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Clinical Evaluation of Fibrin Glue in the Prevention of Anastomotic Leak and Internal Hernia after Laparoscopic Gastric Bypass: Preliminary Results of a Prospective, Randomized Multicenter Trial

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Background: Gastro-jejunal anastomotic leak and internal hernia can be life-threatening complications of laparoscopic Roux-en-Y gastric bypass (LRYGBP), ranging from 0.1-4.3% and from 0.8-4.5% respectively. The safety and efficacy of a fibrin glue (Tissucol®) was assessed when placed around the anastomoses and over the mesenteric openings for prevention of anastomotic leaks and internal hernias after LRYGBP.

Methods: A prospective, randomized, multicenter, clinical trial commenced in January 2004. Patients with BMI 40-59 kg/m^2, aged 21-60 years, undergoing LRYGBP, were randomized into: 1) study group (fibrin glue applied on the gastro-jejunal and jejuno-jejunal anastomoses and the mesenteric openings); 2) control group (no fibrin glue, but suture of the mesenteric openings). 322 patients, 161 for each arm, will be enrolled for an estimated period of 24 months. Sex, age, operative time, time to postoperative oral diet and hospital stay, early and late complications rates are evaluated. An interim evaluation was conducted after 15 months.

Results: To April 2005, 204 patients were randomized: 111 in the control group (mean age 39.0±11.5 years, BMI 46.1±8.2) and 93 in the fibrin glue group (mean age 42.9±11.7 years, BMI 46.9±6.4). There was no mortality or conversion in both groups; no differences in operative time and postoperative hospital stay were recorded. Time to postoperative oral diet was shorter for the fibrin glue group (*P*=0.0044). Neither leaks nor internal hernias have occurred in the fibrin glue group. The incidence of leaks (2 cases, 1.8%) and the overall reoperation rate were higher in the control group (*P*=0.0165).

Conclusion: The preliminary results suggest that Tissucol® application has no adverse effects, is not time-consuming, and may be effective in preventing leaks and internal hernias in morbidly obese patients undergoing LRYGBP.

Key words: Morbid obesity, laparoscopy, gastric bypass, fibrin glue, anastomotic leak, internal hernia

Introduction

Laparoscopic Roux-en-Y gastric bypass (LRYGBP) has gained popularity not only in the U.S.A. but also in Europe as treatment for morbid obesity.[1] The efficacy on long-term weight loss and associated co-morbidities[2] has resulted in LRYGBP being considered as the gold standard for the treatment of morbid obesity. However, LRYGBP can have life-threatening

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complications, as well as anastomotic leaks and internal hernias. Leak can originate from different sources (gastro-jejunal or jejuno-jejunal anastomosis or the staple-line of the isolated gastric pouch or the excluded stomach), but the most common site is the gastro-jejunostomy.[3] The incidence of gastro-jejunal anastomotic leaks ranges from 0.1 to 4.3%,[3] once the learning curve (estimated as 75-100 cases)[4-6] is over. The effects of this leak can be devastating, and require reoperation due to the failure of conservative treatment or due to the gravity of the leakage and prolonged hospitalization in the majority of the cases.[7]

A higher incidence of internal hernia after LRYGBP compared with the open series has been reported[8,9] due to less postoperative intra-abdominal adhesion formation, early mobilization and rapid discharge. Despite standardization of the laparoscopic technique, with closure of all potential mesenteric defects, the possibility of developing internal hernia and bowel obstruction still remains at any time in the postoperative course.

In order to prevent postoperative anastomotic leaks after LRYGBP, different intraoperative techniques have been designed (tension-free anastomosis, hemostasis at the suture-line, reinforcement of the suture-lines).[3] The application of a fibrin sealant on the anastomosis, staple-lines and mesenteric defects has been suggested[7,10-14] (Table 1) and successfully applied. In fact, previous, but non-randomized studies demonstrated the efficacy of the fibrin sealants in prevention of leak after gastric bypass.[7,10,11]

In this study, we sought to assess the safety and efficacy of a fibrin glue (Tissucol®, Baxter AG, Vienna) placed around the anastomoses and over the mesenteric openings, in the prevention of anastomotic leaks and internal hernias after LRYGBP. Fibrin glue is a hemostatic agent derived from human plasma. The agent is designed to reproduce the final steps of the physiological coagulation cascade, to form a stable fibrin clot.

