

Adjustable intragastric balloon for treatment of obesity: a multicentre, open-label, randomised clinical trial



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Summary

Background Intragastric balloons are anatomy-preserving, minimally invasive obesity therapies. Enhanced tolerance and durability could help broaden clinical adoption. We investigated the safety and efficacy of an adjustable intragastric balloon (aIGB) in adults with obesity.

Methods In this prospective, multicentre, open-label, randomised clinical trial done at seven US sites, adults aged 22–65 years with obesity were randomly assigned (2:1) to aIGB with lifestyle intervention or lifestyle intervention alone (control) for 32 weeks. Balloon volume could be increased to facilitate weight loss or decreased for tolerability. Coprimary endpoints included mean percentage total bodyweight loss and responder rate ($\geq 5\%$ total bodyweight loss) at 32 weeks. We used a multiple imputed intention-to-treat population analysis. This study was registered with ClinicalTrials.gov, NCT02812160.

Findings Between Aug 9, 2016, and Dec 7, 2018, we randomly assigned 288 patients to aIGB ($n=187$ [65%]) or control ($n=101$ [35%]) groups. Mean total bodyweight loss at 32 weeks was 15.0% (95% CI 13.9 – 16.1) in the aIGB group versus 3.3% (2.0 – 4.6) in the control group ($p<0.0001$). Clinical response was observed in 171 (92%) patients in the aIGB group. Adjustments to the aIGB occurred in 145 (80%) patients for weight loss plateau or intolerance. Upward volume adjustment facilitated an additional mean 5.2% (4.5 – 5.8) total bodyweight loss. Downward volume adjustment allowed 21 (75%) patients in the aIGB group to complete the full duration of therapy. Intolerance caused early removal of the device in 31 (17%) patients. No micronutrient deficiencies were observed in the aIGB cohort. Device-related serious adverse events were observed in seven (4%) patients, without any deaths.

Interpretation When aIGB was combined with lifestyle modification, significant weight loss was achieved and maintained for 6 months following removal. Balloon volume adjustability permitted individualised therapy, maximising weight loss and tolerance.

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Introduction

Obesity is a disease with an overwhelming negative impact on human health. By 2030, approximately one in two US adults will have obesity, with one in four having severe disease.¹ Obesity's involvement in multiple chronic conditions, including cardiovascular disease, type 2 diabetes, chronic joint disease, obstructive sleep apnoea, and malignancy, causes substantial public health and economic burden.

Behavioural changes to reduce obesity exhibit low durability and patient compliance.² Pharmacological therapies were previously hampered by intolerance, cost, and, given their targeted mechanism within redundant evolutionary pathways defending bodyweight, attenuated response.^{3,4} New treatments using GLP-1 agonists or in combination with other agents such as amylin analogues have shown promise in inducing weight loss in conjunction with lifestyle modification, with trials showing total bodyweight loss ranging between 8% and 16%.^{5–8} However, when the drug is discontinued,

weight gain recurs, necessitating long-term drug dependence and cost.⁹ Bariatric surgery, although durable, is limited by its invasiveness, expense, long-term risks, and patients' acceptance.¹⁰ Moreover, in patients with longer life expectancy, enthusiasm for surgery is quelled by concerns regarding long-term nutrient deficiencies and need for invasive revisions. Additionally, bariatric surgery only reaches around 1% of eligible patients and is not considered for most patients with class I and II obesity without comorbidity.¹¹

An opportunity exists for minimally invasive, anatomy-preserving endoscopic therapies to address widening treatment gaps for obesity and its comorbidities. Intragastric balloons (IGBs) are space-occupying devices endoscopically placed into the stomach to alter appetite. Several IGBs are available worldwide and, although they vary in volume and contour, IGBs generally remain in place for 6 months, facilitating approximately 7.1–10.7% weight loss.¹² Nevertheless, IGBs are limited by gastrointestinal intolerance, reduced efficacy after

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Research in context

Evidence before this study

We searched PubMed from inception to Sept 1, 2021, for publications in English, investigating trends in obesity, its metabolic burden, and available therapeutics, as well as those investigating the effectiveness of endoscopic bariatric treatments, especially those with adjustability features. We used the keywords “weight loss”, “intra-gastric balloons”, “endoscopic obesity treatments”, “bariatric endoscopy”, and “nonsurgical obesity management”. We searched for randomised clinical trials (RCTs) and observational studies, and reviewed important older publications, whether highly regarded or highly referenced in this field. Additionally, we did an individual search of the reference lists of identified publications. A formal systematic review was not conducted for this portion. Obesity and its metabolic burden have been growing unabated with few interventions that increase patient access, engage the patient in a lifelong treatment programme, and ultimately improve the disease burden on health care. Although the number of bariatric surgical interventions is increasing, this increase has not matched the disease burden. This schism promoted the development and investigation of endoscopic bariatric and metabolic therapies. We found no large RCT exploring adjustable intra-gastric devices.

