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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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ORIGINAL ARTICLE

Retrospective Study

Impact of intragastric balloon on blood pressure reduction: A retrospective study in Eastern North Carolina

Gbeminiyi Olanrewaju Samuel, Karissa Lambert, Elijah Asagbra, Glenn Harvin, Eric Ibegbu

ORCID number: Gbeminiyi Olanrewaju Samuel 0000-0002-4108-009X; Karissa Lambert 0000-0002-0663-2549; Elijah Asagbra 0000-0003-0348-5042; Glenn Harvin 0000-0003-1129-8781; Eric Ibegbu 0000-0001-7782-425X.

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Gbeminiyi Olanrewaju Samuel, Glenn Harvin, Eric Ibegbu, Division of Gastroenterology, East Carolina University, Greenville, NC 27834, United States

Karissa Lambert, Department of Internal Medicine, Brody School of Medicine, East Carolina University, Greenville, NC 27834, United States

Elijah Asagbra, Department of Health Services and Information Management, East Carolina University, College of Allied Health Sciences, Greenville, NC 27834, United States

Corresponding author: Gbeminiyi Olanrewaju Samuel, MD, Academic Fellow, Division of Gastroenterology, East Carolina University, 2100 Stantonsburg Road, Greenville, NC 27834, United States. gbeminiyi.samuel@gmail.com

Abstract

BACKGROUND

Obesity has evolved into a global pandemic. The prevalence of obesity and hypertension in eastern North Carolina are comparable, if not higher, than the national prevalence. In the United States, an estimated 34% of adults have hypertension, the most modifiable risk factor for heart disease and stroke. Lifestyle and pharmacological interventions often do not provide sustained weight loss in obese patients. Bariatric surgery offers an effective weight reduction with short-and long-term health improvements; however, a higher body mass index is associated with higher surgical morbidity and mortality, longer hospitalization, and increasing rates of 30-day readmission due to co-morbidities. Intragastric balloon may bridge a critical gap in the treatment of obesity. The objective of this paper is to showcase the impact of endoscopic bariatric therapy on blood pressure reduction.

AIM

To investigate the impact of intragastric balloon on blood pressure reduction.

METHODS

A retrospective chart review was conducted from January 1, 2016 to January 31, 2019 of consecutive adults who received intragastric balloon therapy (IGBT) in a gastroenterology private practice in Eastern North Carolina. The balloon was introduced into the stomach under endoscopic guidance, and while in the region of the gastric body, inflation with saline was performed at increments of 50 mL until target volume between 500 to 650 mL of saline was attained depending on

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the patient's gastric capacity. No procedural complications were noted during endoscopic placement and removal of the balloon. A cohort study design was used for data analysis. A total of 172 patients had the Orbera® intragastric balloon placed. Of the 172 patients who had IGBT at baseline, 11 patients (6.4%) requested early balloon removal due to foreign body sensation (n = 1), and/or intolerable gastrointestinal adverse events (n = 10). The reported gastrointestinal adverse events were nausea, vomiting, abdominal pain, and diarrhea. Eventually, 6-mo follow-up data were available for only 140 patients. As a result, only the 140 available at the 6-mo follow-up were included in the analysis. Univariate, bivariate, and multivariate statistical analyses were performed. Specifically, scatterplots were created to show the relationship between weight and blood pressure, and paired two-sample t-test was carried out to determine if there was a significant reduction in weight before and after the IGBT. Multiple regressions were also performed to examine the association between participants' total body weight and blood pressure. The outcome variables for the multiple regression were systolic and diastolic blood pressure measured as continuous variables. This was followed by logistic regression analyses to determine the association between total body weight and hypertension at 6-mo post-implantation. The outcome variables for the logistic regression were systolic blood pressure–non-hypertensive (140 mmHg or less) or hypertensive (greater than 140 mmHg), and diastolic blood pressure–non-hypertensive (90 mmHg or less) or hypertensive (greater than 90 mmHg). All authors had access to the study data and reviewed and approved the final manuscript. All statistical analyses were done using STATA 14®.

RESULTS

The study included 15% males and 85% females. 50% of the patients were white and just over 22% were non-white, and about 27% declined to give their race. The average baseline patients' weight prior to IGBT was 231.61 Lbs. (SD = 46.53 Lbs.). However, the average patients' weight after IGBT at the 6-mo follow-up was 203.88 Lbs. (SD = 41.04 Lbs.). Hence, on average, the percent total body weight loss at 6-mo is 11.97 after IGBT. The logistic regression performed revealed that weight ($\beta = 0.0140$, $P < 0.000$) and age ($\beta = 0.0534$, $P < 0.000$) are important factors in determining systolic blood pressure after IGBT. None of the other demographic characteristics or indicated comorbidities were found to be significant.

CONCLUSION

IGBT can be an effective short-term weight reduction modality with a relatively little risk of adverse event. Due to its improvement on systolic blood pressure, IGBT may help reduce cardiovascular risk.

Key Words: Intragastric balloon; Orbera®; Obesity; Hypertension; Systolic blood pressure; Diastolic blood pressure

Core Tip: Obesity is one of the leading causes of preventable life-years lost among Americans. Adults who have obesity compared with adults at a healthy weight have an increased risk of developing serious health conditions including hypertension. The treatment of hypertension in obesity is complicated by a high prevalence of resistant hypertension, as well as unpredictable hemodynamic effects of many medications. Weight loss stabilizes neurohormonal activity and causes clinically significant reductions in blood pressure. While lifestyle interventions can improve blood pressure, they fail to consistently yield sustained weight loss and have not demonstrated long-term benefits. Weight loss promotes dramatic declines in blood pressure and attenuation of long-term cardiovascular risk.

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INTRODUCTION

Obesity with its associated devastating consequences has evolved into a global pandemic and a major health concern[1]. In the United States, an estimated 34% of adults have hypertension (approximately 8.7 million people), which is the most modifiable risk factor for heart disease and stroke[2]. Lifestyle interventions often do not provide sustained weight loss for people who are obese[2]. While 4.5%-11% total body weight loss can be achieved with pharmacological agents, some patients cannot achieve enough weight loss with lifestyle modifications and medication alone[3]. The pharmacological agents indicated for weight reduction often have limited data for long term effects or intolerable side effect profile[4]. Bariatric surgery is the most effective weight reduction intervention with short- and long-term health improvements; however, a higher body mass index is associated with higher surgical morbidity and mortality, longer hospitalization, and increasing rates of 30-d readmission due to co-morbidities[5-8]. In addition, risks may outweigh the benefits in those with a greater body mass index. While the mortality rates associated with bariatric surgery have decreased, the complication rates remain high with one meta-analysis citing a complication rate of 17% and a reoperation rate of 7%[9]. In addition, only 1% of patients eligible for bariatric surgery ultimately undergo the procedure[3]. Minimally invasive non-surgical options may bridge a critical gap in the treatment of obesity[10,11].

One of the most widely studied of the endoscopic bariatric therapies is Orbera, which is an intragastric balloon approved for a body mass index of 30-40 kg/m^2[11]. It is a spherical silicone device, filled with saline, that is endoscopically implanted and removed with an approved indication of placement for six months[10,11]. It promotes weight loss by its effect as a space occupying device and altering gut hormones, however the mechanism is not quite clear[11]. One study showed that weight loss achieved with Orbera was 11.3% and excess weight loss measured was 25.4%[9]. Comorbidity improvement occurs at a 10% body weight reduction[1,12,13].

Limited studies have evaluated the efficacy of Orbera and its influence on co-morbidities. Genco *et al*[14] demonstrated in an Italian study significant improvement and resolution of pre-operative complications (hypertension, diabetes, respiratory disorders, osteoarthritis, and dyslipidemia) in 89.1% patients. There was a 44.8% resolution of hypertension; yet, there is an insufficient amount of data analyzing the association of weight loss with blood pressure reduction.

MATERIALS AND METHODS

A retrospective chart review was conducted from January 1, 2016 to January 31, 2019 of consecutive adults who received intragastric balloon therapy (IGBT) in a gastroenterology private practice in Eastern North Carolina. The balloon was introduced into the stomach under endoscopic guidance, and while in the region of the gastric body, inflation with saline was performed at increments of 50 mL until target volume between 500 to 650 mL of saline was attained depending on the patient's gastric capacity (see Figure 1 for placement and removal of gastric balloon)[15]. No procedural complications were noted during endoscopic placement and removal of the balloon.

This study was exempt from institutional review board (IRB) review after institutional IRB review (UMCIRB 19-001002). The data collected consisted of patient demographics and other comorbidities. The patient demographic information collected included race, gender, age, and weight. Race was categorized in three groups-white, non-white, and not reported. The comorbidities considered in this study included hyperlipidemia, depression, coronary artery disease, cardiovascular disease, obstructive sleep apnea, and diabetes mellitus.

The unit of analysis was the patient, and the outcome of interest was hypertension. Both systolic and diastolic blood pressure were obtained to determine hypertension. All blood pressure measurements were assessed by a digital blood pressure machine (GE Dinamap Carescape V100 Vitals Monitor). This study examined the impact of

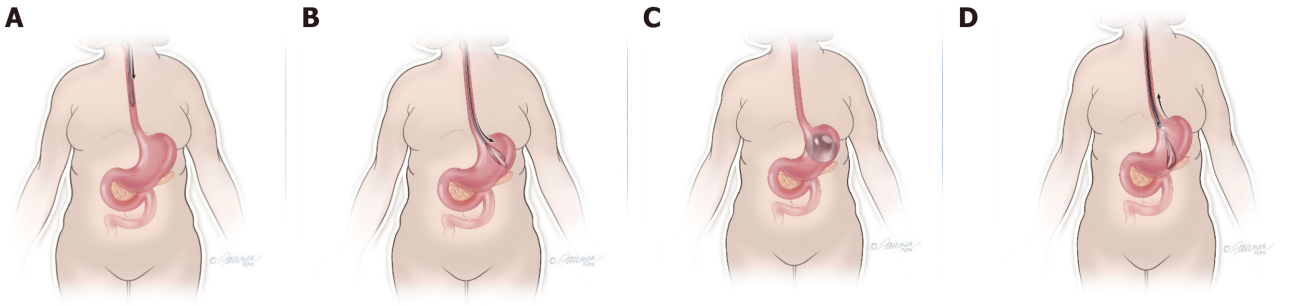

Figure 1 Placement and removal of gastric balloon. A: Showing endoscopic advancement of the balloon in the esophagus; B: Showing endoscopic appearance of deflated balloon in the gastric body; C: Showing endoscopic appearance of inflated balloon in the gastric body; and D: Removal of intragastric balloon after deflation. Citation: Image Library. In: Illustrations [cited 22 March 2021]. Available from: http://apolloresource.wpengine.com/orbera/image-library/. Copyright© The figures 2021. Published by Apollo Endosurgery, Inc.[15].

weight reduction at baseline compared to 6-mo on hypertension. The cut-offs for systolic and diastolic blood pressures were 140 and 90 respectively. This allowed for the creation of binary outcome variables-hypertension and non-hypertension for both systolic and diastolic blood pressures.

A cohort study design was used for data analysis. A total of 172 patients had the Orbera intragastric balloon placed. Of the 172 patients who had IGBT at baseline, 11 patients (6.4%) requested early balloon removal due to foreign body sensation (n = 1), and/or intolerable gastrointestinal adverse events (n = 10). The reported gastrointestinal adverse events were nausea, vomiting, abdominal pain, and diarrhea. Eventually, 6-mo follow-up data were available for only 140 patients. As a result, only the 140 available at the 6-mo follow-up were included in the analysis. Univariate, bivariate, and multivariate statistical analyses were performed. Specifically, scatterplots were created to show the relationship between weight and blood pressure, and paired two-sample t-test was carried out to determine if there was a significant reduction in weight before and after the IGBT. Multiple regressions were also performed to examine the association between participants' total body weight and blood pressure. The outcome variables for the multiple regression were systolic and diastolic blood pressure measured as continuous variables. This was followed by logistic regression analyses to determine the association between total body weight and hypertension at 6-mo post-implantation. The outcome variables for the logistic regression were systolic blood pressure (SBP)–non-hypertensive (140 mmHg or less) or hypertensive (greater than 140 mmHg), and diastolic blood pressure–non-hypertensive (90 mmHg or less) or hypertensive (greater than 90 mmHg). All authors had access to the study data and reviewed and approved the final manuscript. All statistical analyses were done using STATA 14®.

RESULTS

Univariate and bivariate analysis

Of the 172 patients at baseline, follow-up data were available for only 140 patients at 6-mo. Table 1 shows the descriptive statistics for both patient demographic information and presence of comorbidities at baseline unless otherwise stated. The study included 15% males and 85% females. 50% of the patients were white and just over 22% were non-white, and about 27% declined to give their race. Additionally, a few patients were diagnosed with comorbidities including 12.86% patients with hyperlipidemia, 30% with depression, 2.86% with coronary artery disease, 5.71% with cardiovascular disease, 17.86% with obstructive sleep apnea, and 21.43% with Diabetes Mellitus.

The average baseline patients' weight prior to IGBT was 231.61 Lbs. (SD = 46.53 Lbs.). However, the average patients' weight after IGBT at the 6-mo follow-up was 203.88 Lbs. (SD = 41.04 Lbs.). Hence, on average, the percent total body weight loss at 6-mo is 11.97 after IGBT. For comparison, a paired two-sample t-test was performed as shown in Table 2. The result reveals a statistically significant reduction in weight at the 6-mo follow-up after the IGBT. The scatterplot showing the relationship between total body weight and systolic and diastolic blood pressure is presented in Figure 2. The plots reveal a weak but positive correlation between total body weight and systolic blood pressure (r = 0.280), and total body weight and diastolic blood pressure (r =

Table 1 Patient demographical information and comorbidities at baseline

Variables	Description	Frequency	Percent (%)
Race distribution	White	70	50.00
	Non-White	32	22.86
	Declined	38	27.14
Gender distribution	Male	21	15.00
	Female	119	85.00
Age (in year)	mean (SD)	45.56 (10.75)	
Weight in lbs. (At baseline)	mean (SD)	231.61 (46.53)	
Weight in lbs. (At 6-mo)	mean (SD)	203.88 (41.04)	
Systolic blood pressure (At baseline)	Non-hypertensive (140 or less)	76	54.29
	Hypertensive (Greater than 140)	64	45.71
Systolic blood pressure (At 6-mo)	Non-hypertensive (140 or less)	110	78.57
	Hypertensive (Greater than 140)	30	21.43
Diastolic blood pressure (At baseline)	Non-hypertensive (90 or less)	123	87.86
	Hypertensive (Greater than 90)	17	12.14
Diastolic blood pressure (At 6-mo)	Non-hypertensive (90 or less)	125	89.29
	Hypertensive (Greater than 90)	15	10.71
Has hyperlipidemia	No	121	86.43
	Yes	18	12.86
	Missing	1	0.71
Has depression	No	97	69.29
	Yes	42	30.00
	Missing	1	0.71
Has CAD	No	136	97.14
	Yes	4	2.86
Has CVD	No	132	94.29
	Yes	8	5.71
Has OSA	No	115	82.14
	Yes	25	17.86
Has diabetes mellitus	No	110	78.57
	Yes	30	21.43

CAD: Coronary artery disease; CVD: Cardiovascular disease; OSA: Obstructive sleep apnea.

0.132). Given the weak correlation, several cofounders were included in the multivariate analysis as presented below.

Multivariate analysis

This study further analyzed the relationship between weight loss and blood pressure using a multiple regression technique. The findings presented in Table 3 show that after controlling for other cofounders like comorbidities and patient demographic characteristics, weight is an important factor for predicting the systolic blood pressure of the study participants ($\beta = 0.1350$, $P < 0.000$). Conversely, it was revealed that weight was not significantly associated with the diastolic blood pressure of the study participants ($\beta = 0.0295$, $P < 0.138$).

The logistic regression performed revealed that weight ($\beta = 0.0140$, $P < 0.000$) and age ($\beta = 0.0534$, $P < 0.000$) are important factors in determining systolic blood pressure

Table 2 *t*-test: Paired two sample for means

	Weight at baseline	Weight at 6-mo follow-up
Mean	231.61	203.88
t-stat	18.06	
P value	0.0000	

Table 3 Multiple regression showing the association between systolic and diastolic blood pressure and demographics and other comorbidities

	Systolic blood pressure (β)	Diastolic blood pressure (β)
Weight	0.1350[b]	0.0295
Age	0.5135[b]	0.1439
Gender		
Female	-1.1118	-2.9830
Race (White)		
Non-White	-0.9900	1.9809
Declined	0.9093	1.0592
DM	-1.0136	-3.8298
OSA	-1.4531	-0.7374
CVD	-5.5353	-2.4714
Hyperlipidemia	-1.4230	3.5368
CAD	14.9021	-0.4645
Depression	-2.3854	-0.9559

[b]$P < 0.01$. CAD: Coronary artery disease; CVD: Cardiovascular disease; OSA: Obstructive sleep apnea.

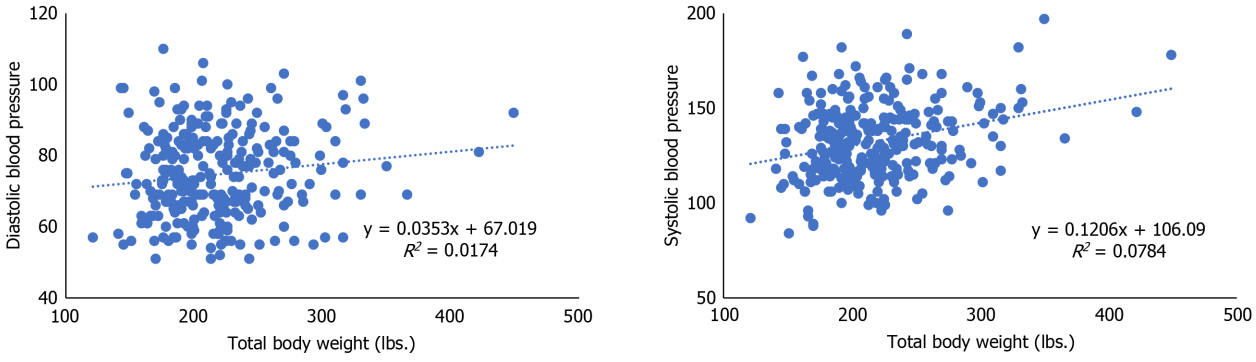

Figure 2 Chart showing the association between total body weight and blood pressure.

after IGBT. None of the other demographic characteristics or indicated comorbidities were found to be significant. The results specifically indicated that for every unit increase in weight, the log odds of SBP will increase by 1.4%. Also, for every unit increase in age, the log odds of SBP will increase by 5.34%. No variable included in the study however showed a significant association with diastolic blood pressure after IGBT. These results are presented in Table 4.

