

An Intra-gastric Balloon in the Treatment Of Obese Individuals With Metabolic Syndrome: A Randomized Controlled Study

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Objective: There are limited controlled data for intra-gastric balloons (IGB) in obesity treatment. This randomized, controlled study evaluated the efficacy and safety of an IGB in obese individuals with metabolic syndrome (MS).

Design and Methods: Sixty-six adults (BMI: 30-40 kg/m²) were randomized to IGB for 6 months, with a 12 month behavioral modification (IGB Group; "IGBG"), or 12 month behavioral modification alone (Control Group; "CG"). The primary outcome was percentage change in body weight.

Results: Thirty-one subjects (female: 68%; mean age: 43; mean BMI: 36.0) were randomized to IGBG and 35 (66%; 48; 36.7) to CG. At 6 months, there was a significantly greater weight loss in the IGBG: -14.2 vs. -4.8; $P < 0.0001$. This was associated with a significantly greater reduction in waist circumference, and an improvement in quality of life, with a trend for a larger %MS remission (50% vs. 30%; n.s.). At month 12, the differences in weight loss were enduring: -9.2 vs. -5.2; $P = 0.007$. Gastrointestinal-related adverse events were common in the IGBG, resolving predominantly within two weeks. The IGB was removed prematurely in three subjects (one for refractory gastrointestinal symptoms).

Conclusions: Statistically significant and clinically relevant improvements in weight loss and health outcomes were observed with the IGBG at 6 months versus behavioral modification alone. The differential weight loss was still evident 6 months after IGB removal.

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Introduction

Overweight and obesity is a global epidemic and is a major public health issue in many countries, accounting for 44% of the global burden of diabetes, 23% of ischemic heart disease, and 7-41% of certain cancers (1). A modest weight loss of 5-10% is associated with clinically significant health benefits including a reduction in risk factors for diabetes and cardiovascular disease (2,3), with more improvement in these risk factors found with greater degree of sustained weight loss (4).

In clinical studies published to date, treatment protocols based on hypo-caloric intake and exercise alone commonly achieve a moderate weight reduction of approximately 5%, which is generally not maintained (5). Pharmacotherapy produces some additional benefit

over behavioral modification alone (6,7), however safety concerns about some of these agents have led to the withdrawal of certain registered drugs and the discontinuation and/or the delay in the development of other experimental agents. Even when long-term behavioral modification programs and pharmacotherapy are offered, multiple neurohormonal and metabolic pathways, controlled both centrally and peripherally, conspire to maintain fat stores and overall weight at pre-ordained levels, providing a strong physiological basis for weight regain (8).

The use of endoscopically inserted gastric balloons as an alternative, non-surgical treatment approach for the management of obesity is not a new concept, having first been tried in the early 1980s (9). These devices are assumed to facilitate weight loss by reducing the gastric reservoir capacity, thereby inducing a premature satiation

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and prolonged satiety, although changes in gastric emptying and gut hormone-mediated signaling cannot be excluded as potential mechanisms. In an early clinical trial conducted by Geliebter et al., a 300 ml fluid filled balloon was employed, which remained in the stomach for three months. This study was the first to show that with a fixed balloon volume, weight loss over time was inversely proportional to gastric capacity, providing the rationale for the use of larger balloon volumes for those with bigger stomach capacities, with specific reference to obese individuals (10). Geliebter had previously demonstrated in a short-term study that balloon volumes of 400 ml or above were associated with a significant reduction in food intake, with a strong correlation between gastric capacity and the balloon volume required to suppress food intake by 50% (11).

Currently available intragastric balloons (IGB) have been designed to remain within the stomach for up to 6 months prior to their removal. The procedure associated with the placement of the balloon is substantially less invasive than bariatric surgery, is totally reversible, and may be repeated if needed, making it attractive treatment for those patients who are looking for an alternative to lifestyle modification alone, and those not ready or suitable for surgical intervention (12). IGBs are used in conjunction with a supervised behavior modification program of diet and exercise, designed to increase the probability of long-term weight-loss maintenance.

Several clinical studies have been conducted with the currently available, more durable IGBs in various overweight and obese populations to assess the safety and efficacy of IGBs. The majority of these studies have been uncontrolled and/or retrospective (13-20). Only three studies published to date employed a prospective, randomized, controlled trial design with a long-term follow-up (≥ 1 year) (21-23); two of which included the use of more than one IGB (21,22). Regardless as to the study design, a mean weight loss of 10% was maintained for up to one year after IGB removal in those studies with an extended post-removal follow-up period (16,21,24). However, the focus of these studies was primarily on weight loss alone, with few reports of the impact of IGBs on relevant health outcomes, based on predefined diagnostic and outcome criteria. These latter issues were addressed specifically in the current study.

Methods and Procedures

Study design and subjects

The study had a prospective, randomized, controlled parallel-arm design, in accordance with ICH-GCP guidelines. Eligible subjects were obese individuals aged between 18 and 60 years, who had had a BMI of 30-40 kg/m² for a minimum of 2 years, and who had provided written informed consent. All had failed supervised weight reduction programs (including diet and exercise), and had the metabolic syndrome (MS) as defined by the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) Criteria (25).

