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REVIEW ARTICLE

Obesity Treatment with Botulinum Toxin-A Is Not Effective: a Systematic Review and Meta-Analysis

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Abstract The effectiveness of gastric injections of botulinum toxin-A (BTA) as primary treatment for obesity is not well known since results in literature are discrepant. Hence, we aimed to systematically review and meta-analyze the available data to assess the real effect of BTA therapy. We searched MEDLINE, Embase, Cochrane, SCOPUS, EBSCO, LILACS, and BVS. We considered eligible only randomized controlled trials enrolling obese patients comparing BTA versus saline injections. Our initial search identified 8811 records. Six studies fulfilled eligibility criteria. After critical appraisal, two articles were excluded and we meta-analyzed the remainder. The mean difference for absolute weight loss and BMI reduction were 0.12 [CI 95%, − 1.14, 1.38] and − 0.06 [95% CI, − 0.92, 0.81], respectively. Therefore, we concluded that treatment of obesity with BTA is not effective.

Keywords Obesity · Botulinum toxins · Endoscopy · Gastric emptying · Systematic review · Meta-analysis

Introduction

Development of cost-effective therapies to control the worldwide pandemic of obesity is a leading priority in modern medicine [1, 2]. Endoscopic therapies focused on weight loss are important allies since they are more effective than pharmacotherapy and lifestyle changes and present lower rate of adverse events compared to bariatric surgery [3, 4].

Current guidelines recommend lifestyle and diet improvement as a first-line therapy to fight overweight [5, 6]. After failure, bariatric surgery is the gold-standard treatment for class III obese (BMI > 40 kg/m^2) and for class II (BMI 35–40 kg/m^2) if associated with a comorbidity related to the overweight [7–9]. Currently, bariatric surgery for Class I (BMI 30-35 kg/m^2) and healthy Class II obese is not a consensus in the world. However, such patients may benefit from minimally invasive treatments such as endoscopic therapies [10].

The injection of botulinum toxin-A (BTA) in the gastric wall is a recent developed endoscopic therapy for obesity. The BTA may potentially delay the gastric emptying and improve satiety

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by causing a temporary paralysis at the injection site. The toxin blocks the acetylcholine release at cholinergic neuromuscular terminations [11]. Its effect is lost gradually over the first 3 to 6 months, and there is no permanent damage [12].

Since 2007, when Foschi et al. found superiority versus placebo in a randomized clinical trial (RCT), non-systematic reviews supporting the use of BTA as primary treatment for obesity have been published on a regular basis [13, 14]. This fact possibly leads doctors around the world to employ such technique in daily practice. The effectiveness of BTA therapy however is not well known since other results presented in the literature are highly discrepant [15].

A systematic review published in 2015 by Bang et al. [16] pooled data from randomized controlled trials and case series. Pooling data from such different studies with incredibly different methodologies and biases may lead to overestimation of effect size. Such approach affects the internal and external validity of the results. Moreover, the estimation of effect sizes of those randomized controlled trials had unexplained substantial heterogeneity thus limiting the strength of their conclusions. Nonetheless, the author chose a subgroup dosage of BTA from the meta-analyzed studies, which may have created a selection bias. Therefore, in our analysis, the results of that review is hasty and literature lack concrete data regarding the effectiveness of BTA therapy. For that reason, we performed a comprehensive systematic review and meta-analysis of available data to assess the real effect of BTA therapy as primary treatment of obesity.

Methods

This review was approved by our Internal Review Board and was registered on the International Prospective Register of Systematic Review—University of York (PROSPERO) under the Registry Number CRD42015023469 [17]. Also, we conducted this study according to the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analyses—the PRISMA Statement [18].

Two independent reviewers thoroughly searched MEDLINE, Embase, Cochrane, SCOPUS, EBSCO, LILACS, BVS, and the Library of University of Sao Paulo from inception to March 2017. Our search was not limited by language or publication date. The search strategy was (overnutrition OR overweight OR obesity OR bariatrics) AND (endoscopy OR endoscopic OR endoluminal OR transoral OR botulinum toxin OR botulinum neurotoxina-A).

