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ORIGINAL CONTRIBUTIONS

The Use of Intraperitoneal Bupivacaine in Laparoscopic Roux-en-Y Gastric Bypass: a Double-blind, Randomized Controlled Trial

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Abstract

Background Several studies have shown a reduction in postoperative pain and length of hospital stay when using intraperitoneal local anesthetics during laparoscopic surgery. In morbidly obese patients, respiratory depression due to opioid use is a serious side effect. Any different type of analgesia is therefore clinically relevant.

Objective To assess the effect of intraperitoneal bupivacaine on postoperative pain after laparoscopic Roux-en-Y gastric bypass (LRYGB).

Methods Between March and November 2017, 130 patients were included and randomly assigned to receive 20 ml or 0 ml of 2.5% bupivacaine hydrochloride sprayed onto the diaphragm. Pain scores for abdominal and shoulder pain were conducted using the visual analogue scale (VAS) for pain score at 0, 1, 6, and 24 h postoperatively. The length of hospital stay and use of analgesics was recorded in digital patient records. The primary outcome is the pain scores and the secondary outcomes are postoperative use of opioids or antiemetics and length of hospital stay.

Results The study and control group contained respectively 66 and 61 patients. Patient characteristics were equal in both groups ($p < 0.05$), except for age. No significant reduction of postoperative pain or opioid use was seen with the use of intraperitoneal bupivacaine. There was also no significant reduction in the use of antiemetics and length of hospital stay.

Conclusion The use of intraperitoneal bupivacaine in LRYGB does not show a statistically significant reduction in postoperative pain or postoperative opioid use. Therefore, using intraperitoneal bupivacaine has no clinical relevance and should no longer be used in LRYGB.

Keywords Obesity · Laparoscopic Roux-en-Y gastric bypass · Intraperitoneal bupivacaine · Postoperative pain

Introduction

Worldwide, the prevalence of overweight and obesity is increasing [1]. This leads to higher medical consumption and medical costs. The laparoscopic Roux-en-Y gastric bypass (LRYGB) is most effective in decreasing these costs and reducing the economic burden [2, 3]. After LRYGB, comorbidities and quality of life improve significantly [4].

The LRYGB is performed laparoscopically to reduce time to recovery, wound problems, and pain. The pain after laparoscopic surgery originates from the incision (parietal pain), the deeper abdomen (visceral pain), and the shoulder (nervus phrenicus irritation by residual carbon dioxide) [5]. Though perioperative and postoperative analgesics are effective, postoperative pain remains a challenge. Reduction of postoperative pain is beneficial as early mobilization decreases postoperative complications, like venous thrombosis and chest infections, and leads to a reduction in length of hospital stay. Only acetaminophen and opioids can be prescribed after LRYGB, since non-steroidal anti-inflammatory drugs (NSAIDs) are prohibited due to the ulcerative effect on the stomach [6]. In morbidly obese patients, respiratory depression due to opioid use is a serious side effect, leading to increased risk of

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respiratory problems. Any different type of analgesia with less side effects is therefore clinically relevant.

Several studies have shown a reduction in postoperative pain and length of hospital stay when intraperitoneal local anesthetics were used during laparoscopic surgery [7–13]. However, for the use of intraperitoneal anesthetics in LRYGB is only a limited amount of evidence. Symons et al. [14], showed a significant reduction of postoperative analgesics (acetaminophen, hydrocodone, anti-epileptic drugs) use when administering bupivacaine over the esophageal hiatus prior to LRYGB. However, this study did not specify whether this reduction was also seen in pain scores or opioid use separately. In 2016 and 2018, two studies were published describing a decrease in postoperative pain, morphine use, time to mobilization, and length of hospital stay following bariatric surgery when using intraperitoneal analgesics [15, 16]. One study used a high dose of intraperitoneal ropivacaine (300 ml) [15] and the other study only included gastric sleeve procedures [16].

Our aim is to assess the effect of intraperitoneal bupivacaine on postoperative pain after LRYGB.

Materials and Methods

This prospective, double-blind, randomized controlled trial was approved by the medical ethical committee in August 2016. Prior to inclusion, all patients were screened by a specialized nurse, endocrinologist, dietician, psychologist, and bariatric surgeon.