Exclusion criteria included any condition which would increase the risks associated with endoscopy and/or insertion of the IGB, inflammatory disease of the gastrointestinal (GI) tract, upper GI bleeding conditions, history or symptoms of oesophageal or GI motility disorders, large hiatus hernia (>5 cm in diameter), structural abnormality of the GI tract, prior gastric surgery or insertion of an IGB, or major surgery within previous three months, cerebrovascular or cardiopul-

monary disease, uncontrolled blood pressure ($\geq 160/95$ mmHg), epilepsy, type 1 diabetes, undiagnosed thyroid disease or hypothyroidism in which the dose of thyroxine replacement had not been stable for at least three months, hepatic or renal insufficiency, psychiatric disorder, or a pregnancy. Subjects were not permitted to take prescription or non-prescription medication or supplements with known effects on appetite or weight, or take aspirin, non-steroidal anti-inflammatory agents (NSAIDs), anticoagulants, or other gastric irritants. Subjects with a history of alcoholism or drug abuse were excluded as were those with a history of weight loss of greater than 5 kg. Enrolment in any formal weight loss program within the 3 months prior to screening was also an exclusion criterion.

All scheduled clinic visits took place at the Clinical Trials Unit of the Boden Institute, University of Sydney, Camperdown, NSW, Australia. The IGB (ORBERA®; Allergan Australia) (Formally known as the BioEnterics® Intragastric Balloon (BIB) was inserted and removed at Sydney Day Surgery (SDS), Royal Prince Alfred Medical Centre, Camperdown, NSW, Australia by the same gastroenterologist (AJK).

Interventions

Subjects were randomized in a 1:1 ratio to receive either the IGB for 6 months in addition to a 12-month behavioral modification program of diet and exercise {IGB Group (IGBG)}, or the behavioral modification program alone {Control Group (CG)}. All subjects returned to the clinic on a monthly basis for assessment of compliance to the behavioral modification program, with scheduled outcome assessments conducted at months 3, 6, 9, and 12.

Behavioral modification program

The same behavioral modification program was employed for both groups, based on the Type 2 Diabetes Lifestyle Intervention Program (26). During the baseline visit, the study dietitian/exercise physiologist (NRF) provided each subject with a written guide as to the specific types of foods and the quantities which could be consumed, in addition to a tailored exercise program. Each subject also received a pedometer and was encouraged to walk at least 10,000 steps daily.

Intragastric balloon group

Baseline Visit (IGB insertion). After the baseline evaluations, subjects in the IGBG were taken to the endoscopy center (SDS) for the IGB insertion. Individuals with no contraindications identified on a preceding endoscopy had the IGB inserted using the standard protocol (27). A volume of 450-700 ml of saline was inserted into each IGB, with the volume predicated on the pre-treatment subjects BMI and stomach anatomy. In this study, the entire insertion procedure took on average 13 min per subject.

The subjects were informed of all symptoms of deflation, gastrointestinal obstruction, ulceration, and other complications which might occur post-insertion and were advised to contact the investigators immediately if such symptoms occurred. Anti-emetics and antispasmodic drugs were prescribed for 5-7 days during the post-insertion period, with a proton pump inhibitor taken daily from 1 to 2 weeks prior to insertion and continued while the IGB was *in situ*.

Subjects were instructed to remain inactive for 3 days post-insertion and to comply with a transitional diet up to day 20 to minimize post-procedure discomfort, prior to commencing their behavioral modification program.

Month 6 Visit (IGB removal). The standard removal protocol was observed (27). The subjects were subsequently followed for a further six months after IGB extraction (ex-IGB group; “Ex-IGBG”).

Control group

After the Baseline visit, all subjects in the CG commenced their prescribed behavioral modification program of diet and exercise, and this was continued over the 12 months of the study.

Primary and secondary outcomes

All assessments were conducted at baseline and every 3 months thereafter to month 12.

Change in weight; other anthropometrics. Body weight was measured using a Tanita BC-418 segmental body composition analyzer (Tanita Corporation of America Inc., Arlington Heights, IL). Change in weight from baseline was expressed as: percentage of initial weight loss; absolute weight loss (kg); percent of excess weight loss (%EWL); change in body mass index (BMI); and proportion with a $\geq 5\%$, $\geq 10\%$, or $\geq 15\%$ weight reduction. Waist circumference was measured midway between the top of the iliac crest and the most inferior part of the rib cage. The primary endpoint for the study was % weight loss at month 6.

Health outcomes. A series of health outcomes were assessed during the study, including: (i) the proportion in remission of MS (< 3 ATP III parameters) (25), (ii) exercise tolerance (6 minute walk test; “6MWT”) (28), (iii) quality of life (Impact Of Weight On Quality Of Life-Lite; “IWQOL-Lite”) (29), and (iv) three domains of eating behavior (cognitive restraint, uncontrolled eating, and emotional eating) as evaluated by the Three Factor Eating Questionnaire-R21 (“TFEQ-R21”) (30).