Materials

Study Design

A prospective, randomized, multicenter, clinical trial was designed to assess the safety and efficacy of the licensed fibrin glue (Tissucol®) in the prevention of gastro-jejunal and jejuno-jejunal anastomotic leaks and internal hernias after LRYGBP. An interim evaluation of the results was conducted after 15 months.

Six academic, specialized centers have been involved in this prospective, randomized study: 3 from Rome (Italy), 1 from Turin (Italy), 1 from Pisa (Italy), and 1 from Nice (France). All participating surgeons are beyong the learning curve.[4-6] It was planned to enroll, starting January 1st, 2004, 322 consecutive morbidly obese patients[14] undergoing LRYGBP, randomized in two treatment groups of 161 subjects each: Tissucol® group versus control group. Each center planned to enroll at least 46 patients in an estimated period of 24 months. The randomization is computer elaborated by the coordinating center (Center of Minimally Invasive Treatment of Morbid Obesity, Policlinico "Umberto I", Rome), and is sent by request the same day of surgery. Inclusion and exclusion to the study criteria are reported in Table 2. The following parameters were evaluated: operative time, time to postoperative oral diet, hospital stay, early and late complications. All data is prospectively recorded in a central database.

Table 1. Use of fibrin sealant in bariatric surgery

Author	Year	Fibrin glue	Patients	Type of study
Liu et al[10]	2003	Tisseel®	120	prospective, non-randomized, controlled
Sapala et al[7]	2004	Tisseel® (Baxter Deerfield, IL, U.S.A)	738	prospective, non-randomized, historic control
Nguyen et al[11]	2004	Tisseel®	66	prospective, non-randomized, non-controlled
Lee et al[12]	2004	–	–	review
Papavramidis et al[13]	2004	Beriplast P (Aventis Behring, King of Prussia, PA, U.S.A.)	3	retrospective
Carbajo et al[14]	2005	Tissucol® (Baxter, Vienna & U.S.A)	124	report, retrospective, non-controlled

Table 2. Inclusion and exclusion criteria to the study

Inclusion criteria	Exclusion criteria
BMI 40-59 kg/m^2	Previous bariatric surgery
Age 21-60 years	Conversion to laparotomy
Surgical technique	Concurrent procedures*
Written informed consent	No compliance

*except cholecystectomy

Device Description, Dosage Regimen, Route of Administration

Tissucol® is composed by two distinct vials containing thrombin and calcium chloride (1st vial); fibrinogen, aprotinin, and factor XIII (2nd vial). Once formed, this clot halts blood and aids normal wound healing (Figure 1). The fibrin clot is then completely reabsorbed within days or weeks by the naturally occurring fibrinolytic enzymes. Tissucol® is provided in sterile, ready to use syringes containing 2 or 5 ml of product, individually packaged (Figure 2). The cost of Tissucol® is 142 euros (171$) for the 2-ml kit and 291 euros (352$) for the 5-ml kit. Each syringe is supplied with a disposable cannula for laparoscopic use (length 35 cm, cost 62.5 euros, 75$). A flexible laparoscopic cannula (length 40 cm, cost 21 euros, 25$) is available.

Figure 1. Tissucol® device, application cannula for laparoscopic use.

Figure 2. Tissucol® clot.

Data Collection

Participants filled in each patient's chart information on demographics, operative data (technique, time, conversion, methylene blue test, use of fibrin glue, time to oral diet initiation), postoperative GI contrast study, length of postoperative hospital stay, early and late complications, and follow-up. Data collection and analysis were performed by the same coordinating center.

