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CLINICAL REPORT

Treatment with Sibutramine prior to Roux-en-Y Gastric Bypass leads to an Improvement of Metabolic Parameters and to a Reduction of Liver Size and Operative Time

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Abstract
Background Previous studies have shown that a preoperative weight loss is associated with better long-term outcome, fewer complications, and less time in the operating room in bariatric patients. However, preoperative weight loss is hard to achieve in many patients.
Methods We, therefore, conducted a study in which 20 bariatric patients received 15 mg of the weight loss medication sibutramine prior to laparoscopic Roux-en-Y gastric bypass (RYGBP) while patients in the control group did not. It was our interest to find out if these patients had a benefit compared to a control group who did not receive medication.
Results Whereas patients in the sibutramine group lost 4.8 kg within 6 weeks, patients in the control group gained 7.0 kg. Along with the change in weight, the size of the left liver lobe decreased in the sibutramine-treated patients and increased in the control group. Glutamic pyruvic transaminase as a parameter of liver function improved with reduction of liver size. Finally, time in the operating room was shorter for patients with preoperative weight loss due to sibutramine intake.
Conclusions Medical therapy with sibutramine in preparation for bariatric surgery can improve the health status of patients and lead to a reduction of liver size and operating time. It should be considered as an alternative or addition to dietary therapy or gastric balloon treatment in the preparation of patients expecting a RYGBP.

Keywords Sibutramine · Preoperative · Weight loss · Obesity · Roux-en-Y gastric bypass · RYGBP

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Introduction

Obesity is a pan-endemic health problem in developed countries with annually increasing numbers of patients. An increasing body mass index (BMI) leads to an accumulating incidence of complications and a decrease in life expectancy [1]. According to the National Institutes of Health Consensus Conference in 1991, surgery is the first-line recommended effective treatment of morbid obesity (defined as a BMI>40 kg/m^2) [2]. Traditional Roux-en-Y gastric bypass (RYGBP) has been shown to be effective in achieving significant and durable long-term weight loss as well as improving medical comorbidities in morbidly obese patients [3]. However, it is a technically challenging procedure and perioperative complications occur in up to 13% of patients [4]. Recent trials have shown that acute preoperative weight loss is associated with a more beneficial perioperative outcome and a better long-term weight reduction. According to data presented by Huerta et al., a preoperative reduction of 10% of initial weight leads to a significant reduction of time in the operating room [5]. Alverado et al. observed a better weight loss outcome after 11 months with preoperative weight reduction [6]. Concordantly, Alger-Mayer et al. described an improvement in weight loss after 3–4 years with preoperative weight reduction [7]. Acute weight loss can reduce liver size and

amount of visceral adipose tissue dramatically [8,9]. In a previous study, Liu et al. have shown a reduction in intraoperative blood loss and deviation from standard operative procedures with preoperative weight reduction [10].

However, dietary advice given to patients scheduled for bariatric surgery often does not lead to a significant weight change. It is our experience that many patients rather increase their meal intake in expectancy of a reduction in portion size postoperatively. Medical therapy has been shown to be effective in patients with BMI between 27 and 40 kg/m^2. Several drugs are available on the European market including sibutramine, amfepramone, or orlistat. Sibutramine has been in use since 1998 and leads to a rapid reduction of about 10 kg of body weight within 6 months [11]. It is the mostly prescribed drug for weight loss in Europe. Side effects can occur but are rarely of serious concern. Few patients suffer from an increase in blood pressure and heart rate. Therefore, vital parameters should be checked under sibutramine treatment. It was our interest to investigate whether a preoperative medical treatment with sibutramine had beneficial effects on metabolic values or surgery-related parameters.

