

Conversion of One-Anastomosis Gastric Bypass (OAGB) to Roux-en-Y Gastric Bypass (RYGB) is Effective in Dealing with Late Complications of OAGB: Experience from a Tertiary Bariatric Center and Literature Review

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Purpose: Both primary and revisional bariatric surgery are on the rise due to global obesity pandemic. This study aimed to assess the indications for revision after one-anastomosis gastric bypass (OAGB) and the outcomes after laparoscopic conversion of OAGB to roux-en-y gastric bypass (RYGB). **Materials and Methods:** Retrospective review on patients that had undergone conversion of OAGB to RYGB between June 2007–June 2019 in a tertiary bariatric center, followed by literature review. **Results:** Out of 386 revisional bariatric surgery, a total of 14 patients underwent laparoscopic conversion of OAGB to RYGB. The mean age was 44.7 with 71% female. The mean pre-revision BMI was 29.2 kg/m². The primary indications for revision were bile reflux (n=7), marginal ulcer (n=3), inadequate weight loss or weight regain (IWL/WR) (n=3) and protein-calorie malnutrition (n=1). Conversion of OAGB to RYGB was completed laparoscopically in all cases. The mean length of stay was 4.1 days. There was no intraoperative or early post-operative complication. The mean total weight loss (rTWL%) after revision at year one, year three and year five post-revision were 11.5%, 18.1% and 29.1%, respectively. All patients achieved resolution of bile reflux and marginal ulcer. There was no mortality in this cohort. **Conclusion:** Bile reflux, marginal ulcer, IWL/WR and malnutrition were the main indications for revision after OAGB in this study. In concordance with the available evidence, laparoscopic conversion of OAGB to RYGB was safe and effective in dealing with late complications of OAGB.

Key Words: Gastric bypass, Revision, Bariatric surgery, Outcomes

INTRODUCTION

Obesity has become a global pandemic, with 39% of adults overweight and 13% obese in 2018 worldwide [1]. Obesity is associated with increased risks of diabetes mellitus (DM), cardiovascular events, cancer and overall mortality [2–4]. Surgical treatment of obesity has been shown to be the most effective in achieving long term

weight loss and resolutions of comorbidities [3–6].

The three commonest bariatric procedures worldwide are sleeve gastrectomy (SG), roux-en-y gastric bypass (RYGB), followed by one-anastomosis gastric bypass (OAGB) [7]. OAGB is mainly being practiced in the UK, Europe and Asian countries since its first development by Rutledge in 1997 [7,8]. It is widely advocated among the proponents due to the technical ease, shorter operating

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time and learning curve, in addition to the promising results in weight loss and resolution of comorbidities [9–15]. OAGB is shown to have low morbidity similar to RYGB and SG, with low mortality rate of 0.1% [15–19]. However, OAGB is also in constant dispute with the concerns on malabsorption, protein-calorie malnutrition, persistent bile reflux and the associated risk of carcinogenesis [20–22].

With the increased number of cases of OAGB worldwide and the longer period of follow up, the need for revision is on the rise. The revision rate after OAGB is around 2.3–4.7%, with malnutrition being the commonest indication [15–19]. Other indications that warrant revision include gastroesophageal reflux disease (GERD), bile reflux, marginal ulcer, inadequate weight loss or weight regain (IWL/WR). The options of revision include conversion to SG, conversion to RYGB, and reversion to normal anatomy, depending on the indication for revision [17–19]. There are numerous publications including three randomized control trials on OAGB to date. However, there are limited literatures on revisional surgery after OAGB, especially in conversion of OAGB to RYGB [16,23–25]. Herein, we study a cohort of patients that presented with late complications after OAGB and underwent conversion of OAGB to RYGB in a tertiary bariatric center. We aimed to assess the indications for revision and the short to mid-term outcomes after conversion of OAGB to RYGB. In addition, a literature search was done on the outcomes following the conversion of OAGB to RYGB.

MATERIALS AND METHODS

1. Study population

A retrospective review was done on the prospectively maintained database in a tertiary bariatric center. Patients that had undergone conversion of OAGB to RYGB between June 2007 to June 2019 were included. Out of 386 revisional surgery, 14 patients were identified. All patients had a history of OAGB done in other centers, as OAGB was not advocated as a primary bariatric procedure in the authors' institution. All patients were included in the initial perioperative data analysis. Patients with follow up

less than 6 months were excluded from the short to mid-term outcome analysis (Fig. 1).