Added value of this study

We report the use of an adjustable intra-gastric balloon (aIGB) and lifestyle modification to treat patients with obesity.

Patients treated using the aIGB had 15.0% total bodyweight loss at 32 weeks, compared with 3.3% for patients in the group receiving lifestyle modification alone. Patients undergoing upward titration of balloon volume because of weight loss plateau lost an additional 5.2% total bodyweight at 32 weeks. Furthermore, accommodative symptoms associated with balloon placement were mitigated in 75% of patients, preventing early removal. Improvement in several obesity-related comorbidities was also observed with this device. Patients receiving the aIGB were able to maintain this weight loss 6 months after balloon removal.

Implications of all the available evidence

An evolving framework of obesity management is an initial weight loss phase sufficient to meaningfully engage patients and improve obesity-related comorbidities, followed by a weight maintenance phase using various interventions, including obesity pharmacotherapies. The aIGB is an anatomy-preserving, novel, safe, and effective weight loss tool that can fit such management and increase access for patients with obesity; thus, augmenting and filling the obesity management gap between lifestyle, pharmacological, and surgical intervention to include endoscopic options.

3 months, limited duration of implantation, and weight regain after balloon removal if not combined with a long-term weight loss maintenance strategy.¹²

The adjustable IGB (aIGB) is a, silicone IGB filled with saline and 1% methylene blue intended for treatment of obesity in those who have not achieved and maintained weight loss in a supervised weight-control programme. This aIGB aims to fulfil standards for IGBs (smooth balloon surface, fluid-filled, adjustable, and containing radio-opaque markers), which were proposed over four decades ago by the comprehensive workshop at Tarpon Springs, FL, USA, on endoscopic therapy for weight loss.¹³ The unique capability to endoscopically increase IGB volume to augment treatment effect and decrease IGB volume to mitigate intolerance is thought to enhance efficacy and prolong therapy duration.

We aimed to investigate safety, efficacy, and utility of the aIGB as an adjunct therapy for obesity in patients with class I and II obesity.

Methods

Study design and participants

In this prospective, open-label, multicentre, randomised clinical trial, we enrolled patients at seven sites in the USA. Inclusion criteria were age 22–65 years; body-mass index (BMI) 30 kg/m² or greater and less than 40 kg/m², with BMI at least 30 kg/m² for at least the

preceding 2 years; history of unsuccessful non-surgical weight loss methods; residence within a reasonable distance from the investigation site; willingness to comply with dietary restrictions required by the procedure; and ability to follow protocol requirements and provide informed consent. Major exclusion criteria included prior gastrointestinal surgery, inflammatory conditions of the gastrointestinal tract including oesophagitis and hiatal hernia greater than 2 cm, and gastroparesis. Full exclusion criteria are listed in the appendix (p 2).

This study was done under a US Food and Drug Administration (FDA) Investigational Device Exemption (IDE G160061), approved on July 29, 2016, in compliance with all FDA regulations, and was registered with Clinicaltrials.gov, NCT02812160. Written informed consent was obtained from participants and each site received institutional review board approval.

Randomisation and masking

Study schematic is shown in the appendix (p 4). Patients were randomly assigned to receive aIGB (Spatz FGIA, Great Neck, NY, USA) plus dietary and exercise counselling or dietary and exercise counselling alone for 32 weeks, with a 2:1 allocation using variable block randomisation, stratified by treatment centre and BMI (<35 kg/m² vs ≥35 kg/m²). The randomisation schedule

See Online for appendix

was created by a study statistician (who was not further involved in the study) and remained confidential. Given the nature of this device and accommodative symptoms following implantation, in conjunction with the US FDA request, masking of patients was deemed infeasible. Patients were instructed to conceal their allocation to weighing personnel and other study participants. Study personnel ascertaining outcomes were masked to treatment allocation of patients.

Procedures

The aIGB was implanted on day 0 via esophagogastroduodenoscopy (EGD) under conscious or monitored anaesthesia sedation, after overnight fasting. Standard EGD was done to rule out contraindications. The aIGB was implanted at an initial volume of 400 mL (patient height <162.56 cm, with gastro-oesophageal reflux disease), 450 mL (height <162.56 cm, without gastro-oesophageal reflux disease), 500 mL (height ≥162.56 cm, with gastro-oesophageal reflux disease), or 550 mL (height ≥162.56 cm, without gastro-oesophageal reflux disease).

All patients followed a 1000–1200 kcal/day diet during the study. Diet plans were reviewed with each patient and adjusted as needed. The exercise plan had three stages that were phased in over the 32-week follow-up period. Full details of diet and exercise plan and weight measurement procedures are in the appendix (pp 15–16). At the end of 32 weeks, the aIGB was removed and patients were followed up for another 24 weeks.

aIGB volume was adjusted according to three different scenarios (appendix p 4). On day 0, aIGB patients received an initial volume that was based on height and history of gastro-oesophageal reflux disease. This volume could be increased by 250 mL if the first 2 weeks did not show treatment effect, or decreased by 100–150 mL (to a minimum volume of 300 mL) for symptoms of intolerance. At 18 weeks (plus or minus 4 weeks), patients meeting prespecified criteria (did not reach goal weight, did not have gastro-oesophageal reflux disease or peptic symptoms, and did not have oesophagitis or erosive gastritis on endoscopy in the first 18 weeks) could undergo additional endoscopic adjustment procedure (to a maximum of 1000 mL) to induce greater weight loss.