Methods

Patients were recruited out of subjects who attended the University Hospital Interdisciplinary Obesity Center's outpatient clinic between April 2007 and September 2008 and who met the 1991 National Institute of Health guidelines for bariatric surgery. All patients signed informed consent for participation in research activities. There were no known diabetics in any of the study groups. All patients were evaluated for surgical treatment of morbid obesity by a multidisciplinary unit with the aid of a visceral surgeon, endocrinologist, and psychiatrist as well as a dietitian. A thorough assessment was performed of each patient's general condition and mental status, complications of obesity, risk factors, and motivation for surgery. All patients seen between April 2007 and September 2008 were instructed to reduce their weight prior to the surgical procedure. A preoperative treatment with 15 mg sibutramine once daily for 6 weeks was offered to all patients who were eligible for RYGP operation and for whom contraindications according to the producers' (Abbott Laboratories. Abbott Park, IL, USA) information did not apply. It was then left to the patient's decision if sibutramine was taken or not. The matching groups were created retrospectively by an independent person. Those patients who went on sibutramine therapy were instructed to check their blood pressure and heart rate at least twice during the 6 weeks of treatment. Recruited patients had a BMI between 40 and 55 kg/m^2. Baseline parameters are shown in Table 1. Patients in the control group had slighter higher blood glucose levels. Evaluation of body composition, blood parameters, and ultrasound of the abdomen with measurement of the maximal diameter of the right liver lobe were performed at day 1 and after 6 weeks (day 42). To rule out interobserver variation, ultrasound was performed by one person and under the supervision of another ultrasound-experienced member of the study group. The technique used for laparoscopic RYGBP was a five-port technique similar to that described by Shauer et al. [12]. We used the CEEA-21 anvil (Tyco, United States Surgical Corporation) which was pulled into the gastric pouch transorally following the technique described by Wittgrove and Clark [13]. Postoperatively, patients were followed up by the aforementioned multidisciplinary team. The outcomes of the case and control patients were compared with unpaired Student's t test for numerical variables and chi-square test for categorical variables. For all statistical tests a

Table 1 Baseline characteristics of patients in the sibutramine and control group

	Sibutramine group (n=20)	Control group (n=20)
Age (years)	40.2±12.2	43.6±11.0
BMI (kg/m^2)	50.5±6.5	47.5±6.7
Weight (kg)	156.2±19.4	152.4±24.1
Liver size (cm) transversal		
RLL	15.4±1.5	15.5±1.3
LLL	11.6±2.4	11.4±1.4
Longitudinal		
RLL	11.7±2.8	10.7±1.8
LLL	7.7±0.9	7.3±0.9
Glucose (mg/dl)	107.9±34.6	122.8±46.6
GOT	32.7±17.6	28.6±8.3
GPT	37.9±21.6	36.0±15.4

Table 2 Values indicate change in parameters after 6 weeks of sibutramine therapy and in the control group

	Sibutramine group (n=20)	Control group (n=20)	p value
BMI (kg/m^2)	1.6±0.6	+2.9±3.0	0.05
Weight (kg)	4.8±2.6	+7.0±9.2	0.06
Liver size (cm) transversal			
RLL	1.6±1.1	0.9±1.8	ns
LLL	0.2±1.6	+1.4±2.1	ns
Longitudinal			
RLL	1.9±2.2	+1.4±2.1	0.04
LLL	0.8±1.3	+3.0±3.5	0.05
Glucose (mg/dl)	10.0±26.9	+26.7±73.5	ns
GOT	2.4±10.3	+8.6±16.6	ns
GPT	2.6±12.2	+7.1±22.8	0.05

$p<0.05$ was considered statistically significant. Data collection was performed on Microsoft Excel 2003. Statistical analysis was performed using SPSS 11.5.

Results

Age or BMI were similar in the two study groups. On average, patients treated with sibutramine prior to bariatric surgery lost 4.8 kg within 6 weeks, whereas patients in the control group gained 7.0 kg (Table 2, Fig. 1). There were no adverse events reported with sibutramine intake. Two patients reported dry mouth and another patient complained about constipation. No increases in blood pressure or heart rate were documented. Liver size (left liver lobe) reduced significantly more in the sibutramine group compared to the control group. Along with the documented weight gain of patients in the control group, size of the left liver lobe increased. Glutamic pyruvic transaminase (GPT) as an indicator of liver function increased during the 6 weeks in the control group, whereas it decreased in the sibutramine group. Moreover, blood glucose levels deteriorated in the control group and remained almost unchanged in the sibutramine subjects. However, this difference did not reach statistical significance. By definition of the International Diabetes Federation, patients in the control group developed diabetes mellitus. Due to the scheduled bariatric surgery, medical treatment was not initiated. No changes were detected in inflammatory parameters (high-sensitivity C-reactive protein, interleukin 6; data not shown). A putative improvement in additional comorbidities was not documented due to the short observation time of only 6 weeks. Time in the operating room as written down in operation reports was around 4 h in most subjects. On average, however, patients in the control group spent an additional 20 min in the operating room compared to the sibutramine-treated patients. No differences were detectable concerning the length of hospitalization. Complication rate was low and similar in both groups (data not shown).