2. Preoperative workup

Routine pre-operative workup consists of full blood count, renal profile, electrolytes, fasting blood sugar, HbA1c, fasting lipid profile, liver function test, esophago-gastroduodenoscopy (OGDS) and electrocardiogram. Diagnosis of bile reflux was made with symptoms of biliary regurgitation or biliary vomiting with confirmation by OGDS visual documentation of bile within the esophagus and mucosal changes like esophagitis, gastritis or Barrett's esophagus. pH study and manometry study were reserved for patients with doubt in diagnosis. Further tests like CT scan or upper GI series were done selectively, on a case-by-case basis. Patients with positive urease test on OGDS were given *Helicobacter pylori* eradication. Patients with persistent reflux symptoms despite best medical therapy including 6 months of proton pump inhibitors, prokinetics, dietary and lifestyle modification were considered for revisional surgery. Marginal ulcer was proven endoscopically and deemed persistent despite 3 months of high dose proton pump inhibitor treatment. Protein-calorie malnutrition was diagnosed with excessive weight loss, persistent diarrhea, low albumin and vitamins level, unresponsive to dietary measures. All patients underwent careful evaluation by bariatric multidisciplinary

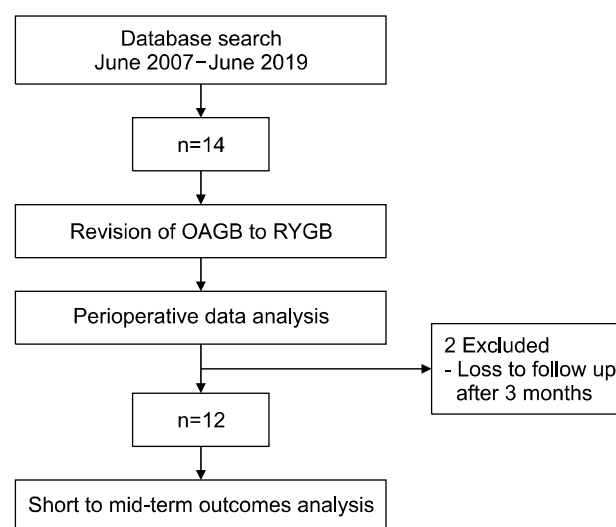


Fig. 1. Patient selection flow chart.

team, validating the indication of surgery and deciding on the type of revisional surgery. All revisional surgeries were done by a single consultant bariatric surgeon.

3. Operative technique

Laparoscopic conversion of OAGB to RYGB was done under general anesthesia in supine position with surgeon on patient's right. Optical entry trocar was used routinely as the first port entry. Standard 4-port technique was used