Participants

Between March and November 2017, 130 patients who presented to the Flevoziekenhuis for bariatric surgery were assessed for eligibility. Inclusion criteria were a body mass index (BMI) > 40 or a BMI > 35 with at least one comorbidity (diabetes mellitus, arthrosis, hypertension, and/or obstructive sleep apnea) and permission for surgery after multidisciplinary bariatric evaluation. Exclusion criteria included psychological unfitness after the screening, American Society of Anesthesiologists (ASA) class 4 or higher, previous bariatric or stomach surgery, age < 18 or > 65 years, and allergy to bupivacaine.

Sample Size

A power analysis was performed using nQuery. The sample size was calculated using the *t* test with an alpha of 0.05 and power of 80%. Bupivacaine has minor risks, a low chance of allergic reactions [17], low costs (2.68 euro [18] per 20 ml at 2.5 mg/ml), and an injection time of 10 s; a decrease of one point on the Visual Analogue Scale (VAS) for pain was considered to be sufficient to provide valuable results. According to the power analysis, at six hours after surgery, both groups should contain 29 patients. With a correction of 10%, 66 patients are needed per group. A double amount of patients was included to provide the ability for subgroup analysis and improve the reliability of the results.

Randomization and Blinding

In the operating room, patients were randomly assigned to receive either 20 ml (study group) or 0 ml (control group) of bupivacaine using sealed envelopes drawn by the scrub nurse. The patient, ward doctor, nurse, and outpatient doctor were fully blinded. Only the operating surgeon and the office manager (without any patient contact) knew to which group the patients were assigned. In the digital records, only participation was recorded, the outcome of randomization was reported to the office manager through closed email. The outcomes were recorded in a database which was handed over to the principal investigator after completion of the study.

Surgical and Postoperative Procedure

The LRYGB was performed by one of four bariatric surgeons at the Department of Surgery, Flevoziekenhuis, Almere, The Netherlands. Anesthetists and nurses worked according to the study protocol. Two hours prior to surgery, 1 g of paracetamol i.v. was administered; 30 min before skin incision, 1 g of cefazoline and 500 mg of metronidazole were given intravenously. The anesthetics used were propofol (200 mg), rocuronium bromide (50 mg), and an ultivapump 20–30 ml/h, which was started 3 min before intubation. Prior to incision, a total of 20 ml of 2.5% bupivacaine hydrochloride was infiltrated into the skin, divided over five skin wounds. After the LRYGB was performed, either 0 ml or 20 ml of 2.5% bupivacaine hydrochloride was sprayed onto the left side of the diaphragm. The standard protocol at the institution before the study was to spray 20 ml of bupivacaine onto the left side of the diaphragm. In the recovery room, acetaminophen, 1 g, was repeated in case of a pain score (VAS) of > 4. When postoperative analgesia (persisting pain score > 4) was insufficient, 2.5 mg sufentanil was additionally administered intravenously. One hour postsurgery, the patients were mobilized. On the ward, all patients received 1000 mg acetaminophen orally four times a day. With a pain score > 4, 50 mg tramadol hydrochloride up to three times a day was prescribed. If the pain still persisted, 15 mg of piritramide was given subcutaneously up to four times a day, instead of the tramadol hydrochloride. The average length of hospital stay was 24 h. Patients were discharged if they were able to walk without pain and drink at least three glasses of water in eight hours (i.e., > 1.5 l/day).

Outcome Measures

Pain scores for abdominal and shoulder pain were documented by a staff nurse using the VAS for pain at 0, 1, 6, and 24 h postoperatively. A score of 0 is defined as no pain at all and a score of 10 as the worst pain imaginable. Data on length of hospital stay, use of analgesics, narcotics and antiemetics, weight, length, BMI, ASA classification, age, comorbidities, duration of surgery, and medical history were recorded in the digital patient records.

Study Endpoints

The primary outcome is postoperative abdominal and shoulder pain defined with the pain scores. The secondary outcomes are postoperative use of opioids (tramadol hydrochloride, piritramide, oxycodone, morphine i.v.) or antiemetics (metoclopramide hydrochloride, dehydrobenzperidol) and length of hospital stay (in days).

Statistical Analysis

Statistical analysis was performed with the IBM SPSS software. The two-tailed *t* test was used to compare the means for patient characteristics. Though the variables were not normally distributed, according to the central limit theory, the groups are large enough to conclude they are asymptotically normally distributed. Thus, the two-tailed *t* test is sufficient in comparing the means. However, a robustness check was performed using the Mann-Whitney *U* and chi-squared tests for the continuous and nominal or ordinal data, respectively. The same analysis was performed for pain scores, use of opioids or antiemetics, and length of hospital stay. An additional analysis was performed on shoulder pain scores, as a result of the shortage of data at 0 h postoperatively, where shoulder pain was converted into a nominal variable (present or not present). In addition, all results were recalculated excluding patients with chronic use of analgesics (excluding acetaminophen). Statistical significance was defined as a p value < 0.05.