Safety. The incidence and severity of adverse events (AEs), reported by the subjects in response to a generic health question or otherwise volunteered, was used to define the safety and tolerability of the study treatments, as were changes in vital signs. Also, on days 8 and 15, the IGB group was telephoned to document AEs during the 1-2 week post-insertion adaptation phase, with specific reference to the impact of these events on daily functioning (time off work/study).

Treatment satisfaction. At months 6 and 12, respectively, subjects in the IGBG/Ex-IGBG were also asked to document their level of satisfaction with the IGB. As the focus of this assessment was to obtain specific information on the subject’s perception of the device, this assessment was not conducted in the CG.

Statistical Analysis

Sample size. Assuming a mean weight reduction at month 6 of 14% and 7% for the IGB and Control groups, respectively, a standard deviation (SD) of 9%, and a drop-out rate of 20%, a total of 66

subjects was required to achieve 80% power of detecting a treatment effect (two-sided significance level of 5%).

Randomization. A computer generated randomization scheme was utilized, with treatment allocations balanced in groups of either 4 or 6, and concealed in consecutively numbered, tamper-proof envelopes.

Data analysis. A longitudinal model was used to estimate change from screening/baseline and the treatment effect at each time point using SAS version 9.1.3 PROC GLIMMIX. The co-variables included: screening/baseline observation, age, gender, and group allocation. Drop-outs and missing visits were assumed to have occurred at random. Results are presented as least squares means with 95% confidence intervals (95% CI). Sensitivity analyses used last observation carried forward (LOCF) and screening observation carried forward (SOCF) methodologies to impute missing data, with a two-sample Wilcoxon test employed to compare treatment outcome. Chi squared or Fisher’s exact test was used to compare categorical outcomes for the treatments. A two-sided P -value of $P < 0.05$ was considered statistically significant.

Results

Trial disposition

A flow chart detailing the subject disposition is provided in Figure 1. The study was conducted between April 2008 and February 2010.

Baseline characteristics

Baseline characteristics of the subjects are detailed in Table 1. Demographic and clinical characteristics were well matched across treatment groups, albeit a significant difference in the 6-minute walk test distance was noted between groups. The mean BMI for the groups was approximately 36 kg/m^2 , with both groups being obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) for over 7 years on average. All subjects met the ATP III criteria for MS.

Primary outcome

Percentage weight loss at month 6. Figure 2 shows the weight change of the two treatment groups at each of the scheduled visits, relative to baseline. A mean weight reduction of -14.2% was achieved by the IGBG prior to IGB removal at month 6, which was significantly greater than the reduction achieved by the Control group: -4.8% ($P < 0.0001$).

Secondary outcomes

Weight loss over 12 months. A significant difference in percentage weight loss in favor of the IGBG was also observed at the first follow-up visit (month 3) with a significant difference between the groups evident during the course of the study, including during the six follow-up month period after IGB removal (Figure 2; Table 2). At 6 months, absolute weight loss for the IGBG was: -14.4 kg versus -5.1 kg for the CG; $P < 0.0001$. Some weight regain was evident for the IGBG post removal of the IGB. At 12 months, this weight loss was: -9.4 kg and -5.3 kg for the Ex-IGBG and CG, respectively ($P = 0.008$). There were also statistically significant reductions for the IGBG group in BMI and %EWL at each scheduled assessment, relative to the Control group (Table 2).