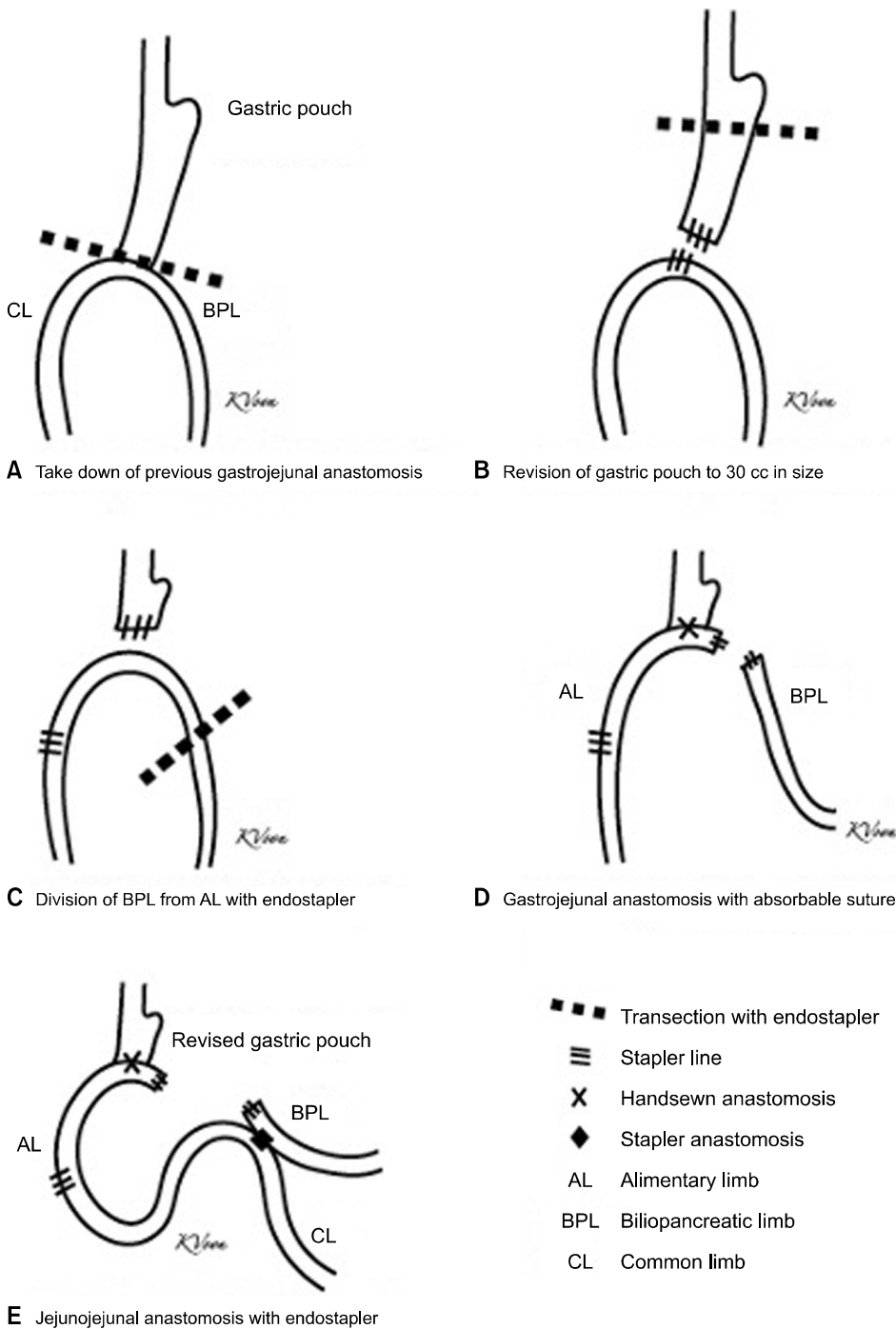


Fig. 2. Laparoscopic conversion of OAGB to RYGB.

and liver suspension was done with the T-suspension tape technique [26]. Adhesiolysis was done with both sharp dissection and energy device. Previous gastrojejunostomy (GJ) was taken down with linear endostapler flush to the stapler line, with care to avoid stenosis of jejunal lumen. Gastric pouch was then resized to 30 cc in volume by using the size 36 Fr bougie, with linear endostapler. A 2 cm antecolic gastrojejunostomy was then constructed with either intracorporeal handsewn technique or linear endostapler. Single layered handsewn anastomosis was done with antegrade method with absorbable monofilament suture (Fig. 2). Omega loop technique was used in construction of gastrojejunostomy with linear endostapler, followed by jejunojejunostomy. Length of alimentary limb (AL) and biliopancreatic limb (BPL) were ranged from 60–100 cm and 20–100 cm, respectively. Isoperistaltic side-to-side jejunojejunostomy of 3cm in length was done with linear endostapler and completed with absorbable monofilament suture. Hiatal hernia reduction and cruroplasty were done with interrupted non-absorbable suture in patients with hiatal hernia. Both mesenteric and Petersen's defects were closed with non-absorbable braided suture. Resected gastric pouch was removed via 12 mm port site. Jackson-Pratt drain was routinely placed posterior to the GJ anastomosis. Post-operatively patients were allowed water on the same day and advanced to liquid diet the following day. Contrast study was not a routine post-op. Follow-up was done at 1 week, 1 month, 3-monthly for first year, followed by yearly thereafter.