Results

Patient Characteristics

Three patients were excluded before analysis (Fig. 1), resulting in a study population of 127 patients for the final analysis, with 66 and 61 patients in the study and control group, respectively. Patient characteristics were equal in the intervention and control group, with the exception of age being significantly higher in the study group (Table 1).

Primary Endpoint

No significant reduction of postoperative abdominal or shoulder pain was achieved with the use of 20 ml of 2.5% bupivacaine (Tables 2 and 3). Although the mean abdominal pain scores are lower in the study group, this difference is not significant. The mean pain score for shoulder pain at 0 h after surgery could not be analyzed due to missing data. Therefore, shoulder pain was analyzed as present or not present. This additional analysis showed no significant difference ($p = 0.586$).

Secondary Endpoints

The use of bupivacaine did not significantly decrease opioid use, antiemetic use, or length of hospital stay in the study

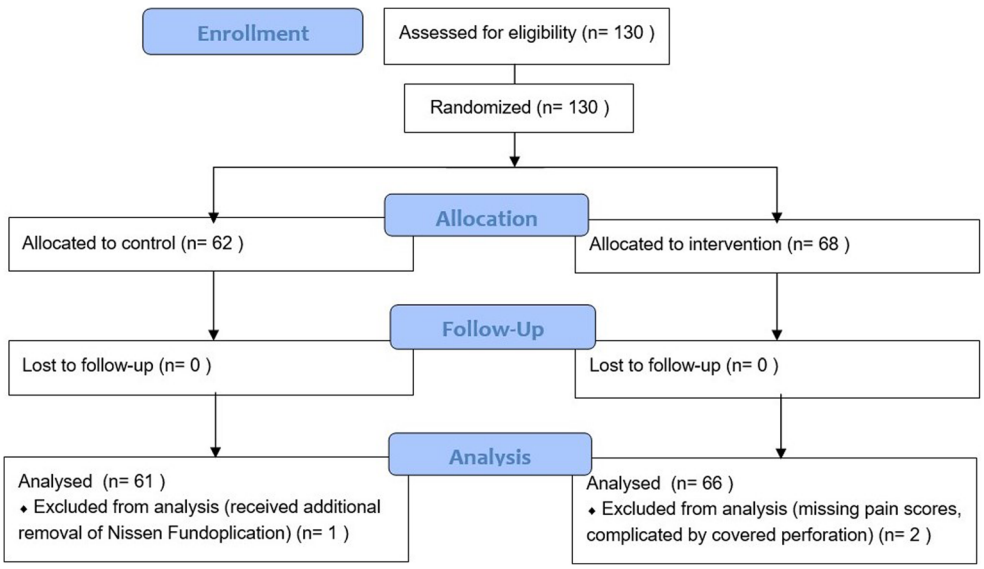

Fig. 1 CONSORT flow diagram

Table 1 Patient characteristics

Patient data	Control	Bupivacaine	*p* value*	*p* value**
Gender (% male)	10/61 (16.4%)	9/66 (13.6%)	0.606	0.663
Age (years)	42.3	46.2	0.033	0.024
Weight (kg)	122.7	119.3	0.321	0.699
BMI	42.5	42.1	0.594	0.417
ASA (mean)	2.59	2.62	0.723	0.720
Diabetes mellitus	11.5%	18.2%	0.293	0.290
Hypertension	24.6%	27.3%	0.733	0.731
Obstructive sleep apnea	24.6%	27.3%	0.733	0.731
Arthrosis	16.4%	19.7%	0.632	0.629
Duration of surgery (minutes)	47.5	46.3	0.102	0.149
Chronic amitriptyline use	3/61 (4.9%)	2/66 (3%)	0.588	0.585
Chronic morphine use	4/61 (6.6%)	1/66 (1.5%)	0.147	0.144

*Outcome of two-tailed *t* test comparing the means

**Robustness check performed with the Mann-Whitney *U* and chi-squared tests for the continuous and nominal/ordinal variables, respectively

group (Table 4). The use of piritramide was slightly more common in the control group; however, this difference was not significant ($p = 0.103$).