We considered eligible only randomized controlled trials (RCTs), controlled clinical trials, and comparative studies enrolling obese patients (BMI greater than 30 kg/m^2). The intervention group must have been the endoscopic treatment with botulinum toxin injection in the gastric wall. The outcomes assessed were absolute weight loss (AWL) in kilograms and BMI reduction (in kg/m^2). Only studies presenting mean with standard deviation were considered eligible.

The two reviewers independently assessed studies for eligibility. Afterwards, we confronted their results and any disagreement was resolved by consensus with a third researcher. We extracted data using an Excel table and included the absolute numbers reported in the articles.

The risk of bias in individual studies was assessed using the JADAD scale [19] and the Methodology Check List: Scottish Intercollegiate Guidelines Network (SIGN) [20]. The SIGN Appraisal Checklist for RCTs is an objective tool to assess the quality of included studies and has three major topics. The first topic aims to determine the suitability of the appraised article to the systematic review. The second one assesses internal validity, and the last part is an overall assessment of the study. Finally, the study is classified as high quality, acceptable, or low quality. We considered eligible only high quality and acceptable articles.

All analyses were carried out using the software Review Manager (RevMan 5.3 - The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) [21]. We employed mean difference as measure of effect for continuous variables. We used the method of inverse variance and fixed-effect model to provide the forest and funnel plots. Data on mean difference and 95% CI for each outcome were calculated using the inverse variance test. We conducted both graphic funnel plot and I^2 analysis to identify true heterogeneity and publication bias across the studies. We considered I^2 higher than 50% as high heterogeneity. If we identified an outlier study in funnel plot analysis, we removed that study from analysis and assessed heterogeneity once again. If we did not identify an outlier, we considered true heterogeneity and changed the model of analysis from fixed to random effect analysis.

Results

We identified 8615 records in MEDLINE and 196 records in Cochrane, Embase, Scopus, EBSCO, LILACS, BVS, and Library University of Sao Paulo. Thirty-six duplicates were removed. We recovered 8787 and selected 11 studies for full-text assessment. Among them, six articles were comparative controlled studies that were appraised according to the criteria of JADAD [19] and Methodology Check List: SIGN [20]. We removed two studies from analysis after critical appraisal, in the first topic of SIGN (Table 1). One of them did not address

Table 1 Exclusion criteria according to JADAD score and Methodology Check List: SIGN

STUDY	JADAD	SIGN
Topazian 2013	3	Acceptable
Maurizio 2010	4	Rejection
Foschi 2008	1	Rejection
Reinhard 2007	4	Acceptable
Foschi 2007	4	Acceptable
Gui 2006	4	Acceptable

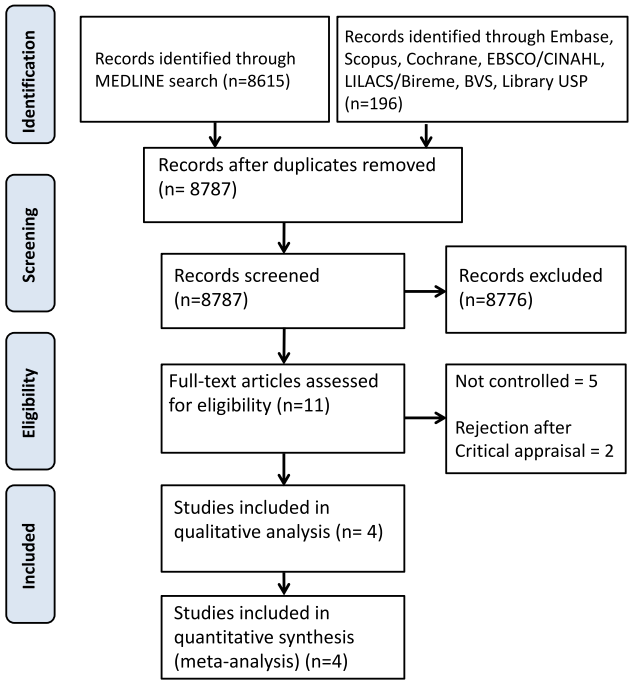

Fig. 1 PRISMA chart

correctly the clinical question to suit our review and did not assess weight loss either. The other article used data from a previous RCT to create a matched cohort and therefore was excluded from this review. The remaining four studies were enrolled in our meta-analysis (Fig. 1).