4. Data analysis

Patients' demography, perioperative parameters, 30-day readmission, morbidity, mortality, total weight loss after revision (rTWL%) and resolution of preoperative symptoms or comorbidities were recorded. The ideal body weight (IBW) and excess weight loss (EWL%) were calculated using a standard formula with ideal BMI equal to 22 kg/m² as per Asian standard. Total weight loss after revision (rTWL%) was calculated based on a standard formula based on the pre-revision body weight, as the initial weight before the OAGB was not available for all patients. Diabetes mellitus remission was defined as

HbA1c <6.0% without medications. While remission of hypertension was defined as blood pressure <140/90 mmHg without medications. Other comorbidity remission was defined as discontinuation of treatment for the condition at 1 year in patients who had received treatment for that condition at baseline. Remission of bile reflux and marginal ulcer was confirmed by both resolution of symptoms and repeat OGDS assessment after revision. Patient data were retrieved from a customized computer database built using Excel (Microsoft Inc., Redmond, WA). Descriptive results for continuous variables were presented as mean ± standard deviation. The categorical data were presented as counts and percentage.

RESULTS

1. Indications for revision after OAGB

Fourteen patients were included in the initial analysis. The mean age was 44.7 with 71% female. Upon revisional surgery, diabetes mellitus (DM) and hypertension were present in three patients (21.4%). Eleven patients (78.6%) had GERD, in which seven of them were diagnosed to have bile reflux (Table 1). Two patients had history of intragastric balloon insertion and vertical band

Table 1. Patients' demography

Demographic data (n=14)	Value
Age, mean (range)	44.7 ± 11.1 (26–66)
Gender (female/male), n (%)	10/4 (71/29)
Mean pre-revision BMI, kg/m ² (range)	29.2 ± 5.8 (17–39.1)
Mean follow up, months (range)	23.1 ± 22.8 (3–75)
Interval between primary & revisional surgery, years (range)	5.3 ± 3.4 (2–10)
Comorbidities, n (%)	
Type 2 DM	3 (21.4)
Hypertension	3 (21.4)
Chronic kidney disease	1 (7.1)
Hyperlipidemia	1 (7.1)
GERD	11 (78.5)
Smoker	0 (0)
Primary indications for revision, n (%)	
Bile reflux	7 (50.0)
Marginal ulcer	3 (21.4)
IWL/ WR	3 (21.4)
Protein-calorie malnutrition	1 (7.1)

DM = diabetes mellitus, GERD = gastroesophageal reflux disease, IWL/WR = inadequate weight loss/weight regain.

gastroplasty prior to the OAGB surgery, respectively. The mean follow-up period was 23.1 months with 60% follow up at 5 years. Two patients were excluded from the short to mid-term outcome analysis due to loss to follow up after 3 months (Fig. 1). The mean interval between the primary OAGB and revisional surgery was 63.6 months (18–120 months). The commonest primary indication for revision was bile reflux (n=7, 50%), followed by marginal ulcer (n=3, 21.4%), IWL/WR (n=3, 21.4%), and protein-calorie malnutrition (n=1, 7.2%). Bile reflux was diagnosed in 7 patients with presence of bile in esophagus with esophagitis changes on OGDS. There was no Barrett's esophagus or dysplasia in the cohort. Four patients with positive urease test on endoscopy were given Helicobacter pylori eradication. Five patients were noted to have iron deficiency anemia with the mean hemoglobin of 8.5 g/dL before revision (Table 2).

2. Perioperative outcomes

All patients successfully underwent laparoscopic conversion of OAGB to RYGB with one patient had additional hiatal hernia repair. The mean operative time was 131.8 minutes. The mean length of the AL and BPL in the revisional surgery were 93 cm and 64 cm, respectively (Table 3). There were no intra-operative or early

post-operative complications. However, two patients were readmitted within 30 days after discharge. One patient with nonspecific abdominal pain while the other patient with poor oral intake and dehydration. Both patients were discharged well after 2 days of hospitalization, after appropriate workup and hydration.

3. Short to mid-term outcomes

The mean pre-revision BMI was $29.2 \pm 5.8 \text{ kg/m}^2$, which reduced to $26.3 \pm 3.4 \text{ kg/m}^2$ and $23.8 \pm 1.2 \text{ kg/m}^2$ at one year and five years follow up, respectively. The mean total weight loss after revision (rTWL%) at year one, year three and year five post-op were 11.5%, 18.1% and 29.1%, respectively. The only patient that presented with protein-calorie malnutrition pre-revision, achieved satisfactory weight regain with increment in BMI from 17 kg/m^2 to 23.3 kg/m^2 with resolution of diarrhea and hypoalbuminemia.

