TITLE: Endoscopic treatment of Gastroesophageal Reflux Disease using a new endoscopic stapling system: Results of a prospective controlled multicenter trial
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ABSTRACT

Introduction: The aim of this prospective multicenter controlled study was to test the safety and efficacy of a new system which is designed for trans-oral endoscopic treatment of Gastro Esophageal Reflux Disease (GERD). The device is a flexible video endoscope coupled with a surgical stapler and an ultrasonic range finder. Using this device, the operator can staple the fundus of the stomach to the esophagus, about 3cm above the GE junction, using 2 or 3 quintuplets of staggered standard 4.8mm surgical staples. The result of the stapling is anatomically equivalent to anterior fundoplication.

Methods: Inclusion criteria: moderate to severe GERD with response to PPI treatment, abnormal 24h esophageal acid exposure and Hill gastro-esophageal valve grade ≥2. Patients with significant comorbidities, esophageal motility disorders and hiatal hernia > 3 cm were excluded. Procedures were performed under general anesthesia at 6 centers using positive end expiratory pressure (PEEP) to reduce the hernia, if present. Anterior fundoplication was performed with two or three stapling sites between the esophagus and the stomach under control of the ultrasonic range finder. Patients were followed at 1, 2 and 4 weeks for safety and at 6 months for efficacy. The primary outcome of the study was safety and reduction of the off-PPI GERD Health Related Quality of Life scores (GERD-HRQL) score by at least 50%. Secondary outcome criteria were elimination or reduction of daily PPI use, improvement in 24h acid exposure and of Hill valve grade.

Results: 69 patients were treated as per protocol. Primary outcome - Safety: There were 2 occult perforations (one transient pneumomediastinum, and one resulting in empyema – treated by chest tube drainage) and one case of bleeding requiring transfusion. All device-related serious adverse events occurred in the first 24 subjects. After refining the technique, none were observed. Other adverse events were mild and transitory.

Primary outcome - Efficacy: 3 subjects were excluded due to major protocol violations, and 64 completed the follow up. 75% patients (48/64) met the primary success criterion – 50% reduction in GERD-HRQL scores. The median GERD-HRQL scores dropped from baseline of 29 to 6 at six months post-procedure (p<0.001). Median acid exposure (percent of time pH<4) dropped from 8.30% (4.7-73.9%) at baseline (mean 11.05±10.8) to a value of 6.75 (0-21.0) (mean of 7.30±5.12) six months following the procedure (p=0.002). Eighty five percent of the 66 patients reduced daily PPI use by 50% or more.

Seventy seven percent (of 60 patients with follow up endoscopy) demonstrated an improved flap valve angle at 6 months.

Conclusions: This study shows that the Medigus SRS™ Endoscopic stapling device is a safe and effective endoscopic treatment for GERD patients with a sliding hiatal hernia of up to 3cm. The procedure under general anesthesia showed acceptable complications rate, high efficacy rates (75%) and can be recommended for patients with up to 3 cm sliding hiatal hernia.

Introduction

Gastro Esophageal Reflux Disease (GERD) is fast becoming a worldwide health problem [1]. The prevalence of endoscopic esophagitis depends on the rate of endoscopies. A population survey in Scandinavia, [2] found erosive esophagitis in 15.5% of randomly selected men and women of the urban population, a third of which were asymptomatic. Population studies in Japan and Korea showed similarly high numbers [3, 4]
The plethora of conflicting opinions on the treatment of GERD testifies that there is no single solution to the many ways this disease adversely affects the quality of life of its victims [5].

Life style and diet modifications can sometimes be effective, but are impractical to the majority of sufferers. Other current available treatment options are either lifelong treatment with proton pump inhibitors (PPI) or surgery [2-4]. Both options have their limitations, although they are about equally effective in controlling the symptoms of GERD and resolving esophagitis, but neither is entirely satisfactory [6], [7]. Recently, FDA issued warnings that using high dose PPI for more than a year increases the risk of long bone fractures and can cause hypomagnesaemia (www.fda.gov).

It is not surprising therefore, that a lot of research has been done during the recent decades to seek an alternative solution. Most techniques relied on the observation that GERD patients who develop a stricture, no longer suffer from heartburn. In view of this observation various endoscopic methods tried narrow the LES. Efficacy has been modest, and widespread use never occurred.