Surgical Technique

All patients received antithrombotic prophylaxis (low-molecular-weight-heparin) combined with sequential compression devices. An isolated gastric pouch (20 cc) was created, followed by measurement and creation of the 50-cm biliopancreatic limb and 75-150 cm alimentary limb. The gastro-jejunal anastomosis was carried out in three different manners: circular-stapled using the 25-mm CEEA (U.S. Surgical Corporation, Norwalk, CT) with the stapler's anvil placed transorally (Gagner technique), linear-stapled, or 2 layers hand-sewn continuous suture. All gastro-jejunal anastomoses were tested intraoperatively with methylene blue injection through the nasogastric tube. The jejuno-jejunostomy was a side-to-side stapled anastomosis (45x25 mm cartridge, 6 rows) with hand-sewn suture of the enterotomies. The closure of the mesenteric defects between the alimentary limb and the transverse colon and between the two limbs was carried out with non-absorbable sutures. Drainage was left in

place, depending on surgeon choice.

Study group: Step 1 and 2 as in the control group and then closure of the mesenteric defects between the alimentary limb and the transverse colon and between the two limbs with Tissucol®. Fibrin glue was prepared with a 2-ml or 5-ml kit and applied intraoperatively with a laparoscopic double syringe dispensing unit provided in the kit. Furthermore, Tissucol® was applied to cover both anterior and posterior lines of the gastro-jejunal and jejuno-jejunal anastomoses. After application, fibrin sealant was allowed to polymerize for 1-3 minutes before releasing the left hepatic lobe from the retractor. The sealant was not applied over the staple-lines of the isolated gastric pouch or the excluded stomach. The surgical operation without application of Tissucol® (standard closure of the mesenteric defects) was considered as reference treatment. If gallstones were detected preoperatively, patients underwent cholecystectomy at the time of the LRYGBP.

Postoperative Care

Postoperative contrast study (Gastrografin® swallow) was done in all patients (day 1-3). Liquid diet was initiated after the confirmed negative contrast study. Postoperative follow-up schedule consisted in 1st, 3rd and then every 6 months clinical and, when needed, instrumental studies for 3 years. Studies were done in the outpatient department.

Primary End-points of the Study

Recorded was: 1) the incidence of the early complication-free patients at follow-up evaluation, defined as clinical and sub-clinical absence of leaks originating from the gastro-jejunal anastomosis, as ascertained by Gastrografin® swallow on the 1st-3rd postoperative day; 2) occurrence of late complications such as small bowel obstruction due to herniation; 3) presence of adverse effects due to fibrin glue application.

Secondary End-points

Recorded were: 1) time to postoperative oral diet; 2) length of the hospital stay; 3) anastomotic stenosis; 4) treatment of other complications; and 5) excess weight loss.

Statistical Analysis

A sample size of 160 subjects per study arm, without drop-outs, was required in order to have a statistical power of 80% (P=.05), to detect a decrease in rate of LRYGBP complications from 5% to 2%. The primary variable for the effectiveness comparison is the incidence of complication-free subjects. The comparison of the two study arms was based on the Chi-square test for homogeneity (or Fisher's exact test where the cell frequencies were small). An interim evaluation after at least 12 months was planned.

Results

A total of 220 patients have been randomized 15 months after the initiation of the study. Sixteen cases were eliminated because they did not meet the inclusion criteria (Table 2). Thus, 204 patients were included in the study: 111 in the control group (mean age 39.0±11.5 years, mean BMI 46.1±8.2) and 93 in the fibrin glue group (mean age 42.9±11.7, mean BMI 46.9±6.4). Patients' characteristics are reported in Table 3. Mortality and conversion were nil in both groups. The 2 groups were homogeneous for sex and BMI distribution, and no differences for operative time, hospital stay and excess weight loss at 6 and 12 months were recorded. Differences between surgical techniques used in different centers are reported in Table 4. With the use of fibrin sealant, there was no statistically significant increase in operative time, nor any local (anastomosis or mesenteric openings) or general adverse effects (no adhesions, nor infection due to its components). Time to postoperative oral diet was shorter in the fibrin glue

Table 3. Patient characteristics

Characteristics	Tissucol® n=93	Control n=111	*P*
Age (years)	42.9 ± 11.7	39.0 ± 11.6	0.0201
Females/males	73/20	92/19	n.s.
BMI (kg/m^2)	46.9 ± 6.4	46.41± 8.2	n.s.
BMI at 6 months	38 ± 6.5	36.8 ± 5.9	n.s.
BMI at 12 months	29.7 ± 4.7	30.4 ± 5.2	n.s.
Operative time	146 ± 41	135.6 ± 42	n.s.
Time to oral diet	3.1 ± 1.8	3.9 ± 1.6	0.0044
Hospital stay	7.0 ± 1.6	7.0 ± 1.8	n.s.

