Surgical Endoscopy (2019) 33:3984–3989
https://doi.org/10.1007/s00464-019-06687-0

Peri-operative, intravenous clindamycin may improve the resolution rate of hypertension after Roux-en-Y gastric bypass in morbidly obese patients

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Received: 30 August 2018 / Accepted: 25 January 2019 / Published online: 7 February 2019

Abstract

Background Recent studies have suggested that potential aberrant alterations in the gastrointestinal microbiome contribute to the development of cardiovascular disease, specifically hypertension. Bariatric surgery produces significant sustained weight loss and hypertension resolution likely through multiple mechanisms which includes beneficial changes in the gut microbiome. We hypothesized that the type of prophylactic antibiotic given for bariatric surgery could impact the resolution rate of hypertension by altering the post-operative gastrointestinal microflora.

Methods A retrospective analysis of adult bariatric patients who underwent Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) between 2012 and 2016 was conducted. The standard antibiotic prophylaxis was cefazolin, or clindamycin in patients with a penicillin allergy. Univariate analyses were performed comparing the differing peri-operative antibiotic treatments with resolution of hypertension at 2-week (± 1 week), 6-week (± 2 weeks), 3-month (± 2 weeks), 6-month (± 6 weeks), and 1-year (± 2 months) follow-up appointments. The criterion for resolution of hypertension was no longer requiring medication at time of follow-up.

Results In total, 123 RYGB and 88 SG patients were included. No significant differences were found between cefazolin and clindamycin regarding hypertension resolution rates after SG. However, patients who underwent RYGB and received clindamycin had a significantly higher rate of hypertension resolution compared to cefazolin. This effect started at 2 weeks post-operatively (52.4% vs. 23.5% respectively, $p = 0.008$) and persisted up to the 1-year (57.9% vs. 44.0% respectively, $p = 0.05$).

Conclusion Prophylactic peri-operative, intravenous clindamycin was associated with significantly increased resolution of post-operative hypertension compared to cefazolin. This finding was not observed in SG patients. Future studies are needed to confirm the mechanism of action for this novel finding is due to the differing modifications of the gastrointestinal microflora after RYGB resulting from the specific peri-operative antibiotic administered.

Keywords Microbiome · Gastric bypass · Antibiotic · Sleeve gastrectomy · Hypertension

Hypertension is the leading cause of cardiovascular and renal diseases and accounts for 13% of all deaths. By the year 2025, an estimated 1.6 billion patients will be diagnosed with hypertension [1]. Despite medications and lifestyle changes with diet and exercise, the prevalence of hypertension remains high with the majority of patients requiring life-long medical treatment. The cause of hypertension is unknown in 90% of cases; however, it is believed that systemic inflammation mediated by alteration in the gut microbiome is an important contributor to hypertension [2].

The human gastrointestinal tract harbors a diverse and rich ecosystem of microbes that affects whole body health [3]. In disease states such as hypertension, there are observed differences in gut microbial composition in patients with hypertension and cardiovascular disease suggesting a link between microbial health and human cardiovascular physiology [4, 5]. Gut microbiota can affect blood pressure by influencing hormones like serotonin, dopamine, norepinephrine, as well as secrete inflammatory metabolites [6]. Gut metabolites such as short chain fatty acids can profoundly impact the cardiovascular system and renal sensory nerves [7]. Administration of antibiotics or probiotics can improve

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blood pressure due to beneficial alterations in the microbiome [8, 9]. This suggests a potential link between the gut microbiome and the pathogenesis of hypertension, and that beneficial modifications to the microbiome may treat and resolve hypertension.

Although the majority of patients require life-long medical treatment for their hypertension, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) result in substantial improvements in hypertension. The resolution rate of hypertension is 50% or higher at 1 year after both RYGB and SG [10, 11]. One mechanism for the dramatic resolution of hypertension after bariatric surgery may include beneficial, post-surgical changes in the gut microbiome. There are profound and consistent changes in the gut microbial composition after RYGB and SG [12–15]. The effect of bariatric surgery on the gut microbiome in hypertensive patients and its role in disease resolution is unknown. One way to explore whether or not the microbiome is responsible for the improvement in hypertension after bariatric surgery is to determine if antibiotics which are secreted into the gastrointestinal tract at the time of surgery alter the post-bariatric resolution rate of hypertension. In this study, we compared the effect of a single dose of cefazolin to clindamycin at the time of a RYGB or SG on the short- and long-term resolution rates of hypertension.