The real foundation for successful mechanical repair of the gastro esophageal valve was laid down in the 50’s and the 60’s by pioneers such as Nissen and Belsey who understood that a successful reflux barrier requires restoration of a flap valve mechanism at the GE junction. The original operation performed by Nissen was a 360 degree fundoplication, which remains the most commonly used anti-reflux operation. But subsequently, other surgeons have demonstrated that a partial fundoplication was equally effective, and reduced the rate of side effects such as gas bloat and dysphagia which are associated with a full wrap [8]. Although less commonly performed, anterior 180 degrees fundoplication was shown in randomized clinical trials to be as effective as a 360 degree wrap in the treatment of GERD [9], and appear to be associated with fewer early and late complications. One randomized controlled trial showed that even a 90 degree fundoplication was efficacious. [10]

The Medigus SRS device was designed to enable the operator to staple the fundus of the stomach to the esophagus anteriorly and on the left side, about 3 cm cephalad to the gastro-esophageal junction. The stapled fundus covers part of the circumference of the distal esophagus, on the left and anterior side. The partial wrap is anatomically similar to the wrap achieved surgically by the laparoscopic anterior fundoplication.

Its main advantage is that the procedure is performed entirely through the mouth, with no incisions. It is still an operative procedure, but one that is carried out by a single operator, using a modified dedicated surgical gastroscope.

The partial wrap restores the angle of His, and restores the flap valve. The resulting flap valve is functionally and anatomically similar to the flap valve created surgically by laparoscopic fundoplication.

This paper reports the results of an international multicenter study designed to assess the safety and efficacy of this new endoscopic method for the treatment of GERD.

**Methods and rationale**

The study was a multi-center international open label prospective trial. A total of six centers participated: three in Europe, two in the US and one in India. The principal investigators at each site
were either gastroenterologists or surgeons with established skills in complex therapeutic endoscopic operations and procedures. All received prior training in the use of the device on a porcine model, at a laboratory certified by the Israeli animal welfare act.

All subjects signed a detailed informed consent form (ICF). In non-English speaking countries, the ICF was translated to the local language, and then retranslated into English by a different translator.

Data collection, monitoring and statistical analysis performed by an independent contract research organization (CRO) (Boston Med-Tech, Boston, MA) and the study was performed in strict compliance with ICH – GCP rules and monitored regularly by the American Food and Drug Administration (FDA) as well as by an independent data safety and monitoring board (DSMB).

**Inclusion and Exclusion Criteria**

The key inclusion criteria were that the subject is at least 18 years old, had a history of GERD related symptoms for at least 2 years, had recent objective evidence of GERD, demonstrated by an abnormal 24 hour pH acid exposure test, and a history of daily intake of PPIs for at least 6 months, with significant relief of symptoms (i.e., a difference of at least 6 points between the GERD-HRQL scores on and off PPI)

Subjects with Hiatal hernia > 3 cm or a paraesophageal hernia, Barrett’s esophagus or grade IV esophagitis, esophageal stricture, ring or web causing symptoms of dysphagia, Grade I Flap valve according Hill’s classification [Hill & Kozarek, 1999] on endoscopy and significant co-morbidity were excluded.