Outcomes

The first coprimary endpoint was percentage total bodyweight loss, with clinical success defined a priori in the aIGB group as total bodyweight loss exceeding 4.5% of the mean total bodyweight loss of the control group at 32 weeks. Total bodyweight loss was defined as day-0 weight minus blinded weight at balloon extraction, divided by day-0 weight, multiplied by 100. The second coprimary endpoint was clinical responder rate, defined a priori as achieving at least 5% total bodyweight loss at 32 weeks. Secondary endpoints were (1) short-term weight loss maintenance, defined as maintenance of 40% of total bodyweight loss at 6 months after device removal,

with success specified a priori as achieving weight loss maintenance of at least 50% of the aIGB group; and (2) excess bodyweight loss, with success specified a priori as at least 25% excess body weight loss at 32 weeks. Weight loss maintenance was calculated as: (day-0 weight–weight 6 months after removal)/(day-0 weight–weight on removal visit). Excess bodyweight loss was calculated using BMI of 25 kg/m² as ideal. Laboratory assessment was done at baseline and 36 weeks. The incidence, frequency, and severity of adverse events related to treatment with the device were reported, with no prespecified safety endpoints. A serious adverse event was defined as life-threatening, requiring hospitalisation, resulting in persistent or significant disability, associated with a congenital anomaly or birth defect, or resulting in death. All adverse events were adjudicated by a centralised data safety and monitoring board. Protocol deviations in this study are highlighted in the consort flow diagram and mostly related to out of window visits without impacting primary or secondary endpoints assertion.

Statistical analysis

True population mean percentage total bodyweight loss in the control group was assumed to be 3.3% on the basis of previous trials of other non-adjustable IGBs.¹⁴ SD of percentage total bodyweight loss was assumed to be approximately 6.6% on the basis of previous data.¹⁴ With these two assumptions, and a true population mean total bodyweight loss in the aIGB group of 10.3%, a total sample size of 240 patients randomly assigned 2:1 (160 in the aIGB group and 80 in the control group) would provide 80% power to show superiority of 4.5% total bodyweight loss over the control group at a one-sided significance of 2.5%. We accounted for a potential dropout rate of 15%.

Primary analysis was done in the intention-to-treat (ITT) population, excluding patients who did not receive IGB implantation because of a contraindication observed on initial endoscopy. ITT analysis was done on a multiple-imputed dataset of blinded weights at week 32. The multiple imputation model included baseline bodyweight, baseline BMI, sex, study centre, treatment group, and all non-missing bodyweights until week 32. Efficacy analysis of the per-protocol population was done on a non-imputed dataset of blinded weights at the aIGB extraction visit (week 32 or an unscheduled visit) and a non-imputed dataset of blinded weights at the end of the 6-month follow-up after removal. The per-protocol population included all ITT-population patients except those with deviations that included the following: did not meet inclusion baseline BMI (≥30 kg/m² and <40 kg/m²); did not receive the intervention of the group to which the patient was randomly assigned; early device removal or early discontinuation from control group; more than three missed or substantially out-of-window visits before week 32; and non-compliance with the device volume adjustment requirements of the study protocol.

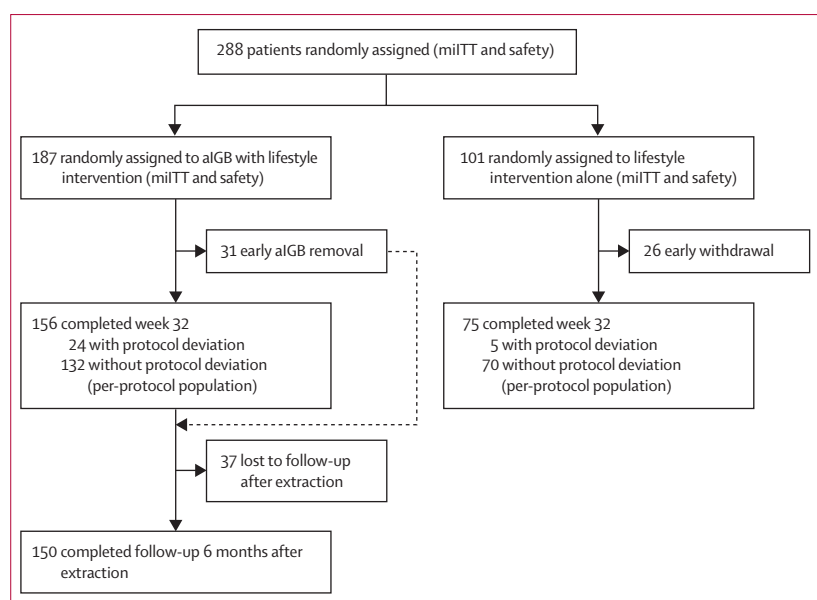


Figure 1: Trial profile

Early balloon removal indicates removal before week 32 and early withdrawal indicates withdrawal of consent by control patients before week 32. aIGB=adjustable intragastric balloon. miITT=multiple imputed intention-to-treat.

