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Multicenter Randomized Study of Obesity Treatment with Minimally Invasive Injection of Hyaluronic Acid Versus and Combined with Intra-gastric Balloon

Jerome Dargent¹ · François Mion² · Vianna Costil³ · René Ecochard² ·
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Abstract

Background Research into minimally invasive techniques is worthwhile for greater acceptance in bariatric surgery, a useful first step being to evaluate the combination of these with current procedures. We suggest that intra-gastric balloon (IGB) can be performed with hyaluronic acid (HA) injections at the level of the gastroesophageal junction.

Methods A submucosal restriction is created by circular injection of an absorbable material within a defined area based on endoscopic anatomy. We included 101 patients in a prospective multicenter randomized trial, with average body mass index (BMI) 33.4 (range 27–44), treated from April 2010 to April 2012 by IGB and/or HA injection, sequentially, and followed for two more years. Patients were divided into group 1 (IGB alone), group 2 (IGB followed by HA at IGB removal, at 6 months), and group 3 (HA and IGB at 6 months).

Results BMI loss at 6 months was inferior in the HA group (32 patients) compared with the IGB groups (68 patients) (2.1

± 0.4 versus 3.4 ± 0.3 , $p < 0.05$). The efficacy of IGB alone compared with combined treatments (groups 2 and 3) was significantly inferior at 18 months only, but the impact of the treatment sequence (HA before or after IGB) on BMI loss was not statistically significant, although in favor of HA first.

Conclusions This study did not demonstrate the efficacy of HA injections as an obesity treatment.

Keywords Obesity classes I–III · Minimally invasive · Endoscopy · Intra-gastric balloon · Hyaluronic acid injection

Introduction

Surgical treatment of morbid obesity has improved markedly since the introduction of laparoscopic procedures. Laparoscopic adjustable gastric banding (LAGB) is a simple operation, but prosthetic complications occur [1, 2]; laparoscopic sleeve gastrectomy (LSG) [3] and gastric bypass [4] are more complex operations but show good results.

No single procedure can benefit all morbidly obese patients, even if one claims that bariatric surgery offers the only long-term solution for class III obesity [5]. The majority of obese people fear the surgical risks and complications, indicating a need to diversify the medical response to obesity [6]. Clinical research should also be oriented toward less invasive procedures that could be widely accepted, e.g., through natural orifices (endoscopy). While desirable, the idea of long-lasting and “simple” minimally invasive procedures is not likely to be promoted in the near future. Although sometimes suggested as stand-alone procedures, these techniques may rather be viewed as preliminary steps before typical surgical procedures or bridges to them. Typical bariatric surgical

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procedures also address class I obesity in select cases with comorbidities, as explained in a recent International Federation for the Surgery of Obesity position statement [7], while endoscopic therapies have not demonstrated long-term efficacy.

Minimally invasive procedures via natural orifice (upper GI endoscopy) are most often performed on an outpatient basis, with or without general anesthesia. Currently, intragastric balloon (IGB) is the only minimally invasive routinely performed bariatric procedure. It is a temporary method and is indicated for rapid weight loss before surgery [8] or for obesity classes I–II [9].

Some endoscopic techniques are proposed primarily in obese patients, although only on an investigational basis currently [10, 11], or combined with bariatric procedures (e.g., after gastric bypass). Endoscopic therapy for gastroesophageal reflux disease is also an interesting model for our purpose [12–14]. Food intake could also be significantly restricted by injecting material beneath the gastroesophageal junction (GEJ). Collagen was tested previously in humans to treat gastroesophageal reflux [15], and a collagen ring has also been used experimentally as an adjuvant to vertical banded gastroplasty [16]. Recently, the endoscopic intragastric injection of botulinum toxin A has been used for the treatment of obesity to impair gastric motility, but the results of a clinical trial by Mittermair et al. are inconclusive [17].

The goal of our study was to evaluate the efficacy of injections at the level of the GEJ of an absorbable filling agent similar to collagen—hyaluronic acid (HA)—as an obesity treatment. The main objective was to assess the effect on weight loss of the injection on its own versus IGB, and the secondary objective was to assess the potential benefit of the combination HA/IGB and vice versa versus IGB alone.