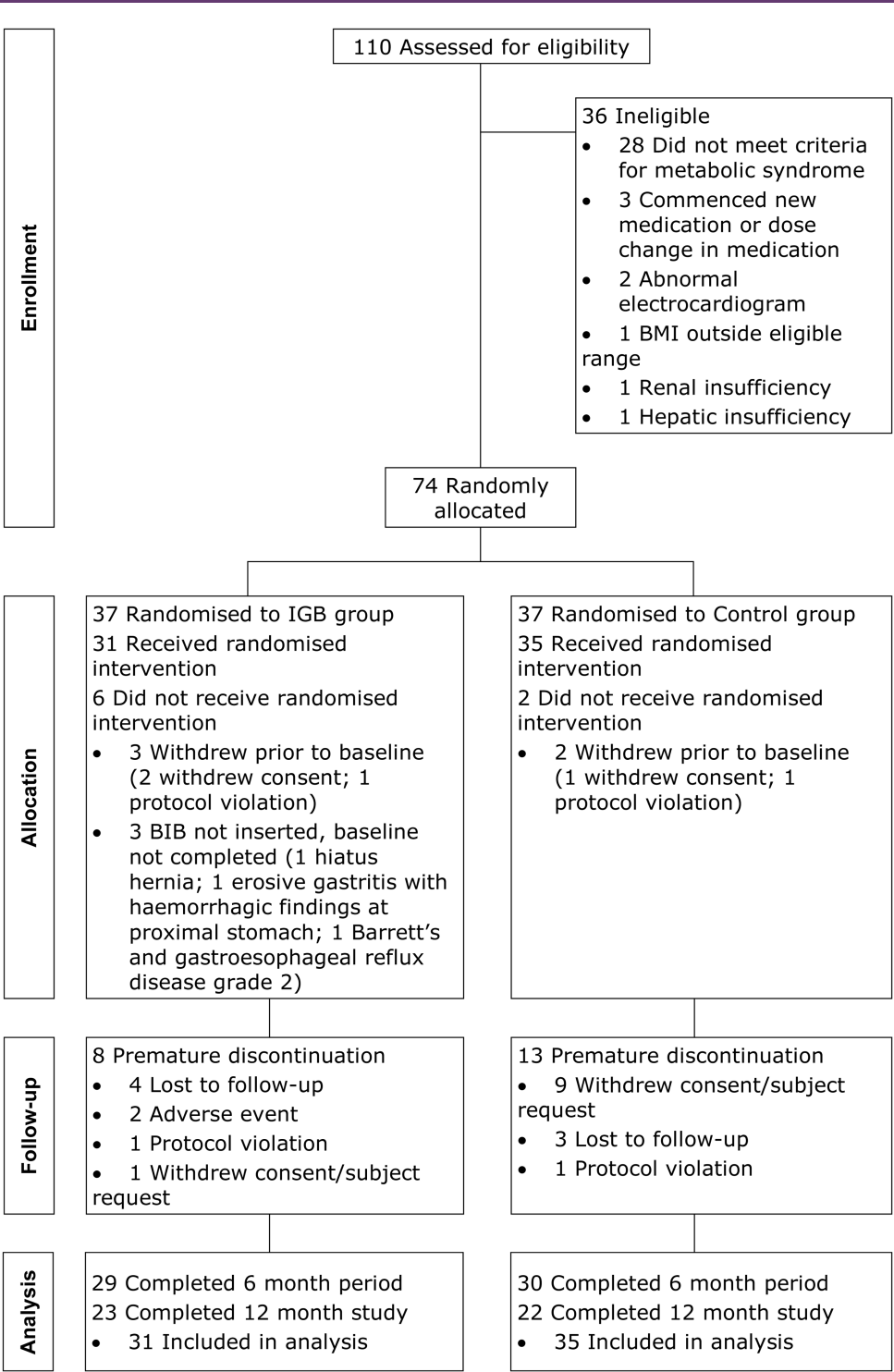


FIGURE 1 Trial disposition.

Waist circumference. The greater weight loss achieved by the IGBG was accompanied by larger reductions in waist circumference at all scheduled clinic visits, with the differences between groups being statistically significant (Table 2).

Proportion of subjects with $\geq 5\%$, $\geq 10\%$, or $\geq 15\%$ weight Loss. At months 3 and 6, the proportion of subjects achieving a $\geq 5\%$, $\geq 10\%$, or $\geq 15\%$ weight loss was significantly greater for the IGBG (Table 2). However, whilst a greater proportion of subjects in the

TABLE 1 Baseline characteristics of study participants ($n = 66$)

Characteristic ^a	IGB group ($n = 31$)	Control group ($n = 35$)
Female gender; n (%)	21 (68)	23 (66)
Age (years)	43.4 (9.4)	48.1 (7.3)
Caucasian; n (%)	26 (83.9)	26 (74.3)
Weight (kg)	104.6 (14.8)	103.4 (13.9)
BMI (kg/m^2)	36.0 (2.7)	36.7 (2.9)
BMI years $> 30 \text{ kg}/\text{m}^2$	7.4 (4.0)	8.3 (5.5)
Waist circumference (cm)	115.4 (10.9)	115.2 (8.8)
Systolic blood pressure (mmHg)	133.7 (10.1)	129.6 (13.2)
Diastolic blood pressure (mmHg)	86.0 (6.3)	83.0 (7.3)
Fasting blood glucose (mmol/l)	5.6 (1.0)	6.2 (2.1)
HDL-cholesterol (mmol/l)	1.23 (0.36)	1.17 (0.30)
LDL-cholesterol (mmol/l)	3.4 (1.0)	3.1 (1.0)
Total cholesterol (mmol/l)	5.6 (1.2)	5.1 (0.9)
Triglycerides (mmol/l)	2.2 (1.2)	1.9 (1.0)
IWQOL-Lite total score	60.7 (16.0)	66.6 (15.1)
TFEQ-R21 cognitive restraint domain	2.3 (0.6)	2.3 (0.5)
TFEQ-R21 emotional eating domain	2.8 (0.8)	2.5 (0.8)
TFEQ-R21 uncontrolled eating domain	2.7 (0.5)	2.3 (0.6)
6-minute walk test distance (meters)	535 (68.7)	470 (67.6) ^b

^aValues are mean (SD) unless otherwise indicated.^b $P = 0.0008$.

Ex-IGB group maintained these outcomes at month 12, the between group difference was not statistically significant at the end of study (Table 2). The proportion of subjects who lost $\geq 10\%$ body weight during this 12 month study is also shown by group in Supporting Information Figure S1, with 36% and 17% for the IGBG and CG, respectively fulfilling this weight loss criterion at month 12.