Total bodyweight loss was analysed by an ANCOVA that included the effects of treatment group, study centre, baseline BMI group ($<35 \text{ kg/m}^2$ vs $\geq 35 \text{ kg/m}^2$), and patient's sex as covariates. Parameter estimates from the five imputations were used to estimate a one-sided lower 97.5% confidence bound on the difference in mean total bodyweight loss (aIGB mean minus control mean). If this lower confidence bound exceeded the super-superiority margin of 4.5%, the aIGB was deemed to have super-superiority over the control group in total bodyweight loss. Clinical responder rates were analysed using the same five imputed datasets created for testing the first primary endpoint but using only the data from patients in the active treatment group. The estimated proportion of patients with at least a 5% total bodyweight loss at week 32, along with their associated variance, from each dataset was combined using Rubin's method to estimate the overall proportion and its variance. This proportion and its variance were then used to estimate the one-sided lower 97.5% confidence bound on the proportion of patients with at least a 5% total bodyweight loss at week 32. If this lower confidence bound exceeded 50%, the aIGB met its second primary endpoint. A significance level of 0.025 was used for testing of the coprimary outcomes as recommended by the US FDA to ensure study conclusions supported regulatory decisions.

Except for cholesterol, a paired *t* test was used to compare screening versus week-36 laboratory results in the aIGB group. Screening versus week-36 cholesterol results were compared by fitting a repeated measure mixed model with factors for visit and increased number or dose of cholesterol-lowering medications.

Systolic and diastolic blood pressure on the last visit (defined as last visit for control patients and balloon removal visit for aIGB patients) were compared between groups using an ANCOVA with factors for the group and increased number or dose of anti-hypertensive medications and a covariate for the screening blood pressure. All analyses were done with SAS (version 9.4).

Role of the funding source

Study funding and design was by Spatz Medical, with US FDA guidance and regulatory approval of this device. Spatz Medical had no role in patient recruitment, data collection, data analysis, data interpretation, or manuscript writing. Individual site investigators controlled study conduct, and each site underwent multiple audits by an independent monitoring agency.

Results

Between Aug 9, 2016, and Dec 7, 2018, we randomly assigned 288 patients either to aIGB ($n=187$ [65%]) or control ($n=101$ [35%]; figure 1). 17 (8%) of 205 intervention patients were deemed ineligible during balloon implantation endoscopy and classified as screen failures. One (<1%) withdrew consent before endoscopy and was classified as early termination during screening. Baseline patient characteristics of the multiple imputed ITT (miITT) population are shown in table 1. Patients in the aIGB group had a mean baseline age of 44.4 years (SD 8.9), were 87% female, 13% male, with a mean BMI of 35.8 kg/m^2 (2.6). Control patients had a mean baseline age of 44.0 years (8.9), were 89% female, 11% male, with a mean BMI of 35.8 kg/m^2 (2.7). 156 (83%) patients in the aIGB group completed the full 32 weeks of device implantation, and 31 (17%) required early device removal. 150 (80%) patients in the aIGB group completed the 6-month follow-up phase after device removal. Among controls, 75 (74%) patients completed week 32 and 26 (26%) withdrew early.

In the aIGB group, the per-protocol population ($n=132$) excluded 29 (22%) patients for early device removal, 14 (11%) for non-compliance with device volume adjustments, nine (7%) for more than three missed or out-of-window visits, two (2%) for out-of-range BMI, and one (<1%) for pregnancy. For the control group ($n=70$), per-protocol analysis excluded 24 (24%) patients for early discontinuation from the study, five (5%) for more than three missed or out-of-window visits, and two (2%) for BMI out of range.

In the miITT population, patients in the aIGB group had 15.0% (95% CI 13.9–16.1) total bodyweight loss at 32 weeks, compared with 3.3% (2.0–4.6) in the control group after the same time period ($p<0.0001$; appendix p 5). The difference in mean percentage total bodyweight loss at week 32 between the aIGB and control groups was 11.7% (9.9–13.5), exceeding the prespecified 4.5% super-superiority margin (appendix p 5). At 32 weeks, mean total bodyweight loss in those in the