Methods

Research Protocol

The endoscopic anatomy of the GEJ shows that the place for injection, beneath the Z line, cannot be correctly defined using direct vision, more evidently in cases of hiatal hernia, commonly observed in obese patients. However, retrovision allows a panoramic view of a distinct circular gastric fold of approximately 4 cm circumference, an area internally matching the area above a hypothetical externally placed LAGB. This area can be assessed for instance by the spherical balloon of the Allergan™ calibration tube (Allergan Inc.), which contains 15 cm³ of air, and is routinely used when placing a LAGB. This location has actually been used in clinical experiments in humans (trans-oral endoscopic restrictive

implant system, Barosense Inc., Redwood City, CA, USA, unpublished data; Hour Glass Technologies Inc., Redwood City, CA, USA, unpublished data).

The appropriate HA injection technique and depth have been satisfactorily defined from the Enteryx™ (Boston Scientific) and similar procedures (submucosal, muscular layers of the GEJ) [13]. We suggest using a kit that is placed within the endoscope.

Prior to the clinical trial (2008–2009), HA injection was tested in human cadavers, then in three pigs, and finally in humans: four patients underwent LSG at the same time as the HA injection, following ethics committee approval. HA was eventually preferred as a bulking material because it is genetically bioengineered, nonallergenic, and currently widely used in cosmetic surgery; the device we implanted is also used for knee arthritis (Sinovial™, Genévrier, France).

The current clinical protocol was approved by an ethics committee (Comité de Protection des Personnes (CPP), Sud-Est III, France) and national health authorities (Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM)). The study was designed as a noninferiority test of HA injection versus IGB at 6 months. Statistically and in order to prove noninferiority, 46 patients per group were necessary (total 138 patients), based on a weight loss of 12 % at 6 months and an acceptable clinical nonsignificance of 17 % between groups.

Patients

The inclusion criteria were male and female patients, age 18–65 years, and body mass index (BMI) >27. Patients with a history of gastric surgery, gastric or duodenal ulcer, or active *Helicobacter pylori* infection were excluded. The trial was a prospective, randomized, controlled study, comparing the effects of HA injection, IGB, and the combination of both sequentially.

Patients were randomly allocated to one of the three treatment sequences at the time of inclusion: group 1 (IGB implanted at day 0 (D0), removed at 6 months), group 2 (IGB implanted at D0, removed at 6 months with HA injection immediately after IGB removal), and group 3 (HA injection at D0, IGB at 6 months, IGB removal at 12 months). The primary endpoints were the safety and weight loss efficacy of the HA injection, IGB placement, and the combination of both, at 6, 12, 18, and 24 months from the initial HA injection or IGB placement. Weight, BMI, comorbidities, and complications were recorded at baseline and at these intervals. The secondary endpoints were the resolution of comorbidities and improved health-related quality of life, evaluated by the Short Form-12 (SF-12) questionnaire (v 2.0).

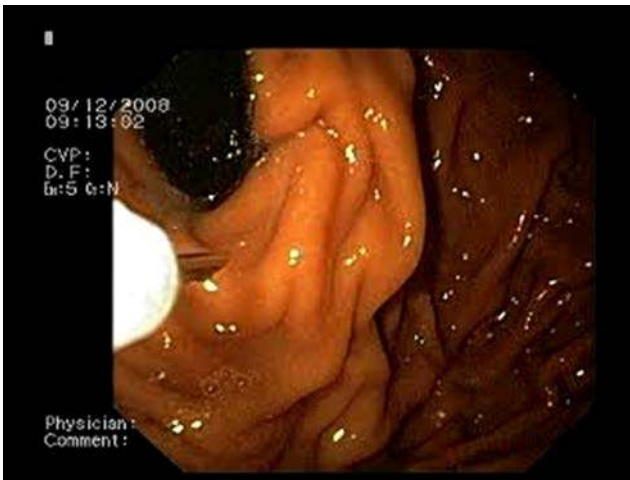


Fig. 1 Gastroesophageal junction before HA injection

Statistics

Statistical analyses were performed using Student's *t* test for numerical variables and χ^2 test for categorical variables. The BMI evolution over time was compared between the groups using ANOVA for repeated measurements (software: R 3.1.1, The Foundation for Statistical Computing, Vienna, Austria (Vienna University of Economics and Business)). $p < 0.05$ was considered significant.