The results of the additional analysis performed after excluding patients with chronic use of analgesics (excluding acetaminophen) were in line with the initial analysis (Table 5).

Discussion

In this double-blind, randomized controlled trial, the use of intraperitoneal bupivacaine does not result in a reduction of postoperative abdominal or shoulder pain at 0, 1, 6, or 24 h after surgery or in a reduction of postoperative opioid use. Furthermore, no significant reduction in the use of antiemetics or decrease in length of hospital stay was demonstrated (Fig. 2).

The difference in age between the study and control group was submitted to multiple testing and there is no doubt in the accuracy of our randomization. Furthermore, a difference of 3.9 years can be considered clinically irrelevant. The primary outcome, abdominal and shoulder pain, measured with the VAS for pain, did not change significantly in the intervention group. A difference of one point or more on the VAS for pain is considered as clinically relevant. Pain scores at 24 h postoperatively were practically equal in both groups. Bupivacaine works up to six hours when administered intraperitoneally, so no difference was to be expected. Length of hospital stay did not change significantly. The slightly higher use of antiemetics in the control group could be associated with the also slightly higher use of opioids. However, both results did not reach statistical significance, so conclusions cannot be drawn. In the control group, piritramide, used in the recovery room, was used more frequently. This might be due to higher pain scores in the recovery room (0 and 1 h postoperatively) in this group (Tables 2 and 3). When analyzing shoulder pain as a nominal variable (Table 4), its prevalence is higher in the control group (33.8% vs. 28.7%), though not significantly. In laparoscopic cholecystectomy, this correlation has been found [7]. In the present study, many shoulder pain scores at 0 h were missing. Follow-up on this correlation is therefore recommended.

Despite several studies indicating a decrease in pain and analgesic use in laparoscopic surgery [7–9, 11, 12] and laparoscopic bariatric surgery [14, 15] when using intraperitoneal local anesthetics, we were unable to

Table 2 Mean pain scores for abdominal pain at 0, 1, 6, and 24 h after surgery

Time after surgery (h)	Control	Bupivacaine	*p* value*	*p* value**
0	3.04	2.98	0.897	0.657
1	3.33	2.97	0.278	0.153
6	3.34	3.06	0.324	0.253
24	2.79	2.83	0.161	0.074

*Outcome of two-tailed *t* test comparing the means

**Robustness check performed with the Mann-Whitney *U* test

Table 3 Mean pain scores for shoulder pain at 0, 1, 6, and 24 h after surgery

Time after surgery (h)	Control	Bupivacaine	*p* value*	*p* value**
1	0.64	0.29	0.368	0.803
6	0.55	0.78	0.498	0.229
24	0.67	0.68	0.975	0.871

*Outcome of two-tailed *t* test comparing the means

**Robustness check performed with the Mann-Whitney *U* test

Table 4 Secondary outcomes

Outcomes	Control	Bupivacaine	*p* value*	*p* value**
Length of hospital stay (days)	1	1	0.620	0.692
Use of antiemetics	39/61	32/66	0.081	0.081
Use of opioids	48/61	45/66	0.184	0.182
Tramadol	18/61	16/66	0.507	0.505
Piritramide	43/61	38/66	0.132	0.132
Oxycodone	2/61	0/66	0.140	0.140
Shoulder pain	16/54	15/43	0.586	0.581

*Outcome of two-tailed *t* test comparing the means

**Robustness check performed with the Mann-Whitney *U* and chi-squared tests for the continuous and nominal/ordinal variables, respectively

demonstrate these benefits. A systematic review and meta-analysis [9] on intraperitoneal anesthetics used in laparoscopic cholecystectomy recommends the use of 20 ml 0.5% (5 mg/ml) bupivacaine as it is effective in reducing pain and is considered safe. When comparing intraperitoneal bupivacaine with a postoperative infusion of pethidine after laparoscopic cholecystectomy, bupivacaine was associated with a decrease in pain scores and oral narcotic use [19]. Most references mentioned in this review [9] administered the intraperitoneal anesthetics right before pneumoperitoneum; however, one study [10] additionally administered 15 ml of 0.5% bupivacaine before the procedure. The most recently published review [13] on intraperitoneal bupivacaine used in laparoscopic cholecystectomy recommends performing a randomized controlled trial using a larger sample size as there are many confounders influencing the correlation between bupivacaine and a decrease in pain. A recent study published in 2017 comparing ropivacaine and bupivacaine [8] demonstrated a stronger decrease in pain scores when using ropivacaine. In contrast to our method, most studies used saline as placebo. It is unknown if this has any influence on the peritoneum and could cause an increase or decrease of pain scores.