**Table 1: Inclusion and exclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient was ≥18 years old</td>
<td>1. Endoscopic hiatal hernia &gt; 3 cm or an irreducible hiatal hernia of any size</td>
</tr>
<tr>
<td>2. Recent objective evidence of GERD, demonstrated by an abnormal ambulatory pH monitoring study taken, off PPI, within 30 days</td>
<td>2. Normal acid exposure test (pH&lt;4.0 for ≤ 4.5% of the time or DeMeester score &lt;14.7%)</td>
</tr>
<tr>
<td>3. History of heartburn symptoms for at least two years</td>
<td>3. Paraesophageal hiatal hernia or an esophageal diverticulum as determined by a barium swallow taken within 6 months of the procedure</td>
</tr>
<tr>
<td>4. Use of daily PPI treatment for at least 6 months, with significant relief of symptoms (i.e., a difference in the GERD Health Related Quality of Life – Velanovich questionnaire (GERD-HRQL) scores on and off PPI medications of ≥6 points)</td>
<td>4. Esophageal stricture, ring or web causing symptoms of dysphagia</td>
</tr>
<tr>
<td>5. GERD-HRQL ≥20 off of PPIs</td>
<td>5. Endoscopic Barrett’s Esophagus (including short segment Barrett’s) or grade IV esophagitis</td>
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<tr>
<td>6. Esophageal manometry study conducted within 30 days demonstrating adequate esophageal peristalsis (defined as a mean amplitude of contraction in the esophageal body of &gt;35 mmHg with at least 8/10 wet swallows demonstrating effective peristalsis)</td>
<td>6. Esophageal or gastric varices</td>
</tr>
<tr>
<td>7. Patient understands the study requirements and the treatment procedures and provides written informed consent before any study-specific tests or procedure are performed</td>
<td>7. Esophageal dysmotility, as determined by esophageal manometry</td>
</tr>
<tr>
<td>8. Willing to comply with all specified follow-up evaluations</td>
<td>8. Achalasia</td>
</tr>
<tr>
<td>9. Good general health status, except for GERD</td>
<td>9. Hill’s classification Grade I</td>
</tr>
<tr>
<td></td>
<td>10. BMI &gt;35</td>
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<tr>
<td></td>
<td>11. Positive test for H. Pylori – could be included after eradication</td>
</tr>
<tr>
<td></td>
<td>12. History of co-morbidity with</td>
</tr>
<tr>
<td></td>
<td>a. Any heart disease with NYHA classification</td>
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</table>
Procedure:
The procedure was performed under general anesthesia. After induction of general anesthesia, a preliminary standard endoscopy was performed, to ensure that the subject was still eligible for the procedure, i.e. that none of the exclusion criteria had developed in the interim period between screening and procedure day.

Positive End Expiratory Pressure (PEEP) was used to reduce any observed hiatal hernia (after the first 14 subjects a PEEP of 5mmHg was used for all subjects, upon induction of anesthesia). If a hiatal hernia was identified, PEEP was increased up to 10mmHg until the hernia was reduced. If any of the exclusion
criteria was identified, the procedure was terminated and the subject excluded from the intention to treat analysis.

If the subject was not excluded, an 18 mm over-tube was passed into the esophagus over the standard endoscope, the standard gastroscope was removed and the SRS device is inserted through the over-tube to begin the procedure.

The SRS Endoscope

The device itself is a modified flexible endoscope (Figure 1) which includes five core components: a handle with controls, a 80 cm long flexible shaft, a short (5cm) rigid section, holding a cartridge with 5 standard 4.8 mm titanium surgical staples, a ratchet controlled bending section, and a distal tip, which houses an anvil, an ultrasonic transducer and two screws.

There is also a suction and irrigation channel, a camera and a light source at the tip (Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Figure 2)

Operating the SRS Endoscope

The SRS endoscope is a single operator device. It is advanced to the stomach under visual control. Once the bending section is in the stomach it is retro-flexed to about 180 degrees, so that the operator can see the endoscope entering the stomach from the esophagus, including the rigid section (Figure 3). The ratchet mechanism is now activated, so that the bending angle of the bending section (from the cartridge to the tip) remains steady, and the device is pulled back, until the staple line in the cartridge is located about 3 cm above the GE junction, in the esophagus, while the distal tip is in the stomach. The operator now uses the knob on the handle to approximate the tip in the stomach to...
the cartridge. The bending angle is displayed on the monitor. At 270 degrees of bending, the tip in the stomach abets on the cartridge, with the full thickness of the stomach and the esophagus between the two.

As the endoscope tip abets the gastric mucosa, vision is lost. However, the ultrasonic signal from the transducer on the tip is reflected back by the ultrasonic mirror on the cartridge. The timing of the reflected signal corresponds to the distance between the mirror and the transducer (the combined tissue thickness), while the signal amplitude and its stability indicate that the anvil and the staples are properly aligned.

This information is displayed on the monitor. The operator then compresses the tissues by further turning the bending knob, click by click, until the tissues are compressed to a combined thickness of 3mm or less.

Once the distance is 3 mm or less, the operator may begin to extract the screws. The screws penetrate the stomach and the esophagus, and engage nuts in the cartridge. Further turning of the screws allows compression of the tissues to stapling thickness, which is about 1.5mm for a 4.8mm staple to form a B shape. At that distance, a quintuplet of staples is fired simultaneously.