Table 4 Logistic regression showing the association between systolic and diastolic blood pressure and demographics and other comorbidities at 6-mo post-implantation

	Systolic blood pressure (β)	Diastolic blood pressure (β)
Weight	0.0140[b]	0.0081
Age	0.0534[b]	0.0262
Gender		
Female	0.0002	0.2519
Race (White)		
Non-White	-0.3575	0.0558
Declined	0.1795	-0.3747
DM	-0.1462	-0.2354
OSA	-0.4340	-0.3993
CVD	-0.4240	0.3402
Hyperlipidemia	-0.0603	0.4243
CAD	0.3749	0.0000
Depression	-0.3549	-0.3365

[b]$P < 0.01$. CAD: Coronary artery disease; CVD: Cardiovascular disease; OSA: Obstructive sleep apnea.

DISCUSSION

The intragastric balloon is used for those patients who have failed to achieve and maintain the weight loss with conservative measures or prefer a less invasive approach. In addition, it can have a significant role in the preoperative management of morbidly obese patients prior to bariatric surgery to reduce mortality and morbidity.

We observed an average loss of 11.97% from baseline weight at 6-mo post implantation, which is sufficient for comorbidity improvement. The present data indicate that Orbera® intragastric balloon significantly reduced weight, and systolic blood pressure at the time of balloon removal at 6-mo; although there was a decrease in diastolic blood pressure, it was not statistically significant. Furthermore, weight and age appear to be important factors in determining systolic blood pressure after intragastric balloon therapy. The weight reduction observed was analogous to other studies. Yorke *et al*[12] demonstrated a 15 kg and 5.9 ± 1.0 kg/m^2 reduction post-implantation in a systematic review of 26 studies. Herve *at al*[16] demonstrated a 12 kg weight reduction at the time of balloon removal and 8.6 kg reduction at 1 year follow up. A Brazilian multicenter study also cited a significant weight reduction of 15.2 ± 10.5 kg, however, Ganesh *et al*[17] reported a 5.9 kg reduction after 6 mo[18]. While the intragastric balloon can induce short-term weight reduction, the weight loss sustainability is often difficult to achieve. Despite weight regain observed, Crea *et al*[19] reported improvement in metabolic syndrome and the sustained 10% body weight loss.

Obesity plays a key role in metabolic syndrome[20]. The development of hypertension in obesity involves multiple mechanisms such as insulin resistance, increased inflammatory markers, oxidative stress, the sympathetic nervous system, and the renin-angiotensin aldosterone system. The mentioned effects in the setting of obesity induce endothelial dysfunction thus contributing to elevated blood pressure[20]. While patients who undergo lifestyle interventions often have blood pressure improvement, its sustainability on weight loss is limited; therefore, it may fail to decrease long-term adverse cardiovascular effect[20]. While there are conflicting data regarding the influence of pharmacological agents for weight reduction on blood pressure improvement, there is evidence that bariatric surgery improves blood pressure by mechanisms such as decreasing plasma leptin and sympathetic nervous system activity[20]. Given the relatively new field of endoscopic bariatric therapies, there is limited data regarding the influence of intragastric balloon therapy on blood pressure. It is known that the intragastric balloon adopts the gastric restriction mechanism through the space-occupying design, while increasing post-prandial satiety and decreasing pre-prandial hunger. It has also been reported to alter hormone

release, such as leptin and ghrelin, leading to weight loss; however, it appears to be a transitory affect[21,22].

Orbera has a relatively good safety profile with the commonest adverse events being abdominal pain, nausea, vomiting, and gastroesophageal reflux disease[8,12,23]. While there is a cited early balloon removal rate of 9%, in our study, there was a 6.4% early balloon removal rate due to intolerable gastrointestinal adverse events[9].

The study has several limitations. They include the retrospective analysis of a single-center analysis and the absence of a control group. The frequency of the other comorbidities may be an underestimate. In addition, the follow-up period was only at the six-month time period of balloon removal, and therefore, weight loss sustainability cannot be concluded.

CONCLUSION

IGBT can be an effective short-term weight reduction modality with a relatively little risk of adverse event. Due to its improvement on systolic blood pressure, IGBT may help reduce cardiovascular risk.

ARTICLE HIGHLIGHTS

Research background

In the United States, about a third of adults have hypertension, which is the most modifiable risk factor for heart disease and stroke. The prevalence of obesity and hypertension in eastern North Carolina are comparable, with obesity being an established risk factor for hypertension. Lifestyle interventions and pharmacological agents often are not sufficient to achieve enough weight loss. Bariatric surgery offers the most effective weight reduction intervention, however patients with higher body mass index may have higher surgical morbidity and mortality, longer hospitalization, and high rates of 30-d readmission due to co-morbidities. Minimally invasive non-surgical options like the intragastric balloon may bridge a critical gap in the treatment of obesity.

Research motivation

The weight loss mechanism of the intragastric balloon therapy is restrictive, and this leads to weight reduction due to reduced food intake from early post-prandial satiety. Weight loss helps to lower the risk of potentially serious obesity-related health problems like heart disease, stroke, hypertension, diabetes and osteoarthritis. Aside from long-term health benefits, weight reduction is cost-effective and promotes substantial health-care cost savings.

Research objectives

Our study focused on the impact of intragastric balloon therapy (IGBT) on blood pressure reduction. IGBT leads to statistically significant weight and systolic blood pressure reduction at 6-mo. Also, the degree of weight reduction by IGBT is sufficient to effect improvement in comorbidities.

Research methods

A retrospective chart review was conducted from January 1, 2016 to January 31, 2019 of consecutive adults who received IGBT in a gastroenterology private practice in eastern North Carolina. The balloon was introduced into the stomach under endoscopic guidance, and while in the region of the gastric body, inflation with saline was performed at increments of 50 mL until target volume between 500 to 650 mL of saline was attained depending on the patient's gastric capacity. No procedural complications were noted during endoscopic placement and removal of the balloon.

Of the 172 patients who had IGBT at baseline, 11 patients (6.4%) requested early balloon removal due to foreign body sensation (n = 1), and/or intolerable gastrointestinal adverse events (n = 10). The reported gastrointestinal adverse events were nausea, vomiting, abdominal pain, and diarrhea. Eventually, 6-mo follow-up data were available for only 140 patients. As a result, only the 140 available at the 6-mo follow-up were included in the analysis. Univariate, bivariate, and multivariate statistical analyses were performed. Specifically, scatterplots were created to show the

relationship between weight and blood pressure, and paired two-sample *t*-test was carried out to determine if there was a significant reduction in weight before and after the IGBT. Multiple regressions were also performed to examine the association between participants' total body weight and blood pressure. The outcome variables for the multiple regression were systolic and diastolic blood pressure measured as continuous variables. This was followed by logistic regression analyses to determine the association between total body weight and hypertension at 6-mo post-implantation. The outcome variables for the logistic regression were systolic blood pressure–non-hypertensive (140 mmHg or less) or hypertensive (greater than 140 mmHg), and diastolic blood pressure-non-hypertensive (90 mmHg or less) or hypertensive (greater than 90 mmHg). All authors had access to the study data and reviewed and approved the final manuscript. All statistical analyses were done using STATA 14®.

Research results

Weight is an important factor for predicting the systolic blood pressure of the study participants ($\beta = 0.1350$, $P < 0.000$). Conversely, weight was not significantly associated with the diastolic blood pressure of the study participants ($\beta = 0.0295$, $P < 0.138$). On average, the percent total body weight loss at 6-mo is 11.97 after IGBT. The logistic regression performed revealed that weight ($\beta = 0.0140$, $P < 0.000$) and age ($\beta = 0.0534$, $P < 0.000$) are important factors in determining systolic blood pressure after IGBT. The results specifically indicated that for every unit increase in weight, the log odds of SBP will increase by 1.4%. Also, for every unit increase in age, the log odds of SBP will increase by 5.34%.

IGBT can be an effective short-term weight reduction modality with a relatively little risk of adverse event. Due to its improvement on systolic blood pressure, IGBT may help reduce cardiovascular risk. Study limitations include the retrospective analysis of a single-center and the absence of a control group. In addition, the follow-up period was only at the six-month time period of balloon removal, and therefore, weight loss sustainability cannot be concluded.

Research conclusions

IGBT engenders short-term weight reduction modality with a relatively little risk of adverse event. Its improvement on systolic blood pressure may help reduce cardiovascular risk.

Research perspectives

Given the increasing global prevalence of obesity, it is envisioned that bariatric devices such as intragastric balloons will continue to evolve. Though intragastric balloons can bring about short-term morbidity/mortality benefits, the long-term benefits are questionable. Further studies will focus on promoting the long-term weight benefits of intragastric balloons.

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ORIGINAL ARTICLE

Observational Study

Comparison of endoscopic gastritis based on Kyoto classification between diffuse and intestinal gastric cancer

Osamu Toyoshima, Toshihiro Nishizawa, Shuntaro Yoshida, Tomonori Aoki, Fumiko Nagura, Kosuke Sakitani, Yosuke Tsuji, Hayato Nakagawa, Hidekazu Suzuki, Kazuhiko Koike

ORCID number: Osamu Toyoshima 0000-0002-6953-6079; Toshihiro Nishizawa 0000-0003-4876-3384; Shuntaro Yoshida 0000-0002-9437-9132; Tomonori Aoki 0000-0003-0794-9940; Fumiko Nagura 0000-0001-5138-7768; Kosuke Sakitani 0000-0002-4537-6023; Yosuke Tsuji 0000-0001-9537-4993; Hayato Nakagawa 0000-0002-6973-5094; Hidekazu Suzuki 0000-0002-8994-6163; Kazuhiko Koike 0000-0002-9739-9243.

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Osamu Toyoshima, Toshihiro Nishizawa, Shuntaro Yoshida, Kosuke Sakitani, Department of Gastroenterology, Toyoshima Endoscopy Clinic, Tokyo 157-0066, Japan

Toshihiro Nishizawa, Department of Gastroenterology and Hepatology, International University of Health and Welfare, Narita Hospital, Narita 286-8520, Japan

Tomonori Aoki, Yosuke Tsuji, Hayato Nakagawa, Kazuhiko Koike, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan

Fumiko Nagura, Internal Medicine, Chitosefunabashi Ekimae Clinic, Tokyo 157-0054, Japan

Kosuke Sakitani, Department of Gastroenterology, Sakiatani Endoscopy Clinic, Narashino 275-0026, Japan

Hidekazu Suzuki, Department of Gastroenterology and Hepatology, Tokai University School of Medicine, Isehara 259-1193, Japan

Corresponding author: Osamu Toyoshima, MD, PhD, Director, Doctor, Department of Gastroenterology, Toyoshima Endoscopy Clinic, 6-17-5 Seijo, Setagaya-ku, Tokyo 157-0066, Japan. t@ichou.com

Abstract

BACKGROUND

Gastric cancers can be categorized into diffuse- and intestinal-type cancers based on the Lauren histopathological classification. These two subtypes show distinct differences in metastasis frequency, treatment application, and prognosis. Therefore, accurately assessing the Lauren classification before treatment is crucial. However, studies on the gastritis endoscopy-based Kyoto classification have recently shown that endoscopic diagnosis has improved.

AIM

To investigate patient characteristics including endoscopic gastritis associated with diffuse- and intestinal-type gastric cancers in *Helicobacter pylori* (*H. pylori*)-infected patients.

METHODS

Patients who underwent esophagogastroduodenoscopy at the Toyoshima

anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Toyoshima Endoscopy Clinic.

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Endoscopy Clinic were enrolled. The Kyoto classification included atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. The effects of age, sex, and Kyoto classification score on gastric cancer according to the Lauren classification were analyzed. We developed the Lauren predictive background score based on the coefficients of a logistic regression model using variables independently associated with the Lauren classification. Area under the receiver operative characteristic curve and diagnostic accuracy of this score were examined.

RESULTS

A total of 499 *H. pylori*-infected patients (49.6% males; average age: 54.9 years) were enrolled; 132 patients with gastric cancer (39 diffuse- and 93 intestinal-type cancers) and 367 cancer-free controls were eligible. Gastric cancer was independently associated with age ≥ 65 years, high atrophy score, high intestinal metaplasia score, and low nodularity score when compared to the control. Factors independently associated with intestinal-type cancer were age ≥ 65 years (coefficient: 1.98), male sex (coefficient: 1.02), high intestinal metaplasia score (coefficient: 0.68), and low enlarged folds score (coefficient: -1.31) when compared to diffuse-type cancer. The Lauren predictive background score was defined as the sum of +2 (age ≥ 65 years), +1 (male sex), +1 (endoscopic intestinal metaplasia), and -1 (endoscopic enlarged folds) points. Area under the receiver operative characteristic curve of the Lauren predictive background score was 0.828 for predicting intestinal-type cancer. With a cut-off value of +2, the sensitivity, specificity, and accuracy of the Lauren predictive background score were 81.7%, 71.8%, and 78.8%, respectively.

CONCLUSION

Patient backgrounds, such as age, sex, endoscopic intestinal metaplasia, and endoscopic enlarged folds are useful for predicting the Lauren type of gastric cancer.

Key Words: Gastric cancer; Lauren classification; Endoscopy; Pathology; Gastritis; Kyoto classification

Core Tip: Accurately assessing the Lauren classification before the treatment of gastric cancer is crucial. Factors independently associated with intestinal-type cancer were age ≥ 65 years, male sex, high endoscopic intestinal metaplasia score, and low endoscopic enlarged folds score when compared to diffuse-type cancer. The Lauren predictive background score was defined as the sum of +2 (age ≥ 65 years), +1 (male), +1 (intestinal metaplasia), and -1 (enlarged folds) points. Area under the curve of the Lauren predictive background score was 0.828 (cut-off: +2) for predicting intestinal-type cancer. Age, sex, intestinal metaplasia, and enlarged folds are useful for predicting tumor type.

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INTRODUCTION

The International Agency for Research on Cancer reported in GLOBOCAN 2018 that stomach cancer was the third leading cause of mortality worldwide[1]. Gastric cancers are epidemiologically crucial and can be categorized into two types based on the

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Lauren histopathological classification: diffuse and intestinal-types[2]. Intestinal-type cancers are associated with a *Helicobacter pylori (H. pylori)*-induced chronic inflammatory process, known as the Correa pathway, which includes atrophy, metaplasia, dysplasia, and cancer[3], whereas diffuse-type gastric cancers directly undergo a highly active inflammation-based carcinogenesis without having to pass through the Correa pathway[4,5]. The two histological subtypes of gastric tumors proposed by Lauren exhibit several distinct clinical and molecular characteristics[6-8]. Depending on the Lauren type, the frequency of lymph node metastasis[2,9,10] and peritoneal metastasis[11,12], application of endoscopic mucosal dissection[13,14], recommended surgical margin[15], response to chemotherapy[16], and prognosis[2,16,17] differ. The Lauren classification is diagnosed by pathology; however, it would be useful if subtypes could be endoscopically predicted.

In recent years, advancement in endoscopy has enabled diagnosis that is highly consistent with histology[18,19]. In 2013, the endoscopy-based Kyoto classification of gastritis was advocated by the Japan Gastroenterological Endoscopy Society with the aim of unifying the endoscopic diagnosis of gastritis in clinical practice and match it with the pathological diagnosis of gastritis[20]. The Kyoto classification adopted and scored atrophy, intestinal metaplasia, enlarged folds, nodularity, diffuse redness, and the regular arrangement of collecting venules (RAC) as endoscopic findings of gastritis. Among them, the Kyoto score, which is the sum of the scores of these factors, has been vigorously reported to be associated with gastric cancer[21,22], gastric cancer risk[20,23], and *H. pylori* infections[24]. Evaluating the risk of gastric cancer on the basis of endoscopic findings is an important alternative to biopsy.

Since there are few reports regarding the relationship between the Lauren classification and endoscopic findings based on the Kyoto classification[21,22], we investigated the background patient characteristics and endoscopic gastritis of patients with diffuse- and intestinal-type gastric cancers, focusing on *H. pylori* infected patients. Based on these outcomes, a score was created to predict the Lauren classification, and its accuracy was examined.

MATERIALS AND METHODS

Study design and oversight

We conducted a retrospective case-control study at the Toyoshima Endoscopy Clinic, which is an outpatient endoscopy-specialized clinic located in Tokyo, an urban area in Japan. This study was approved by the certificated review board of the Hattori Clinic on September 4, 2020 (approval No. S2009-U04, registration number UMIN000018541). Written informed consent was obtained from all patients. All clinical investigations were conducted in accordance with the ethical guidelines of the Declaration of Helsinki. This study received no financial support.

Study population

Eligibility criteria included patients with gastric cancer and an *H. pylori* infection who underwent esophagogastroduodenoscopy at the Toyoshima Endoscopy Clinic from September 2008 to February 2020. We excluded patients who did not have *H. pylori* infection, patients in whom *H. pylori* was successfully eradicated, and those whose *H. pylori* status was unavailable. Patients with gastric cancer and past gastrectomy were also excluded. As control group, patients with *H. pylori*-positive gastritis and without gastric cancer were enrolled. This criterion included patients who underwent esophagogastroduodenoscopy and initial assessments for an *H. pylori* infection from December 2013 to March 2016 and from January 2018 to February 2019.

Diagnosis of Lauren classification and H. pylori infection

The Lauren classification was diagnosed from resected specimens or, if unresectable, biopsy specimens.