Procedures

IGB placement and HA injection were performed under unconscious sedation, and IGB extraction was performed under deep sedation with tracheal intubation 6 months after balloon placement. Proton pump inhibitors were given for 3 weeks after IGB implantation. The Orbera™ system (Allergan Inc., Irvine, CA, USA) water-filled

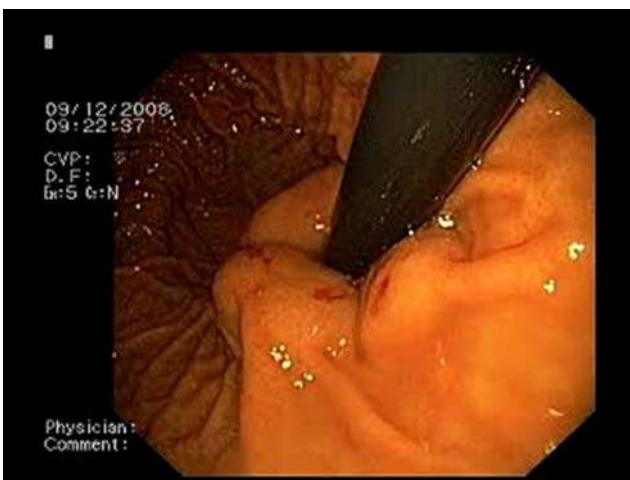


Fig. 2 HA injection

Table 1 Demographics

Sex	93 females, 8 males
Age	36.8 years (19–66)
Weight	Mean value 91.1 kg (SD=13.6, range 70–148)
Excess weight	34.2 kg (17–68)
BMI	Mean value 34.1 (SD=3.7, range 27–48.3)

balloon was used in all cases and filled with 500 ml isotonic saline. The Orbera™ is CE-approved for patients with BMI >27. Four milliliters of HA (16 mg in 2 ml of KCl solution, Sinovial™, Genévrier, France) was injected at four locations beneath the GEJ, under endoscopic vision with the endoscope retroflexed in the stomach (Figs. 1 and 2, before and after injection). The operators were Jerome Dargent and Frédéric Pontette in center 1 (Polyclinique Lyon-Nord, 69140 Rillieux), François Mion in center 2 (Hospices Civils de Lyon, Hôpital E. Herriot, 69437 Lyon), and Vianna Costil in center 3 (Clinique du Trocadéro, 75016 Paris). Each center had individually approved the protocol.

Results

Demographics

A total of 101 patients (93 female and 8 male) were included from April 2010 to May 2012: 89 in center 1 (Rillieux), 10 in center 2 (Lyon), and 2 in center 3 (Paris). The mean age was 36.8 years (range 18–66), and mean BMI 33.4 (range 27–44) (Table 1). Comorbidities were present in 34 patients (33.7 %) (Table 2), and there were no differences in age, sex, and BMI among the three groups.

Safety and Adverse Events

The HA injection procedure was uneventful in all primary cases (group 3). When the balloon was implanted secondarily (6 months after HA), we found no abnormality at the

Table 2 Comorbidities

	Number (%)
Osteoarticular	15 (14.8)
Cardiovascular	10 (9.9)
Respiratory	6 (5.9)
Hepatic steatosis	2 (1.9)
Dyslipidemia	10 (9.9)
Type 2 diabetes	4 (3.9)
Depression	4 (3.9)

Table 3 Weight loss %, mean (standard error of mean, SEM), over time in each group

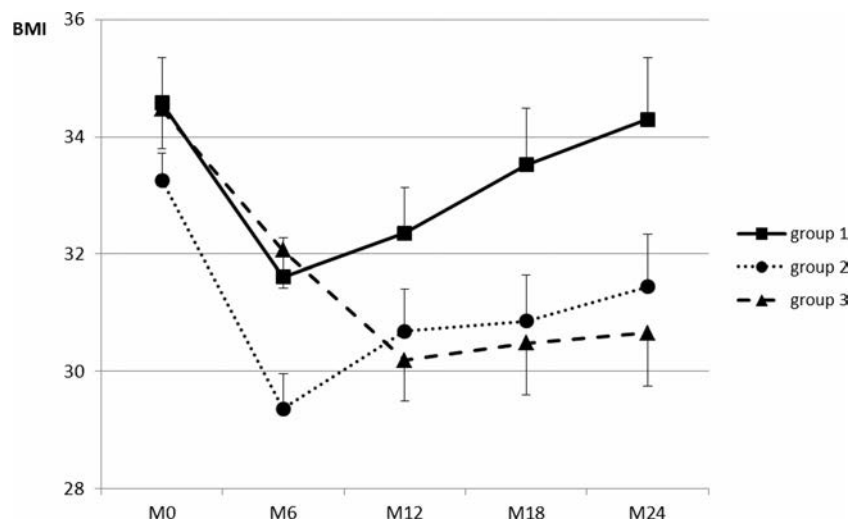
	6 months	12 months	18 months	24 months
Group 1	(N=34) 8 (1.6)	(N=30) 6.5 (1.1)	(N=24) 3.2 (1.0)	(N=22) 3.3 (1.2)
Group 2	(N=34) 10.8 (1.2)	(N=29) 8.8 (1.8)	(N=26) 6.9 (1.8)	(N=24) 6.6 (1.8)
Group 3	(N=32) 5.8 (1.1)	(N=29) 11.1 (2.7)	(N=28) 10.5 (1.8)	(N=26) 9.3 (1.8)