Health outcomes

Proportion in remission of metabolic syndrome.. Consistent with significant weight reduction documented in the IGBG, approximately half of this group achieved remission of MS throughout the study, with this outcome documented from the first follow-up visit at month 3 (Figure 3). This compared to a remission rate of approximately 30% in the CG during the study. However, the difference between the IGBG/Ex-IGBG and CG did not reach significance during the course of the study (Table 3).

Exercise tolerance. Both groups improved their walk distance over 6 minute from baseline during the study, with a significant difference in favor of the IGBG at months 3 and 6. However, this statistical difference between groups was not detected during 6-month post-removal follow-up period (Table 3).

Quality of life. A significant differential improvement in quality of life (QOL), based on the IWQOL-Lite questionnaire, was documented for the IGBG by month 6 with this between group difference

maintained for the 6 months following IGB removal (Supporting Information Figure S2; Table 3).

Eating behaviors. Improvements from baseline in all three eating behavior domains of the TFEQ-R21 were also noted in the IGBG, with a statistical difference observed between groups at months 3 and 6, while the IGB was *in situ*, and with the difference still significant 3 months after IGB removal (month 9). At month 12, the between group difference was only significant for the emotional eating domain (Table 3).

Safety

No between group differences in blood pressure (BP), or heart rate (HR) were found between groups during the study, with BP and HR improving for both groups (data not shown). Treatment-emergent AEs over the 12-month study are presented by group in Supporting Information Table S1. Most of those in the IGBG experienced GI-related AEs. These were mainly reported during the initial adaptation phase (days 1-14) and mostly resolved during the second week post-insertion (Figure 4). Consistent with this, when an analysis was conducted of the impact of the three most common symptoms (nausea, vomiting, and abdominal pain) on daily functioning (defined as: days off work or study), the mean (SD) number of days impacted during week 1 was: 3.7 (0.9), reducing to 0.6 (1.4) days during week 2. The IGB was removed prematurely in three subjects. One was due to excessive vomiting, abdominal cramps, and gastro-esophageal reflux at month 1. The other two cases were not safety-related; (i) at the insistence of the subject's spouse (day 8), and (ii) after the refusal of the subject to have a pregnancy test (month 4).

Treatment satisfaction

At month 6, 73% of IGBG were satisfied or very satisfied with the IGB, with 86% indicating that they would recommend the device to others. At month 12, 6 months after removal of the IGB, 68% of subjects in the Ex-IGBG were satisfied or very satisfied, whilst 83% would recommend the device to others.

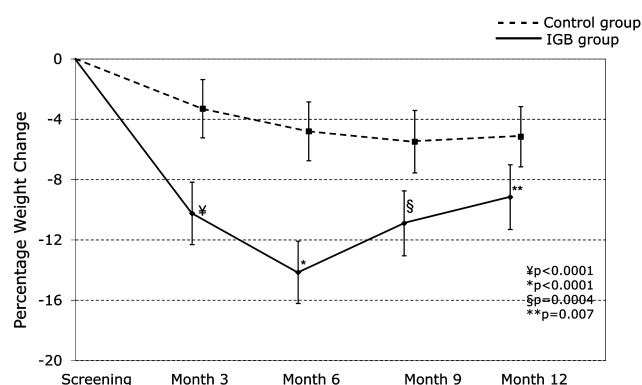
**FIGURE 2** Percentage weight loss for the two treatment groups over the 12 month period of the study.

TABLE 2 Change from baseline for the anthropometric parameters at months 3, 6, 9, and 12, based on a longitudinal analysis