Study Characteristics

Four randomized clinical trials were enrolled in our quantitative analysis. Patients in those studies received injections with either saline or BTA. The number of injections varied from 8 to 20 in the antrum [22, 24], antrum and fundus [23], or antrum and distal body [15]. The dose of BTA injected ranged from 100 to 500 IU. Only one study [23] instructed the patients to follow a hypocaloric diet, in both intervention and control groups. Follow-up ranged from 5 to 24 weeks after the procedure. All studies reported the primary outcomes (AWL and BMI reduction) as means with standard deviation (Table 2).

PART I: Individual analysis of studies

Topazian M. Clin Gastroenterol Hepatol. 2013 [24]

Sixty obese patients were enrolled in a 24-week, double-blind, randomized, placebo-controlled trial to compare the effects of gastric antral injections of BTA (100, 300, or 500 U) or saline. Patients were given one set of injections of BTA or saline into the gastric antral muscularis propria using endoscopic ultrasound guidance. Sixteen weeks after the procedures, mean absolute weight losses were 2.2, 0.2, 2.3, and 3.0 kg in those groups, respectively. This study showed no significant difference among therapies.

Table 2 Characteristics of included studies

Study	Population	Intervention	AWL/Follow-up	BMI Reduction/Follow-up
Topazian M. (2013)	BMI higher than 30, n = 60, no diet	100 UI BTA antrum and body, n = 15; 20 injections	0.4 ± 3.1 kg/4 months	–
		300UI BTA antrum and body, n = 15; 20 injections	2.3 ± 3.4 kg/4 months	–
		500UI BTA antrum and body, n = 15; 20 injections	3 ± 5.1 kg/4 months	–
		Saline 0.9% antrum and body, n = 15; 20 injections	2.2 ± 3.5 kg/4 months	–
Mittermair R. (2007)	BMI 30–35, n = 10 female, no diet	200UI BTA antrum and body, n = 5, 16 injections	− 1.6 kg/6 months	− 0.1 kg/m^2/6 months
		Saline 0.9% antrum and body, n = 5, 16 injections	0/6 months	0/6 months
Foschi D. (2007)	BMI higher than 35 with complication or higher than 40, n = 24, 1200Kcal diet	200UI BTA antrum and body, n = 12, 20 injections	11.08 kg/2 months	4 kg/m^2/2 months
		Saline 0.9% antrum and body, n = 12, 20 injections	5.48 kg/2 months	2 kg/m^2/2 months
Gui D. (2006)	BMI higher than 30, n = 14, no diet	133UI BTA antrum, n = 6, 8 injections	7.4 kg/1 month	2.5 kg/m^2/1 month
		200UI BTA antrum, n = 4, 8 injections	5.8 kg/1 month	1.7 kg/m^2/1 month
		Saline 0.9% antrum, n = 4, 8 injections	0/1 month	0/1 month

Mittermair R. Obes Surg. 2007 [15]

In this double-blind trial, 10 female patients with class I obesity (BMI 30-35 kg/m^2) were randomly assigned into 2 groups (BTA and 0.9% saline). In intervention group, the endoscopists injected 200 U BTA into the antrum and the distal gastric body. Meanwhile, the control group had saline injections. Body weight was assessed monthly in 6 months' follow-up. There was no significant weight loss in both groups (BTA and saline).

Foschi D. Int J Obes (Lond). 2007 [23]

Twenty-four class III obese patients were blindly randomized to receive 200 U BTA or saline injections into the antrum and fundus through endoscopy. The outcomes assessed were absolute weight loss and BMI reduction. The two groups were homogeneous for anthropometric characteristics. Eight weeks after treatment, BTA patients had significantly higher absolute weight loss (11 ± 1.09 vs 5.7 ± 1.1 kg, $P < 0.001$) and BMI reduction (4 ± 0.36 vs 2 ± 0.58 kg/m^2).