	Control (n=101)	Adjustable intra-gastric balloon (n=187)
Age, years	44.0 (8.9)	44.4 (8.9)
Sex		
Female	90 (89%)	162 (87%)
Male	11 (11%)	25 (13%)
Race		
Asian	1 (1%)	1 (1%)
Black or African American	26 (26%)	49 (26%)
Native Hawaiian or Pacific Islander	0 (0%)	1 (0%)
White	72 (71%)	132 (71%)
Other	2 (2%)	4 (3%)
BMI (kg/m ²)	35.8 (2.7)	35.8 (2.6)
Sleep apnoea		
No	93 (92%)	165 (88%)
Yes	1 (1%)	1 (1%)
Non-insulin-dependent type 2 diabetes		
No	97 (96%)	174 (93%)
Yes	4 (4%)	13 (7%)
Hypertension		
No	69 (68%)	146 (78%)
Yes	32 (32%)	41 (22%)
Increased lipids		
No	78 (77%)	146 (78%)
Yes	23 (23%)	41 (22%)

Data are n (%) or mean (SD). miITT=multiple imputed intention to treat.

Table 1: Baseline patient characteristics in the miITT population

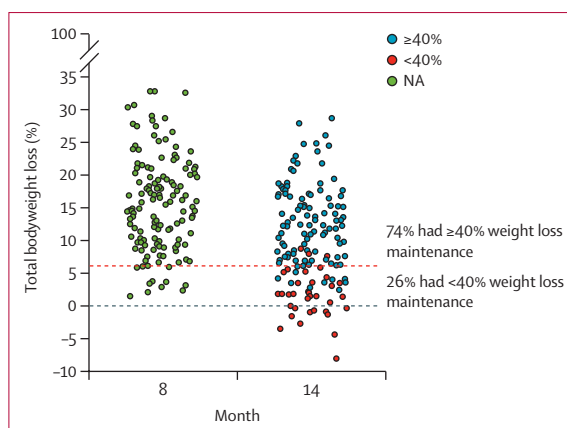


Figure 2: Weight loss maintenance at 6 months after aIGB removal

Dots depict participant weight at aIGB removal (8 months, non-imputed) and at 6 months after removal (14 months, non-imputed). The horizontal dotted line (at 6% total bodyweight loss) depicts the total bodyweight loss corresponding to the goal of 40% weight loss maintenance. Maintenance of at least 40% of weight lost at 8 months by 14 months in at least 50% of patients in the aIGB group was a prespecified secondary endpoint. aIGB=adjustable intra-gastric balloon. NA=not applicable.

aIGB group was 14.5 kg (7.5 kg), compared with 3.2 kg (6.5) in the control group. Weight loss in the aIGB group ranged from 0 kg to 34 kg (total bodyweight loss 0–32.8%), whereas control patients ranged from gaining 7 kg to losing 23 kg (total bodyweight loss –6.7% to 21.7%). The per-protocol population showed a mean of 15.2% total bodyweight loss at 32 weeks in the aIGB group and 4.1% in the control group ($p < 0.0001$; appendix p 6). Percentage total bodyweight loss by month over the duration of aIGB implantation or control is shown in the appendix (p 6), showing little distinction between miITT and per-protocol results.

In the miITT population, clinical response was observed in 171 (92%) patients in the aIGB group, clinical success defined as clinical response rate exceeding 50% of patients in the aIGB group (appendix p 7). In the per-protocol population, clinical response was observed in 127 (96%) of patients in the aIGB group at 32 weeks. At 32 weeks, 34 (34%) patients in the control group (miITT) had clinical response, and 27 (27%) patients gained weight.

144 (77%) patients in the aIGB group had weight loss results available 6 months after device removal and were included for analysis of weight loss maintenance. A prespecified secondary endpoint stipulated that more than 50% of patients in the aIGB group should achieve weight loss maintenance. Of the 144 patients who

underwent aIGB and had weight loss data at 14 months, weight loss maintenance was achieved in 107 (74%) patients, satisfying the prespecified endpoint goal (figure 2).

In the miITT population, mean excess bodyweight loss was 53.6% in the aIGB group at 32 weeks. 157 (84%) patients in the aIGB group had excess bodyweight loss of at least 25%, exceeding the prespecified performance outcome dictating that at least 35% of patients in the aIGB group achieve this clinical response.

Baseline blood laboratories for the control and aIGB groups are shown in the appendix (p 10). Among 11 patients with type 2 diabetes and mean baseline HbA_{1c} 7.5% mmol/mol (SD 1.0), the observed improvement at 36 weeks was –0.73% (95% CI –1.49 to 0.02; $p = 0.055$). Adjusted for the number or dose of cholesterol-lowering medications, total cholesterol improved by –6.8 mg/dL (–11.1 to –2.6; $p = 0.0018$) among 155 patients in the aIGB group at 36 weeks (appendix p 11). Additionally, alkaline phosphatase concentrations, aspartate aminotransferase concentrations, alanine aminotransferase concentrations, and white blood cell count significantly decreased, whereas 25-Hydroxy vitamin D concentrations and, vitamin B₁₂ concentrations significantly improved after 36 weeks of aIGB treatment (appendix p 11). Patients in the aIGB group ($n = 132$) had a reduction in systolic blood pressure of –6.1 mm Hg (–9.8 to –2.3; $p = 0.0016$) and a reduction in diastolic blood pressure of –3.7 mm Hg (–6.4 to –1.0; $p = 0.0078$) compared with those in the control group ($n = 70$), adjusted for the number or dose of anti-hypertensive medications and screening blood-pressure measurements.