An *H. pylori* infection was diagnosed using pathology (hematoxylin and eosin staining) or the urea breath test.

Endoscopic gastritis based on the Kyoto classification

The Kyoto score for endoscopic gastritis, which ranges from 0 to 8, is based on the total scores of the following five endoscopic findings: atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. A high score represents an increased risk of gastric cancer[20-23] and *H. pylori* infection[24].

Endoscopic atrophy was classified based on the extent of mucosal atrophy (the Kimura Takemoto classification)[26]. Non-atrophy and C1 atrophy were scored as atrophy score 0, C2, and C3 atrophies as atrophy score 1, and O1 to O3 atrophies as atrophy score 2.

Endoscopically, intestinal metaplasia typically appears as grayish-white and slightly elevated plaques surrounded by mixed patchy pink and pale areas of the mucosa, forming an irregular uneven surface. A villous appearance, whitish mucosa, and rough mucosal surface are useful indicators for the endoscopic diagnosis of intestinal metaplasia. Intestinal metaplasia score 0 was defined as the absence of intestinal metaplasia, score 1 as the presence of intestinal metaplasia within the antrum, and score 2 as intestinal metaplasia extending into the corpus. The intestinal metaplasia score was calculated based on the diagnosis of metaplasia using white-light imaging.

An enlarged fold is defined as ≥ 5 mm width that is not flattened or is only partially flattened by stomach insufflation. The absence and presence of enlarged folds were scored as enlarged fold scores of 0 and 1, respectively.

Nodularity is a condition in which a miliary pattern similar to "goosebumps" is mainly located in the antrum. The absence and presence of nodularity were scored as nodularity scores of 0 and 1, respectively.

Diffuse redness refers to uniformly reddish mucosa with continuous expansion located in the non-atrophic mucosa, mainly in the corpus. The RAC is a condition in which collecting venules are arranged in the corpus. From a distance, the venules look like numerous dots; however, up close, the venules appear like a regular pattern of starfish-like shapes. The absence of diffuse redness, presence of mild diffuse redness or diffuse redness with RAC, and severe diffuse redness or diffuse redness without RAC were scored as diffuse redness scores of 0, 1, and 2, respectively.

Data collection and outcomes

We obtained data for cancer and participants background information from the endoscopic database of the Toyoshima Endoscopy Clinic from September 2008 to February 2020. Two expert endoscopists reviewed all images and scored them according to the Kyoto classification.

Clinical data of this study consisted of variables including gastric cancer type according to the Lauren classification, age, sex, and endoscopic gastritis score based on the Kyoto classification (Kyoto score, atrophy score, intestinal metaplasia score, enlarged folds score, nodularity score, and diffuse redness score).

The main outcome of this study was the differences in patient backgrounds and the endoscopic gastritis between patients with diffuse- and intestinal-type gastric cancers. To predict the Lauren type of cancer, this study developed a Lauren predictive background score using variables associated with the Lauren classification. We assessed the discrimination of the Lauren predictive background score using the receiver operating characteristic (ROC) curve, the corresponding area under the ROC curve (AUC), and the diagnostic accuracy of predicting the Lauren type of tumor.

We also compared *H. pylori*-infected patients with cancer (whole, diffuse-, and intestinal-type cancers, respectively) and cancer-free *H. pylori*-infected controls.

Statistical analyses

Univariate and multivariate analyses were conducted using a binomial logistic regression analysis. The multivariate analysis included age, sex, and each score of the Kyoto classification, excluding the Kyoto score. Age was categorized based on the average number of patients with gastric cancer. A multivariate analysis was conducted, using a backward stepwise logistic regression, for variables with P values < 0.1; these values were determined by a univariate analysis. Regarding missing data, we used complete case analysis.

We developed the Lauren predictive background score based on the coefficients of a logistic regression model, using variables with P values < 0.05 in a multivariate analysis. The AUC for predicting intestinal-type cancer and the sensitivity, specificity, and accuracy of the Lauren predictive background score were measured. The optimal cut-off value of the ROC curve was calculated using the Youden index.

A two-sided P value of < 0.05 was considered statistically significant. Statistical analyses were performed using Ekuseru-Toukei 2015 (Social Survey Research Information company, Limited, Tokyo, Japan).

RESULTS

Patient characteristics

A total of 132 patients with *H. pylori*-positive gastric cancers (39 diffuse- and 93 intestinal-type, 105 early, and 27 advanced cancers) were included; 11 patients were excluded as they did not have an *H. pylori* infection, 104 due to successful eradication, and 16 due to an unavailable *H. pylori* status. The control group comprised 367 patients with *H. pylori*-positive gastritis (gastric cancer free controls). A total of 499 patients were enrolled in this study. We show patient flowchart in Figure 1. The mean age in this study was 54.9 ± 14.1 (range: 23-89) years, and 49.6% of patients were male; the Kyoto score was 4.93 ± 1.58, (atrophy: 1.53 ± 0.61; intestinal metaplasia: 0.83 ± 0.92; enlarged folds: 0.42 ± 0.49; nodularity: 0.33 ± 0.47; and diffuse redness: 1.83 ± 0.48).

H. pylori-positive gastritis with vs without gastric cancer

Univariate analysis showed that patients with *H. pylori*-infected cancer patients were older (66.4 *vs* 50.9 years) and had a higher Kyoto score (5.63 *vs* 4.69) than *H. pylori*-infected non-cancer patients. Among the scores of the items of the Kyoto classification, atrophy and intestinal metaplasia scores for gastric cancer were higher than those for cancer-free gastritis; however, nodularity scores for gastric cancer were lower than those for cancer-free gastritis. There was no significant difference in the enlarged folds and diffuse redness scores. Based on the results of a multivariate analysis, *H. pylori*-infected gastric cancer was independently associated with an age of 65 years or more [odds ratio (OR): 4.01], a high atrophy score (OR: 2.80), high intestinal metaplasia score (OR: 1.57), and a low nodularity score (OR: 0.51, Table 1).

H. pylori-infected gastritis with diffuse-type gastric cancer vs without gastric cancer

On comparing *H. pylori*-infected patients with diffuse-type cancer and those without gastric cancer (gastric cancer-free controls), a univariate analysis showed that patients with diffuse-type cancer were older (58.0 *vs* 50.9 years) and had a higher Kyoto score (5.33 *vs* 4.69), higher atrophy score, and higher intestinal metaplasia score than gastric cancer-free patients. In a multivariate analysis, a high atrophy score was independently associated with diffuse-type gastric cancer (Table 2).

H. pylori-infected gastritis with intestinal-type gastric cancer vs without gastric cancer

H. pylori-infected intestinal-type gastric cancer and *H. pylori*-infected non-cancer gastritis were compared. Univariate analysis showed that *H. pylori*-infected patients with intestinal-type gastric cancer were older (69.9 *vs* 50.9 years), comprised more of males (62.4% *vs* 47.7%), and had a higher Kyoto score (5.75 *vs* 4.69), higher atrophy score, higher intestinal metaplasia score, lower enlarged folds score, and lower nodularity score than those with non-cancer gastritis. Similar results were obtained in multivariate analysis (Table 3).

H. pylori-infected gastritis with diffuse- vs intestinal-type gastric cancer

Table 4 shows a comparison of endoscopic background gastritis between *H. pylori*-infected patients with diffuse- and intestinal-type cancers. Univariate analysis showed that patients with intestinal-type cancer were older (69.9 *vs* 58.0 years), comprised more of males (61.5% *vs* 37.6%), had a higher atrophy score (1.95 *vs* 1.69), higher intestinal metaplasia score (1.58 *vs* 0.97), lower enlarged folds score (0.28 *vs* 0.56), and lower nodularity score (0.10 *vs* 0.28). There was no significant difference in the Kyoto and diffuse redness scores. In a multivariate analysis, factors independently associated with intestinal-type cancer were an age of 65 years or more (coefficient: 1.98; OR: 7.26), male sex (coefficient: 1.02; OR: 2.78), high intestinal metaplasia score (coefficient: 0.68; OR: 1.97), and low enlarged folds score (coefficient: -1.31; OR: 0.27).

Based on the coefficients of a multivariate analysis, the equation for the scoring system was calculated based on an assumption that patients receive +2 points if they were aged 65 years or more, +1 point if they were male, +1 point if they had intestinal metaplasia, and -1 point if they had enlarged folds. We defined the Lauren predictive background score as the sum of these points, ranging from -1 to +4.

The ROC curve based on the Lauren predictive background score in 132 patients with diffuse- or intestinal-type cancer is shown in Figure 2. AUC of the Lauren predictive background score for predicting intestinal-type cancer was 0.828 (95% confidence interval: 0.744-0.912). The optimal cut-off value of the Lauren predictive background score for correlation with intestinal-type gastric cancer was +2, based on

Table 1 Endoscopic gastritis based on Kyoto classification of *Helicobacter pylori*-infected patients with *vs* without gastric cancer

	Gastric cancer (+)	Cancer (-)	Univariate analysis			Multivariate analysis		
			Odds ratio	95%CI	*P* value	Odds ratio	95%CI	*P* value
n	132	367						
Age, mean (SD), yr	66.4 (12.4)	50.9 (12.4)	1.099	1.078-1.120	< 0.001			
Age ≥ 65 yr, %	60.6	15.3	8.544	5.446-13.405	< 0.001	4.010	2.436-6.603	< 0.001
Male sex, %	55.3	47.7	1.357	0.910-2.024	0.134			
Atrophy score, mean (SD)	1.871 (0.336)	1.411 (0.642)	6.173	3.635-10.486	< 0.001	2.800	1.583-4.954	< 0.001
Intestinal metaplasia score, mean (SD)	1.402 (0.809)	0.624 (0.878)	2.570	2.031-3.253	< 0.001	1.567	1.188-2.067	0.001
Enlarged folds score, mean (SD)	0.364 (0.483)	0.441 (0.497)	0.723	0.480-1.090	0.121			
Nodularity score, mean (SD)	0.152 (0.360)	0.387 (0.488)	0.283	0.168-0.476	< 0.001	0.508	0.282-0.913	0.024
Diffuse redness score, mean (SD)	1.841 (0.507)	1.823 (0.466)	1.085	0.706-1.667	0.709			
Kyoto score, mean (SD)	5.629 (1.149)	4.687 (1.637)	1.568	1.342-1.831	< 0.001			

P value was calculated using the binomial logistic regression analysis. CI: Confidence interval; SD: Standard deviation.

Table 2 Endoscopic gastritis based on Kyoto classification of *Helicobacter pylori*-infected patients with diffuse-type gastric cancer *vs* without gastric cancer

	Diffuse-type cancer (+)	Cancer (-)	Univariate analysis			Multivariate analysis		
			Odds ratio	95%CI	*P* value	Odds ratio	95%CI	*P* value
n	39	367						
Age, mean (SD), yr	58.00 (13.00)	50.88 (12.41)	1.044	1.018-1.072	0.001			
Age ≥ 65 yr, %	28.2	15.3	2.182	1.027-4.634	0.042	1.434	0.633-3.246	0.388
Male sex, %	38.5	47.7	0.686	0.348-1.349	0.275			
Atrophy score, mean (SD)	1.692 (0.468)	1.411 (0.642)	2.327	1.223-4.428	0.010	2.327	1.223-4.428	0.010
Intestinal metaplasia score, mean (SD)	0.974 (0.903)	0.624 (0.878)	1.516	1.065-2.158	0.021	1.313	0.905-1.906	0.152
Enlarged folds score, mean (SD)	0.564 (0.502)	0.441 (0.497)	1.638	0.842-3.186	0.146			
Nodularity score, mean (SD)	0.282 (0.456)	0.387 (0.488)	0.622	0.300-1.290	0.202			
Diffuse redness score, mean (SD)	1.821 (0.556)	1.823 (0.466)	0.990	0.495-1.978	0.976			
Kyoto score, mean (SD)	5.333 (1.402)	4.687 (1.637)	1.306	1.044-1.632	0.019			

P value was calculated using the binomial logistic regression analysis. CI: Confidence interval; SD: Standard deviation.

the Youden index. The sensitivity, specificity, and accuracy of the Lauren predictive background score were 81.7%, 71.8%, and 78.8%, respectively.

DISCUSSION

This study showed that old age, male sex, the presence of endoscopic intestinal metaplasia, and the absence of endoscopic enlarged folds were independently associated with intestinal-type gastric cancer compared to diffuse-type cancer among *H. pylori*-infected patients. The Lauren predictive background score created based on these variables was good, with AUC of 0.828, sensitivity of 81.7%, and accuracy of 78.8%. It is well known that old age, male sex[2,27], and endoscopic intestinal metaplasia[28] are indicators of intestinal-type cancers and that endoscopic enlarged folds[5,29] are characteristics of diffuse-type tumors. The strength of this study is that

Table 3 Endoscopic gastritis based on Kyoto classification of *Helicobacter pylori*-infected patients with intestinal-type gastric cancer *vs* without gastric cancer

	Intestinal-type cancer (+)	Cancer (-)	Univariate analysis			Multivariate analysis		
			Odds ratio	95%CI	*P* value	Odds ratio	95%CI	*P* value
n	93	367						
Age, mean (SD), yr	69.86 (10.29)	50.88 (12.41)	1.138	1.107-1.169	< 0.001			
Age ≥ 65 yr, %	74.2	15.3	15.967	9.261-27.527	< 0.001	6.220	3.394-11.400	< 0.001
Male sex, %	62.4	47.7	1.818	1.140-2.900	0.012	1.794	0.955-3.372	0.069
Atrophy score, mean (SD)	1.946 (0.227)	1.411 (0.642)	15.312	6.147-38.144	< 0.001	6.167	2.321-16.382	< 0.001
Intestinal metaplasia score, mean (SD)	1.581 (0.697)	0.624 (0.878)	3.368	2.499-4.539	< 0.001	1.683	1.166-2.430	0.005
Enlarged folds score, mean (SD)	0.280 (0.451)	0.441 (0.497)	0.491	0.299-0.808	0.005	0.453	0.237-0.867	0.017
Nodularity score, mean (SD)	0.097 (0.297)	0.387 (0.488)	0.170	0.083-0.348	< 0.001	0.323	0.141-0.742	0.008
Diffuse redness score, mean (SD)	1.849 (0.488)	1.823 (0.466)	1.135	0.681-1.891	0.626			
Kyoto score, mean (SD)	5.753 (1.007)	4.687 (1.637)	1.696	1.407-2.004	< 0.001			

P value was calculated using the binomial logistic regression analysis. CI: Confidence interval; SD: Standard deviation.

independent variables related to cancer type were investigated using the currently vigorously studied endoscopic gastritis evaluation method (Kyoto classification), and Lauren predictive background score was newly created using these variables; moreover, the score was accurate. Predicting cancer types without a biopsy may lead to faster treatment choices. A pathological diagnosis before endoscopic resection, surgery, or chemotherapy is vital to determine the line of treatment of lesions[13-16]. However, cases in which there are differences between the histological diagnoses of biopsy and resected specimens amount to 20%–30% of all cases[30-32]. Biopsy results are supported when the Lauren predictive background score is consistent with the biopsy diagnosis; however, the treatment should be carefully selected when discrepancies are observed. Furthermore, some endoscopic features of cancer are indicated by the Lauren classification. For example, diffuse-type cancers are frequently located in the proximal stomach[33]. The endoscopic gross appearance of an elevated-type cancer predominantly indicated intestinal-type cancer, whereas flat and depressed types of cancers indicated difuse-type cancer[34,35]. In the early stages of gastric cancer, intestinal-type cancer is usually reddish, whereas diffuse-type cancer is pale. While magnifying with narrow-band imaging, a well-demarcated area[36] and a white opaque substance[37] serve as an indicator of intestinal-type cancer, an ill-defined area[36] and a high proportion of the area with an absent microsurface pattern[38] are specific markers for diffuse-type cancer. In contrast, our study is unique in predicting the Lauren classification from background information rather than tumor information. In the future, a combination of both background and tumor information may allow for more accurate predictions, and a diagnosis by artificial intelligence may help.

We previously showed that corpus-predominant gastritis (5.96) has a higher Kyoto score than pangastritis (5.21)[20]. Corpus-predominant gastritis and pangastritis are risk factors for intestinal- and diffuse-type cancers, respectively[39], and a similar tendency was observed in this study.

Next, this study demonstrated that the Kyoto score of gastric cancer patients was higher than that of cancer-free patients among *H. pylori*-infected participants, regardless of whether the cancer was diffuse- or intestinal-type. This result is concordant with that of a previous report by Sugimoto *et al*[21]. While examining each item of the Kyoto classification, atrophy and intestinal metaplasia showed a positive association with gastric cancer; however, nodularity was negatively correlated with gastric cancer. This tendency is also the same as that reported in a previous study[21]. Nodularity has been reported as a risk factor for stomach cancer in young patients[40]; however, our observation might indicate a negative association since it covers all ages. When we previously investigated the association of the ABC classification, which consisted of a combination of serum *H. pylori* antibody and pepsinogen,

Table 4 Endoscopic gastritis based on Kyoto classification of *Helicobacter pylori*-infected patients with diffuse- *vs* intestinal-type gastric cancer

	Diffuse-type	Intestinal-type	Univariate analysis			Multivariate analysis				
			Odds ratio	95%CI	*P* value	Coefficient	95%CI	Odds ratio	95%CI	*P* value
n	39	93								
Age, mean (SD), yr	58.00 (13.00)	69.86 (10.29)	1.091	1.051-1.132	< 0.001					
Age ≥ 65 yr, %	28.2	74.2	7.318	3.166-16.917	< 0.001	1.983	1.045, 2.921	7.263	2.843-18.553	< 0.001
Male sex, %	38.5	62.4	2.651	1.228-5.724	0.013	1.021	0.069, 1.973	2.776	1.071-7.193	0.036
Atrophy score, mean (SD)	1.692 (0.468)	1.946 (0.227)	7.822	2.530-24.188	< 0.001	0.727	-0.927, 2.381	2.069	0.396-10.816	0.389
Intestinal metaplasia score, mean (SD)	0.974 (0.903)	1.581 (0.697)	2.473	1.544-3.959	< 0.001	0.678	0.128, 1.228	1.970	1.136-3.413	0.016
Enlarged folds score, mean (SD)	0.564 (0.502)	0.280 (0.451)	0.300	0.138-0.653	0.002	-1.308	-2.261, -0.356	0.270	0.104-0.701	0.007
Nodularity score, mean (SD)	0.282 (0.456)	0.097 (0.297)	0.273	0.102-0.726	0.009	-0.237	-1.621, 1.147	0.789	0.198-3.149	0.737
Diffuse redness score, mean (SD)	1.821 (0.556)	1.849 (0.488)	1.116	0.545-2.288	0.764					
Kyoto score, mean (SD)	5.333 (1.402)	5.753 (1.007)	1.355	0.987-1.860	0.060					

P value was calculated using the binomial logistic regression analysis. CI: Confidence interval; SD: Standard deviation.