Ten patients with GERD achieved remission of symptoms after conversion to RYGB with the remaining one had improvement with reduced use of proton pump inhibitors. All patients with bile reflux and marginal ulcer achieved remission, evidenced by the resolution of reflux symptoms and OGDS confirmation within 1 year post revision (Table 4). Five patients had iron deficiency

Table 2. Indications for revision after OAGB

No.	Indications	OGDS pre-revision	Pre-revision BMI (kg/m ²)	Interval between surgeries (years)	Initial BPL length (cm)
1.	Marginal ulcer, IWL	Anastomotic ulcer, CLO -	29.7	2	200
2.	Protein-calorie malnutrition, anemia, diarrhea	Anastomotic ulcer, CLO -	17.0	2	200
3.	Bile reflux	Bile reflux, CLO -	32.0	2	150
4.	Bile reflux	Bile reflux, CLO +	22.0	2	100
5.	Bile reflux, diarrhea, HTN, DM	Bile reflux CLO +	24.1	3	150
6.	Marginal ulcer, GERD	Anastomotic ulcer, CLO -	28.9	3	200
7.	IWL, GERD, diarrhea	Esophagitis, CLO +	30.1	3	150
8.	IWL, HTN, DM	Normal, CLO -	39.6	3	150
9.	Bile reflux, anemia, HTN, CKD, DM	Bile reflux, CLO +	26.0	3	150
10.	Bile reflux, anemia	Hiatal hernia, bile reflux, CLO -	29.9	9	250
11.	Bile reflux, anemia	Bile reflux, CLO -	27.3	9	250
12.	Marginal ulcer, anemia, GERD	Anastomotic ulcer, CLO -	29.8	10	200
13.	Bile reflux, WR	Bile reflux, CLO -	39.1	10	150
14.	WR, GERD, hyperlipidemia	Esophagitis CLO -	33.6	10	100

Bold = primary indication for revision, GERD = gastroesophageal reflux disease, IWL = inadequate weight loss, WR = weight regain, HTN = hypertension, DM = diabetes mellitus, CKD = chronic kidney disease, BPL = biliopancreatic limb, CLO = campylobacter-like organism test (urease test).

Table 3. Perioperative data

Measures	Value
Surgery	
LOAGB-RYGB, n (%)	10 (90.1)
LOAGB-RYGB + HHR, n (%)	1 (9.9)
Operative time (min), mean (range)	131.8±30.5 (85–180)
Prerevision BPL length (cm), mean (range)	164.3±39.8 (100–250)
AL in RYGB (cm), mean (range)	93±14 (60–100)
BPL in RYGB (cm), mean (range)	64±28 (20–100)
Gastric pouch size (cc)	30
Gastrojejunostomy length (cm)	2
RYGB gastrojejunostomy technique, n (%)	
Intracorporeal handsewn	10 (71)
Endostapler	4 (29)
Blood loss (ml), mean (range)	38±14 (20–50)
Conversion to open surgery, n (%)	0 (0)
Intraoperative complication, n (%)	0 (0)
Length of stay (days), mean (range)	4.1±1.8 (3–8)
Readmission in 30 days, n (%)	
Nonspecific abdominal pain	1 (50)
Poor oral intake with dehydration	1 (50)
Late complications, n (%)	
Intestinal obstruction	1 (25)
Perforated marginal ulcer	1 (25)
Persistent anemia	1 (25)
Inadequate weight loss	1 (25)
Mortality, n (%)	0 (0)

LOAGB-RYGB = laparoscopic conversion of OAGB to RYGB, HHR = hiatal hernia repair, AL = alimentary limb, BPL = biliopancreatic limb.

anemia pre-revision and there was improvement of anemia in all five patients, with the raise in mean hemoglobin from 8.5 g/dL pre-revision to 10.1 g/dL post-revision. For the patients with DM, two patients achieved complete remission while the other one achieved partial remission at 5-year follow up. Similarly, two out of three patients achieved remission for hypertension (Table 4).