Initial aIGB volume was 400–550 mL. 145 (78%) of 187 patients in the aIGB group had one or more adjustments during the study. Those starting at 400 mL

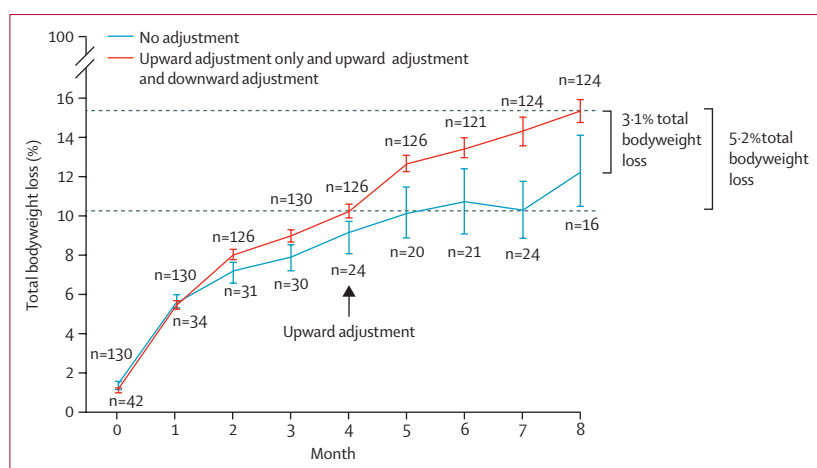


Figure 3: Weight loss effect of upward adjustment of the aIGB

The 5.2% (95% CI 4.5–5.8) total bodyweight loss is the mean of the per-subject differences of percentage total bodyweight loss between 4 months and 8 months (immediately before upward adjustment) among those who underwent upward adjustment. Error bars denote SE. aIGB=adjustable intragastric balloon.

	Adjustable intragastric balloon (n=187)		Control (n=101)	
	n (%)	Events, n	n (%)	Events, n
Total	7 (4%)	24	1 (1%)	1
Gastrointestinal disorders	7 (4%)	19	0	..
Nausea	6 (3%)	7	0	..
Vomiting	5 (3%)	5	0	..
Abdominal pain	2 (1%)	2	0	..
Diarrhoea	2 (1%)	2	0	..
Abdominal discomfort	1 (<1%)	1	0	..
Gastro-oesophageal reflux disease	1 (<1%)	1	0	..
Abdominal pain upper	1 (<1%)	1	0	..
Metabolism and nutrition disorders	4 (2%)	5	0	..
Dehydration	3 (2%)	3	0	..
Failure to thrive	1 (<1%)	1	0	..
Hypokalaemia	1 (<1%)	1	0	..
Musculoskeletal and connective tissue disorders	0	0	1 (1%)	1
Spinal column stenosis	0	0	1 (1%)	1

Table 2: Serious adverse events

did not receive downward adjustments but mostly upward adjustments to 650 mL. 37 (84%) of 44 patients starting at 450 mL had adjustments, and 27 (61%) were removed at 700 mL. 25 (78%) of 32 patients had adjustments and 17 (53%) were explanted at 800 mL. Of those starting at 550 mL, the most common volume at removal was 850 mL (n=47 [48%]). No aIGB volume exceeded 850 mL.

130 (70%) of 187 patients in the aIGB group underwent upward adjustment or upward and downward adjustments at 4 months per protocol resulting in an additional mean 5.2% (95% CI 4.5–5.8) total bodyweight loss between week 18 (time of adjustment) and week 32 (including only upward adjustment and both upward adjustment and downward adjustment; (figure 3).

Consequently, at week 32 the percentage total bodyweight loss of those who were adjusted was 3.1% greater than in those who were not adjusted (figure 3).

52 (28%) patients in the aIGB group reported symptoms that required consideration of device adjustment or extraction. In 24 (46%) of these patients, immediate intervention included device removal with no opportunity for adjustment as per patient's request. In the remaining 28 (54%) patients, downward adjustment of the aIGB volume was attempted first. 21 (75%) of those patients completed the 32 weeks of the study, five (18%) required device removal within 100 days from the adjustment, and two (7%) required device removal later than 100 days from the adjustment (appendix p 8). Of 31 (17%) of 187 patients who underwent early device removal (<32 weeks), 26 (84%) removals were for adverse events; of the remaining five (16%) early explants, three (10%) were for patient preference, one (3%) for pregnancy, and one (3%) for patient relocation. Upon early removal (11 [35%] of 31), abnormal endoscopic findings in the oesophagus (5 [45%] of 11) and stomach (6 [55%] of 11) were noted, with complete resolution on later endoscopic follow-up.