Gui D. Aliment Pharmacol Ther. 2006 [22]

In this double-blind trial, 18 obese patients (BMI > 30 kg/m^2) were randomly assigned into one of three groups (BTA 133 U, BTA 200 U or saline), and received BTA or saline injections in the antrum. Absolute weight loss was assessed 5 weeks after the procedure. Fourteen patients completed the study. Both BTA groups had higher AWL at 5 weeks compared to saline, but the difference was not statistically significant.

PART II: Synthesis of Results (Meta-analysis)

Absolute Weight Loss

Four studies with seven subgroups of different BTA dosage were analyzed versus saline; the Higgins test (I^2) was 89%, suggesting high heterogeneity. Funnel plot analysis identified Foschi D. et al. [23] as the outlier responsible for the high heterogeneity. After removal of this study, I^2 became 33% suggesting homogeneity. Therefore, we kept the fixed-effects model and the MD was − 0.12 (95% CI − 1.14, 1.38) (Fig. 2). Consequently, there was no difference in AWL between groups treated with BTA and groups treated with saline injection.

BMI Reduction

Three studies with four subgroups of different BTA dosage were analyzed against saline; the Higgins test (I^2) was 86%, suggesting high heterogeneity. The funnel plot analysis identified Foschi D. et al. [23] again as the outlier responsible for the high heterogeneity. After removal of this study, I^2 became 0% suggesting homogeneity. Therefore, we kept the fixed-effects model and the MD was − 0.06 (95% CI − 0.92, 0.81) (Fig. 3). Consequently, there was no difference in BMI reduction between groups treated with BTA and groups treated with saline injection.

Risk of Bias within and across Studies

We identified and evaluated biases of each study according to the criteria of JADAD scale [19] and Methodology Check List: SIGN [20]. Results of bias assessment are outlined in Table 1. We extracted data into a table encompassing all studies and identified all other potential bias. Then, we analyzed them graphically (Fig. 4) using the software RevMan5 [21].

The key points to determine the internal validity of a randomized clinical trial are the randomization process and double-blindness of the study. As shown in the graph, we considered all RCTs enrolled on our analysis to be at low risk of bias (no red bars in the first 4 lines). The main issue we found in the studies was the significant loss to follow-up of Gui D. et al. [22], what may have created bias due to incomplete outcome data. Finally, another potential bias is related to the small size of population enrolled in the studies once small-sized studies may not show a real difference simply because of the few events analyzed.

Discussion

Currently, BTA treatment is performed worldwide despite the uncertainty of its effectiveness. This review is the first unbiased systematic review with meta-analysis regarding obesity treatment with BTA injections. A thorough search was performed, surely encompassing all available literature. We performed a meta-analysis including only high-quality articles. Consequently, the herein results are concrete and homogenous. Finally, our study is an important step to a more evidence-based practice.

Endoscopic techniques may induce weight loss by many different ways. Some methods lead to weight loss by altering intake, digestion, and absorption of food. Other methods modify distention, gastric emptying, and the release of gut hormones, especially cholecystokinin [25]. All those modalities affect satiety, reduce appetite, and improve weight loss [26–28].

The most attractive characteristic of the BTA therapy, however, is the absence of serious adverse events and procedure-related complications regardless of the technique, dose, or injection site [22, 23, 29, 30]. If effective, it would be the perfect therapy. The mechanism of action of BTA is inhibition