Group 1: IGB alone; group 2: IGB followed by HA injection; group 3: HA injection followed by IGB. No statistical difference between groups at any time point

GEJ. Biopsies were performed in five cases, revealing no adverse effect. Likewise, endoscopy at the time of balloon removal in group 3, i.e., at 12 months, showed no abnormality. One major complication occurred in a group 2 patient (HA injection at the time of balloon removal) as a left hepatic abscess. The patient was hospitalized for 7 days, after having a radiologically placed drain for 3 months, with antibiotics and anticoagulants because of concurrent phlebitis of the left hepatic vein. She recovered fully after 4 months, with normal CT scan results. HA injection had to be postponed three times in group 2 patients because of food residues at the junction.

We encountered IGB side effects and complications that were similar to those described in the literature: 30 % experienced vomiting, abdominal pain, and/or reflux, but less frequently when the IGB was placed after HA injection (group 3, 21 %). Nine patients were readmitted during the first postoperative week (2–4 days) after IGB for intravenous rehydration and medical therapy. In five patients in groups 1 and 2 and 1 patient in group 3, the balloon had to be removed before 6 months because of food intolerance and/or abdominal pain.

Fig. 3 Evolution of BMI over time according to the three treatment sequences (group 1: IGB alone; group 2: IGB followed by HA injection; group 3: HA injection followed by IGB). Dots indicate the mean BMI at each time point, and the vertical bars the SEM



Follow-up

Data were missing or excluded for 26 patients at 24 months. Two cases were excluded before 6 months after inclusion (pregnancy), 12 cases between 6 and 12 months (1 LAGB, 1 hepatic abscess, 10 lost to follow-up), 7 cases between 12 and 18 months (2 LAGB, 5 lost to follow-up), and 5 cases between 18 and 24 months (2 LSG, 1 additional IGB, 2 lost to follow-up). These patients were excluded from analysis after protocol deviation.

Weight Loss

Total weight loss (WL %) according to each group is presented in Table 3, and BMI loss over time in Fig. 3. BMI loss at 6 months was clearly inferior in the HA group (31 patients) compared with the IGB groups (68 patients) (2.1 ± 0.4 versus 3.4 ± 0.3 , $p=0.0071$). Nonresponder patients, defined as having less than 5 % WL in 6 months, were 16/31 (51.6 %) in group 3 versus 19/68 (27.9 %) in groups 1 and 2. The global efficacy in terms of BMI loss with IGB alone compared with the combined treatments (groups 2 and 3) was significantly inferior at 18 months only (Table 4). The impact of the treatment sequence (HA before or after IGB) on BMI loss was not statistically significant at any time point (Table 5). At 2 years, weight regain above baseline was observed in 11 patients, with some having surgery shortly after the end of our study.

Quality of Life

The mental and physical dimensions of the SF-12 questionnaires were similar in the three groups before treatment, and the evolution of the two dimensions was similar in each group (data not shown).

Table 4 Global efficacy (BMI loss, mean±SEM) of IGB alone versus combined treatment

	M12	M18	M24
Group 1	(N=30) -2.1 (0.5)	(N=24) -1.0 (0.7)	(N=22) -0.8 (0.8)
Groups 2 and 3	(N=58) -3.1 (0.4)	(N=54) -2.8 (0.5)	(N=50) -2.3 (0.5)
<i>p</i> value	0.120	0.04*	0.099

Group 1: IGB alone; group 2: IGB followed by HA injection; group 3: HA injection followed by IGB

**p*<0.05 difference, ANOVA test

Evolution of Comorbidities

Related diseases were improved in 16 patients, equal in 17, and worsened in 1 of 34 patients.