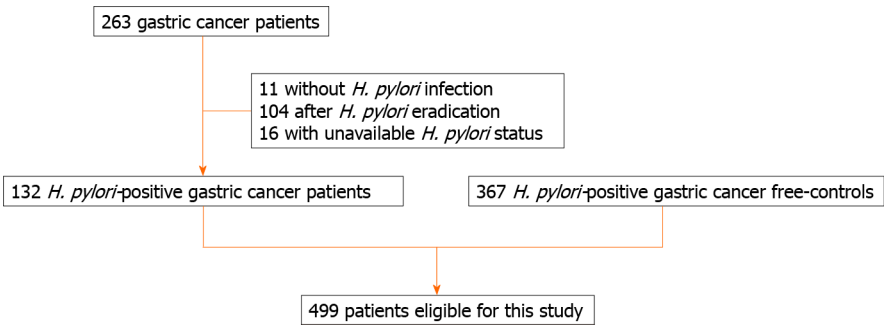

Figure 1 Patient flowchart. *H. pylori: Helicobacter pylori.*

with endoscopic gastritis, the simplified Kyoto score using only atrophy and intestinal metaplasia scores was more dramatically related to the ABC classifi-cation[27]. Combined with the results of this study, we suggest that nodularity and diffuse redness scores be not included in the gastric cancer risk score. Particularly, enlarged folds scores should be excluded from the risk score for intestinal-type cancer. However, further verifications are required for this matter.

This study has some limitations. The subjects of our study were limited to *H. pylori*-infected patients. Gastric cancer is detected even after *H. pylori* eradication[41]. Take *et al*[42] described an increased incidence of diffuse-type cancer more than 10 years after *H. pylori* eradication. Studying subjects after *H. pylori* eradication or *H. pylori*-uninfected subjects in the future is warranted. The gastric cancer-free control group in this study was extracted from a shorter period than the gastric cancer group. In the future, comparisons between the endoscopic background diagnosis of patients with gastric cancer (especially according to the Lauren classification) and that of non-cancer controls during the same period is desired. In addition, further investigations using prospective study designs are needed to evaluate the accuracy of the Lauren predictive

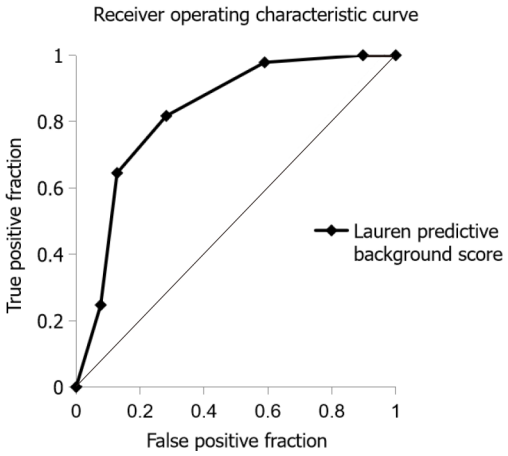

Figure 2 Receiver operating characteristic curve for predicting intestinal-type gastric cancer. Receiver operating characteristics curve was based on the Lauren predictive background score in 132 patients with diffuse- or intestinal-type gastric cancer according to Lauren classification. The Lauren predictive background score was defined as a sum of the following points: +2 points for an age of 65 years or older, +1 point for male sex, +1 point for endoscopic intestinal metaplasia, and -1 point for endoscopic enlarged folds.

background score. The sample size for that study would be 26 (8 patients with diffuse type cancer, and 19 patients with intestinal type cancer).

CONCLUSION

In conclusion, patient backgrounds, such as age, sex, endoscopic intestinal metaplasia, and endoscopic enlarged folds are useful for predicting tumor type.

ARTICLE HIGHLIGHTS

Research background

The accurate diagnosis of gastric cancer using the Lauren classification is crucial.

Research motivation

The relationship between the Lauren classification and endoscopic findings based on the Kyoto classification is not clear.

Research objectives

To investigate the background patient characteristics and endoscopic gastritis of patients with diffuse- and intestinal-type gastric cancers, focusing on *Helicobacter pylori (H. pylori)*-infected patients.

Research methods

This study included participants who underwent esophagogastroduodenoscopy at the Toyoshima Endoscopy Clinic. The endoscopy-based Kyoto classification of gastritis consisted of atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. The effects of age, sex, and Kyoto classification score on gastric cancer according to the Lauren classification were analyzed.

Research results

A total of 499 *H. pylori*-infected patients (49.6% males; average age, 54.9 years) were enrolled. A total of 132 patients with gastric cancer (39 diffuse- and 93 intestinal-type) and 367 cancer-free controls were eligible. Gastric cancer was independently associated with age ≥ 65 years, high atrophy score, high intestinal metaplasia score, and low nodularity score when compared to the control. Factors independently associated with intestinal-type cancer were age ≥ 65 years, male sex, high intestinal metaplasia score, and low enlarged folds score when compared to diffuse-type cancer. The Lauren predictive background score was defined as the sum of the following points: +2 points for an age of ≥ 65 years, +1 point for male sex, +1 point for intestinal

metaplasia, and -1 point for enlarged folds. The area under the curve of the Lauren predictive background score was 0.828 for predicting intestinal-type tumors. With a cut-off of +2, the sensitivity and specificity of the Lauren predictive background score were 81.7% and 71.8%, respectively.

Research conclusions

Patient backgrounds such as age, sex, endoscopic intestinal metaplasia, and endoscopic enlarged folds are useful for predicting tumor type.

Research perspectives

Studying subjects after *H. pylori* eradication or *H. pylori*-uninfected subjects in the future is warranted. Furthermore, comparisons between the endoscopic background diagnosis of patients with gastric cancer (especially according to Lauren classification) and that of non-cancer controls is desired.

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META-ANALYSIS

Meta-analysis and trial sequential analysis of randomized evidence comparing general anesthesia *vs* regional anesthesia for laparoscopic cholecystectomy

Peter Asaad, Adam O'Connor, Shahab Hajibandeh, Shahin Hajibandeh

ORCID number: Peter Asaad 0000-0002-6603-468X; Adam O'Connor 0000-0001-5267-2819; Shahab Hajibandeh 0000-0002-3294-4335; Shahin Hajibandeh 0000-0001-6159-1068.

Author contributions: Asaad P and Hajibandeh Shahi designed the research study; Asaad P, O'Connor A and Hajibandeh Shaha collected the data for the meta-analysis; Hajibandeh Shaha and Hajibandeh Shahi analysed and interpreted the data; Hajibandeh Shaha and Hajibandeh Shahi did the statistical analysis; Asaad P, Hajibandeh Shaha and Hajibandeh Shahi wrote the article; all authors critically revised the article and provided final approval for the article.

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Peter Asaad, Department of General and Colorectal Surgery, Wythenshawe Hospital, Manchester M23 9LT, United Kingdom

Adam O'Connor, Department of General Surgery, Royal Blackburn Hospital, Blackburn BB2 3HH, United Kingdom

Shahab Hajibandeh, Department of General Surgery, Glan Clwyd Hospital, Rhyl LL18 5UJ, United Kingdom

Shahin Hajibandeh, Department of General Surgery, Wye Valley NHS Trust, Hereford HR1 2ER, United Kingdom

Corresponding author: Shahin Hajibandeh, MD, Senior Researcher, Surgeon, Department of General Surgery, Wye Valley NHS Trust, Hereford, Hereford HR1 2ER, United Kingdom. shahin_hajibandeh@yahoo.com

Abstract

BACKGROUND

In an effort to further reduce the morbidity and mortality profile of laparoscopic cholecystectomy, the outcomes of such procedure under regional anesthesia (RA) have been evaluated. In the context of cholecystectomy, combining a minimally invasive surgical procedure with a minimally invasive anesthetic technique can potentially be associated with less postoperative pain and earlier ambulation.

AIM

To evaluate comparative outcomes of RA and general anesthesia (GA) in patients undergoing laparoscopic cholecystectomy.

METHODS

A comprehensive systematic review of randomized controlled trials with subsequent meta-analysis and trial sequential analysis of outcomes were conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards.

RESULTS

Thirteen randomized controlled trials enrolling 1111 patients were included. The study populations in the RA and GA groups were of comparable age (P = 0.41),

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gender (P = 0.98) and body mass index (P = 0.24). The conversion rate from RA to GA was 2.3%. RA was associated with significantly less postoperative pain at 4 h [mean difference (MD): - 2.22, P < 0.00001], 8 h (MD: -1.53, P = 0.0006), 12 h (MD: -2.08, P < 0.00001), and 24 h (MD: -0.90, P < 0.00001) compared to GA. Moreover, it was associated with significantly lower rate of nausea and vomiting [risk ratio (RR): 0.40, P < 0.0001]. However, RA significantly increased postoperative headaches (RR: 4.69, P = 0.03), and urinary retention (RR: 2.73, P = 0.03). The trial sequential analysis demonstrated that the meta-analysis was conclusive for most outcomes, with the exception of a risk of type 1 error for headache and urinary retention and a risk of type 2 error for total procedure time.

CONCLUSION

Our findings indicate that RA may be an attractive anesthetic modality for day-case laparoscopic cholecystectomy considering its associated lower postoperative pain and nausea and vomiting compared to GA. However, its associated risk of urinary retention and headache and lack of knowledge on its impact on procedure-related outcomes do not justify using RA as the first line anesthetic choice for laparoscopic cholecystectomy.

Key Words: Laparoscopic cholecystectomy; Regional anesthesia; General anesthesia; Laparoscopy; Level 1 evidence; Meta-analysis

Core Tip: Despite the existence of solid level 1 evidence from multiple randomized controlled trials on comparative outcomes of general anesthesia and regional anesthesia (RA) in laparoscopic cholecystectomy and demonstration of feasibility of laparoscopic cholecystectomy under RA, lack of knowledge on the impact of RA on specific procedure related outcomes may discourage surgeons from selecting RA as the first choice of anesthesia for laparoscopic cholecystectomy. Considering our findings, we encourage use of RA in patients who are not fit for general anesthesia but do not hesitate to highlight that available evidence does not justify using RA as the first line anesthetic choice for laparoscopic cholecystectomy.

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INTRODUCTION

Gallstone disease is thought to occur in approximately 15% of the population of whom 20% are symptomatic[1]. Laparoscopic cholecystectomy is the gold standard treatment for symptomatic gallstone disease and one of the most commonly performed general surgical procedures[1]. This minimally invasive procedure results in a shorter length of hospital stay and quicker overall recovery compared with the traditional open approach[2].

Traditionally, laparoscopic cholecystectomy is carried out under general anesthesia (GA). Some argue the endotracheal intubation is required to prevent aspiration or respiratory complications secondary to the induction of pneumoperitoneum[3]. Furthermore, GA is associated with rapid onset of action and reduces the procedure related stress[4].

In an effort to further reduce the morbidity and mortality profile of laparoscopic cholecystectomy, the outcomes of such procedure under regional anesthesia (RA) have been evaluated[5]. RA, including spinal anesthesia (SA) and epidural anesthesia (EA), confers the advantages of avoidance of both paralytic agents and endotracheal intubation[6]. Although combining a minimally invasive surgical procedure with a minimally invasive anesthetic technique would appear attractive, it's use is currently

limited[7]. Nevertheless, it has been demonstrated that the use of neuraxial anesthetics decreases postoperative thromboembolic events, myocardial infarction as well as overall mortality[8]. Moreover, RA has been demonstrated to be associated with less postoperative pain and earlier ambulation in patients undergoing laparoscopic cholecystectomy[7].

The purpose of our study was to conduct a comprehensive review of the current literature and conduct a meta-analysis of randomized trials to evaluate comparative outcomes of RA and GA in patients undergoing laparoscopic cholecystectomy. Furthermore, we aimed to conduct a trial sequential analysis to assess the robustness of our meta-analysis findings.

MATERIALS AND METHODS

Design

We highlighted our eligibility criteria, methods, and evaluated outcomes in a review protocol. Our study was carried out in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards[9].

Inclusion criteria

(1) Randomized controlled trials (RCTs); (2) Including patients aged > 18 years old of any gender; (3) Including patients undergoing laparoscopic cholecystectomy under RA; and (4) Comparing laparoscopic cholecystectomy under GA.

Exclusion criteria

(1) Observational studies, case series, case reports, and letters; (2) Including patients undergoing open cholecystectomy; and (3) Including patients undergoing laparoscopic intraoperative cholangiogram with or without common bile duct exploration.

Outcomes

Primary outcome measures were defined as the post-operative pain intensity assessed on a 10 mm visual analogue scale (VAS) at 4 h, 6 h, 12 h and 24 h. The pain intensity data described by other means than a 10 mm VAS were standardized to such a scale. Operative time, total operative and anesthetic time, urinary retention (defined as inability to urinate spontaneously during the early postoperative period requiring application of heat or urinary catheterization), nausea and vomiting, headache, and hypotension (defined as a reduction of > 30% in mean arterial pressure or systolic blood pressure < 90 mmHg) were the secondary outcome parameters.

Literature search strategy

Three authors independently searched the following electronic databases: MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL). The literature search was performed on 08 March 2019. Our search strategy was adapted according to thesaurus headings, search operators and limits in the aforementioned databases (Supplementary Table 1). Furthermore, we searched World Health Organization International Clinical Trials Registry (http://apps.who.int/trialsearch/), ClinicalTrials.gov (http://clinicaltrials.gov/), and ISRCTN Register (http://www.isrctn.com/) to identify ongoing and unpublished studies. Moreover, the reference lists of identified articles were screened for further potentially eligible trials.

Selection of studies

The yielded search results were evaluated by two reviewers. Following evaluation of their titles, abstracts and full-texts of identified articles, those studies that met the inclusion criteria of our study were selected for inclusion in data synthesis. Disagreements in selection of studies were resolved by discussion between the reviewers. However, if the discrepancies remained unresolved, a third reviewer was involved.

Data extraction and management

We created an electronic data extraction spreadsheet according to the Cochrane's recommendations for intervention reviews. The data extraction spreadsheet was pilot-tested in randomly selected articles and adjusted accordingly. The following information were extracted from the included studies by two independent authors: (1)

Study-related data (first author, publication year, country of origin of the corresponding author, journal in which the study was published, study design, and study size); (2) Baseline demographic and clinical information of the study populations (age, gender, weight, height, body mass index, American Society of Anesthesiologists classification); (3) Type of anesthetic agent used in the RA group or any additional medications used, conversion from SA to GA; (4) Primary and secondary outcome data; and (5) Disagreements during data extraction and management were resolved following consultation with a third independent author.

Assessment of risk of bias

The methodological quality and risk of bias assessment were carried out by two authors using the Cochrane's tool[10]. The Cochrane's tool classifies studies into low, unclear and high risk of bias following evaluating and determining the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. We resolved discrepancies in risk of bias assessment by discussion between the assessing authors. Nevertheless, if no agreement could be reached, a third reviewer was involved as an adjudicator.

Summary measures and synthesis

For urinary retention, nausea and vomiting, and headache we calculated the risk ratio (RR) as the summary measures. The RR is the risk of an adverse event in the RA group compared to the GA group. An RR of less than one would favor the SA group. For VAS score at 4 h, 6 h, 12 h and 24 h, operative time, and total operative and anesthetic time we calculated the mean difference (MD) between the two groups.

The number of individual patients was used as the unit of analysis for all outcome parameters. Information with regards to dropouts, withdrawals and any other missing data were recorded. We planned to contact authors of the included studies where information about our outcome of interest was not reported. Our final analysis respected the intention-to-treat concept.

One independent review author entered the extracted data into Review Manager 5.3 software for data synthesis[10]. The entered data were subsequently checked by a second independent review author. Random-effects or fixed-effect modelling were used, as appropriate, for analysis. Only when significant between-study heterogeneity existed, random-effects models were applied. This has previously been defined by Higgins *et al*[10]. We reported the results of our analysis for each outcome parameter in a forest plot with 95% confidence intervals (CIs).

Heterogeneity among the studies was assessed using the Cochran Q test (χ^2). We quantified inconsistency by calculating I^2 and interpreted it using the following guide: 0% to 25% might not be important; 25% to 75%: may represent moderate heterogeneity; 75% to 100% may represent substantial heterogeneity. Moreover, where more than 10 studies were available in analysis of an outcome parameter, funnel plots were planned to be constructed in order to assess their symmetry to visually evaluate publication bias.

We conducted sensitivity analyses to explore potential sources of heterogeneity and assess the robustness of our results. For each outcome parameter, we repeated the primary analysis using random-effects or fixed-effect models. Moreover, for each of our defined dichotomous variable, we calculated the pooled odds ratio or risk difference. Finally, we evaluated the effect of each study on the overall effect size and heterogeneity by repeating the analysis following excluding one study at a time.