After the stapling, the screws are retracted back into the device, the ratchet is released, the bending section is straightened, and the device is pulled out for reloading.

The same procedure is repeated at least one more time. The decision of whether to use two or three quintuplets depends on the patient’s particular anatomy, but is usually evident at the initial gastroscopy or after the first stapling. Therefore, the operator can choose the location of the 2nd stapling accordingly. The total circumference of the wrap should be about 180 degrees. Two applications may produce a satisfactory wrap, but 3 were more commonly used.

The exact location of the second and third application is determined by the particular anatomy of the patient’s gastro-esophageal junction. However, each quintuplet is placed at least 60 degrees away from the previous quintuplet. The leftmost is always placed as close to the left crux of the diaphragm as possible, while the rightmost is placed just to the left of the lesser curve.

The order of stapling locations (i.e.: left, center, right, or center, left, right etc.) also depends on the particular anatomy, and is selected by the operator. The goal is to achieve a Hill Grade I valve, so that after the last stapling, no esophageal mucosa is seen around the scope in retrograde view.
Upon completion of the procedure, the stomach is stapled to the esophagus by standard 4.8 mm titanium staples, which are the same staples as have been in use for creating surgical gastro-esophageal anastomoses for over 30 years.

**Safety Assessment**

Serious adverse events were defined as any adverse event requiring hospitalization beyond 72h post procedure (i.e. longer than the median hospitalization after LPF[11]), re-hospitalization, or death occurring within 30 days of the procedure. Adverse events were classified as non-procedure or device related, procedure related, or device related by the primary investigator at each site.

**Primary Efficacy Criterion**

The primary efficacy endpoint was a > 50% reduction (compared to pre-treatment) of the OFF Proton pump inhibitors (PPI) GERD health related quality of life score (GERD-HRQL -Velanovich)[12] at six months post procedure. Patients who still used PPI at 6 months, were allowed to use H2 blockers for up to 3 days before the test and rescue treatment with Gaviscon™ up to the day of the test (same as for the baseline test).

**Secondary Efficacy Criteria:**

The following secondary efficacy success criteria were also defined and used:

1. Median change from baseline in the percent of time in which esophageal pH was <4.
   
   In the study protocol, each center was allowed to use its own method of pH monitoring, as long as the same method was used at baseline and at six months later. Two centers used impedance and two centers used the Bravo capsule. The others used standard trans-nasal electrode. Consequently, only the median change from baseline was chosen as an endpoint.

2. PPI usage reduction: Ratio between two patient populations: patients who reduced PPI use by 50% or more and patients who reduce PPI use by less than 50% at six months compared to baseline.

3. Proportion with persistent flap valve on immediate post procedure endoscopy 6 months (using Hill grade (Hill and Kozarek 1997)). Hill valve grades were assessed by the PI, and endoscopic images before and after procedure and at follow-up (6mo) were scored by an independent observer. Additionally, where available, photographic images of the valve were used to assess the Hill grade, by an independent observer.

Results
Seventy-two patients were enrolled and consented to take part in this study in six centers. The chief investigator was a surgeon in three centers, and a gastroenterologist in the other three. There were 30 female patients (41.7%) and 42 male patients. Three subjects were excluded before any staples were placed, and three more subjects were excluded because of serious protocol violations in the inclusion criteria (At screening, there was no difference between the pre-procedure on and off PPI acid exposure test). The latter three subjects were included in the safety analysis, but excluded from the intention to treat analysis.

The demographics are presented in Table 2.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Male</th>
<th>Female</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (yrs)</td>
<td>Height (cm)</td>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Mean</td>
<td>44.2</td>
<td>175.4</td>
<td>82.5</td>
</tr>
<tr>
<td>Minimum</td>
<td>23.5</td>
<td>153.0</td>
<td>54.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>73.7</td>
<td>190.0</td>
<td>109.9</td>
</tr>
</tbody>
</table>

Table 2: Demographic data

There were some statistically significant differences (p<0.01) between the sites regarding the BMI of subjects: the subjects from India were thinner and less tall [mean (SD) BMI of 22.2 32 kg/m² (3.98)] than the subjects from Indianapolis and Vienna [mean (SD) BMI of 28.32 (3.5) kg/m² and 28.6 (3.4) kg/m² respectively]. However, these differences did not seem to affect the outcome.