No patient deaths; balloon deflations with migration into the small intestine; obstructions; pancreatitis; or oesophageal or gastric perforations were reported. One balloon was found deflated within the stomach at the time of extraction at 32 weeks. The most commonly reported non-serious adverse events were nausea (90%), dyspepsia (74%), vomiting (72%), and abdominal pain (56%; appendix p 9). Most of these symptoms were restricted to the first few days after balloon placement and were managed successfully with medication or downward aIGB adjustment. Device-related serious adverse events were observed in seven (4%) patients in the aIGB group over 24 separate events (table 2), the most common of which included nausea (3%), vomiting (3%), metabolic or nutritional disorders (2%), dehydration (2%), abdominal pain (1%), and diarrhoea (1%; table 2). All serious adverse events resolved with no long-term consequences.

Discussion

The aIGB in conjunction with diet and exercise achieved 15% total bodyweight loss at 32 weeks with a substantial margin over diet and exercise alone. Response rate exceeded 90% at 32 weeks, with 74% of patients in the aIGB group maintaining weight loss at 14 months. The volume adjustability function of this IGB enhanced device tolerance, prevented 75% of early removals, and improved weight loss. The safety profile was favourable with no deaths or invasive interventions.

A multifaceted spectrum of interventions targeting peripheral and central pathways, which control energy intake and expenditure, are required to combat excess adiposity. The counter-regulatory physiological response to calorie restriction in response to anti-obesity therapies can result in plateauing weight loss and weight regain.¹⁵

The prevailing management strategy involves a continuum of care starting with intensive weight loss intervention sufficient to produce significant early weight loss, while engaging the patient in life-long weight stabilisation and re-intensification efforts.¹⁶ This strategy recognises that anti-obesity medications, endoscopic bariatric therapies, and bariatric surgery are important tools to be administered together or sequentially, with a focus on personalising the initial intervention choice to the predominant obesity phenotype and severity of disease. Lifestyle changes, including physical activity and a reduced calorie diet remain the cornerstones of treatment. The aIGB can serve as an anatomy-preserving and scalable tool for improving obesity and engaging the patient in life-long weight stabilisation and re-intensification efforts. Most patients who underwent treatment with this aIGB in conjunction with a protocolised diet and lifestyle modification programme surpassed the 10% threshold of total bodyweight loss sufficient to show improvement in obesity-related comorbidities. Although this aIGB therapy can induce the weight loss needed to improve obesity-related comorbidities, long-term weight maintenance with lifestyle modification or pharmacological therapy after the device is removed is important for sustained improvement in obesity-related comorbidities and reduction in associated mortality.

Although this is the largest and first randomised controlled trial of this IGB, others have investigated earlier generations with dwelling time of 12 months, and two prospective cohort studies^{17,18} relayed that first experience. In one report, 73 patients from the UK with obesity had a mean of 20·1% total bodyweight loss and 45·8% excess bodyweight loss after 12 month implantation.¹⁷ In another report, 18 patients with obesity in the Czech Republic had 48·8% excess bodyweight loss at 12 months.¹⁸ A subsequent prospective study investigated the most recent version of this IGB in the UK and Czech Republic in which 77 patients had a mean total bodyweight loss of 15·9% and 40·1% excess bodyweight loss at 12 months.¹⁹ Finally, a retrospective review in 165 patients (79% female, 21% male, mean age 42·4 years, mean BMI 35·7 kg/m²) in the UK and Czech Republic found a mean total bodyweight loss of 16·4% and 67·4% excess bodyweight loss at 12 months.²⁰ With this precedent, a safe, longer dwell time of this aIGB can be envisioned, ostensibly facilitating even more robust weight loss and the opportunity to reinforce complementary behavioural practices, which might be addressed in future studies.

IGB therapy can have both weight-loss-dependent and weight-loss-independent mechanisms of action resulting in a metabolic benefit. By triggering weight loss of greater than 10%, the IGB leads to reductions in total and visceral adiposity, insulin resistance, HbA_{1c}, and improvement or resolution of non-alcoholic steatohepatitis as assessed by liver histology.²¹ Additionally, IGB therapy is associated

with weight-independent mechanisms, positively affecting metabolic homeostasis.^{22,23} Fluid-filled IGB delays gastric emptying, reducing post-prandial hyperglycaemia, a major contributor to glycaemic control.^{22,23} We observed improvements in blood pressure, liver biochemical tests, total cholesterol, and diabetes control among a small cohort with type 2 diabetes. Larger studies that are focused on obesity comorbidities with longer follow-up are needed to ascertain resolution of these comorbidities and maintenance of response.