Strengths and Limitations

The reliability of our results is high due to a large study population, robustness checks for all results, and the double-blind randomization. Patients with chronic use of

Table 5 Mean pain scores for abdominal and shoulder pain and the means for the secondary outcomes, excluding patients with chronic use of analgesics. ($n = 97$)

Time after surgery (h)	Control	Bupivacaine	*p* value*	*p* value**
Abdomen				
0	3.08	3.02	0.911	0.637
1	3.22	3.31	0.808	0.959
6	3.28	3.06	0.475	0.596
24	2.65	2.32	0.307	0.291
Shoulder				
1	0.59	0.24	0.396	0.692
6	0.55	0.59	0.907	0.596
24	0.71	0.65	0.863	0.832
Secondary outcomes				
Length of hospital stay (days)	1	1	0.868	0.585
Use of antiemetics	28/46	25/51	0.246	0.242
Use of opioids	34/46	33/51	0.332	0.372
Tramadol	13/46	12/51	0.599	0.595
Piritramide	30/46	28/51	0.306	0.301
Oxycodone	1/46	0/51	0.295	0.290
Shoulder pain	15/42	10/31	0.762	0.785

*Outcome of two-tailed *t* test comparing the means

**Robustness check performed with the Mann-Whitney *U* and chi-squared tests for the continuous and nominal/ordinal variables, respectively

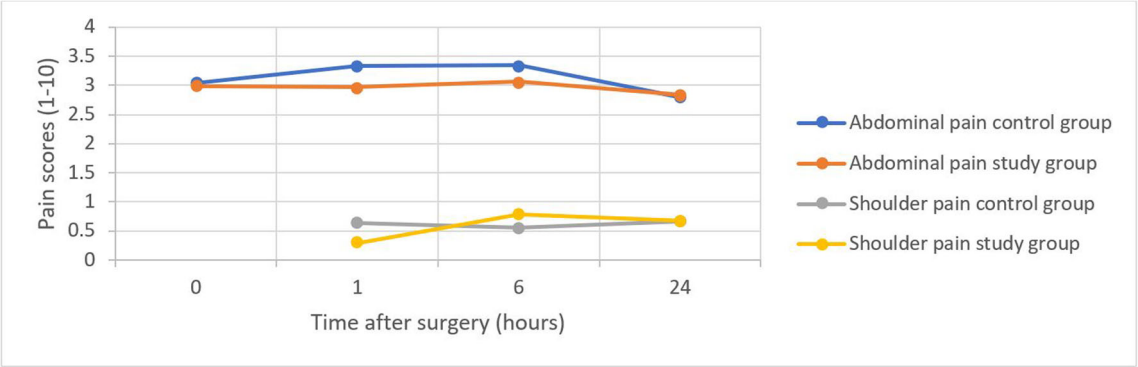

Fig. 2 Mean abdominal and shoulder pain scores at 0, 1, 6, and 24 h postsurgery

analgesics were also included, thus increasing the generalizability of the results. To exclude bias caused by these patients, results were recalculated after excluding them from the database. To reduce bias, the operating surgeon was excluded from the measurement of pain scores and postoperative care. To be able to analyze the data on shoulder pain with many missing values at 0 h postoperatively, shoulder pain was converted into a nominal variable. The subjectivity of the VAS for pain scores is a limitation to this study. Analyzing the use of opioids instead decreases the subjectivity of the results. However, as opioids are prescribed based on pain scores, the results remain sensitive to subjectivity. Another limitation is that the standard use of acetaminophen per protocol, prescribed up to 4 times a day to all patients, was not included in the database. All known confounders were included and where necessary corrected for.

Conclusion

The administration of intraperitoneal bupivacaine in LRYGB does not show a statistically significant reduction of postoperative pain or postoperative opioid use. Neither does it decrease the length of hospital stay or the use of antiemetics. Therefore, using intraperitoneal bupivacaine has no clinical relevance and should no longer be used in patients undergoing LRYGB.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This prospective, double-blind, randomized controlled trial was approved by the medical ethical committee in August 2016.

Informed Consent Informed consent was obtained from all individual participants included in this study.

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