Methods

A retrospective analysis of adult bariatric patients who underwent a primary Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) between 2012 and 2016 at a single academic medical center was conducted. Patients were identified through the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program database, and data were supplemented using the institution's electronic medical records. Peri-operative data were gathered on variables including age, sex, pre-operative BMI (body mass index), smoking status within 1 year of surgery, number of hypertension medications pre-operatively, and %BMI change within 1 year of surgery. %BMI change was calculated using the following formula:

$$(12 \text{ month follow-up BMI} - -\text{Pre-Op BMI})/\text{Pre-Op BMI} \times 100\%.$$

The standard antibiotic prophylaxis for the study interval was cefazolin. Patients with a penicillin allergy received clindamycin. Antibiotic prophylaxis was delivered through a single pre-operative dose, within 1 h of surgery. For cefazolin dosing, patients weighing ≤ 100 kg received 2 g, and patients weighing > 100 kg received 3 g. For clindamycin, 900 mg was the standard fixed prophylactic dose. Re-dosing was performed for cefazolin if the intra-operative case was continuing at 4 h and for clindamycin if the case was continuing at 6 h.

Patients were excluded from the study if they had received oral or intravenous antibiotics or immunosuppressive therapy within 30 days of surgery, or at any point upon completion of the surgery up to 30 days following surgery. Patients were also excluded if there were no data available to properly monitor changes in their hypertension status. Patients were only included if they were on medications for their hypertension prior to surgery. If patients missed a follow-up appointment, they were excluded from analysis for only that specific time-point. We excluded these patients on the premise of not being able to definitively track their hypertension resolution or recurrence.

The Medical College of Wisconsin Institutional Review Board (Milwaukee, Wisconsin) approved this study. SPSS, version 21 (IBM Corp.) was used for all statistical analyses. A p value of ≤ 0.05 was considered statistically significant for all analyses. Categorical data were analyzed using Chi-square tests and continuous data were analyzed using independent samples t tests. Univariate analyses were performed to determine whether the type of antibiotic influenced resolution of hypertension at standard post-operative intervals including: 2-weeks ($\pm$ 1 week), 6-weeks ($\pm$ 2 weeks), 3-months ($\pm$ 2 weeks), 6-months ($\pm$ 6 weeks), and 1-year ($\pm$ 2 months). The criterion for resolution of hypertension was no longer requiring medication at the time of follow-up in clinic. Post-operative changes in hypertension medication regimens were provided by the bariatric surgeon at patients' follow-up appointments, or through their prescribing provider during visits that occurred between their regularly scheduled bariatric surgery follow-ups.

Results

In total, 286 RYGB and 217 SG patients underwent surgery between 2012 and 2016. Of these, 123 RYGB and 88 SG patients had pre-operative medication-controlled hypertension and were included in our analyses. Of the 88 SG patients, 71 patients received cefazolin (80.7%) and 17 patients received clindamycin (19.3%). Three SG patients received a second, intra-operative dose of intravenous cefazolin per the intra-operative re-dosing protocol. There was no difference in the gender distribution of SG patients who received cefazolin versus clindamycin (Table 1). The mean BMI for SG patients who received cefazolin was 48.9 ± 9.54 kg/m^2 and the mean BMI for SG patients who received clindamycin was 46.0 ± 9.68 kg/m^2 ($p = 0.27$). There were no significant differences in the mean age, number of hypertension medications, or %BMI change at one year post surgery for SG patients who received cefazolin versus clindamycin (Table 1).