Trial sequential analysis

Trial sequential analysis was performed for the outcomes reported by at least 5 trials using the trial sequential analysis software 0.9.5.5 Beta (Copenhagen Trial Unit, Copenhagen, Denmark). In order to control the risk of type 1 error, we planned to adjust the thresholds for the *Z* values using O'Brien-Fleming α-spending function; allowing the type I error risk to be restored to the desired maximum risk. Crossing the O'Brien-Fleming α-spending boundaries by a Z-curve would indicate statistical significance. Moreover, we penalised the *Z* values according to the strength of the available evidence and the number of repeated significance tests as defined by the law of the iterated logarithm. The risk of type 2 error was controlled using the β-spending function and futility boundaries. Crossing the futility boundaries by a Z-curve would indicate that the two interventions do not differ more than the anticipated intervention effect. Random or fixed effects modelling were applied as appropriate for the analyses. We handled the zero event trials by constant continuity correction which involved adding a continuity correction factor to the number of events and non-events in each

intervention group. A two-sided CI with 95% confidence level was used to indicate statistical significance. We estimated the information size for the analyses based on achievement of 80% power and 10% relative risk reduction between the two groups.

RESULTS

The literature search identified 1267 articles. After further evaluation of the identified articles, 13 RCTs[4,5,11-21] met our inclusion criteria (Figure 1). The included studies reported the outcomes of 1111 patients of whom 554 patients underwent laparoscopic cholecystectomy under RA and the remaining 557 patients had laparoscopic cholecystectomy under GA.

The date of publication and country of origin, journal, and study design of the included studies are presented in Table 1. Table 2 presents baseline demographic and clinical characteristics of the study populations. There was no significant difference in mean age (P = 0.41), gender (P = 0.98) and body mass index (P = 0.24) between two groups. There were 13 conversion from RA to GA. Table 3 demonstrates details of anesthetic agent used in the RA group in the included studies

Methodological appraisal

Figure 2 presents the risk of bias assessment of the included RCT. Eleven studies had low risk of selection bias and the remaining two had unclear risk of selection bias due to not providing information about the allocation concealment. All included studies had high risk of performance bias due to lack of blinding. Three studies had low risk of detection bias as they blinded the outcome assessor. However, 9 studies had high risk of such bias. All included studies had low risk of attrition and reporting bias.

Data synthesis

Outcomes are summarized in Figure 3.

VAS score at 4 h: Seven studies (539 patients) reported the VAS score at 4 h postoperatively as one of their outcomes. The pooled analysis demonstrated that RA was associated with significantly less postoperative pain at 4 h following surgery (MD: -2.22, 95%CI: -3.10 to -1.34, P < 0.00001). The heterogeneity among the studies was significant (I^2 = 94%, P < 0.00001).

VAS score at 8 h: Five studies reported the VAS score at 8 h as an outcome. The pooled analysis which included 430 patients demonstrated that RA was associated with significantly lower pain 8 h following laparoscopic cholecystectomy (MD: -1.53, 95%CI: -2.41 to -0.66), P = 0.0006). The between-studies heterogeneity was significant (I^2 = 89%, P < 0.00001).

VAS score at 12 h: Five studies including 473 patients reported this outcome. The meta-analysis demonstrated RA was associated with significantly lower postoperative pain at 12 h following surgery when compared to GA (MD: -2.08, 95%CI: -2.58 to -1.58, P < 0.00001). Significant heterogeneity existed among the included studies (I^2 = 84%, P < 0.0001).

VAS score at 24 h: Seven studies (583 patients) reported postoperative VAS score at 24 h in their study groups. The pooled analysis demonstrated that there was a significantly lower postoperative pain at 24 h in favor of RA (MD: -0.90, 95%CI: -1.28 to -0.53, P < 0.00001). The heterogeneity among the included studies was considerable (I^2 = 87%, P < 0.00001).

Nausea and vomiting: Nine studies (811 patients) reported postoperative nausea and vomiting as an outcome in their intervention groups. The nausea and vomiting rates in the RA and GA groups were 6.2% and 15.7%, respectively. There was a significantly lower rate of nausea and vomiting in favor of RA compared to GA (RR: 0.40, 95%CI: 0.26-0.61, P < 0.0001). Low heterogeneity existed among the included studies (I^2 = 0%, P = 0.49).

Headache: Four studies (631 patients) reported post-operative headache as one of their outcomes. The rate of headache in the RA group was 3.2% while it was only 0.3% in the GA group. The pooled analysis demonstrated that RA was associated with significantly higher rate of postoperative headaches compared to GA (RR: 4.69, 95%CI: 1.21-18.21, P = 0.03). The between-study heterogeneity was low (I^2 = 0%, P = 0.98).

Table 1 Summary characteristics of included studies

Ref.	Year	Country	Journal	Design	Total number of patients	GA	RA
Majedi *et al*[15]	2019	Iran	*Advanced Biomedical Research*	RCT	80	40	40
Sharaf *et al*[19]	2018	Pakistan	*Anaesthesia, Pain and Intensive Care*	RCT	120	60	60
Donmez *et al*[11]	2017	Turkey	*Annals of Surgical Treatment and Research*	RCT	49	25	24
Kalaivani *et al*[14]	2014	India	*Journal of Clinical and Diagnostic Research*	RCT	50	25	25
Prasad *et al*[17]	2014	India	*Journal of Evolution of Medical and Dental Sciences*	RCT	60	30	30
Ellakany *et al*[12]	2013	Egypt	*Egyptian Journal of Anaesthesia*	RCT	40	20	20
Tiwari *et al*[20]	2013	India	*Journal of Minimal Access Surgery*	RCT	235	114	110
Bessa *et al*[5]	2012	Egypt	*Journal of Laparoendoscopic and Advanced Surgical Techniques*	RCT	180	90	90
Ross *et al*[18]	2012	United States	*Surgical Endoscopy*	RCT	20	10	10
Mehta *et al*[16]	2010	India	*Anesthesia, Essays and Researches*	RCT	60	30	30
Imbelloni *et al*[13]	2010	Brazil	*Revista Brasileira de Anestesiologia*	RCT	68	33	35
Bessa *et al*[21]	2010	Egypt	*Journal of Laparoendoscopic and Advanced Surgical Techniques*	RCT	60	30	30
Tzovaras *et al*[4]	2008	Greece	*Archives of Surgery*	RCT	100	50	50

RCT: Randomized controlled trial; GA: General anesthesia; RA: Regional anesthesia.

Table 2 Demography and clinical characteristics of the patients

Ref.	Age		Male:female ratio		BMI		ASA I: II: III	
	GA	RA	GA	RA	GA	RA	GA	RA
Majedi *et al*[15]	50.1 ± 9.78	52.06 ± 15.03	14:26	16:24	NR	NR	NR	NR
Sharaf *et al*[19]	44.07 ± 5.62	42.57 ± 5.77	0:60	0:60	25.41 ± 2.36	26 ± 2.31	14:46:0	22:38:0
Donmez *et al*[11]	45 ± 13	45 ± 14	18:07	18:6	28.75 ± 4.5	30.63 ± 3.6	18:7:0	16:6:2
Kalaivani *et al*[14]	47.84 ± 10.49	45 ± 11.73	08:17	10:15	NR	NR	NR	NR
Prasad *et al*[17]	38.5 ± 9.83	35.06 ± 7.5	25:5	17:13	23.5 ± 1.98	22.96 ± 2.98	23:7:0	22:8:0
Ellakany *et al*[12]	44.3 ± 13.2	45.9 ± 13.6	07:13	8:12	30 ± 3.9	29.8 ± 4.1	NR	NR
Tiwari *et al*[20]	46.1 ± 12.9	45.07 ±13.19	16:98	13:96	NR	NR	NR	NR
Bessa *et al*[5]	44 (19-50)	40 (16-50)	8:82	11:79	29.1 (23.4-33.1)	28.7 (22.8-34)	NR	NR
Ross *et al*[18]	39.4 ± 11.7	44.9 ± 12.5	3:7	2:8	25.1 ± 4.6	26.1 ± 5.5	1:6:3	3:5:2
Mehta *et al*[16]	38.3	39.1	10:20	14:16	NR	NR	NR	NR
Imbelloni *et al*[13]	45.2 ± 12.1	41.1 ± 12.4	10:23	9:26	NR	NR	NR	NR
Bessa *et al*[21]	40.9 ± 11	41.4 ± 11.1	6:24	5:25	30.8 ± 6.6	31.3 ± 4.1	NR	NR
Tzovaras *et al*[4]	46 (26-65)	44 (23-65)	18:30	20:29	26 (19-30)	25 (18-30)	37:11:0	40:9:0

GA: General anesthesia; RA: Regional anesthesia; NR: Not reported; ASA: American Society of Anesthesiologists; BMI: Body mass index.

Urinary retention: Seven studies reported postoperative urinary retention as an outcome. The urinary retention rates in the RA and GA groups were 4.1% and 1.1%, respectively. The pooled analysis of 751 patients demonstrated that RA was associated with significantly higher postoperative urinary retention when compared to GA (RR: 2.73, 95%CI: 1.13-6.56), $P = 0.03$). There was low between-study heterogeneity ($I^2 = 0\%$, $P = 0.54$).

Operative time: Six studies reported the operative time as one of their outcomes. The pooled analysis included 681 patients and demonstrated that there was no significant

Table 3 Anesthetic agents used in the regional anesthesia group in each study

Ref.	Anesthetic agent used
Majedi *et al*[15]	18 mL of lidocaine 2% plus epinephrine (1:200000) plus 2 mL of sodium bicarbonate 8.4% and fentanyl 50 μg
Sharaf *et al*[19]	15 mg of hyperbaric bupivicaine and 25 μg fentanyl
Donmez *et al*[11]	hyperbaric bupivicaine 16mg and fentanyl 10 micrograms
Kalaivani *et al*[14]	15 mg of hyperbaric bupivicaine and 20 μg fentanyl
Prasad *et al*[17]	15 mg of heavy bupivicaine and 25 μg fentanyl
Ellakany *et al*[12]	5 mg plain bupivicaine and 25 μg fentanyl
Tiwari *et al*[20]	12.5 mg to 17.5 mg of hyperbaric bupivicaine
Bessa *et al*[5]	15 mg of hyperbaric bupivicaine and 20 mcg fentanyl
Ross *et al*[18]	20-25 mL of lidocaine 2%
Mehta *et al*[16]	0.3 mg/kg of hyperbaric bupivicaine 0.5%
Imbelloni *et al*[13]	15 mg of hyperbaric bupivicaine and 20 μg fentanyl
Bessa *et al*[21]	15 mg of hyperbaric bupivicaine and 20 μg fentanyl
Tzovaras *et al*[4]	15 mg of hyperbaric bupivicaine, 0.25 mg morphine and 20 μg fentanyl

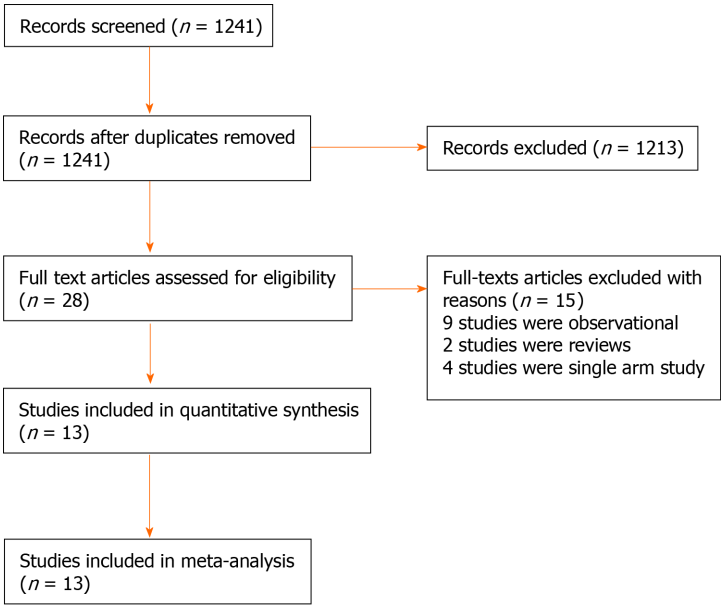


Figure 1 Study flow diagram.

difference in operative time between RA and GA (MD: -2.29, 95%CI: -7.00-2.41, P = 0.34). The heterogeneity among the included studies was significant (I^2 = 90%, P < 0.00001).

Total operative and anesthetic time: Six studies (491 patients) reported the total operative and anesthetic time as one of their outcomes. The meta-analysis demonstrated that there was no significant difference in total operative and anesthetic time between two groups (MD: -1.43, 95%CI: -5.39-2.53, P = 0.48). The heterogeneity between studies was high (I^2 = 77%, P = 0.0005).

Considering the data provided by the included studies, it was not possible to conduct analysis on hypotension which was one of our secondary outcomes.

Sensitivity analysis

Using random-effects fixed-effect models did not affect the pooled effect size in analysis of any of the reported outcomes, except urinary retention where the increased rate of urinary retention in the RA group became insignificant. Nevertheless,

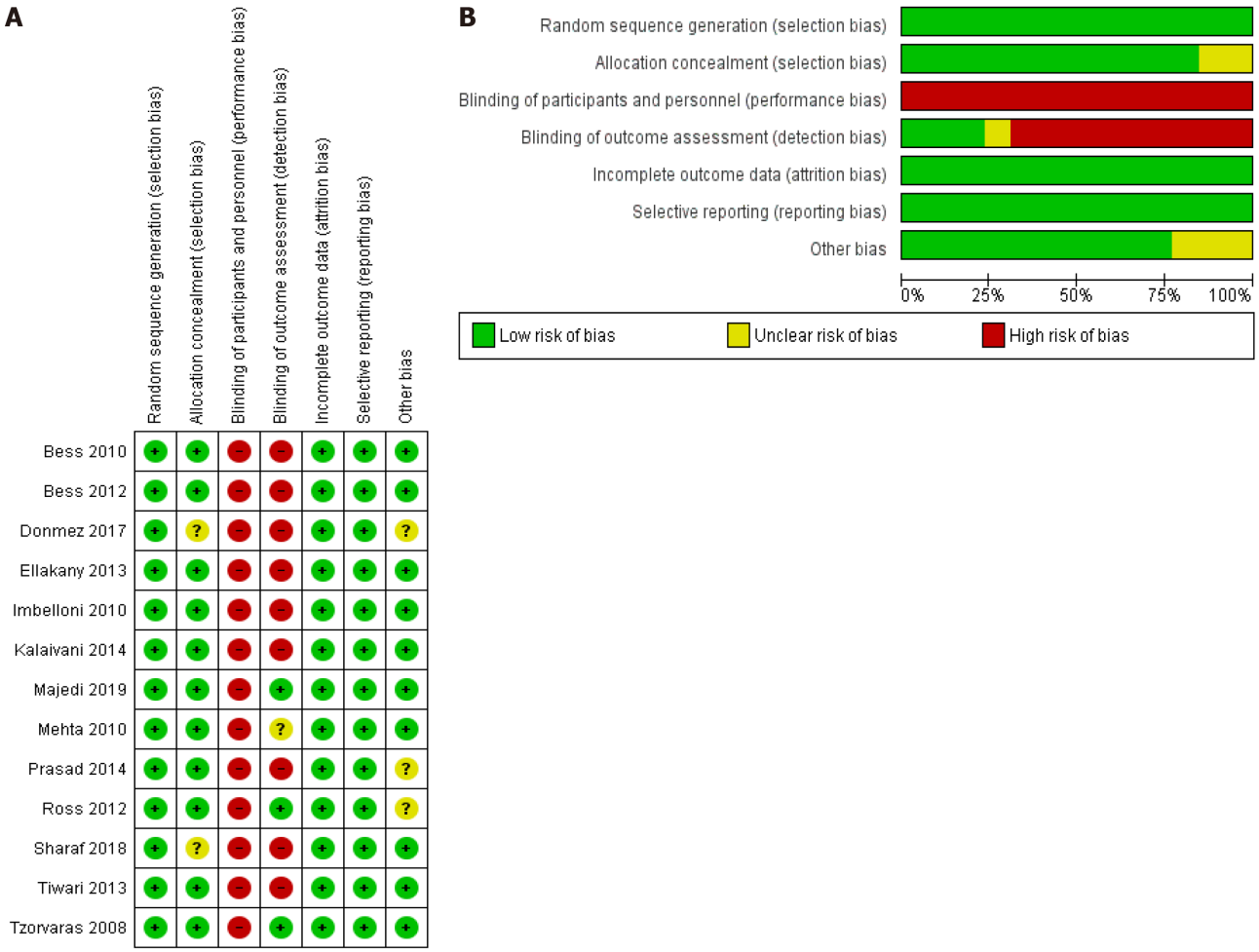


Figure 2 Risk of bias summary and graph showing authors' judgments about each risk of bias item. A: Risk of bias summary; B: Risk of bias graph.

considering heterogeneity of 0%, fixed-effect model was deemed more appropriate. The direction of pooled effect size remained unchanged when odds ratio, RR, or risk difference were calculated for dichotomous variables.

As two of our included studies, Bessa *et al*[21] and Bessa *et al*[5] were conducted by the same group, in order to ensure that potential overlapping patients are not included, we repeated all analyses with exclusion of Bessa *et al*[5] which did not change the direction of pooled effect size in any of our outcomes

Trial sequential analysis

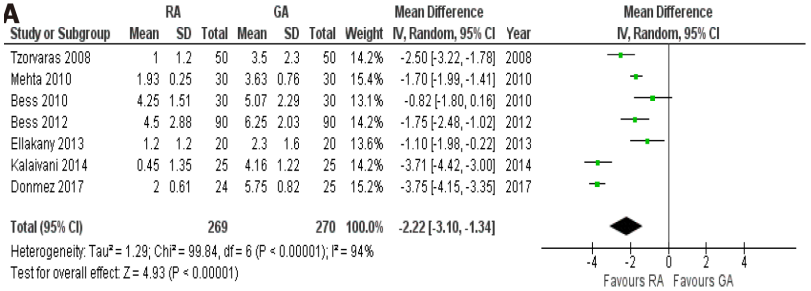
Outcomes are summarised in Figure 4.

VAS score at 4 h: The information size was calculated at 330 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favor of RA before and after the information size was reached and the penalized Z value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.