Procedure Performance
A total of 69 subjects underwent the procedure. Of these, 57 subjects had 3 quintuplets placed, and the rest only two. The mean (SD) net (excluding technical preparations) and overall procedure times were 58(38.6) min and 77.7 (42.4) min. In 4 subjects the resulting flap valve was deemed unsatisfactory (Hill grade of 3 or 4) immediately post procedure due to misplaced staples. The primary specialty of the operator was gastroenterology in 36 cases, and general surgery in 33. In 33 cases, the procedure was performed in an endoscopy suite equipped for providing general anesthesia, and the rest were performed in a standard operating theater. There was a slight difference in the success and complication rates in favor of the gastroenterologists, but it did not reach statistical significance.

Safety
In terms of safety, the study can be divided into 2 phases within the study duration. The first 14 subjects had 7 serious adverse events (SAE) (as defined by protocol), six of which were device or procedure
related. Four of these were mild and transitory, but were counted as SAE’s by protocol definition. Three of these subjects were kept in the hospital until the 4th day, for non-specific symptoms and one was counted as SAE because of a one day readmission for fever and sore throat. All four had normal endoscopies and radiological studies.

One subject had a persistent air bubble in the mediastinum, which was asymptomatic, but required 12 days to resorb. A second subject returned to the hospital 3 days after the procedure because of empyema and pneumothorax (immediate post procedure chest roentgenogram was normal) The perforation was not demonstrated on endoscopy or by radiological (contrast CT and fluoroscopy) studies, but the drained fluid had high amylase concentration. The subject had a severe retching upon awakening from anesthesia. It is likely that the perforation was due to post procedure retching, leading to excessive tension on one or both of the stapling sites. The subject was successfully treated by chest tube drainage and antibiotics.

As a result of these two SAE’s, the instructions for use were modified. Prophylaxis against nausea and vomiting was made mandatory, to prevent retching. The air insufflation pump was turned off before screw insertion, and a PEEP of 5mmHg was used during anesthesia for all subsequent patients, to prevent air leak during screw insertion. As can be seen in Figure 5, these measures effectively reduced the rate of complications. In the remaining 52 subjects, there were only two procedure related SAE’s. One was post procedure bleeding (the patient presented 8 days after the procedure with anemia weakness and tarry stools. The bleeding source was not identified, the patient was treated with 2 units of packed red cell blood and the hematocrit remained stable over the follow up period. The last patient had fever on the first day, and elevated CRP for 3 days following a particularly long procedure (over 210 minutes, compared to the mean 77.7 minutes) The subject was discharged on the 4th day.
Other adverse events were mild, consisting mostly of temporary chest and abdominal pain lasting 1-7 days post procedure. Following the modifications of the IFU described above, there were no device or procedure related SAEs among the last 48 patients. For these 48 subjects, the protocol was modified to improve early detection of complications. The modified protocol prescribed a pre-discharge upright chest roentgenogram and hematocrit level, and the discharge instructions were expanded.

The procedure does not preclude having laparoscopic fundoplication in case the desired outcome has not been accomplished. Two subjects of the intention to treat group, who had a clinical failure, underwent laparoscopic fundoplication after completing the follow up period. The surgeon reported that in both cases the operation was uncomplicated, and did not require take-down of the previous staples.

**Efficacy**

66 subjects were included in the intention to treat efficacy analysis (excluding the 3 subjects with the major protocol violation in the inclusion or exclusion criteria). Of these, 64 subjects completed the follow up. The mean (SD) OFF-PPI HRQL dropped from 29.7 (6.16) at baseline to 8.97 (9.137) (p< 0.001) at 6 months.

Twenty two percent decreased their GERD-HRQL to 0 at six months (100% improvement). A total of 48 of the 64 (75%) available patients had a six month HRQL improvement of greater than 50%, when
assessed off all acid reducing medications and 10 additional subjects showed a 40% improvement. (for patients still on PPI at six months, the PPI’s were stopped 7 days before testing. H2 blockers were allowed up to 3 days before, and rescue treatment with Gaviscon™ was allowed up to 24h before answering the questionnaire).