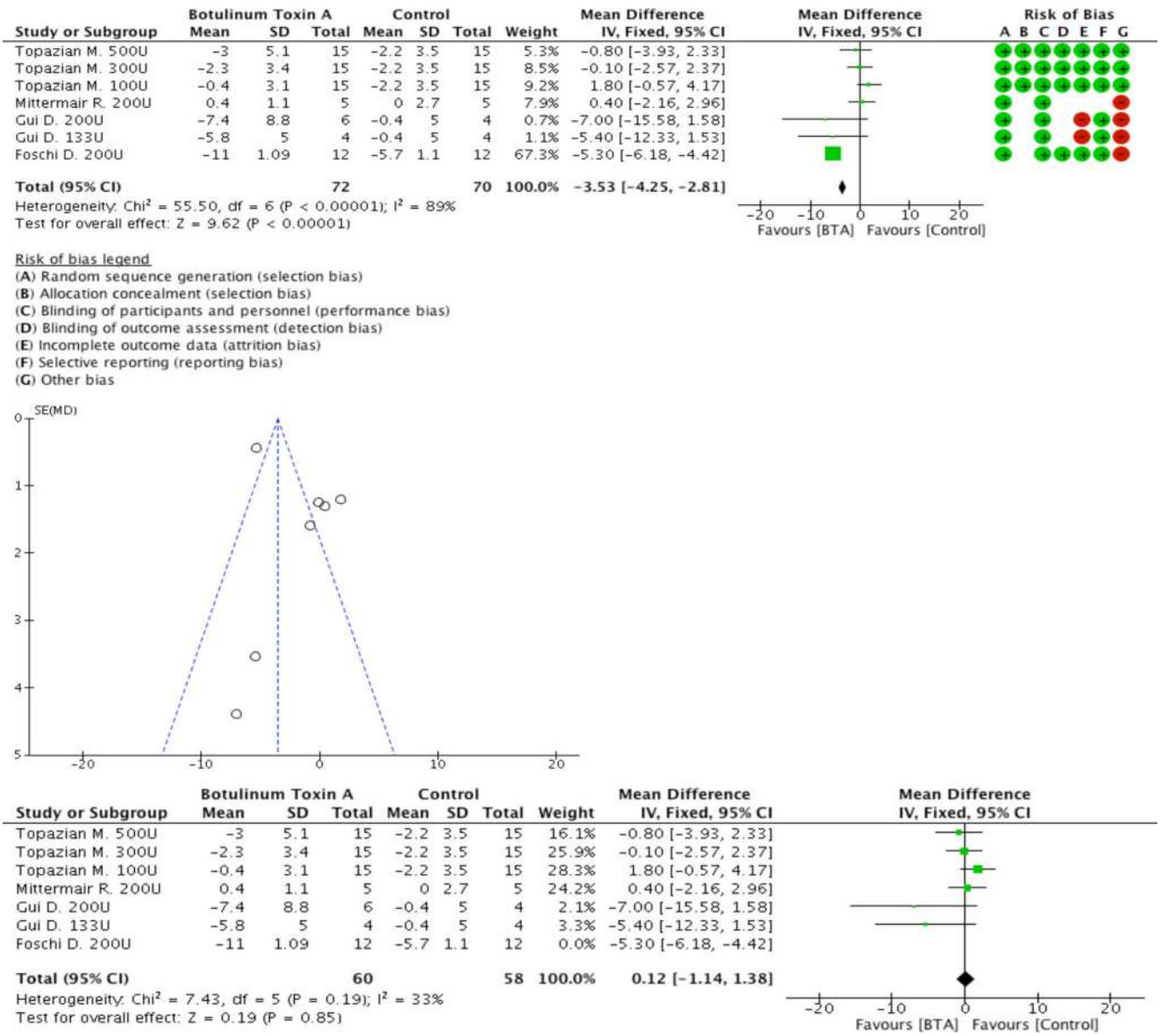

Fig. 2 Absolute weight loss: forest plot and funnel plot

of acetylcholine-mediated gastric antral motility, leading to delayed emptying and early satiety [8]. As discussed herein, the effectiveness of BTA was not proven in medical literature yet, and our results stimulate the abandonment of such method.

Our meta-analysis enrolled 96 patients and 118 events with low I^2. This fact highlights our highly homogenous studies and supports our result. BMI reduction analysis enrolled fewer patients, but we advocate that AWL analysis is enough to claim the equivalence of placebo and BTA therapy.

The US Food and Drug Administration (FDA) establishes effectiveness targets for bariatric devices according to the risk related to the treatment. The higher the risk, the higher the benefit must be. BTA therapy would be classified as Level 1 risk, meaning no serious adverse events reported. FDA expects Level 1 risk devices to provide 5% of total body weight loss (TBWL) and statistical superiority to diet and exercise control [31]. The group in our analysis with the highest AWL is the 133UI of Gui D. et al. [22], which presented an average AWL of − 7.4 kg. The mean baseline weight of that group was 138 kg. That group reached the established threshold of 5% TBWL but did not achieve statistical superiority.