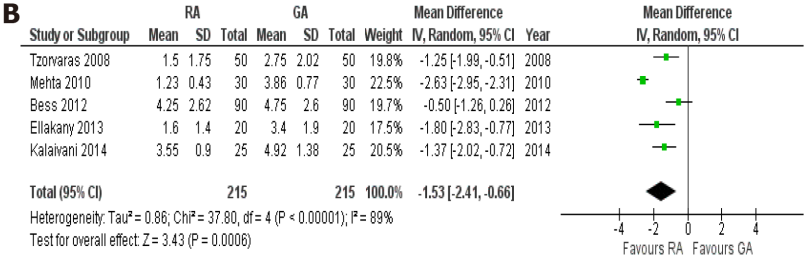
VAS score at 8 h: The information size was calculated at 324 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favor of RA before and after the information size was reached and the penalized Z value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.

VAS score at 12 h: The information size was calculated at 112 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favor of RA before and after the information size was reached and the penalized Z value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.

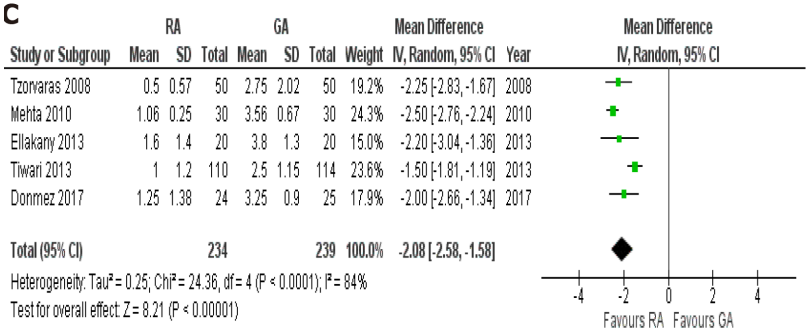
A


RA GA Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year IV, Random, 95% CI
Tzorvaras 2008 1 1.2 50 3.5 2.3 50 14.2% -2.50 [-3.22, -1.78] 2008
Mehta 2010 1.93 0.25 30 3.63 0.76 30 15.4% -1.70 [-1.99, -1.41] 2010
Bess 2010 4.25 1.51 30 5.07 2.29 30 13.1% -0.82 [-1.80, 0.16] 2010
Bess 2012 4.5 2.88 90 6.25 2.03 90 14.2% -1.75 [-2.48, -1.02] 2012
Ellakany 2013 1.2 1.2 20 2.3 1.6 20 13.6% -1.10 [-1.98, -0.22] 2013
Kalaivani 2014 0.45 1.35 25 4.16 1.22 25 14.2% -3.71 [-4.42, -3.00] 2014
Donmez 2017 2 0.61 24 5.75 0.82 25 15.2% -3.75 [-4.15, -3.35] 2017
Total (95% CI) 269 270 100.0% -2.22 [-3.10, -1.34]
Heterogeneity: Tau² = 1.29; Chi² = 99.84, df = 6 (P < 0.00001); I² = 94%
Test for overall effect: Z = 4.93 (P < 0.00001)
-4 -2 0 2 4
Favours RA Favours GA

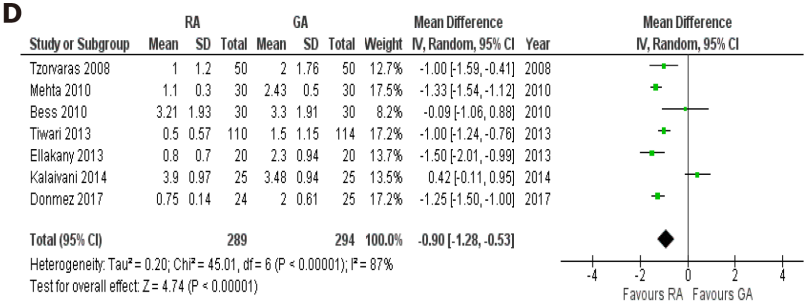
B


RA GA Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year IV, Random, 95% CI
Tzorvaras 2008 1.5 1.75 50 2.75 2.02 50 19.8% -1.25 [-1.99, -0.51] 2008
Mehta 2010 1.23 0.43 30 3.86 0.77 30 22.5% -2.63 [-2.95, -2.31] 2010
Bess 2012 4.25 2.62 90 4.75 2.6 90 19.7% -0.50 [-1.26, 0.26] 2012
Ellakany 2013 1.6 1.4 20 3.4 1.9 20 17.5% -1.80 [-2.83, -0.77] 2013
Kalaivani 2014 3.55 0.9 25 4.92 1.38 25 20.5% -1.37 [-2.02, -0.72] 2014
Total (95% CI) 215 215 100.0% -1.53 [-2.41, -0.66]
Heterogeneity: Tau² = 0.86; Chi² = 37.80, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.43 (P = 0.0006)
-4 -2 0 2 4
Favours RA Favours GA

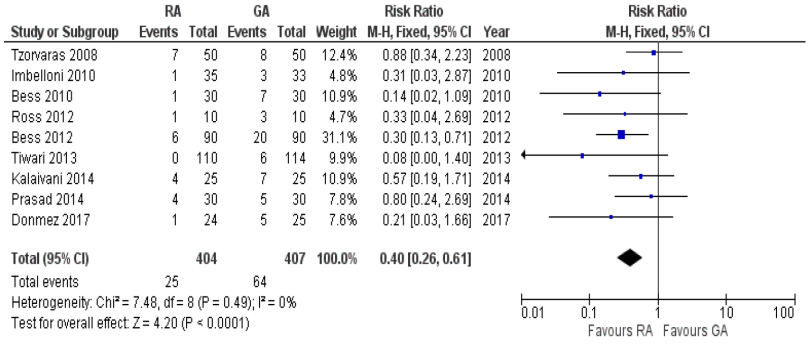
C


RA GA Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year IV, Random, 95% CI
Tzorvaras 2008 0.5 0.57 50 2.75 2.02 50 19.2% -2.25 [-2.83, -1.67] 2008
Mehta 2010 1.06 0.25 30 3.56 0.67 30 24.3% -2.50 [-2.76, -2.24] 2010
Ellakany 2013 1.6 1.4 20 3.8 1.3 20 15.0% -2.20 [-3.04, -1.36] 2013
Tiwari 2013 1 1.2 110 2.5 1.15 114 23.6% -1.50 [-1.81, -1.19] 2013
Donmez 2017 1.25 1.38 24 3.25 0.9 25 17.9% -2.00 [-2.66, -1.34] 2017
Total (95% CI) 234 239 100.0% -2.08 [-2.58, -1.58]
Heterogeneity: Tau² = 0.25; Chi² = 24.36, df = 4 (P < 0.0001); I² = 84%
Test for overall effect: Z = 8.21 (P < 0.00001)
-4 -2 0 2 4
Favours RA Favours GA

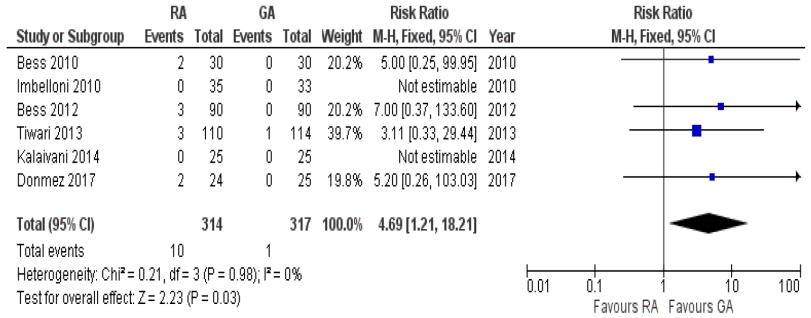
D


RA GA Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year IV, Random, 95% CI
Tzorvaras 2008 1 1.2 50 2 1.76 50 12.7% -1.00 [-1.59, -0.41] 2008
Mehta 2010 1.1 0.3 30 2.43 0.5 30 17.5% -1.33 [-1.54, -1.12] 2010
Bess 2010 3.21 1.93 30 3.3 1.91 30 8.2% -0.09 [-1.06, 0.88] 2010
Tiwari 2013 0.5 0.57 110 1.5 1.15 114 17.2% -1.00 [-1.24, -0.76] 2013
Ellakany 2013 0.8 0.7 20 2.3 0.94 20 13.7% -1.50 [-2.01, -0.99] 2013
Kalaivani 2014 3.9 0.97 25 3.48 0.94 25 13.5% 0.42 [-0.11, 0.95] 2014
Donmez 2017 0.75 0.14 24 2 0.61 25 17.2% -1.25 [-1.50, -1.00] 2017
Total (95% CI) 289 294 100.0% -0.90 [-1.28, -0.53]
Heterogeneity: Tau² = 0.20; Chi² = 45.01, df = 6 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.74 (P < 0.00001)
-4 -2 0 2 4
Favours RA Favours GA

E


RA GA Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year M-H, Fixed, 95% CI
Tzorvaras 2008 7 50 8 50 12.4% 0.88 [0.34, 2.23] 2008
Imbelloni 2010 1 35 3 33 4.8% 0.31 [0.03, 2.87] 2010
Bess 2010 1 30 7 30 10.9% 0.14 [0.02, 1.09] 2010
Ross 2012 1 10 3 10 4.7% 0.33 [0.04, 2.69] 2012
Bess 2012 6 90 20 90 31.1% 0.30 [0.13, 0.71] 2012
Tiwari 2013 0 110 6 114 9.9% 0.08 [0.00, 1.40] 2013
Kalaivani 2014 4 25 7 25 10.9% 0.57 [0.19, 1.71] 2014
Prasad 2014 4 30 5 30 7.8% 0.80 [0.24, 2.69] 2014
Donmez 2017 1 24 5 25 7.6% 0.21 [0.03, 1.66] 2017
Total (95% CI) 404 407 100.0% 0.40 [0.26, 0.61]
Total events 25 64
Heterogeneity: Chi² = 7.48, df = 8 (P = 0.49); I² = 0%
Test for overall effect: Z = 4.20 (P < 0.0001)
0.01 0.1 1 10 100
Favours RA Favours GA

F


RA GA Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year M-H, Fixed, 95% CI
Bess 2010 2 30 0 30 20.2% 5.00 [0.25, 99.95] 2010
Imbelloni 2010 0 35 0 33 Not estimable 2010
Bess 2012 3 90 0 90 20.2% 7.00 [0.37, 133.60] 2012
Tiwari 2013 3 110 1 114 39.7% 3.11 [0.33, 29.44] 2013
Kalaivani 2014 0 25 0 25 Not estimable 2014
Donmez 2017 2 24 0 25 19.8% 5.20 [0.26, 103.03] 2017
Total (95% CI) 314 317 100.0% 4.69 [1.21, 18.21]
Total events 10 1
Heterogeneity: Chi² = 0.21, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)
0.01 0.1 1 10 100
Favours RA Favours GA

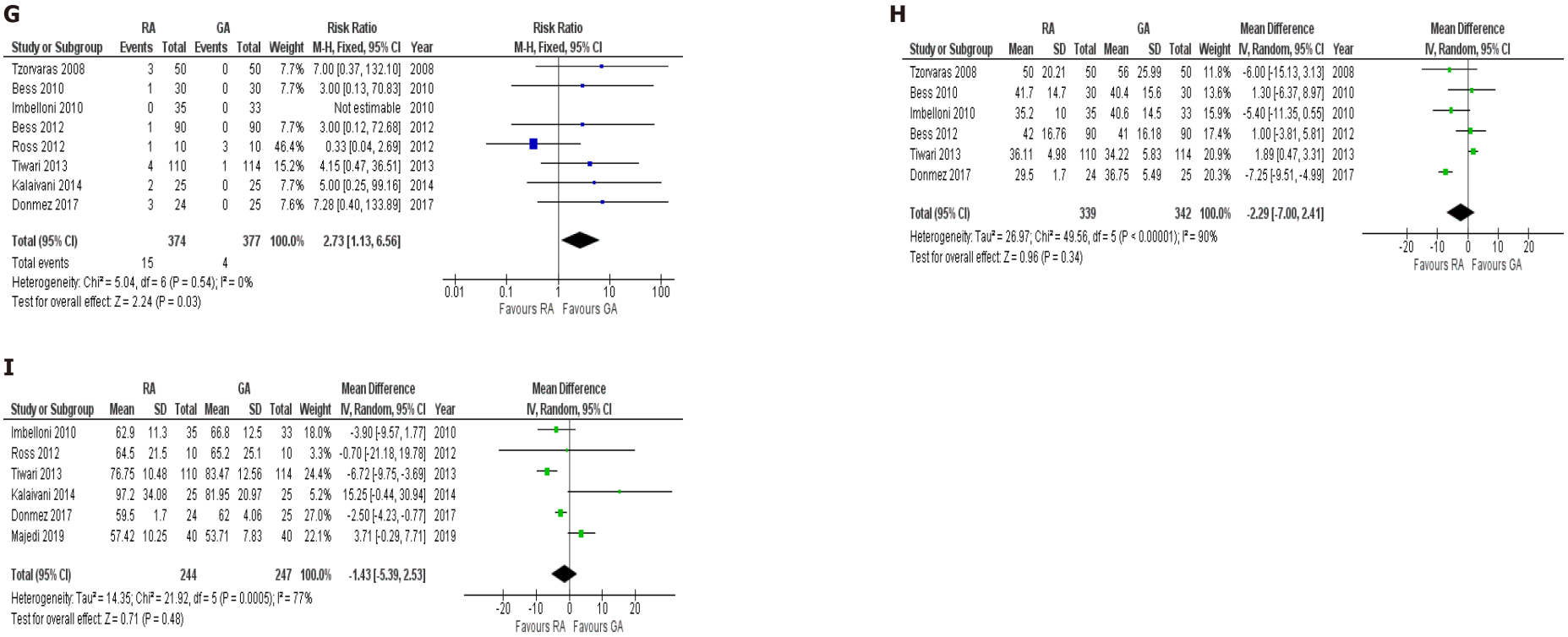
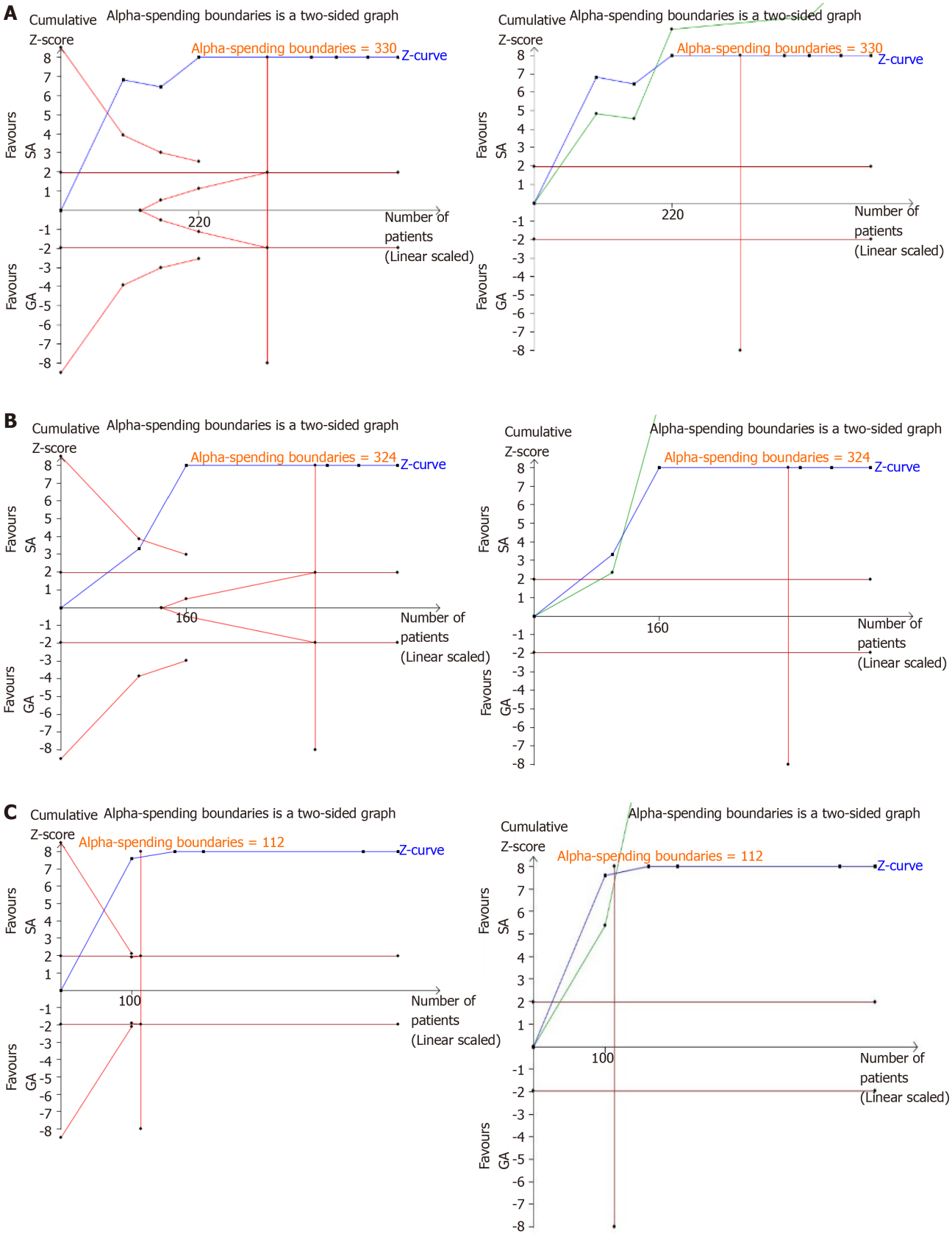
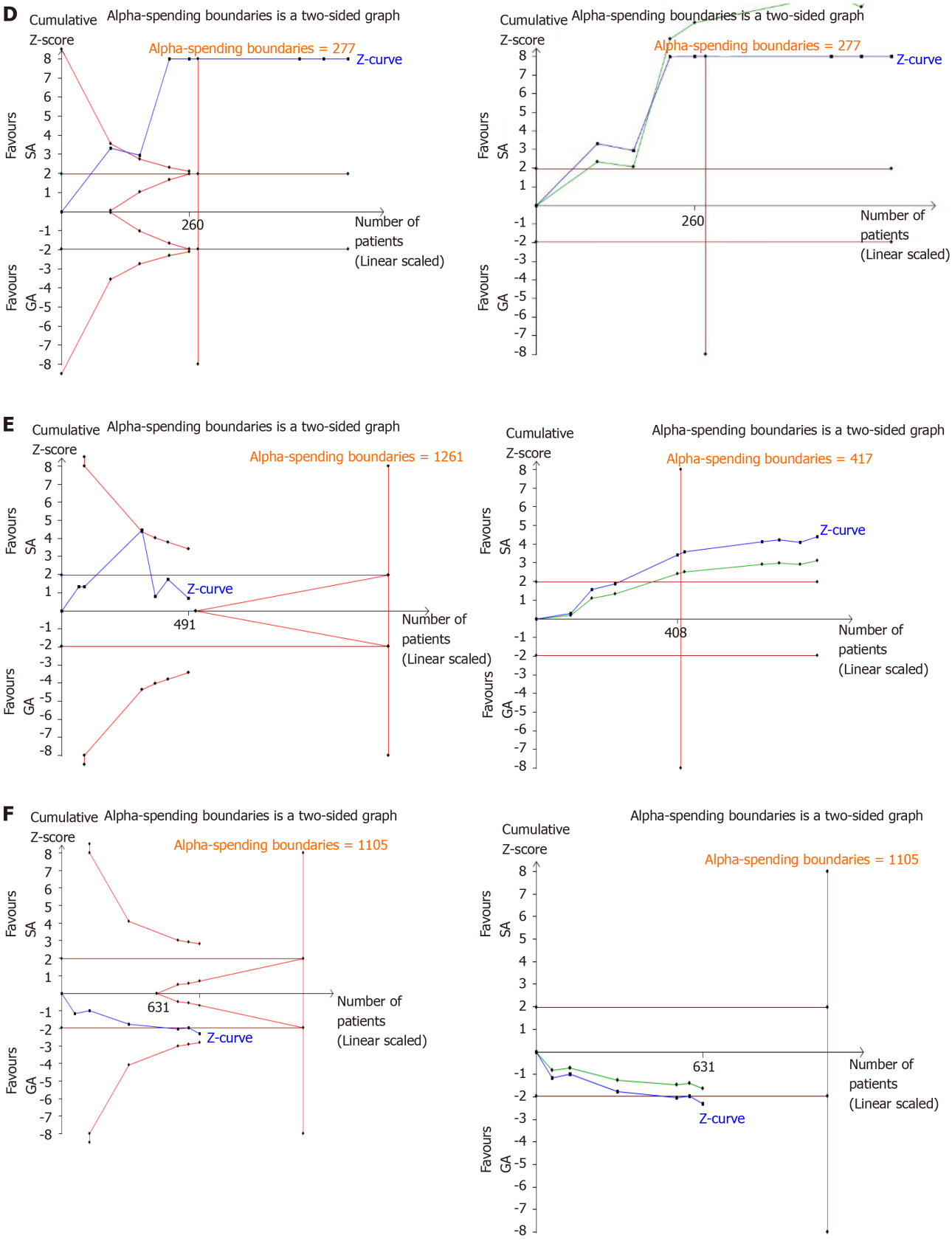


