessation, avoidance of late-night meals, and cessation of foods that can potentially aggravate reflux symptoms including caffeine, coffee, chocolate, spicy foods, highly acidic foods such as oranges and tomatoes, and foods with high fat content[15]."

4. **The authors described the disadvantages of laparoscopic Nissen Fundoplication (LNF) procedure compared to MSA in the introduction. The authors should describe the previous outcomes numerally of LNF compared to MSA.**

Yes, thank you. We have added the following to the paragraph describing the disadvantages of laparascopic Nissen fundoplication:

"Sixty-seven percent of patients undergoing LNF (54/87) reported new symptoms (i.e., excessive gas, abdominal bloating, dysphagia) after surgery[28]. LNF is associated with up to 15% reoperation rates and a cumulative surgery failure rate of up to 27.1%[26,29]."

5. **The authors described the diagnostics to determine surgical eligibility of GERD patients in the Findings. The authors should mention the indication for use of MSA and its differences in comparison with LNF.**

Differences in indication would be patients who do not want an irreversible procedure such as LNF (non-fundic-sparing) and patients in whom LINX is contraindicated. We have added the following paragraph to incorporate the indication and contraindications for MSA:

"The LINX® Reflux Management System is a laparoscopic, fundic-sparing anti-reflux procedure indicated for patients diagnosed with GERD as defined by abnormal pH testing, and who are seeking an alternative to continuous acid suppression therapy (i.e. proton pump inhibitors or equivalent) in the management of their GERD. LINX is contraindicated in patients with suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials."

6. **If possible, the readers and I'd like to know the cost-effectiveness of MSA compared to conventional treatment, such as LNF and PPI intake should be described.**

Yes, we agree that the cost-effectiveness is an important consideration and have included the following paragraph in the Discussion section:

"In regards to the economic consequences associated with MSA, a meta-analysis by Chen and colleagues (2017)[48] showed that MSA had a significantly shorter operative time (MSA and fundoplication: RR = -18.80 minutes, 95% CI: -24.57 to -13.04, and p=0.001) and length of stay (RR = -14.21 hours, 95% CI: -24.18 to -4.23, and p=0.005) compared to fundoplication. A

retrospective analysis of 1-year outcomes of patients undergoing MSA and LNF by Reynolds and colleagues (2016)[34] showed that LNF and MSA were comparable in overall hospital charges ($48,491 vs. $50,111, p = 0.506). The charge for the MSA device was offset by lower charges in pharmacy/drug use, laboratory/tests/radiology, OR services, anesthesia, and room and board. There were significant differences in OR time (66 min MSA vs. 82 min LNF, p < 0.01) and LOS (17 h MSA vs. 38 h LNF, p < 0.01)."

7. The authors should mention the endoscopic therapy (Esophyx®) in the introduction.

Yes, we agree that the discussion of endoscopic therapies would improve the manuscript and we have added the following paragraph:

"Endoscopic therapies for GERD have been developed but evidence for their long-term efficacy is limited[15]. These therapies include radiofrequency augmentation to the LES, silicone injection into the LES, and endoscopic suturing of the LES[15]. Recent alternative approaches have included transoral incisionless fundoplication, a suturing device designed to create a full thickness gastroesophageal valve from inside the stomach[15]. Unfortunately, long-term data regarding efficacy of this device are limited to a small number of subjects and short duration of follow-up[15]."

Reviewer #3 (03724099) – Minor Revision

This is a very well written review on magnetic sphincter augmentation. Few comments:
-The review seems to focus on patient selection for anti-reflux surgery in general and not necessarily MSA.

Thank you for your kind remarks

- **It will be interesting to know which patients should be referred for MSA and which patients can be referred for traditional antireflux surgery such as Nissen's fundoplication.**

Differences in MSA vs. LNF indication would be patients who do not want an irreversible procedure such as LNF (non-fundic-sparing) and patients in whom LINX is contraindicated. We have added the following paragraph to incorporate the indication and contraindications for MSA:

"The LINX® Reflux Management System is a laparoscopic, fundic-sparing anti-reflux procedure indicated for patients diagnosed with GERD as defined by abnormal pH testing, and who are seeking an alternative to continuous acid suppression therapy (i.e. proton pump inhibitors or equivalent) in the management of their GERD. LINX is contraindicated in patients with suspected or known allergies to titanium, stainless steel, nickel, or ferrous materials."

- **The authors should also mention endoscopic therapies such as Stretta, TIF, MUSE etc in their introduction section as available treatment options for GERD.**

Yes, we have added the following paragraph:

"Endoscopic therapies for GERD have been developed but evidence for their long-term efficacy is limited[15]. These include radiofrequency augmentation to the LES, silicone injection into the LES, and endoscopic suturing of the LES[15]. Recent alternative approaches have included transoral incisionless fundoplication, a suturing device designed to create a full thickness gastroesophageal valve from inside the stomach[15]. Unfortunately, long-term data regarding efficacy of this device are limited to a small number of subjects and short duration of follow-up[15]."

- **A short section on complications related to MSA will be highly desirable for readers who plan to refer patients for MSA.**

Thank you for this helpful suggestion. We have added the following paragraph:

"The 5-year reoperation rate with MSA has been shown to range from 6.8%-7.0%[30,33]. The 5-year reoperation rate with MSA has been shown to range from 6.8%-7.0%[30,33]. The most common side effects of MSA were gas/bloating (26.7% with MSA vs 53.4% with LNF; p = 0.06) and postoperative dysphagia (33.9% with LINX vs 47.1% with LNF; p = 0.43)[35]."

Reviewer #4 (02573214) – Accept (High Priority)

This manuscript is a good minireview of the state of art about the optimal patient population for magnetic sphincter augmentation (MSA) in patients with gastroesophageal reflux disease.

We are very grateful for your kind remarks. Thank you for your interest in our manuscript!

Reviewer #5 (00058401) - Rejection

Congratulations for the effort.

We appreciate your review of our manuscript. We hope that the changes that we have made based on the reviewers' comments have substantially improved it.

Reviewer #6 (03667297) – Accept (High Priority)

This is a well written mini review paper concerning the optimal patient's selection, who suffer under gastro-esophageal reflux disease (GERD), for magnetic sphincter augmentation (MSA) and the related patient care pathways. The authors have reviewed and analyzed a sufficient amount of literature (a total of 86 articles were identified for inclusion after comprehensive searches with the timeframe 01.01.2000 to 16.12.2018). In this review authors described the main points which should be taken into account: the optimal population who experience GERD symptoms of heartburn and /or uncontrolled regurgitation despite optimal medical management, have abnormal pH and have normal esophageal motility. Also the authors underlines that it should be taken into consideration improving primary care providers, physician training curricula and developing an evidence –based, multidisciplinary referral network.

Thank you for your thoughtful review of our manuscript. We appreciate it very much.