Safety remains paramount for any obesity intervention. Early iterations of this IGB were associated with rare instances of gastric perforation requiring surgical intervention.¹⁸ An upgraded design in 2012 included a soft rather than rigid catheter metal chain, decreasing this risk. In our study, the safety profile was favourable with no observed death, gastric perforation, balloon hyperinflation, pancreatitis, or balloon migration. Few device-related serious adverse events occurred and were largely from expected accommodative symptoms. Non-serious adverse events are both expected and common, manifesting as accommodative symptoms. Such symptoms can be limitations for IGB therapy; however, advancement in therapeutics, careful patient selection, the transient nature of these symptoms, and downward adjustability of this IGB renders it tolerable and effective in most patients.

The bidirectional volume adjustability and longer dwelling time of this IGB compared with that of previous iterations and other IGBs personalises treatment to individual patients and improves tolerability and efficacy. Studies show that weight loss plateau, typically seen 2–3 months after implantation, could be overcome by sequential use of non-adjustable IGBs.²⁴ Predicated on this concept, the upward adjustments delivered in this study at week 18 afforded those patients an additional 5·2% total bodyweight loss by month 8 of implantation, and an overall 3·1% greater total bodyweight loss than in those patients who did not undergo any adjustments. These results are congruent with those observed in two international studies, in which 45 (62%) patients had successful upward adjustment yielding a mean of 9·4 kg weight loss after adjustment,¹⁷ and 15 (20%) patients had successful upward adjustment, yielding a mean of 8·2 kg weight loss after adjustment.¹⁹ The decision to increase IGB volume should be balanced against the presence and degree of ulcers and oesophagitis. Decrease in aIGB volume offers an effective method for patient adherence and avoiding premature extraction, provided it is done after a thorough risk stratification and severity assessment, should a complication occur. In this study, most patients who selected downward adjustment for refractory symptoms subsequently tolerated IGB therapy at reduced balloon volume. These results align with those observed in previous studies.^{17,19} In the first, ten (71%) of 14 patients had downward adjustment for intolerance, all of whom continued to month 9 of the study, losing an additional

mean of 12.3 kg after adjustment.¹⁷ In the second, six patients had earlier intolerance, three who had downward adjustment and were able to complete the 12 month study.¹⁹ The adjustability of this IGB could have facilitated the considerably greater efficacy observed compared with that of other non-adjustable gastric balloons. However, in the absence of head-to-head comparative trials, relative effectiveness compared with non-adjustable IGBs is hypothetical. Finally, the requirement of multiple endoscopies to implant, adjust, and remove the aIGB should be considered, especially in the context of swallowable IGBs not requiring endoscopy.²⁵ However, the safety of implanting a device in the stomach without adequate endoscopic examination has not been indubitably shown in prospective randomised trials, and dwelling time of the swallowable IGB is 3–4 months without the ability to adjust volume for intolerance or enhanced efficacy.

Limitations of this study include no blinding or sham intervention. Given the short-term accommodative symptoms associated with implantable gastric devices, masking is infeasible.²⁶ The study cohort included a higher proportion of women, which is consistent with most obesity-treatment literature.¹⁰ This study was not powered to investigate improvement in obesity-associated comorbidities, which play a substantial role in the burden of obesity on clinical outcomes, quality of life, and health-care expenditure. Future studies should gauge long-term safety and whether the weight loss achieved with this temporary therapy can be sustained in the contexts of other interventions (eg, pharmacologic, behavioural, or surgical). This strategy of additive therapies and dynamic follow-up might capitalise on short-term influence of the aIGB. A temporary device such as the aIGB allowing rapid weight loss could serve as a bridge to improve the patient's candidacy for another intervention such as orthopaedic arthroplasty, transplant, and bariatric surgery.^{27–29}

The aIGB combined with lifestyle modification facilitated clinically significant weight loss with acceptable safety profile and weight loss maintenance 6 months after device removal. The novel feature of upward or downward volume adjustment affords a patient-tailored approach to improve efficacy and tolerability. The results of this multicentre, randomised, US trial further add to the available safe and effective obesity therapies.

Contributors

BKA was involved in study design, conceptualisation, study conduct, patient recruitment, data collection, data interpretation, statistical analysis, writing of manuscript, creation of figures, and drafting and critical review of the manuscript. DBM, BR, EJV, FB, and ACS were involved in study conduct, writing the manuscript, literature search, data interpretation, creation of figures, and critical review of the manuscript. PJ, TL, MN, HH, CGC, VP, MR, EJV, AA, and FB were involved in data collection and critical review of the manuscript. DM was responsible for statistical analysis and development of figures. CCT was involved in study design, conceptualisation, patient recruitment, data collection, data interpretation, and critical review of the manuscript. BKA and DM

fully accessed and verified the underlying data. All authors verify this study was done per protocol and vouch for data accuracy and completeness.

Declaration of interests

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Data sharing

Data from this study can be requested from Daniel Molina (dmolina@tech-res.com) after publication of this study. Deidentified participant data, data dictionary, and other specified data sets can be requested. The study protocol, statistical analysis plan, and informed consent form will also be made available upon request. Specific requests for data will require approval of a proposal and signed data access agreement.

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