Figure 3 Forest plots of comparison. A: Visual analogue scale (VAS) at 4 h; B: VAS at 8 h; C: VAS at 12 h; D: VAS at 24 h; E: Nausea and vomiting; F: Headache; G: Urinary retention; H: Operative time; I: Total operative and anesthetic. The solid squares denote the risk ratios or mean difference. The horizontal lines represent the 95% confidence intervals, and the diamond denotes the pooled effect size. M-H: Mantel Haenszel test; RA: Regional anesthesia; GA: General anesthesia; CI: Confidence interval; SD: Standard deviation.

VAS score at 24 h: The information size was calculated at 277 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favour of RA before and after the information size was reached and the penalized *Z* value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.

Nausea and vomiting: The information size was calculated at 417 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favor of RA before and after the information size was reached and the penalized *Z* value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.


A
Cumulative Z-score
Alpha-spending boundaries is a two-sided graph
Alpha-spending boundaries = 330
Z-curve
Favours SA
Favours GA
220
Number of patients (Linear scaled)
B
Alpha-spending boundaries = 324
160
C
Alpha-spending boundaries = 112
100


D
Cumulative Z-score
Alpha-spending boundaries is a two-sided graph
Alpha-spending boundaries = 277
Z-curve
Favours SA
Favours GA
260
Number of patients (Linear scaled)
E
Alpha-spending boundaries = 1261
491
Alpha-spending boundaries = 417
408
F
Alpha-spending boundaries = 1105
631

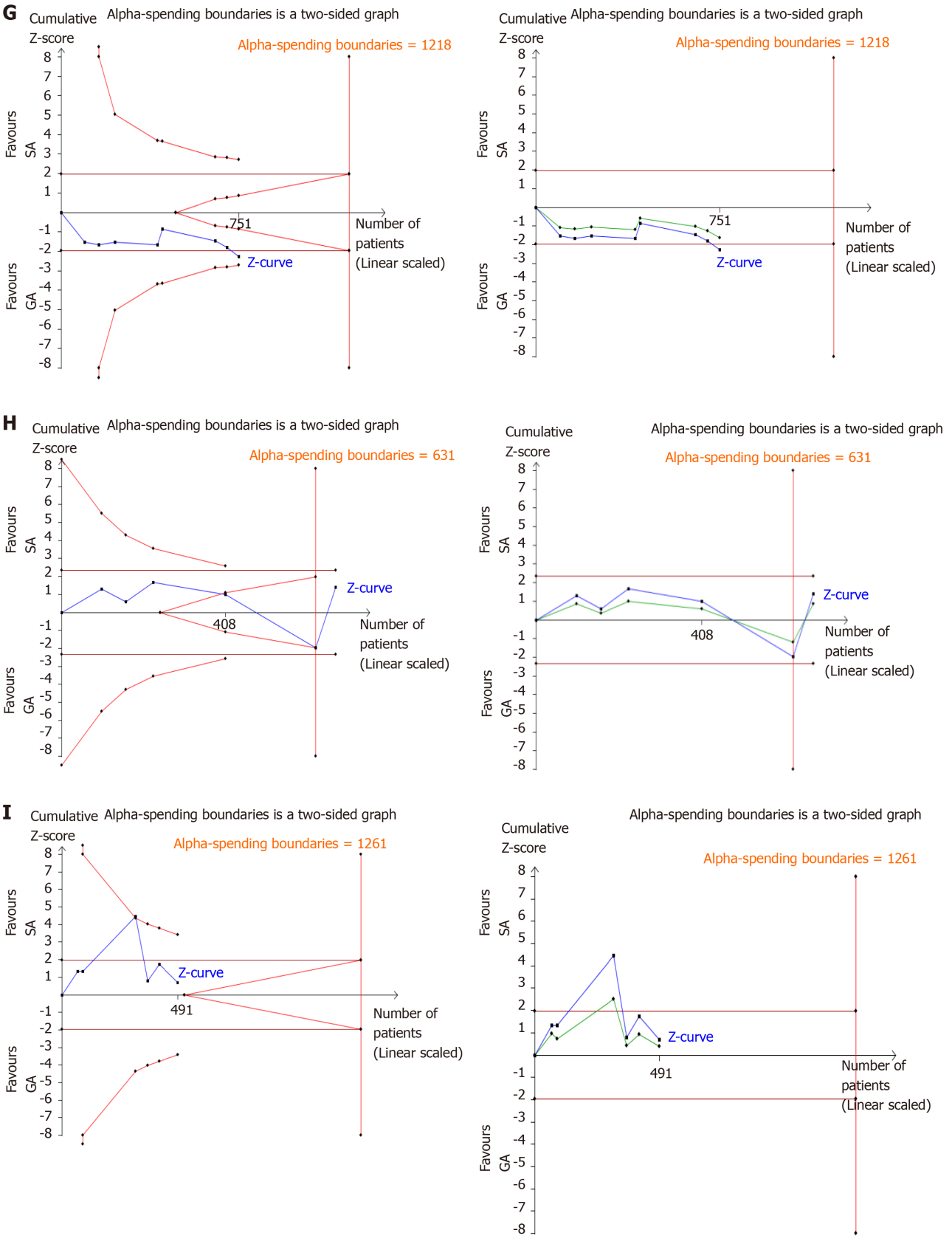


Figure 4 Results of trial sequential analysis. A: Visual analogue scale (VAS) at 4 h; B: VAS at 8 h; C: VAS at 12 h; D: VAS at 24 h; E: Nausea and vomiting; F: Headache; G: Urinary retention; H: Operative time; I: Total operative and anesthetic time. The red inward-sloping dashed lines make up the trial sequential monitoring boundaries. To the right, the outward sloping red dashed lines make up the futility region. The solid blue line is the cumulative *Z* curve. The solid green line presents penalised *Z* value.

Headache: The information size was calculated at 1105 patients. The Z-curve crossed

the conventional boundaries in favor of GA before the information size is reached. However, the Z-curve did not cross the α-spending boundaries and the futility boundaries before the information size is reached and the absolute number for penalized Z value remained smaller than 1.96; therefore, the meta-analysis was not conclusive and the results for this outcome were subject to type 1 error.

Urinary retention: The information size was calculated at 1218 patients. The Z-curve crossed the conventional boundaries in favor of GA before the information size is reached. However, the Z-curve did not cross the α-spending boundaries and the futility boundaries before the information size is reached and the absolute number for penalized Z value remained smaller than 1.96; therefore, the meta-analysis was not conclusive and the results for this outcome were subject to type 1 error.

Operative time: The information size was calculated at 631 patients. The Z-curve did not cross the conventional boundaries and the absolute number for penalized Z value remained smaller than 1.96 in both sides after the information size is reached; therefore, the meta-analysis was conclusive and the risk of type 2 error was minimal.

Total operative and anesthetic time: The information size was calculated at 1261 patients. The Z-curve did not cross the α-spending boundaries and the futility boundaries before the information size is reached and the absolute number for penalized Z value remained smaller than 1.96; therefore, the meta-analysis was not conclusive and the results for this outcome were subject to type 2 error.

DISCUSSION

We have conducted a comprehensive literature review and meta-analysis of the best available evidence to evaluate the comparative outcomes of RA and GA in laparoscopic cholecystectomy. We identified 13 RCTs[4,5,11-21] reporting on a total of 1111 patients who underwent laparoscopic cholecystectomy under RA (n = 557) and GA (n = 554). Our subsequent analysis of outcomes demonstrated that RA was associated with significantly lower postoperative pain within 24 h following the surgery, and lower nausea and vomiting compared to GA. However, it was associated with significantly higher rates of urinary retention and headache. Moreover, there was no significant difference in operative and total procedural (surgical and anesthetic) time between two groups. The heterogeneity between studies for post-operative nausea and vomiting, headaches, and urinary retention were all low, demonstrating the robustness of these results. The between-study heterogeneity in analysis of VAS score was high indicating that our findings on these outcomes may be less robust.

We also conducted a trial sequential analysis to assess for risk of Type 1 and Type 2 errors in our meta-analysis. Overall, we found that the meta-analysis is conclusive for most of the outcomes. The exceptions to this are headache and urinary retention, which have a risk of a type 1 error, and total procedure time, which has a risk of a type 2 error.

There have been two previous systematic reviews and meta-analyses analysing the outcomes between GA and RA for laparoscopic cholecystectomy[7,22]. Yu *et al*[22] in 2015 included 7 RCTs and Wang *et al*[7] in 2016 included 8 RCTs in their meta-analysis, whilst our meta-analysis included 13 RCTs. Yu *et al*[22] found that postoperative pain was significantly lower at 12 h in favor of RA but they did not find any difference in postoperative pain at 24 h between RA and GA. Consistent with our findings, Wang *et al*[7] found significantly lower postoperative pain in favor of RA in the first 24 h of postoperative period. Moreover, Yu *et al*[22] reported that there was no difference in operative time between RA and GA which is in agreement with our findings on operative time. Considering the potential impact of the type of anesthesia on overall procedure time, we analysed total operative and anesthetic time independently and demonstrated that there was no significant difference between two groups. This was not considered by previous meta-analyses. Both studies reported a significant reduction in postoperative nausea and vomiting associated with RA, but an increase in risk of postoperative urinary retention. These results are similar to our findings. Considering that dural puncture is believed to induce distension of intracranial vessels and an increase in brain blood flow playing a primary role in post-dural pain headache formation[23], unlike other meta-analyses, we evaluated the headache as an outcome and found that the use of RA was associated with significantly higher postoperative headache than GA. This has previously been

demonstrated in other laparoscopic procedures carried out under RA[24].

The growing evidence in favour of use of RA in laparoscopic cholecystectomy with regards to postoperative pain convinced us to not only meta-analyse the outcomes but also to evaluate the robustness of the findings of the meta-analysis by a trial sequential analysis. This is the first meta-analysis of the best available evidence complemented by a trial sequential analysis which demonstrated that the findings of our meta-analysis with regard to the postoperative pain are robust.

Postoperative pain is the most common complaint after surgery[22]. It has a unique pathophysiology and is believed to be due to peripheral and central sensitisation, as well as other humoral factors[22]. In day-case surgery, postoperative pain is problematic even when oral analgesia is optimised, as ongoing pain can lead to delayed discharges. In our analysis of the best available evidence, patients undergoing laparoscopic cholecystectomy under RA, have had significantly less postoperative pain when assessed at 4, 8, 12, and 24 h. Only 2.3% of patients had conversions from RA to GA showing that performing laparoscopic cholecystectomy under RA was well-tolerated. Furthermore, the type of anesthetic did not increase the anesthetic time or the surgical time. This further supports the argument that the use of RA for day-case laparoscopic cholecystectomy is feasible.

The second most common complaint after surgery is post-operative nausea and vomiting[25]. It is another cause of delayed discharges following day-case surgery. It has a complex pathophysiological mechanism and is influenced by multiple pre-operative, intraoperative, and postoperative factors, as well as general patient factors. Cholecystectomies in particular are known to have a high incidence of postoperative nausea and vomiting[25]. According to our meta-analysis, there is clear robust evidence that the use of RA for laparoscopic cholecystectomy has led to a significant reduction in postoperative nausea and vomiting. In turn, this should lead to a larger number of patients being successfully discharged on the day of surgery.

Postoperative urinary retention is a common finding after surgery with an incidence up to 70% in some procedures[26]. It is transient in most cases. Catheterisation is the primary treatment for this. Multiple risk factors for this including increasing age, longer surgery, use of postoperative analgesia, as well as the use of RA have been described[27]. The inherent pharmacology of anesthetic drugs can cause changes in the physiology of micturition. Spinal, general and regional nerve blocks can cause postoperative urinary retention by decreasing micturition control at the pontine micturition center and peripherally by blocking neural transmission in the spinal cord[28]. GA relaxes smooth muscle and reduces bladder contractility by interfering with autonomic regulation of the detrusor muscle[29]. This is physiologically apparent given the fact that bladder capacity substantially increases when a patient is subjected to GA[30]. SA and EA affect micturition *via* a different mechanism. They interfere with efferent and afferent nerves of micturition and disrupt the reflex arcs peripherally. The available evidence suggests that SA is associated with highest risk for postoperative urinary retention, followed by EA followed by GA[26]. The results of our meta-analysis are in agreement with this as it showed a significant increase in urinary retention in those patients undergoing laparoscopic cholecystectomy under RA. This finding may discourage some surgeons and patients from using RA.

The use of RA in laparoscopic cholecystectomy should be seen as a “half-full glass”. It is feasible with promising potential to reduce the postoperative pain and nausea or vomiting. Nevertheless, the increased risk of urinary retention and headache associated with RA can potentially cancel-out its effectiveness in pain control in early postoperative period by prolonging the length of hospital stay or need for outpatient assessment. Moreover, the impact of RA compared with GA on surgical outcomes of laparoscopic cholecystectomy is yet to be determined. Unfortunately, the available RCTs have not provided appropriate data about the indication for procedure, procedure related difficulties, and procedure related complications. Performing a laparoscopic cholecystectomy for a gallbladder polyp would be less challenging than doing the procedure for a complex cholecystitis or gallstone pancreatitis. We encourage future randomized studies to evaluate the comparative procedure related outcomes of laparoscopic cholecystectomy under RA and GA.

It is important to consider the limitations of our meta-analysis when interpreting its results. Although we included only RCTs to ensure high quality data, we found that there remained significant between-study heterogeneity when assessing operative time, total procedure time, and post-operative VAS scores. Furthermore, although our trial sequential analysis demonstrated that our meta-analysis was conclusive for most outcomes, it demonstrated a risk of type 1 error for two outcomes: headache and urinary retention. It also demonstrated a risk of type 2 error for total procedure time. Some of the include studies reported their VAS score and procedure time as median

and interquartile range. We have calculated their mean and standard deviation using the method described by Hozo *et al*[30]. This might have subjected our findings to some degree of bias. Moreover, some the included studies excluded patients who had failure of RA which is not consistent with intention to treat concept. This might have significantly affected the results in favor of RA and subsequently introduced bias to our findings. Finally, all the risk of performance and detection bias was high among the included studies due to lack of blinding. With regards to the performance bias, the blinding of participants and surgeons would have been impossible; however, blinding of outcome assessor would have been possible to reduce the risk of detection bias.

CONCLUSION

Our meta-analysis of the best available evidence (Level 1 evidence) demonstrated that RA may be a safe and feasible anesthetic modality for laparoscopic cholecystectomy considering its associated lower postoperative pain and nausea and vomiting compared to GA. This makes it a potentially attractive option to expedite discharge planning in day-case surgery. However, its associated risk of urinary retention and headache may not help facilitating such aim. Moreover, lack of knowledge on the impact of RA on specific procedure related outcomes may discourage surgeons from selecting RA as the first choice of anesthesia for laparoscopic cholecystectomy. Most importantly, intention-to-treat principle has been breached in some of the included studies by excluding failed RA attempts. Considering our findings and the limitations of the available evidence, we do not hesitate to highlight that available evidence does not justify using RA as the first line anesthetic choice for laparoscopic cholecystectomy although it may be an option in patients who are not fit for GA. Future research should focus on procedure related outcomes of RA and GA in laparoscopic cholecystectomy with respect to intention-to-treat concept.