Three patients required repeat surgery during the 5-year follow up. One patient presented with intestinal obstruction 3 months after surgery and diagnosed with AL obstruction due to kinking at previous gastrojejunostomy (GJ) take down site, which was treated with laparoscopic jejunojunal bypass. The same patient again presented with perforated marginal ulcer three years later, in which a laparoscopic repair of the ulcer was done. Two other patients underwent repeat revisional surgery due to persistent anemia and IWL, respectively. The first patient

Table 4. Clinical parameters and comorbidities after conversion of OAGB to RYGB

Variables	Pre-revision	Post-revision
Hemoglobin, mean (g/dl)	11.2±2.4	11.9±1.5
Fasting blood sugar, mean (mg/dl)	105.8±30.2	93.4±18.6
HbA1c, mean (%)	5.7±0.8	5.4±0.5
LDL, mean (mg/dl)	95.8±46.3	80.3±11.9
Triglyceride, mean (mg/dl)	89.4±27.7	81.4±15.8
Hypertension (n)	3	1
GERD (n)	11	1
Bile reflux (n)	7	0
Marginal ulcer (n)	4	0
Diarrhea (n)	3	0

LDL = low density lipoprotein, GERD = gastroesophageal reflux disease.

had persistent anemia despite improvement in hemoglobin from 7.7 g/dL to 9.0 g/dL after revision of OAGB to RYGB. Laparoscopic conversion of RYGB to sleeve gastrectomy was done three years later. The second patient had IWL and chronic constipation after conversion of OAGB to RYGB. Laparoscopic distalization of BPL was done two years later. There was no mortality in this study.

DISCUSSION

Revisional surgeries are usually indicated for late complications of the primary procedure, IWL/WR or impaired quality of life. The common late complications of OAGB include bile reflux, GERD, anemia, marginal ulcers and malnutrition [12–18]. Parmar and Mahawar [15] reported post-operative GERD rate of 2.0%, marginal ulcer 2.7%, anemia 7.0% and malnutrition in 0.71% of patients after OAGB [15]. The overall revision rate for OAGB reported in the literature ranged from 1–5% and the commonest indications for revision are malnutrition and IWL/WR [14–18]. In consistent with the literature, the indications for revision in this study were bile reflux, marginal ulcer, IWL/WR and protein-calorie malnutrition.

1. Bile reflux

Incidence of bile reflux after OAGB ranged from 0.6% to 10% [16–19]. Stagnation of the biliopancreatic content

and duodenogastroesophageal reflux (DGER) are pathological as it can lead to gastritis, esophagitis, Barrett's esophagus and significant reflux symptoms [21,22]. Moreover, the potential risk of carcinogenesis associated with chronic bile reflux is still under study. Two recent case reports reported the occurrence of cardioesophageal junction (COJ) adenocarcinoma 2 years after OAGB [27,28]. However, the significant relation between OAGB, bile reflux and COJ adenocarcinoma was questionable in these reports as there was no detailed information on the pre-operative condition of the COJ. Diagnosis of bile reflux is challenging as there is no standardized diagnostic tool for bile reflux [22,29,30]. Bile reflux is usually a clinical diagnosis with symptom-based and endoscopic findings of bile in the esophagus with esophagitis changes. Bile reflux scintigraphy, catheter based fiberoptic spectrophotometer (Bilitec) and multi-channel intraluminal impedance-pH monitoring may be helpful in differentiating acid vs biliary reflux [29,30]. However, their uses are limited by patient's compliance, lack of anatomical resolution, cost and labor-intensive data interpretation.

Conversion of OAGB to RYGB is effective in treating bile reflux, by converting the omega loop into roux-en-y reconstruction. Kassir et al. [23] reported 93.8% of patients achieved resolution of bile reflux after conversion of OAGB to RYGB. Moreover, 100% resolution was reported by Landreneau et al. [24]. Similarly, resolution of bile reflux was 100% in this study.

2. Marginal ulcers

All patient with marginal ulcers achieved resolution after conversion of OAGB to RYGB in this study. Similarly, Landreneau et al. [24] and Bolckmans et al. [25] reported 100% resolution in marginal ulcer after conversion of OAGB to RYGB. However, there was a case of new onset marginal ulcer which occurred 3 years after revision of OAGB to RYGB in this cohort. Occurrence of marginal ulcer after gastric bypass is multifactorial, including large gastric pouch size, mucosal ischemia, stapler line disruption, gastrogastic fistula and foreign body reaction [31]. Pyke et al. [32] reported the incidence of marginal ulcers of 6.28% after RYGB. In comparison, Mahawar et al. [33] reported a lower incidence (2.24%) of

marginal ulcer after OAGB. The lower incidence of marginal ulcer in OAGB could be due to the buffering effect of biliopancreatic content on gastric acid in OAGB. In the authors' institution, intracorporeal handsewn GJ anastomosis with absorbable suture was preferred over stapler anastomosis to reduce the risk of marginal ulcer formation secondary to foreign body reaction.