Our funnel plot analysis identified Foschi D. et al. [23] as an outlier. That was only study that associated dietary orientations to BTA therapy and the only one to

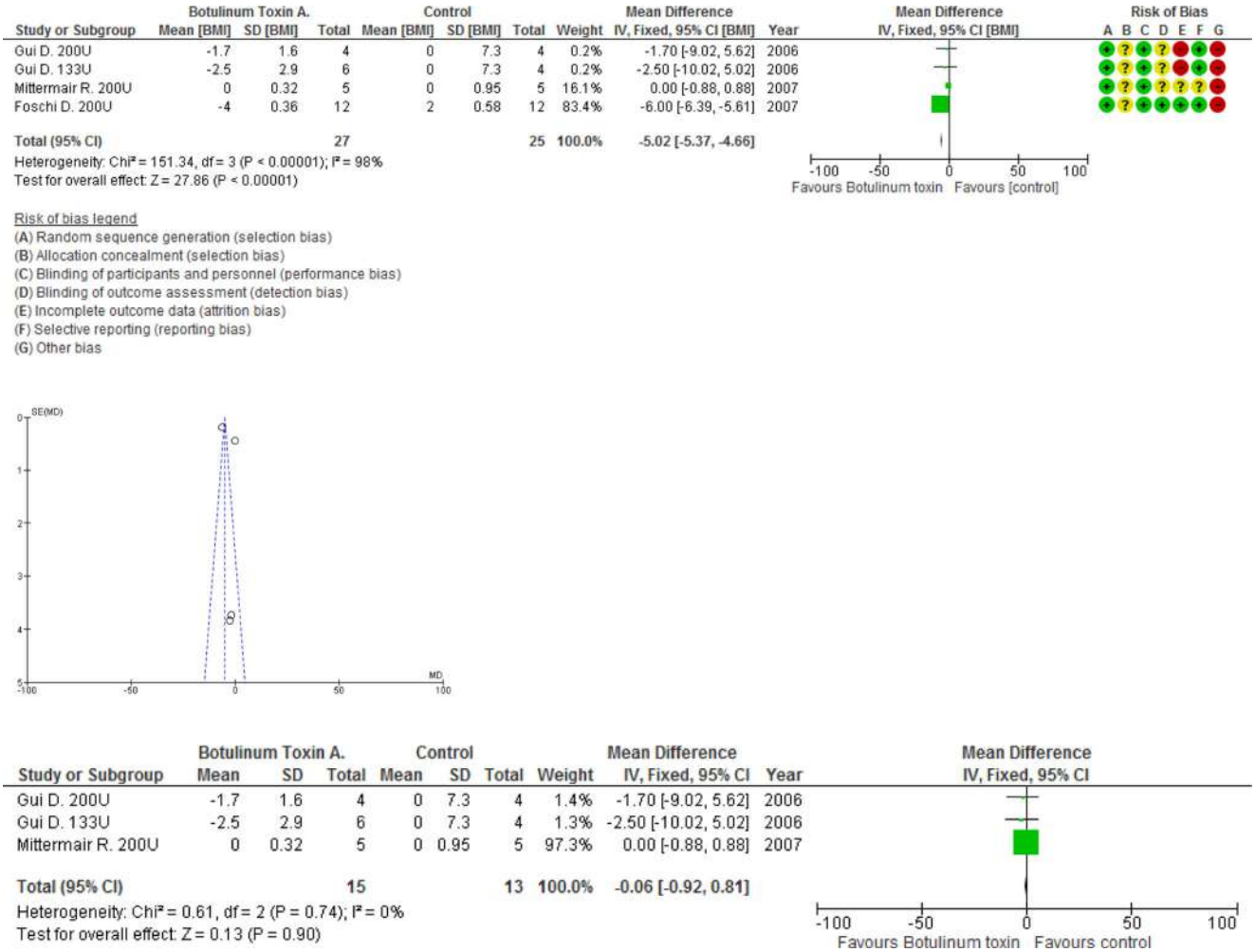

Fig. 3 BMI reduction: forest plot and funnel plot

show statistical superiority of BTA versus control. This fact either points out a publication bias or suggests that a combined approach of BTA therapy and lifestyle improvement is better than a single intervention. Moreover, it might favor the activity of the toxin effect [15, 16, 23, 32].