ARTICLE HIGHLIGHTS

Research background

In an effort to further reduce the morbidity and mortality profile of laparoscopic cholecystectomy, the outcomes of such procedure under regional anesthesia (RA) have been evaluated.

Research motivation

In the context of cholecystectomy, combining a minimally invasive surgical procedure with a minimally invasive anesthetic technique can potentially be associated with less postoperative pain and earlier ambulation.

Research objectives

The main objective of this meta-analysis was to evaluate comparative outcomes of RA and general anesthesia (GA) in patients undergoing laparoscopic cholecystectomy.

Research methods

A comprehensive systematic review of randomized controlled trials (RCTs) with subsequent meta-analysis and trial sequential analysis of outcomes were conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards.

Research results

Thirteen RCTs enrolling 1111 patients were included. The study populations in the RA and GA groups were of comparable age (P = 0.41), gender (P = 0.98) and body mass index (P = 0.24). The conversion rate from RA to GA was 2.3%. RA was associated with significantly less postoperative pain at 4 h [mean difference (MD): -2.22, P < 0.00001], 8 h (MD: -1.53, P = 0.0006), 12 h (MD: -2.08, P < 0.00001), and 24 h (MD: -0.90, P < 0.00001) compared to GA. Moreover, it was associated with significantly lower rate of nausea and vomiting [risk ratio (RR): 0.40, P < 0.0001]. However, RA significantly increased postoperative headaches (RR: 4.69, P = 0.03), and urinary retention (RR: 2.73, P = 0.03). The trial sequential analysis demonstrated that the meta-analysis was conclusive for most outcomes, with the exception of a risk of type 1 error for headache

and urinary retention and a risk of type 2 error for total procedure time.

Research conclusions

Our findings indicate that RA may be an attractive anesthetic modality for day-case laparoscopic cholecystectomy considering its associated lower postoperative pain and nausea and vomiting compared to GA. However, it associated risk of urinary retention and headache and lack of knowledge on its impact on procedure-related outcomes do not justify using RA as the first line anaesthetic choice for laparoscopic cholecystectomy.

Research perspectives

The available RCTs have not provided appropriate data about the indication for procedure, procedure related difficulties, and procedure related complications. We encourage future randomised studies to evaluate the comparative procedure related outcomes of laparoscopic cholecystectomy under LA and GA.

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CASE REPORT

Peroral endoscopic myotomy in a pregnant woman diagnosed with mitochondrial disease: A case report

Alexander A Smirnov, Maya M Kiriltseva, Mariya E Lyubchenko, Vladimir D Nazarov, Anna V Botina, Aleksandr N Burakov, Sergey V Lapin

ORCID number: Alexander A Smirnov 0000-0002-6440-2370; Maya M Kiriltseva 0000-0003-3821-3805; Mariya E Lyubchenko 0000-0003-1110-1379; Vladimir D Nazarov 0000-0002-9354-8790; Anna V Botina 0000-0001-5991-0066; Aleksandr N Burakov 0000-0002-6530-9127; Sergey V Lapin 0000-0002-4998-3699.

Author contributions: Smirnov AA and Lyubchenko ME performed peroral endoscopic myotomy, reviewed the literature and contributed to manuscript drafting; Kiriltseva MM performed the gastroenterology consultation; Burakov AN and Kiriltseva MM reviewed the literature and contributed to manuscript drafting; Nazarov VD and Lapin SV performed the genetic tests and interpretation and contributed to manuscript drafting; Botina AV provided the histology report; Burakov AN and Kiriltseva MM were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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Alexander A Smirnov, Maya M Kiriltseva, Mariya E Lyubchenko, Aleksandr N Burakov, Department of Endoscopy, Pavlov First Saint Petersburg State Medical University, Saint Petersburg 197022, Russia

Vladimir D Nazarov, Sergey V Lapin, Center for Molecular Medicine, Pavlov First Saint Petersburg State Medical University, Saint Petersburg 197022, Russia

Anna V Botina, Department of Pathology, Pavlov First Saint Petersburg State Medical University, Saint Petersburg 197022, Russia

Corresponding author: Aleksandr N Burakov, Research Fellow, Department of Endoscopy, Pavlov First Saint Petersburg State Medical University, L'va Tolstogo Str. 6-8, Saint Petersburg 197022, Russia. aleksandr.medox@yandex.ru

Abstract

BACKGROUND

Achalasia is a primary esophageal motility disease characterized by impairment of normal esophageal peristalsis and absence of relaxation of the lower esophageal sphincter. Sometimes is can be a part of some genetic disorders. One of the causes of gastrointestinal motility disorders, including achalasia, is mitochondrial defects.

CASE SUMMARY

We report about a pregnant woman with a history of symptoms associated with inherited mitochondrial disease, which was confirmed by genetic tests, and who was treated *via* peroral endoscopic myotomy.

CONCLUSION

Peroral endoscopic myotomy is possible treatment option for a pregnant woman with achalasia caused by mitochondrial disease.

Key Words: Mitochondrial disease; Pregnancy; Esophagus; Peroral endoscopic myotomy; Achalasia; Biopsy; Case report

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Core Tip: Achalasia is a primary esophageal motility disease. Sometimes is can be a part of some genetic disorders. One of the causes of gastrointestinal motility disorders, including achalasia, is mitochondrial defects. We report about a pregnant woman with a history of symptoms associated with inherited mitochondrial disease, which was confirmed by genetic tests, and who was successfully treated *via* peroral endoscopic myotomy.

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INTRODUCTION

Achalasia is a primary esophageal motility disease characterized by impairment of normal esophageal peristalsis and absence of relaxation of the lower esophageal sphincter[1]. It can exist as an independent disease or part of some genetic disorders. One of the causes of gastrointestinal (GI) motility disorders, including achalasia, is mitochondrial defects[2,3]. Peroral endoscopic myotomy (POEM) is the safest and most effective method for achalasia treatment[4-7].

CASE PRESENTATION

Chief complaints

A 30-year-old woman presented to our hospital complaining of swallowing difficulty.

History of present illness

A patient had a violation of physical development and constipation from an early age. At the age of 7 years, she was diagnosed with partial bilateral symmetric ptosis. At the age of 8 years, she was referred to the hospital with diagnoses of generalized viral infection of unspecified etiology, postinfectious encephalopathy, cerebro-asthenic syndrome, neurosis, urinary bladder and gut atony, chronic pyelonephritis, mydriasis, semiptosis, and dystrophy. At the age of 9 years, she had suspected high intestinal obstruction which was followed by surgery. The obstruction was not revealed during the surgery. In the postoperative period, signs of intestinal obstruction persisted, and they were managed conservatively. After the surgery, she developed meningeal signs, gaze paresis, double vision, and reduced vision. Electrocardiogram showed an incomplete type of blockade of the right branch of the bundle of His. Esophago-gastroduodenoscopy (EGD) showed gastric hypotony. Computed tomography scans of the head revealed moderate diffuse cortex atrophy. Cerebrospinal fluid was clear with 0.066. The patient was seen by a neurologist, ophthalmologist, infectious diseases specialist, and neurosurgeon. However, the diagnosis remained unclear. The following pathologies were excluded: neuro infections, intestinal infections, oncohematology, and endocrine pathologies. Further generalized pathology persisted. At the age of 10 years, a second laparotomy was performed followed by a temporary ileostomy because of signs of acute intestinal obstruction. From the ages of 11 years to 14 years, the patient was annually referred to the surgery department with signs of acute intestinal obstruction, which were managed conservatively. At the age of 11 years, she was diagnosed with intestinal pseudo-obstruction. From the age of 11 years, paradontosis began. From the age of 14 years, the patient had daily dysphagia while eating solid and liquid food. She lost 5 kg and began feeling weak and fatigued. At the age of 15 years, resection of the jejunum was performed two times with an overall resection length of 90 cm because of acute intestinal obstruction which was not managed conservatively. The patient was dystrophic, which was thought to be because of malabsorption as a consequence of the resection of the jejunum. At the age of 25 years, the patient lost all her teeth because of progressive paradontosis. From the age of 26 years, she developed amenorrhea. At the age of 29 years, esophagography

showed signs of achalasia, gastroptosis, and delayed gastric and duodenum emptying time. At the age of 30 years, the patient was referred to the endoscopy department of Pavlov Medical University for achalasia treatment.

History of past illness

History of present illness includes the patient's entire life. That is why we suppose that this part is irrelevant in this case.

Personal and family history

The mother, father, and sister are healthy. There was no family history of GI or autoimmune pathologies or allergic disorders. The niece (4 years of age) had sensorineural hearing loss.

Physical examination

Eckardt score was 4. Her weight was 38 kg. Her body mass index was 16.9, and she had protein energy malnutrition. During preoperative preparation, the patient was revealed to be 16 wk pregnant. She was not aware of the pregnancy. In addition, intraventricular blockage was diagnosed. High-resolution esophageal manometry showed achalasia type I (Figure 1). Hemoglobin and total blood protein levels were 106 g/L and 64 g/L, respectively. Creatine phosphokinase and lactate levels were normal. Neurologic and ophthalmologic disorders were not observed. Considering all data, we suspected mitochondrial disease: incomplete Kearns-Sayre syndrome (KSS) or mitochondrial neurogastrointestinal encephalopathy (MNGIE) disease.

Laboratory examinations

Histology of the esophageal muscular layer specimens: There were myocytes of different thicknesses with sites of wave-like deformation and dystrophic changes. There were also single myocytes with necrobiotic changes and small vessels with "edge standing" leukocytes (Figure 2 and 3).

Genetic testing of mitochondrial DNA (lymphocytic): It showed segment deletion in mitochondrial DNA (mDNA) which affected the genes *RNR1* (MTRNR1) and *RNR2* (MTRNR2). This aberration is considered to be pathogenic and most frequently observed in patients with KSS[8]. Unfortunately, after discharge, the patient refused further genetic testing.

FINAL DIAGNOSIS

Achalasia. Mitochondrial disease. KSS? MNGIE?

TREATMENT

Considering the severe dysphagia and cachexia, a multidisciplinary team decided to perform POEM. After performing a submucosal tunnel myotomy of 8 cm in the esophageal muscular layer, a myotomy of 3 cm in the gastric muscular layer was also performed. From the region of the lower esophageal sphincter, 5 mm × 5 mm specimens of the lower and middle parts of the esophageal muscle (circular and longitudinal muscles) were obtained for further histological investigation. After the procedure, the endoscope was able to freely pass the lower esophageal sphincter.

OUTCOME AND FOLLOW-UP

The postoperative period was unremarkable. On postoperative day (POD) 2, liquid intake was initiated. It was later followed by eating liquid food. On POD 6, she was discharged in a satisfactory condition with a continuing pregnancy. The first follow-up was performed 3 mo after POEM: Eckardt score was 2, weight was 39 kg (+ 1 kg), EGD was normal, and pregnancy was 29 wk without any ultrasound findings of fetal pathology.

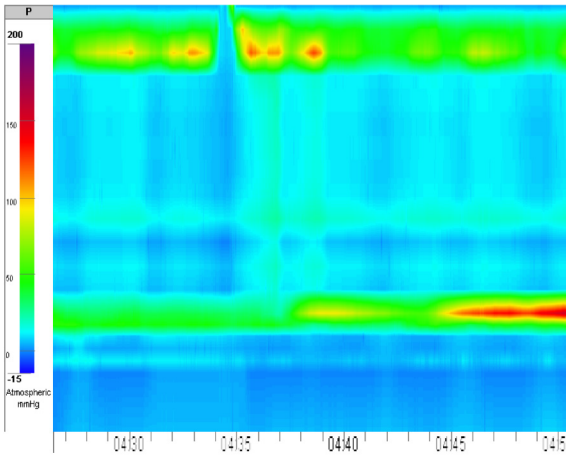

Figure 1 High-resolution esophageal manometry, manometric signs of achalasia type I.

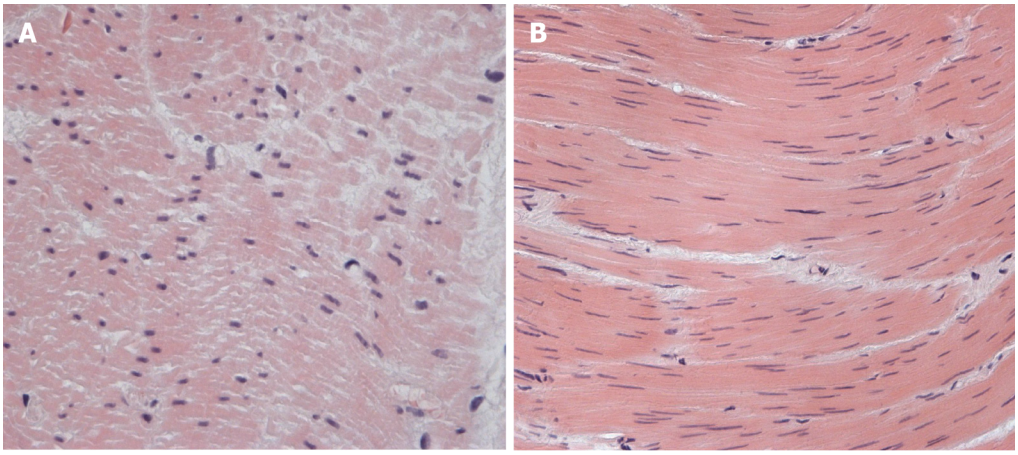

Figure 2 Muscle specimen of the upper part of the esophagus. A: Wave-like deformation of the myocytes, hematoxylin-eosin, magnification × 200; B: Myocytes of different thicknesses, hematoxylin-eosin, magnification × 100.

DISCUSSION

There are no guidelines on achalasia management in pregnant women. In the literature, achalasia cases in pregnant women were treated in different ways based on the duration of gestation, severity of the disease, and maternal and fetal risk. The most common are botulotoxin injections[9], balloon dilatation[10], Heller myotomy, or in some cases, treatment was delayed until childbirth, and patients received parenteral or enteral nutrition. Concerning nasojejunal feeding tube, the patient was in the beginning of second trimestr of pregnancy. Thus we decided that enteral nutrition is impractical for that long period because it can cause erosions and ulcers in stomach and esophagus. In addition to, long-term usage of nasojejunal feeding tube can also be a source of psychological stress to the patient. As far as dilatation concerned, the first course of dilatation with the use of 30 mm balloon has an efficacy of no more than 80% over the next 6 mo after surgery, resulting in an esophageal perforation rate of 1.1%[11,12]. The patient had not undergone Balloon Dilatation before, and we know from the literature that initiating dilatation is 10 times more likely to result in perforation, with a rate of up to 9.7%[13]. At the same time, the immediate clinical efficacy of POEM in some studies is more than 1.5 times higher than the efficacy of Balloon Dilatation (94% and 52%, respectively), and POEM is less likely to cause significant complications[14].

To the best of our knowledge, there are no cases of POEM in pregnant women published in the literature. A study by Vogel *et al*[15] showed a significant deterioration of the disease when achalasia developed and was not treated before pregnancy.

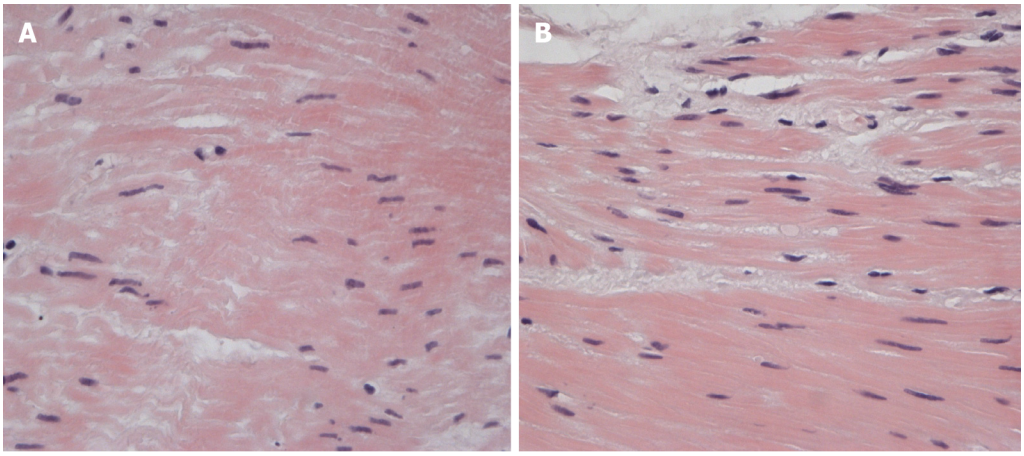

Figure 3 Muscle specimen of the esophagus. A: Muscle specimen of the upper part of the esophagus. Dystrophic and necrobiotic changes with focal myocytolysis of muscle fibers, hematoxylin-eosin, magnification × 400; B: Muscle specimen of the lower part of the esophagus. Intracellular edema, myocytes of different thicknesses, hematoxylin-eosin, magnification × 400.

In our case, we chose POEM as the treatment method because we have extensive experience in such endoscopic procedures (more than 150 POEMs). In addition, we have a multidisciplinary team taking care of patients with achalasia.

We revealed a deletion in mDNA; however, this phenotype can as well be observed when mDNA damage is caused by a primary mutation in nuclear DNA (nDNA). These genetic disorders, unlike sporadic isolated mDNA mutations, usually have autosomal recessive inheritance, are less frequently autosomal dominant, and steadily progress[16]. Mutations in *TYMP* (MNGIE syndrome) and gene *POLG* (MNGIE–like syndrome) are the most common mutations of nDNA, which cause impairment of mDNA replication, resulting in severe GI motility disorders, cachexia, polyneuropathy, leukoencephalopathy, ptosis, ophthalmoplegia, and sensorineural hearing loss. In addition, mutations in the *RRM2B* gene[17-20]. In all aberrations listed above according to the literature, the most common symptom is severe GI motility disorders.

CONCLUSION

To the best of our knowledge, this is the first case of a pregnant woman with a mitochondrial disorder treated successfully with POEM and the first histology of the esophageal muscle layer of a patient with achalasia caused by mitochondrial disease.

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