Parameter, mean [95% CI]	Month 3				Month 6				Month 9				Month 12			
	IGB group	Control group	Between group comparison ^a	IGB group	Control group	Between group comparison ^a	Ex-IGB group	Control group	Between group comparison ^a	Ex-IGB group	Control group	Between group comparison ^a	Ex-IGB group	Control group	Between group comparison ^a	
% weight (Primary Efficacy)	-10.2	-3.3	-6.9 [-9.8, -4.1]; <i>P</i> < 0.0001	-14.2	-4.8	-9.4 [-12.2, -6.5]; <i>P</i> < 0.0001	-10.9	-5.5	-5.4 [-8.4, -2.5]; <i>P</i> = 0.0004	-9.2	-5.2	-4.0 [-6.9, -1.1]; <i>P</i> = 0.007				
kg	-10.5	-3.5	-7.1 [-9.9, -4.2]; <i>P</i> < 0.0001	-14.4	-5.1	-9.4 [-12.2, -6.5]; <i>P</i> < 0.0001	-11.0	-5.7	-5.3 [-8.3, -2.3]; <i>P</i> = 0.0006	-9.4	-5.3	-4.0 [-7.0, -1.1]; <i>P</i> = 0.008				
Waist circumference (cm)	-8.8	-3.4	-5.4 [-8.7, -2.0]; <i>P</i> = 0.002	-13.1	-4.8	-8.3 [-11.7, -4.9]; <i>P</i> < 0.0001	-11.4	-6.2	-5.3 [-8.8, -1.7]; <i>P</i> = 0.004	-11.1	-6.4	-4.7 [-8.2, -1.3]; <i>P</i> = 0.008				
BMI (kg/m ²)	-3.5	-1.2	-2.2 [-3.3, -1.2]; <i>P</i> < 0.0001	-5.1	-1.7	-3.4 [-4.5, -2.4]; <i>P</i> < 0.0001	-4.0	-2.0	-1.9 [-3.1, -0.8]; <i>P</i> = 0.0008	-3.4	-1.9	-1.4 [-2.5, -0.3]; <i>P</i> = 0.01				
%EWL	36.4%	12.1%	24.3 [14.2, 34.5]; <i>P</i> < 0.0001	50.3%	16.9%	33.4 [23.2, 43.6]; <i>P</i> < 0.0001	39.0%	19.2%	19.8 [9.1, 30.5]; <i>P</i> = 0.0003	32.7%	17.8%	14.8 [4.3, 25.3]; <i>P</i> = 0.006				
≥5% weight loss	80.7%	34.3%	RR = 2.4 [1.4, 3.8]; <i>P</i> = 0.0002	77.4%	48.6%	RR = 1.6 [1.1, 2.4]; <i>P</i> = 0.0159	67.7%	37.1%	RR = 1.8 [1.1, 3.0]; <i>P</i> = 0.0130	48.4%	28.6%	RR = 1.7 [0.9, 3.2]; <i>P</i> = 0.0977				
≥10% weight loss	41.9%	5.7%	RR = 7.3 [1.8, 30.0]; <i>P</i> = 0.0005	71.0%	17.1%	RR = 4.1 [1.9, 8.9]; <i>P</i> < 0.0001	41.9%	17.1%	RR = 2.4 [1.1, 5.7]; <i>P</i> = 0.0264	35.5%	17.1%	RR = 2.1 [0.9, 5.0]; <i>P</i> = 0.0890				
≥15% weight loss	12.9%	0.0%	N/A, <i>P</i> = 0.0437 ^b	41.9%	5.7%	RR = 7.3 [1.8, 30.0]; <i>P</i> = 0.0005	25.8%	8.6%	RR = 3.0 [0.9, 10.4]; <i>P</i> = 0.0608	16.1%	8.6%	RR = 1.9 [0.5, 7.2]; <i>P</i> = 0.3478				

All values are means (95% CI), unless otherwise indicated. *P*-values represent the differences between the treatment groups at each time point. A mixed effects model was used for the longitudinal analysis, with age, gender, screening observation, and treatment group used as covariates.

^aBetween group comparisons are expressed as relative risk (RR) at each time point assuming patients with missing data did not meet the criteria for response.

^bRelative risk could not be calculated because there were no responders in the control group. *P*-value derived using Fisher's exact test.

TABLE 3 Change from baseline for the health outcomes at months 3, 6, 9, and 12, based on a longitudinal analysis

Parameter mean [95% CI]	Month 3			Month 6			Month 9			Month 12		
	IGB group	Control group	Between group comparison ^a	IGB group	control group	Between group comparison ^a	Ex-IGB group	Control group	Between group comparison ^a	Ex-IGB group	Control group	Between group comparison ^a
% Remission of metabolic syndrome (ATPIII<3)	51.6%	28.6%	RR = 1.8 [1.0, 3.4]; P = 0.0559	51.6%	34.3%	RR = 1.5 [0.9, 2.7]; P = 0.1552	48.4%	28.6%	RR = 1.7 [0.9, 3.2]; P = 0.0977	45.2%	28.6%	RR = 1.6 [0.8, 3.0]; P = 0.1620
6 minute walk test (meters)	53.3	19.2	34.1 [1.4, 67.0]; P = 0.041	77.6	42.0	35.6 [2.4, 68.8]; P = 0.036	64.1	53.7	10.4 [-25.5, 46.3]; P = 0.569	87.6	59.3	28.3 [-6.4, 63.1]; P = 0.110
IWQOL-Lite (total score)	11.9	7.8	4.1 [-1.6, 9.8]; P = 0.160	20.9	10.2	10.6 [4.9, 16.3]; P = 0.0003	20.7	14.0	6.8 [0.7, 12.8]; P = 0.030	22.2	13.1	9.1 [2.8, 15.3]; P = 0.005
TFEQ-R21 cognitive restraint domain	0.9	0.4	0.5 [0.3, 0.7]; P < 0.0001	0.8	0.5	0.3 [0.1, 0.5]; P = 0.002	0.7	0.4	0.2 [0.0, 0.4]; P = 0.038	0.7	0.5	0.2 [-0.1, 0.4]; P = 0.146
TFEQ-R21 emotional eating domain	-0.6	-0.1	-0.5 [-0.7, -0.2]; P = 0.001	-0.6	-0.2	-0.4 [-0.7, -0.2]; P = 0.002	-0.5	-0.03	-0.5 [-0.8, -0.2]; P = 0.002	-0.6	-0.1	-0.4 [-0.7, -0.1]; P = 0.004
TFEQ-R21 uncontrolled eating domain	-0.5	-0.2	-0.3 [-0.6, -0.1]; P = 0.005	-0.6	-0.3	-0.3 [-0.6, -0.1]; P = 0.005	-0.5	-0.3	-0.3 [-0.5, 0.0]; P = 0.023	-0.5	-0.4	-0.2 [-0.4, 0.1]; P = 0.172

All values are means (95% CI), unless otherwise indicated. P-values represent the differences between the treatment groups at each time point. A mixed effects model was used for the longitudinal analysis, with age, gender, screening observation and treatment group used as covariates.