Our limitations are mostly related to the available literature. The studies included in our analysis used a wide variety of BTA doses, sites, and number of injections, what may have created some heterogeneity. We expected to reduce the impact of such heterogeneity by analyzing all dosage groups separately against placebo, instead of selecting a specific group.

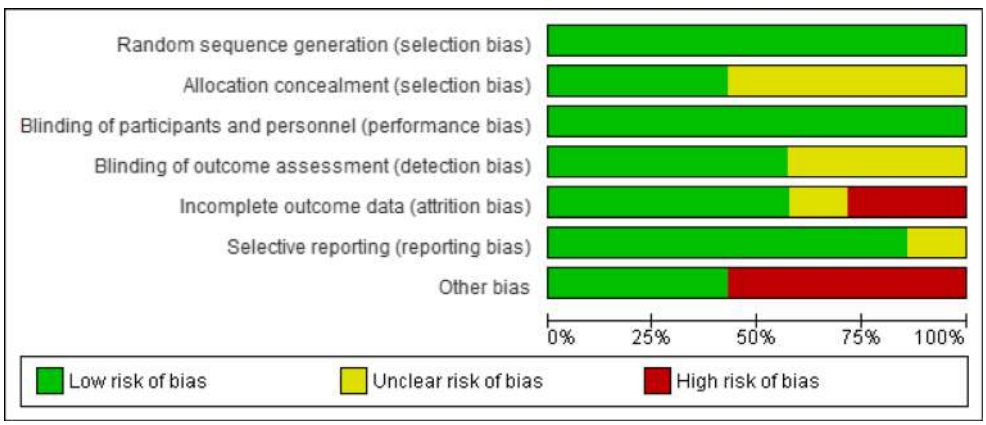

Fig. 4 Risk of bias across the studies

Moreover, only one study provided hypocaloric dietary instructions to patients [23]. As expected, however, this study was identified as an outlier. Its results showed significantly greater benefit of BTA group compared to the three other trials. We reduced the impact of this heterogeneity by removing that study from pooled analysis. Finally, our analysis is limited by the small number of patients enrolled. We advocate, however, that this is the real data currently available in literature and includes only articles with high quality of evidence. As a consequence, the consistency of our results is encouraging and supports our conclusions.

Three independent high-quality and homogenous RCTs did not find superiority of BTA versus placebo. As expected, neither did our pooled analysis. Hence, further studies are unlikely to change our results.

Conclusion

The available literature demonstrates that BTA therapy alone is not effective for the primary treatment of obesity.

Compliance with Ethical Standards

Funding None.

Conflict of Interest Dr. GALVAO NETO reports personal fees from APOLLO ENDOSURGERY, personal fees from FRACTYL LABS, personal fees from GI WINDOWS, personal fees from GI DYNAMICS, personal fees from ETHICOM ENDOSURGERY, personal fees from ALACER BIOMEDICA outside the submitted work. All the other authors have nothing to declare.

Ethical Approval Statement All procedures performed in 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 Statement Does not apply.