Table 1 Pre- and post-operative variables for sleeve gastrectomy patients

Sleeve gastrectomy	Cefazolin ($n=71$)	Clindamycin ($n=17$)	p value
Age (years)	44.0 ± 12.5	50.4 ± 10.5	0.06
Female	77.7%	76.5%	0.93
Number of HTN medications	1.9 ± 0.88	2.5 ± 1.24	0.15
Pre-operative BMI (kg/m^2)	48.9 ± 9.54	46.0 ± 9.68	0.27
%BMI change after 1 year	26.8 ± 9.10	25.7 ± 8.70	0.71

Statistical significance determined at $p<0.05$ comparing cefazolin and clindamycin sleeve gastrectomy patients

HTN hypertension, *BMI* body mass index

Table 2 Pre- and post-operative variables for Roux-en-Y gastric bypass patients

Gastric bypass	Cefazolin ($n=102$)	Clindamycin ($n=21$)	p value
Age (years)	47.2 ± 11.5	47.0 ± 11.1	0.92
Female	80.6%	92.0%	0.18
Number of HTN medications	2.03 ± 1.03	1.81 ± 0.87	0.53
Pre-operative BMI (kg/m^2)	46.9 ± 7.0	46.9 ± 6.7	0.99
%BMI change after 1 year	32.9 ± 8.6	31.4 ± 7.07	0.50

Statistical significance determined at $p<0.05$ comparing cefazolin and clindamycin gastric bypass patients

HTN hypertension, *BMI* body mass index

Of the 123 RYGB patients, 102 patients received cefazolin (82.9%) and 21 patients received clindamycin (17.1%). Nine RYGB patients received a second, intra-operative dose of intravenous cefazolin per the intra-operative re-dosing protocol. As shown in Table 2, there was no difference in the gender distribution of RYGB patients who received cefazolin versus clindamycin. The mean BMI for RYGB patients who received cefazolin was 46.9 ± 7.0 kg/m^2 and the mean BMI for RYGB patients who received clindamycin was 46.9 ± 6.7 kg/m^2 ($p=0.996$). There was no difference in the mean age, number of hypertension medications, or %BMI change at 1 year post surgery for RYGB patients who received cefazolin versus clindamycin (Table 2).

No significant differences were found in the rate of hypertension resolution following SG, based on whether the pre-operative antibiotic was cefazolin or clindamycin (Fig. 1). However, there was a significant and persistent difference in the resolution rate of hypertension after RYGB with the use of prophylactic clindamycin compared to cefazolin. Patients who underwent RYGB and received clindamycin experienced a significantly increased rate of hypertension resolution when compared to those who were administered cefazolin (Fig. 2). This effect was significant beginning at 2-weeks after surgery (52.4% clindamycin vs. 23.5% cefazolin, $p=0.008$) and persisted through 1-year (57.9% clindamycin vs. 33.3% cefazolin, $p=0.05$).

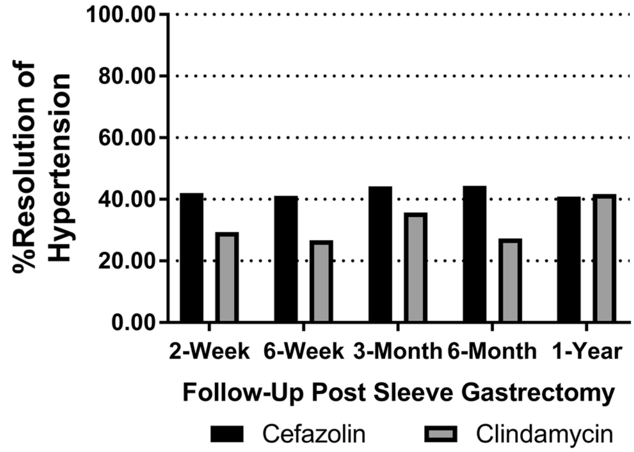

Fig. 1 Sleeve gastrectomy rate of hypertension resolution for 1 year post-operatively based on the type of peri-operative antibiotic used (cefazolin-black, clindamycin-gray)