^aBetween group comparisons are expressed as relative risk (RR) at each time point assuming patients with missing data did not meet the criteria for response. IWQOL-Lite = Impact of Weight on Quality of Life Questionnaire-Lite Version; TFEQ-21 = Three Factor Eating Questionnaire-21 item inventory.

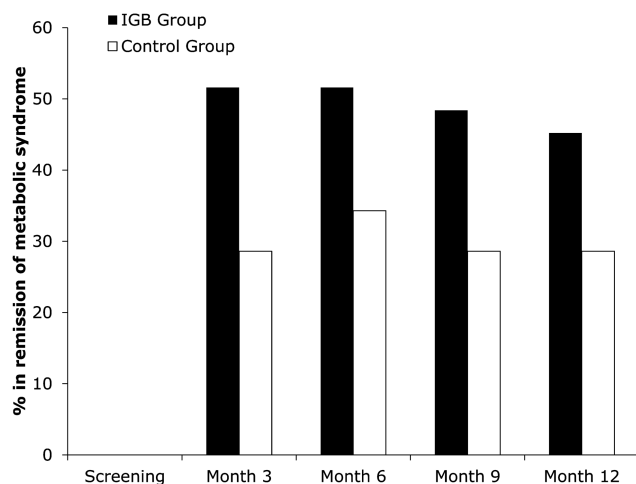


FIGURE 3 Percentage of participants in remission of metabolic syndrome.

Discussion

There is an urgent need to both prevent and effectively manage the epidemic of obesity in order to reduce the emerging personal and societal burden of the associated co-morbidities. Treating obesity is no different from treating any chronic, relapsing, and disabling disease; a range of effective therapies are needed, and combinations of these therapies are often required to provide long-term control (31).

Based on the published research to date, IGBs potentially fulfill such as role as an adjunct to ongoing behavioral modification programs (14) and obesity-specific pharmacotherapy (23). However, more studies are needed directed toward methodologies which optimize the maintenance of weight loss following removal of the IGB. Specific dietary interventions, physical activity, staged pharmacotherapy, and timed re-application of an IGB should be examined as part of a long-term strategy for the overall management of obesity, focused on the initial induction of weight loss with an IGB.

The current prospective, randomized controlled trial was designed to address some of the deficiencies of the previously published IGB studies. At the time of the IGB removal (month 6) a clinically relevant weight loss had been achieved in the IGBG, with a mean reduction of 14.2% (14.4 kg). This is consistent with a recent meta-analysis of 15 studies of the same IGB (14.7 kg) (32). In the current study, weight regain was evident at month 12 (6 months after removal of the IGB) with a mean weight loss, relative to baseline, of 9.2% (9.4 kg). Whilst few of the published studies report on post-removal outcomes, the weight regain reported in the current study is similar to that found by Herve et al. (11.1 kg) at 1 year after removal of the IGB in a similar cohort of subjects (24). The weight loss obtained in the IGBG in the current study, 6 months after removal, is greater than that reported at 12 months for behavioral modification alone (5), or for currently available pharmacotherapy (6). Importantly, this degree of weight loss at 12 months is associated with a reduction in the risk of cardiovascular events and mortality (3), and prevents the progression to type 2 diabetes in those at high risk (33).

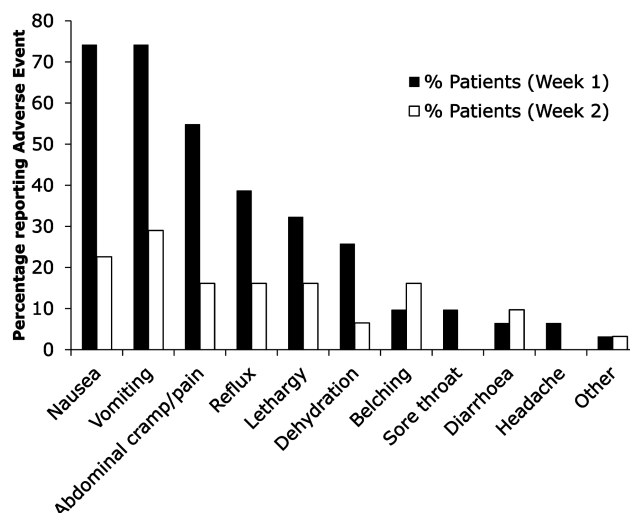
It is important to recognize that the CG also achieved clinically relevant weight loss in this study. This was in excess of those achieved

in studies of similar study design but with different investigational products (34,35). This greater sustained weight loss may be attributed to the frequency and quality of interaction with dietitian/exercise physiologist. Consistent with this, 17% of subjects in the CG achieved a weight loss of $\geq 10\%$ at month 12.