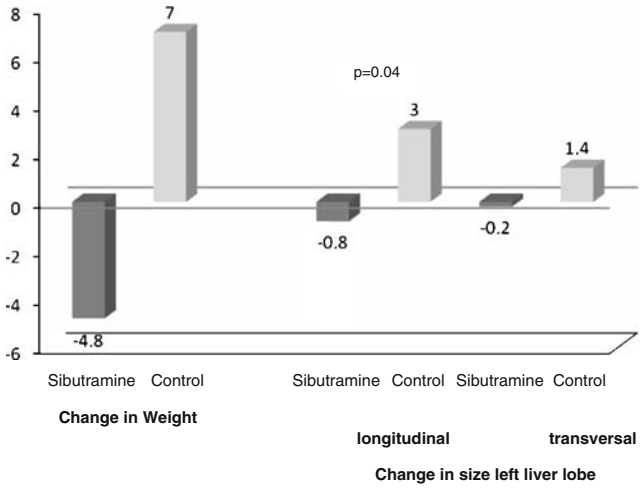

Fig. 1 Change in weight and in the size of the left liver lobe before and after treatment with sibutramine and in the control group

Discussion

In the current study, we found that treatment with sibutramine prior to RYGBP operation was associated with several beneficial effects. The grade of obesity is an independent risk factor for minor and major complications during bariatric procedures [14]. Preoperative weight reduction may improve the course of bariatric surgery through different means. First of all, a reduction in liver size and visceral tissue can improve intra-abdominal view and working space for laparoscopic surgery. Especially, a reduction of the size of the left liver lobe facilitates operative procedures performed on the proximal stomach. Moreover, a reduction in fat content of the liver reduces hepatic fragility when liver is mobilized during operative procedures. Moreover, a small reduction or increase in body

weight is associated with major metabolic effects [15]. Blood glucose levels were reduced in the group of sibutramine-treated patients whereas it was higher after 6 weeks in the control group. In general, patients with diabetes have a higher complication rate during invasive procedures and an increased risk for infectious complications after surgery [15]. The fact that we did not see a difference in the rate of complications is likely to be attributable to the size of our study groups. Complications occur in about 10–15% after gastric bypass [16]. Therefore, larger groups are necessary to examine whether perioperative or postoperative complication rate can be reduced by medical treatment prior to bariatric surgery.

Generally, a preoperative reduction in body weight of obese patients is believed to reduce the complication rate by a reduction in inflammatory parameters. Although we were able to detect a trend towards an improvement in the sibutramine group, these observations did not reach statistical significance.

The intake of sibutramine for weight loss leads to a steady decrease of body weight until a maximum is reached after about 6 months. Therefore, it is possible that a longer pretreatment phase augments beneficial effects. This has been demonstrated for super obese patients using the intragastric balloon therapy [17,18]. Complication and conversion rate were lower in patients with preoperative weight loss. The amount of weight loss (26.4 and 18.2 kg, respectively) can also be achieved by medical treatment. A higher BMI is generally associated with a greater absolute weight loss following medical obesity treatment. A preparation of obese patients through medical therapy is, therefore, an alternative to gastric balloon treatment. Although all subjects were encouraged to reduce weight in expectation of the scheduled operation, patients in the control group gained 7.0 kg within 6 weeks. According to our experience, this is due to a “last meal” emotion of assigned bariatric patients. However, as demonstrated by our data, even a relatively small increase in body weight leads to a deterioration of liver size and liver function parameters as well as metabolic traits. Since dietary advice was not different in both groups, subjects in the sibutramine group had an equal probability to gain weight prior to surgery. The intake of sibutramine, which in part suppresses appetite, could, therefore, possibly abate this effect. In conclusion, treatment with sibutramine prior to bariatric surgery exerts beneficial effects for assigned patients. Indication criteria and follow-up should be under the supervision of an interdisciplinary obesity team. Further studies should be performed in larger groups over a longer time to confirm our preliminary result.

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