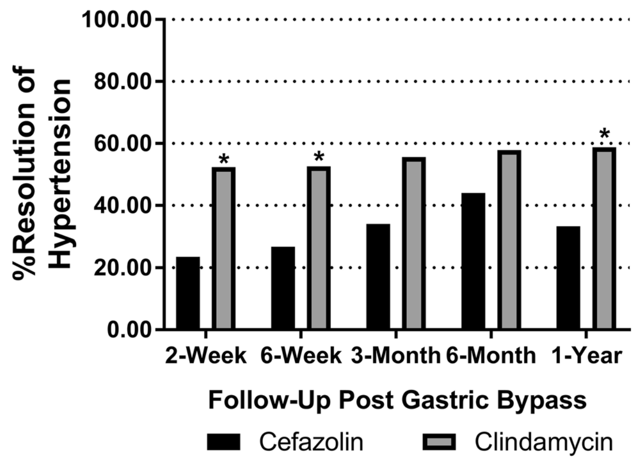

Fig. 2 Roux-en-Y gastric bypass rate of hypertension resolution for 1 year post-operatively based on the type of peri-operative antibiotic used (cefazolin-black, clindamycin-gray). *Statistical significance at $p \le 0.05$

Discussion

In this study, we compared the short- and long-term resolution rates of hypertension after RYGB and SG between patients who received peri-operative cefazolin or clindamycin. Although the type of peri-operative antibiotic administered did not affect sleeve gastrectomy hypertension resolution rates, we observed significantly increased rates of hypertensive resolution up to 1 year post-operatively in RYGB patients receiving a single, peri-operative dose of clindamycin. The impact of antibiotic class on hypertension resolution after RYGB was not due to differences in groups related to age, sex, severity of pre-operative hypertension, or starting BMI. Furthermore, both antibiotic groups lost a similar amount of weight after RYGB, therefore the difference in hypertension resolution rates appears to be independent of surgical weight loss. These findings suggest a novel mechanism for hypertension resolution after RYGB related to gut microbial alterations that may be further beneficially manipulated through peri-operative antibiotic treatment.

The ability of an antibiotic to affect hypertension is in concordance with previous literature that systemic antibiotics can alter the gastrointestinal flora and improve blood pressure. Administration of minocycline improved blood pressure and decreased dysbiosis by increasing the Firmicutes to Bacteroidetes ratio in two rodent models of hypertension [8]. A meta-analysis of nine randomized trials found a significant decrease in both systolic and diastolic blood pressure in patients who took probiotics [8]. Effects of probiotics were greatest for patients with treatment-resistant hypertension, multiple species probiotic use, duration of treatment > 8 weeks or use of a ≥ 1011 colony forming units [9].

Although the peri-operative antibiotics in this study were delivered systemically and not orally, both antibiotics are excreted into the gastrointestinal tract with intravenous administration due to biliary excretion. Once excreted into the bile, they can reach high concentrations in the intestinal lumen leading to major disruptions of the gut microbiota [16, 17]. Clindamycin is a broad-spectrum antibiotic that primarily targets anaerobic bacteria as well as Gram-positive aerobic bacteria. Clindamycin administration in post-surgical patients caused a temporary decrease of streptococci, enterococci, and anaerobes which returned to normal after 2 weeks [18]. In healthy volunteers, clindamycin administration induced a marked decrease in anaerobic bacteria including Bacteroidetes with an increase in Enterococci and Enterobacteria [19]. Cefazolin is a broad-spectrum antibiotic with Gram-positive and Gram-negative coverages. In patients undergoing cefazolin treatment, Firmicutes dominated the fecal microbiota, but later samples revealed decreased diversity with displacement of Firmicutes by Bacteroidetes followed by eventual restoration of the pre-operative flora [20]. Although not previously studied in bariatric patients, we would speculate oral antibiotics could also have the same potential to alter the microbiome and affect hypertension resolution and select antibiotics could be used to improve the efficacy of the surgery on metabolic disease. As the gastrointestinal tract is permanently altered at the time of peri-operative antibiotic administration during a RYGB, this could support our hypothesis that a single dose of antibiotic in conjunction with a gastric bypass could have long-lasting shifts in the gut microbiome.