Figure 6: Distribution, sorted by %change in score, in HRQL change (percents) among the intention to treat cohort (100% means a score of 0 at 6 months)

PPI Utilization

Sixty-five of the sixty-six procedure-treated patients were taking one or more PPIs on a daily basis at baseline (the single exception switched to high dose H2 blockers a few weeks before the procedure, and was therefore not excluded). The average dose (standardized to 40 mg of Omeprazole) per patient was 58.5mg/day (median=40mg/day, SD=33.02mg/day). At the six month follow-up only 23 patients continued to take PPIs on a daily basis. This is a 65% reduction in the number of patients taking PPI on a daily basis.
For the cohort of 23 subjects that continued taking PPI daily for GERD symptoms at six-month the average dose was 31.3mg/day (median=30mg/day, SD=11.40mg/day). For these 23 patients a paired t-test was performed. The results of the test indicated that there was a significant decrease in PPI usage of 31.3mg/day ($t = -3.88$, DF=22, $p=0.001$). A total of 85% of the patients (56/66) who reported daily use of PPI medication at baseline, reported a reduction of at least 50% in the daily medication dose.

Figure 7 illustrates graphically the proportional change in PPI use six months following the procedure for all study patients in the ITT group. Positive numbers represent a reduction in use, while negative numbers represent an increase in use. The reduction in PPI use for the vast majority of patients, including the large group of patients (almost two thirds) that saw a complete elimination of the use of the medication is evident.

**Acid Exposure:**

The median (range) percentage of time pH was < 4.0 dropped from 8.30% (4.7-73.9%) to a value of 6.75% (0-20.5%). (The mean (SD) dropped from 11.05% (10.8) to 7.30% (5.12).) The differences were statistically significant by the Wilcoxon ranked sign test ($p<0.002$). The maximum percent of time dropped from 73.9% to 20.5%. However, there was no significant correlation between acid exposure
time and either PPI utilization or HRQL scores (Spearman correlation coefficient -0.12 and -0.29 respectively)

**Hiatal Hernia Reduction**

In twenty seven subjects, a hiatal hernia was still evident on the immediate pre-procedure endoscopy despite positive pressure ventilation. All reduced completely by increasing PEEP up to 10 mmHg, and remained reduced during the procedure.

In eighteen of these subjects (66.7%) no hiatal hernia was identified on endoscopy at six months when examined under normal, negative pressure breathing.

**Gastro-esophageal Flap Valve Restoration**

The Hill GEFV grade was used to assess the quality of the flap valve. Immediately post procedure, only 4 subjects remained with a Hill grade of 3-4, seemingly due to incorrect staple placement. As expected, these 4 subjects account for 4 of the cases who did not show clinical improvement.

Sixty patients had Hill Grade Scores at the six-month follow-up. **Error! Reference source not found.** demonstrates the joint distribution of bifurcated Hill Grades at the end of the procedure and at the six-month follow-up. At baseline the proportion of the sixty-three patients with a Hill Grade of 1 or 2 was 0.933 (56/60). At six months follow-up the proportion with a Hill Grade of 1 or 2 was 0.766 (46/60). Since the data are correlated a McNemar test was performed to determine if the baseline rate was statistically different from the six month rate. The exact probability of the McNemar statistic was p=0.00024. This indicates that the rate at six months had significantly declined from baseline. However, the rate of unsatisfactory flap valve was significantly reduced from 66% before treatment to 28% at 6 months (before treatment, all subjects had grade 2 or higher Hill grade).

<table>
<thead>
<tr>
<th></th>
<th>Grade ≤ 2</th>
<th>Grade &gt; 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the end of the procedure</td>
<td>43</td>
<td>13</td>
<td>56</td>
</tr>
<tr>
<td>Grade &gt;2</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>17</td>
<td>60</td>
</tr>
</tbody>
</table>

*Table 3: Hill Grades at Baseline: Pre- and Post-procedure*

Since the Hill grade is largely dependent on the individual observer, a sample of 43 pictures was blindly introduced to an independent observer. Images for the remaining 23 subjects were not available.
The success rate (Hill grade 2 or less) based on the PI scoring was 0.98 (95%CI = [0.88-0.99]). The corresponding rate based on the Independent Observer’s scoring was 0.95 (95%CI = [0.84-0.99]). A McNemar test indicates that there is no difference in these proportions (Exact p associated with the McNemar test statistic is 1.0)

**Discussion**

The main goal of any treatment for GERD is to improve the quality of life of the patient. Although GERD has been associated with a number of comorbidities, ranging from sleep apnea to adenocarcinoma of the esophagus, a significant decrease in the life expectancy of GERD patients has not been demonstrated[13].