In the current study, it was anticipated that some weight regain would occur because of the predicted loss of early satiation with the removal of the IGB and the return of neurohormonal adaptive changes promoting weight regain (8). It is therefore encouraging that the subjects in the IGB group still maintained approximately 10% weight loss at month 12. As stated previously, this degree of weight loss is associated with positive health outcomes (36), and as documented in the IGBG, with approximately 50% of the subjects in remission from the metabolic syndrome from the first follow-up visit (month 3) to the end of the study (month 12). This compares to a remission rate of approximately 30% in the CG over the same period. As the current study was not powered to formally evaluate this outcome, a controlled study with an adequate sample size, in a cohort with metabolic syndrome or indeed in patients with other co-morbidities, such as type 2 diabetes, would be an appropriate objective in a future trial of the IGB.

Despite a weight regain after removal of the IGB, the mean waist circumference increased only marginally from months 6 to 12. Considering that central adiposity is more strongly associated with risk factors for cardiovascular disease than generalized obesity (37), this may suggest a longer durability for IGBs beyond that documented by overall weight loss alone. This so-called “metabolic memory effect” has also been shown previously in Diabetes Treatment and Prevention Outcome Studies (33,38) and it could be anticipated that such metabolic benefit would occur with the weight loss achieved in our trial.

One of the hypotheses tested in the current study was that the degree of weight loss achieved with the IGB would have a positive



Other include the following adverse events in week 1: anxiety x 1 patient; cough x 1; hiccups x 1; ribcage pain x 1; chest congestion x 1; constipation x 1
Include the following in week 2: cough x 1; constipation x 1

FIGURE 4 Proportion of patients in the intragastric balloon group reporting adverse events during first 14 days post-insertion.

psychological impact beyond the time of its removal. Consistent with this, the IWQOL-Lite questionnaire score improved by a mean of 20.9 points at month 6, with this improvement maintained at month 12 (22.2 points) in the IGBG. Changes above 12 points on this scale have been previously shown to be clinically relevant (39). These are important data as changes in QOL in obese individuals have not been well documented in studies of the IGB or with other therapeutic interventions, with only two publications in the case of the former, neither of which included post-removal outcomes (12,40).

Regarding the other health outcomes, significant improvements in eating behaviors were noted in each of the three domains of the TFEQ-R21 for the IGBG, relative to the CG, and this persisted for three months after its removal. However, a significant difference was maintained for the emotional eating domain only at month 12, consistent with the increase in hunger and reduced satiety following IGB removal.

While subjects in both groups experienced improved exercise tolerance, with a significant difference observed for the IGBG while the balloon was *in situ*, this statistical difference between groups was not maintained after removal. Both groups maintained improved 6 minute walk scores at month 12, compared to baseline, highlighting the success of the exercise component of the behavioral modification program.

The IGB was safe, though most subjects experienced gastro-intestinal related symptoms with these events declining during the second week corresponding to an adaptation to the IGB. No incidences of spontaneous deflation or other serious complications were reported, consistent with our selection criteria for this study which focused on excluding subjects at risk of complications related to an endoscopy and/or the insertion of the IGB. In one subject, a serious adverse event occurred (persistent vomiting, abdominal pain, and gastro-esophageal reflux), leading to premature removal of the IGB. These findings are similar to previous studies, where gastrointestinal events were experienced post-insertion (32). Our proactive management of these events with pharmacotherapy, commenced at the time of IGB insertion (for 1-2 weeks prior in the case of PPIs), plus the implementation of a specific transitional diet focused on limiting foods which might irritate the stomach, are important in reducing the severity and/or duration of these events.

A potential limitation of this study was the relatively short follow-up (6 months) after removal of the IGB. The assumed loss of the premature satiation following the removal of the IGB does predict some weight regain, perhaps related to a significant physiologically derived defense of fat stores which is believed to exist in obese individuals (8). This weight regain may have been more apparent if the study had a longer post-removal observational period. To address this, the potential use of serial balloons, with the replacement of the old with new at the time the former is removed, may be a possible approach for weight maintenance after the initial weight loss with the primary IGB, or even progressive weight loss. Some evidence for the utility of this procedure has been provided in other earlier studies (21,22). Further, as also recently reported (23), a “step down” to pharmacotherapy which would help to control appetite after IGB removal is also a possible approach for weight maintenance. The impact of these long-term approaches on health outcomes, including QOL, metabolic, and other risk factors defining co-mor-

bidity, would also be an important focus of any formal investigation using one or more of the above mentioned approaches.

Further, in future controlled studies of the IGB, the use of meal replacements aimed at matching the caloric intake of the IGBG in a CG during the initial post-insertion period is an important consideration since the former receives a predominantly fluid-based diet during initial adaptation to the IGB.

In summary, the results from this study confirm the IGB as a safe and effective modality to achieve clinically relevant weight loss in obese patients. This weight loss was generally maintained for at least 6 months after IGB removal. This weight loss was associated with approximately 50% achieving remission of metabolic syndrome, and with a clinically relevant improvement in disease-specific QOL. Given these results, further analyses of the existing database from this study focusing on the cost effectiveness of this weight loss approach is planned. ○

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