Table 4. Surgical technique

Surgical technique	Tissucol®	Control
Gastro-jejunal circular-stapled anastomosis	21	41
Gastro-jejunal linear-stapled anastomosis	33	31
Gastro-jejunal manual anastomosis	39	39
Antecolic, antegastric limb	87	96
Antecolic, retrogastric limb	6	15

group (P=0.0044). BMI at 6 and 12 months for both groups is shown in Table 3, with no difference between them. The 2-ml kit was used in 26 patients (27.9%), the 5-ml kit in 36 patients (38.7%), while in 31 patients (33.3%) 2 kits of 2 ml were used.

Neither anastomotic leak, nor internal hernia was recorded in the fibrin glue group. Of the 111 patients in the control group, 2 presented gastro-jejunostomy leak and underwent reoperation. A third leak occurred in the control group from the excluded stomach. In Patient 1 (male, 25-years-old, BMI 40.1 kg/m^2), the 3rd postoperative day contrast study showed leakage from the gastro-jejunal anastomosis, with concomitant bleeding from the anastomotic staple-line that required laparotomy. The defect was repaired with hand-sewn stitches and hemostasis, with no further complications.

Patient 2 (female, 36-years-old, BMI 46 kg/m^2) was discharged after an uneventful LYRGBP and postoperative course. She presented to the emergency room on the 14th postoperative day complaining fever and abdominal pain. At laparotomy (15th postoperative day) leak from the gastro-jejunal anastomosis was identified, and the isolated gastric pouch was resected and a new end-to-side hand-sewn esophago-jejunal anastomosis was created with a Roux-en-Y limb. Even this new anastomosis was complicated by fistula, conservatively treated with full recovery. Two months after reoperation, an anastomotic stricture was diagnosed, and was successfully treated with 3 endoscopic dilations.

Patient 3 (male, 40-years-old, BMI 56.8 kg/m^2), with a negative 5th day contrast study, developed a fistula from the excluded stomach that required laparotomy for suture of the staple-line. The excluded stomach leakage was not considered a primary end-point.

Further specific complications recorded in both groups are reported in Table 5. One intraoperative complication was recorded in one patient (control group) due to trapping the nasogastric tube in the staple-line. Intraoperative bleeding required hemostasis, with no need for conversion, but the postoperative course was complicated by bleeding from the staple-line and pulmonary emboli that required admission to the intensive care unit. One bowel obstruction at the level of the jejuno-jejunal anastomosis was recorded in the control group, and was followed by a laparoscopic reoperation on the 7th postoperative day. Causes of reoperation are reported in Table 6. Overall reoperation rate was higher in the control group (P=0.0165).

Long-term complications included gastro-jejunal anastomotic stenosis (2.2% in the fibrin glue group vs 4.5% in the control group). The mean time to diagnose a gastro-jejunal anastomotic stenosis was 30 days in the fibrin glue group and 51 days in the control group. One gastric pouch-excluded stomach fistula was radiologically diagnosed in the 5th postoperative month in the fibrin glue group. A reoperation is planned.

Discusson

In this study, we showed the preliminary results of the first prospective, randomized, multicenter, clinical trial designed to assess the safety and efficacy of a fibrin glue used around the anastomoses and over the mesenteric openings for the prevention of anastomotic leaks and internal hernias in morbidly obese patients undergoing LRYGBP.