This study demonstrates that the Medigus SRS procedure significantly improves the quality of life of GERD patients, and reduces their use of PPI: Using intention to treat analysis, 75% of the subjects had a greater than 50% improvement in their off PPI GERD HRQL scores, and an additional 10 had a 40% improvement. This symptomatic improvement was associated with a substantial decrease in usage of PPI drugs, which were eliminated by nearly two thirds of subjects, and reduced by at least 50% in 85% of subjects.

A few studies measure HRQL before and after Laparoscopic Fundoplication (LPF). One study, by Pidoto et al [14], found that HRQL improved from 17.1 +/- 4.0 to 1.9 +/- 4.8 in a cohort of 25 patients at 6 months. The magnitude of the drop is similar to that found in this trial. Another study[15], looked at longer term results of LPF, showed that 71% of patients had normal (<10) HRQL scores 6 years after the operation (this study did not measure baseline HRQL). This number is similar to our results at six months.

Thus, in terms of quality of life – as measured by the GERD HRQL scores – and PPI usage, the results presented herein are one of the better ever reported for a trans-oral endoscopic method, and approximate the results of laparoscopic Nissen Fundoplication (LNF), although this may change with time.

Although there was a significant improvement in acid exposure, there was poor correlation between acid exposure time and symptomatic relief. One possible explanation is that since the procedure only does a partial wrap, it only prevents reflux when the stomach is full. Thus it does not prevent short episodes of reflux, which do not cause symptoms, although this hypothesis was not tested in this study. Composite scores, such as the DeMeester score, may have been better suited, but their use is controversial, and was not tested in this study.

Another possible explanation is that a partial wrap may not be as effective as a full wrap if the subject over-indulges in food and drink. A few patients in this study reported that this is indeed the case. This is not necessarily a bad outcome. Heartburn after heavy meals is a common experience, and may be construed as a physiological admonition against overeating.
Although objective reflux control is not as good as that of LNF as reported by the most experienced centers, the lack of dysphagia with the SRS procedure may compensate for this mismatch and the overall quality of life improvement is similar, at least in the first six months. The results of LNF are reported by centers of excellence with known reputation for this particular procedure. The results of LNF in smaller centers may not be as good[16]. In contrast, this is the first large scale study of the Medigus SRS device (the largest center has performed 21 cases). The procedure is relatively simple, but as can be expected with any surgical procedure, there was a tendency of improved results with growing operator experience.

Two observations support this hypothesis; first, in the center with the largest number of subjects, the success rate in terms of 50% reduction in HRQL was 80.2% vs. 70% for the center with the lowest number of subjects. The difference was not statistically significant, due to the small number of patients, but it points to a trend.

The second observation is that there were four subjects who remained with a Hill grade of 3 or 4 flap valves immediately after the procedure due to incorrect placement of the staples. As expected, these four procedure failures, which were probably due to the learning curve, failed to meet the primary success criterion, and also included the subjects who required an increased or unchanged dosage of PPI. Excluding these four procedure failures from the analysis, the success rate would have been 80%.

It is possible that placing additional staples in the correct location would have resulted in improved success. However, placing a 4\textsuperscript{th} quintuplet was disallowed by protocol restrictions. In open label use, this would seem possible.

Data from the pilot study patients[17] suggest that the results have been stable over the last three years. In addition, the procedure employs the same staples that have been in use for creating gastroesophageal anastomoses for over four decades; there are no reported cases of late breakdown of these anastomoses. Therefore it is likely that the stapling will continue to hold as well as the sutures used in LFP.

That said, many patients who had LFP return to medications after a few years[18]. This effect may be true for all surgical procedures that repair the valve, including the current procedure. After all, no surgical intervention can alter the stresses of daily living and the changes in eating habits that are associated with the increasing worldwide prevalence of GERD. These stresses remain, and deterioration is probably inevitable in some cases.