As patients who received clindamycin were penicillin allergic, it possible that a penicillin allergy somehow alters the microbiome or other factors which affect the resolution rate of hypertension after RYGB. However, Jahansouz et al. recently published the impact of antibiotics on metabolic health after SG in mice. The authors found that antibiotic use of any kind (fidaxomicin, streptomycin, or ceftriaxone) decreased bacterial diversity and uniquely altered the microbial composition compared to no antibiotic use [21]. All antibiotic groups had significantly increased subcutaneous adiposity and impaired glucose homeostasis compared to no antibiotic administration after SG [21]. As peri-operative antibiotic administration is part of our routine clinical protocol, we do not have a control group in either RYGB or SG patients to determine if hypertension resolution would be superior or inferior without antibiotics compared to clindamycin or cefazolin. We feel this study supports the concept that antibiotics at the time of bariatric surgery can have beneficial or deleterious effects on the microbiome to alter metabolic disease improvements, and it is likely not due to some unique underlying physiology in penicillin allergic patients mediating the difference in hypertension resolution rates.

Interestingly, our finding was unique to RYGB patients only. Although both procedures change the post-operative gut microflora, previous studies have proposed these alterations are different and specific for each procedure type [22, 23]. Similarly, Medina et al. found both RYGB and SG had more pronounced changes in intestinal microbiota than dietary treatment alone. In this study, RYGB patients experienced an increase in Bacteroidetes phylum diversity, whereas it was reported SG patients actually have decreased diversity in regard to the Bacteroidetes phylum [24]. In rodent models of bariatric surgery, RYGB and SG produce similar improved diversity but different composition changes at 10 weeks after surgery [25]. Several studies have found that RYGB uniquely shifts the microbiota to a higher relative abundance of Proteobacteria, specifically Gammaproteobacteria [12, 13, 26]. Zhang et al. observed a significant decrease of Firmicutes and increase in Gammaproteobacteria 6 months post RYGB in three normotensive patients [13]. Graessler et al. found a significant alteration in inflammatory activity, changes in 22 microbial species, 11 genera, and 1 phylum at 3 months after RYGB in diabetic patients. There was an abundance of Proteobacteria and a decrease in relative abundance of Firmicutes post-operatively [12]. Currently, the specific role of Gammaproteobacteria in the metabolic effect of RYGB is unknown.

The most important limitation of this study is the lack of prospectively collected stool samples to document causation rather than theoretical changes linking an antibiotic to the microbiome and subsequently hypertension resolution. Future studies will prospectively validate the impact of peri-operative antibiotics on hypertension resolution after

RYGB and specifically study how different antibiotics affect the microbiome in the short- and long-term after surgery. Another limitation involves the measurement of hypertension and definition for hypertension resolution. Hypertension resolution was determined when patients were off all hypertensive medications and not based on normotensive blood pressure readings off medications. Adding to this limitation, individual blood pressures were not analyzed to determine if the patient had un-treated hypertension despite being off medications. Further, we did not have the ability to discern if anti-hypertensive medications were being used post-operatively for another diagnosis other than hypertension if not noted in the medical record. Future prospective studies should be conducted using actual office blood pressure measurements to determine normotension on and off medications. Finally, based on our effect size of clindamycin compared to cefazolin on hypertension resolution rate at 2 weeks, 46 patients would be needed per group to be appropriately powered. Therefore, this study is underpowered to detect pre-operative differences among the two groups which may account for this finding beyond the antibiotic.

Conclusions

This study represents the first clinical report to suggest a critical relationship between the altered gut microbiome and hypertension resolution after bariatric surgery. We hypothesize the difference in hypertension resolution rates between the different antibiotic groups which represents superior long-term alterations in the gut microbiome with clindamycin in RYGB patients. Further studies will validate these findings prospectively and determine the impact of peri-operative antibiotics on the gut microbial composition both short and long term after RYGB. This research provides the opportunity to learn mechanistic information about how a RYGB affects hypertension as well as the potential application of these mechanisms to improve disease treatment by beneficially manipulating the microbiome at the time of RYGB with antibiotics or probiotics to achieve superior disease resolution.

Compliance with ethical standards

Disclosures Dr. Goldblatt is a consultant for WL Gore, is a consultant and has received research funding from Medtronic, has received research funding from Merck, is a consultant for Allergan, and has received research funding from BD. Dr. Gould is a consultant for ETHICON/TORAX. Jacob J. Patz BS, Melissa C. Helm MS, Rana M. Higgins MD, Matthew I. Goldblatt MD, Jon C. Gould MD, and Tammy L. Kindel MD PhD have no conflicts of interest or financial ties to disclose.

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