References

1. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. Arch Intern Med. 2000;160(7):898–904.
2. Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. Obes Surg. 2013;23(4):427–36.
3. Douketis JD, Macie C, Thabane L, et al. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. Int J Obes (Lond). 2005;29(10):1153.
4. Leslie WS, Hankey CR, Lean ME. Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review. QJM. 2007;100(7):395.
5. Lau DC. Synopsis of the 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. CMAJ. 2007;176(8):1103.
6. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(2):342.
7. Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: surgical treatment of obesity. Ann Intern Med. 2005;142(7):547.
8. Elder KA, Wolfe BM. Bariatric surgery: a review of procedures and outcomes. Gastroenterology. 2007;132(6):2253.
9. Roman S, Napoléon B, Mion F, et al. Intragastric balloon for "non-morbid" obesity: a retrospective evaluation of tolerance and efficacy. Obes Surg. 2004;14(4):539.
10. Busetto L, Segato G, De Luca M, et al. Preoperative weight loss by intragastric balloon in super-obese patients treated with laparoscopic gastric banding: a case-control study. Obes Surg. 2004;14(5):671.
11. García-Compean D, Maldonado Garza H. Intragastric injection of botulinum toxin for the treatment of obesity. Where are we? World J Gastroenterol. 2008;14:1805–9.
12. Topazian M, Camilleri M, De La Mora-Levy J, et al. Endoscopic ultrasound-guided gastric botulinum toxin injections in obese subjects: a pilot study. Obes Surg. 2008 Apr;18(4):401–7.
13. Pero R, Coretti L, Lembo F. Botulinum toxin A for controlling obesity. Toxins (Basel) 2016 8(10).
14. Klobucar Majanovic S, Brozovic B, Stimac D. Bariatric endoscopy: current state of the art, emerging technologies, and challenges. Expert Rev Med Devices. 2017;14(2):149–59.
15. Mittermair R, Keller C, Geibel J. Intragastric injection of botulinum toxin for the treatment of obesity. Obes Surg. 2007;17:732–6.
16. Bang CS, Baik GH, Shin IS, et al. Effect of intragastric injection of botulinum toxin A for the treatment of obesity: a meta-analysis and meta-regression. Gastrointest Endosc. 2015;81(5):1141–9.e1–7.
17. PROSPERO—International prospective register of systematic reviews. University of York. Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013170.
18. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9, W64.
19. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
20. Scottish Intercollegiate Guidelines Network, Healthcare Improvement Scotland. SIGN 50: A guideline developer's handbook. 1st ed. Scotland. 2011 56-60p. Available from http://www.sign.ac.uk/guidelines/index.html.
21. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
22. Gui D, Mingrone G, Valenza V, et al. Effect of botulinum toxin antral injection on gastric emptying and weight reduction in obese patients: a pilot study. Aliment Pharmacol Ther. 2006;23(5):675–80.
23. Foschi D, Corsi F, Lazzaroni M, et al. Treatment of morbid obesity by intraparietogastric administration of botulinum toxin: a randomized, double-blind, controlled study. Int J Obes. 2007;31(4):707–12.
24. Topazian M, Camilleri M, Enders FT, et al. Gastric antral injections of botulinum toxin delay gastric emptying but do not reduce body weight. Clin Gastroenterol Hepatol. 2013;11(2):145–50.e1.
25. Lal S, McLaughlin J, Barlow J, et al. Cholecystokinin pathways modulate sensations induced by gastric distension in humans. Am J Physiol Gastrointest Liver Physiol. 2004;287(1):G72–9.
26. Geliebter A, Westreich S, Gage D. Gastric distention by balloon and test-meal intake. Am J Clin Nutr. 1988;48:592–4.
27. Genco A, Bruni T, Doldi SB, et al. BioEnterics Intragastric balloon: the Italian experience with 2,515 patients. Obes Surg. 2005;15(8):1161–4.
28. Sallet JA, Marchesini JB, Paiva DS, et al. Brazilian multicenter study of the intragastric balloon. Obes Surg. 2004;14(7):991–8.
29. Júnior AC, Savassi-Rocha PR, Coelho LG, et al. Botulinum A toxin injected into the gastric wall for the treatment of class III obesity: a pilot study. Obes Surg. 2006;16(3):335–43.

30. Albani G, Petroni ML, Mauro A, et al. Safety and efficacy of therapy with botulinum toxin in obesity: a pilot study. J Gastroenterol. 2005;40(8):833–5.
31. Lerner H, Whang J, Nipper R. Benefit-risk paradigm for clinical trial design of obesity devices: FDA proposal. Surg Endosc. 2013;27(3):702–7. Erratum in: *Surg Endosc*. 2013 Mar;27(3):708
32. Foschi D, Lazaron M, Sangaletti O, et al. Effects of intramural administration of botulinum toxin A on gastric emptying and eating capacity in obese patients. Dig Liver Dis. 2008;40:667–72.