Table 5. Major complications registered in patients undergoing LRYGBP (excepted those studied)

Early complications (<30 days)	**Tissucol® n=93**	**Control n=111**
Pulmonary emboli	0	1
Gastro-jejunal anastomotic bleeding	4	5
Extraluminal bleeding	0	1
Bowel obstruction (kinking limb)	0	1
Jejunal microperforations	0	1
Pleural effusion	0	3
Long-term complications		
Gastro-jejunostomy stenosis	2	5
Gastro-jejunostomy ulcer	1	0
Gastro-gastric fistula	1	0

Table 6. Causes of reoperation registered in patients undergoing LRYGBP

Reoperation for	Tissucol®	Control	*P*
Gastro-jejunal anastomotic leak	0	2	n.s.
Gastric remnant leakage	0	1	n.s.
Gastro-jejunal anastomotic bleeding	0	3	n.s.
Bowel obstruction (no internal hernia)	0	1	n.s.
Jejunal microperforations	0	1	n.s.
Total	**0**	**8**	**0.0165**

Anastomotic leak is the second cause of death (after pulmonary embolus) as a complication of LRYGBP. Internal hernia after LRYGBP determines reoperation in almost all cases.[8,9] In the present study, the rate of these 2 complications in a group of patients undergoing LRYGBP is compared with a group of patients in which the gastro-jejunal and jejuno-jejunal anastomosis was protected with a layer of fibrin glue and the mesenteric defects were closed with the same glue. The interim analysis of the preliminary results (15 months) recorded two gastro-jejunal anastomotic leaks in the control group, while no leak occurred in the Tissucol® group. Both leaks (1.8% from 111 patients) required laparotomy for repair of the anastomotic defect, with prolonged hospital stay (13 days vs mean 7 days). In one case, it was necessary to create a new esophago-jejunal anastomosis, after complete resection of the gastric pouch, which was complicated by stricture 2 months postoperatively that required three endoscopic dilatation sessions. At the moment of the interim analysis, neither jejuno-jejunal anastomotic leak nor internal hernia has been recorded in both groups (204 patients). Leak from the jejuno-jejunal anastomosis is very rare, although described.[11] Internal hernia has a much higher frequency, up to 4.5%.[9] No internal hernia occurred, demonstrating the sealant properties of Tissucol®. The overall rate of reoperation in the control group (for leak, bleeding and bowel obstruction) was statistically higher than in the study group (no reoperation).

In addition to the intraoperative surgical techniques, the use of new products to avoid postoperative complications after LRYGBP has been reported. Staple-line hemorrhage and anastomotic leaks were reduced after reinforcement of the gastric staple-line with non-absorbable bovine pericardial strips.[15,16] Seamguard® bioabsorbable material used as staple-line reinforcement in gastric resections has been shown to potentially prevent hemorrhage and leakage.[17] Another proposed technique is the application of fibrin sealants. Fibrin sealants have been used in various surgical interventions, such as biliary tract,[18] hernia repair and skin grafts,[19,20] repair of perforated peptic ulcer,[21] as well in urologic, cardiovascular and thoracic surgery.[22-24] Besides the certified hemostatic and wound healing capacities, Tissucol® has the property of a fibrin sealant and a decrease in the incidence of leak after LRYGBP has been also reported.[11] Additionally, fibrin glue has been used as endoscopic treatment for postoperative anastomotic leaks.[25] The use of fibrin glue has been recommended in high-risk patients, such as the super-obese (BMI >50 kg/m^2), diabetics, males, patients on low-dose steroids, patients with obstructive sleep apnea syndrome (OSAS), and revisional bariatric surgery. The initiation of a laparoscopic gastric bypass experience has been suggested as an additional indication for the use of glue.[10] Also, where methylene blue or air tests have been positive or in the presence of ischemia or tension at the gastro-jejunal anastomosis, the use of a fibrin sealant to prevent postoperative leaks has been advocated.[11] The cost-effectiveness of the use of a fibrin sealant in 99 non-complicated patients undergoing gastric bypass resulted in less cost than a single leak complication with reoperation and intensive care unit treatment.[3,11]

Our preliminary results suggest that Tissucol® may be an effective suture tool in the closure of the mesenteric defects to prevent internal hernia. The application of fibrin glue on the various gastro-jejunal anastomoses (hand-sewn, circular or linear stapled) appears to be useful in the prevention of anastomotic leaks. The intraoperative use of the fibrin glue did not prolong the overall operative time and seems not to interfere with the normal postoperative course (no stenosis, no infection).

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