3. IWL/WR

The mean total weight loss after revision (rTWL%) at year one and year five post-op were 11.5% and 29.1%, respectively. It was in accordance with the report by Lee et al. [16] which showed a 14% of EWL and 3.2 kg/m² of BMI loss 24 months after revision of OAGB to RYGB. In comparison to Lee et al., the gastric pouch was routinely resized to 30cc in this cohort, which had more restrictive effect in promoting weight loss. The reasons for IWL/WR after OAGB could be multifactorial. Patients' compliance to dietary and exercise regime were first evaluated and reinforced. Secondly, it could be due to non-standardization of surgical technique in the primary OAGB with variations in gastric pouch size, diameter of gastrojejunostomy anastomosis and BPL length. The mean BPL length constructed in the primary OAGB was 140 cm (100–150 cm) among the 5 patients that had IWL/WR in this cohort. In the revisional surgery, a standard approach with 30 cc gastric pouch, 2 cm gastrojejunostomy, AL of 100 cm and BPL of 100 cm was advocated for this group of patients with IWL/WR (Table 3). This approach had led to satisfactory weight loss after the conversion of OAGB to RYGB.

4. Malabsorption and malnutrition

Decision was made against conversion to normal anatomy by the bariatric MDT team for the only patient with protein-calorie malnutrition in this study, in view of the young age, strong family history of diabetes mellitus and possibility of excessive weight regain in future. Hence, revision of OAGB to RYGB was done. The BPL length was noted to be 200 cm from the primary OAGB, which was then converted to RYGB with 60 cm AL and 20 cm BPL. This resulted in resolution of diarrhea, hypoalbuminemia with significant improvement of iron level and hemoglobin

from 6.7 g/dL and 10.2 g/dL at 1-year post-revision.

The incidence of iron deficiency anemia after OAGB ranged between 1–15% [9–15]. Lee et al. [10] reported a decrease in hemoglobin after both OAGB and RYGB but with a significant lower level of hemoglobin after OAGB (10.1 ± 2.8 vs 12.5 ± 1.4 g/dL). The higher incidence of iron deficiency anemia is due to the longer BPL in OAGB leading to increased malabsorption as compared to the standard RYGB. Five patients in the present study had iron deficiency anemia pre-revision, with the mean increment in hemoglobin of 1.6 g/dL after conversion to RYGB.

Revisional surgery is technically challenging and associated with higher risk of perioperative complications [34,35]. Choices of revision, gastric pouch size, gastro-jejunostomy size, AL length, BPL length, common limb (CL) length and anastomotic technique are of important considerations in the planning of revisional RYGB. Patients' symptoms and indications for revision, lifestyle and diet habit, as well as surgeons' experience and availability of resources are the determining factors in individualized strategy for revision. All patients were assessed in a multidisciplinary team meeting and the revision was done by a single consultant surgeon with standardized approach in this study. Laparoscopic revisional surgery is safe and feasible in experienced hands as shown in the literature and current study [34,35].

5. Limitations

There were several limitations in this study. Firstly, this was a single center experience with small cohort of patients. It was a retrospective analysis of the prospectively collected data. Diagnosis of bile reflux was mainly based on clinical features as there was no standard diagnostic tool. Despite the shortcomings, this was a significant study showing the safety and effectiveness of laparoscopic conversion of OAGB to RYGB, in dealing with late complications of OAGB especially for bile reflux and marginal ulcers. Although all the index OAGB were done at other centers with variations in operative technique, the revisional surgery was performed by a single surgeon with vast experience in performing more than 300 revision. Furthermore, it was the only study in the literature with 5-year outcomes after laparoscopic conversion of OAGB

to RYGB.

CONCLUSION

In conclusion, bile reflux, marginal ulcer, IWL/WR and malnutrition were the main indications for OAGB revision in this study. In concordance with the available evidence, laparoscopic conversion of OAGB to RYGB was safe, technically feasible and effective in dealing with late complications of OAGB. Laparoscopic revisional bariatric surgery could be technically challenging and should be done by experienced surgeons in a tertiary center with multidisciplinary team management and individualized approach.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONSENT

Waiver of consent was obtained for this retrospective cohort study.

AUTHORS' CONTRIBUTIONS

All authors are in agreement with the content of the manuscript.

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