Discussion

Our main objective was to evaluate the impact of a single injection of HA versus IGB at 6 months. To our knowledge, HA injection at the GEJ had not been described previously as an obesity treatment nor in sequential mode with IGB or any other bariatric procedure. O'Connor and Lehman discussed collagen injection for gastroesophageal reflux treatment using the endoscopic placement of collagen at the lower esophageal sphincter [15]. The study included 10 patients and repeated collagen injections over 1 year, without adverse events. In combination with LSG during a preliminary stage to the current study, we concluded that the procedure was feasible, simple (10 min), and reproducible and added no risk to LSG (unpublished personal data).

Our results showed that HA injection was inefficient comparatively to IGB to induce weight loss, possibly the result of the rather low injection volume (4 ml) and the rather low viscosity of the HA that we used. Regarding the efficacy of combined treatments using HA, our results are in favor of this approach compared with IGB alone, although the difference in BMI loss was

significant only at 18 months. A longer duration of restriction (beyond 6 months) could be achieved by balloons claiming a longer period of implantation, e.g., Spatz™ balloon (Spatz FGIA Inc., Jericho, NY, USA) [18], or with consecutively repeated IGB as advocated by Genco et al. [19, 20].

The efficacy of such devices is believed to decrease over time, increasing the interest in treating with two different device types, provided the sequence remains minimally invasive. Perhaps the fact that ghrelin secretion is not diminished with IGB explains the difficulty in ensuring weight maintenance after balloon removal [21].

Combination of HA and IGB

Combined endoscopic procedures, as well as successive IGB, increase the number of procedures with anesthesia over time and possibly explain the additional weight loss during sequential treatments. Group 2 (IGB followed by HA injection) was an attractive concept but was irrelevant in the end: the GEJ at the time of balloon removal was often inflamed, and therefore, the injection was more difficult and barely efficient. The severe complication observed (hepatic abscess) in this group led us not to recommend this sequence. Endoscopic injections have been performed for years with various materials in order to treat esophageal varicosae or esophageal motility disorders (e.g., botulinum toxin): the risk of transperitoneal infection is very low but not nil [22] and must be taken into consideration for any further trial involving injections at the level of the GEJ.

Differences Between Our Series and the Literature

Weight loss after IGB has been analyzed in a meta-analysis by Imaz et al. [23], with a mean weight loss at 6 months of 14.4 kg (range 12–17 kg), WL of 12.2 % (range 10–14 %), and BMI loss of 32.1 % (range 26.9–37.2 %). The mean BMI in our series was fairly low compared with other series. IGB is not reimbursed in France, whereas eligible patients with BMI >40 and >35 with comorbidities are reimbursed if they undergo surgery. We included a real-life component in our study, and instead of promoting a low-calorie diet, diet advice was provided, and physical exercise encouraged, but with no

Table 5 Global, early, and late efficacy; BMI loss; and mean (SEM) of treatment sequences: comparison of BMI loss between groups 2 (IGB followed by HA) and 3 (HA followed by IGB)

BMI loss	M12-D0	M18-D0	M24-D0	M18-M12	M24-M12
Group 2	(N=29) -2.6 (0.6)	(N=26) -2.0 (0.7)	(N=24) -1.7 (0.7)	(N=26) +0.7 (0.4)	(N=24) +1.2 (0.5)
Group 3	(N=29) -3.6 (0.6)	(N=28) -3.5 (0.7)	(N=26) -2.9 (0.7)	(N=28) +0.3 (0.4)	(N=26) +0.8 (0.5)
<i>p</i> value	0.19	0.13	0.25	0.47	0.56

oversight beyond the recommendation of monthly supervision. This can be considered a limitation compared with other balloon studies with a strict diet [24]; however, such diets may achieve the same amount of weight loss on a short-term basis and prevent us from drawing relevant conclusions.

Conclusion

Our randomized study has demonstrated that HA injection is not as efficient as IGB in terms of weight loss. While most surgical procedures offer long-term weight loss at the cost of a balanced risk/benefit ratio, simpler devices should not be implemented on a large scale outside of clinical trials and should not be favored unless they prove efficient on the same basis [25, 26].

Ethical Approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

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