The SRS procedure offers further advantage over LFP in such cases. Re-do LFP are difficulty and are associated with more complications and lower patient satisfaction than primary LFP[19]. In contrast, it appears that following the SRS procedure, a remedial LFP is feasible, using standard technique.

Two subjects with clinical failure of the SRS procedure underwent laparoscopic fundoplication after the conclusion of the study. The surgeons reported no difficulty, and did not have to take down the previously placed staples. It thus appears that conversion to a standard fundoplication is a valid option.
in cases of unsatisfactory outcome, or if deterioration should occur at a later date. Based on this limited experience, late conversion should be easier and safer to perform than a re-do LNF.

Another alternative in case of deterioration is to repeat the procedure and add another row of staples more cephalad. This option has not been tested in humans, although it is feasible in the swine model.

The procedure does not attempt to treat sliding hiatal hernias. For many years, GERD and hiatal hernia were almost synonyms. However this is clearly not the case. Sliding hiatal hernia by itself should not be viewed as a disease. It occurs in over 60% of older population (10% in younger than 40 years, 70% in people older than 70 years) [20]. Most cases are discovered incidentally, and the great majority of people with hiatal hernia do not have GERD symptoms.

Although many GERD patients do not have hiatal hernia, there is a high correlation of erosive esophagitis with hiatal hernia [21] Thus a large sliding hiatal hernia may worsen the severity of GERD.

In a prospective study of 57 patients 2 years after laparoscopic surgery, Donkervoort et al. [22], found that 55% had some degree of anatomical failure, and that 27% had complete herniation. The anatomical failure had no effect whatsoever on the clinical outcome. In an ex vivo study, Richardson et al [23] demonstrated that either complete or partial fundoplication provide a complete reflux barrier independent of supporting structures.

It can be concluded from these data that if the LES is competent, hiatal hernia has no clinical importance, but when the valve is incompetent, a hiatal hernia may worsen the symptoms or sequelae of GERD.

There were some patients in the study who were apparently cured of their hiatal hernia by the procedure. This could be explained by either the added bulk to the GE junction with the stapled stomach, or that one of the quintuplets incorporated the left crux of the diaphragm, preventing the stomach from sliding up into the chest. One way or the other this was not a goal of the procedure.

In terms of safety, there were a few serious complications early on in this study. As a result, the protocol and IFU were modified. To prevent accidental insufflation of air during screw insertion, the air pump was turned off during the stapling stage, and PEEP of 5 mmHg was used for all cases. Universal prophylaxis measures against post anesthesia nausea and vomiting were made mandatory, to prevent retching. In addition, pre-discharge chest roentgenogram and hematocrit levels were obtained for all subjects to allow early detection of such complications, although none were observed. It should be noted that only one complication (empyema) was potentially life threatening and it was treated without surgery, resulting in complete recovery (both from the complication and from GERD).

Analysis of the adverse events showed that most serious adverse events occurred when only 2 quintuplets were used. In the final analysis, this was not statistically significant, perhaps because of the small number of cases. However, it does suggest that placing an additional quintuplet may not increase the risk of the procedure. It is possible that in some cases adding additional quintuplet may be advisable.
and improve the outcome. Nonetheless, the correlation between the first few procedures and the smaller number of quintuplets, may point to a learning curve effect rather than number of staples used.

Lastly, the results demonstrate that although the procedure is in fact a trans-oral operation, and requires general anesthesia, it can be performed equally well by either gastroenterologists or surgeons, and that it may be safely performed in the endoscopy suite. It is therefore more widely accessible than alternative procedures.

**Conclusions**

In terms of quality of life improvement and reduced PPI usage, the results, at least at six months, approximate those of LNF, as reported from centers of excellence in the latter procedure[24].

At least four of the clinical failure were due to misplaced staples and probably reflect the learning curve. Although not tested in humans, placing additional quintuplets of staples in such cases may improve the results, without compromising safety.

This is the first report of a new procedure to treat GERD entirely through the mouth by a single operator. We believe that the results suggest that the procedure is a relatively safe and effective alternative to LFP or lifelong high dose PPI treatment for patients with moderate to severe GERD and sliding hiatal hernia < 3cm.
References


