



Safety and Efficacy of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Used for Analgesia After Bariatric Surgery: A Retrospective Case-Control Study

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Published online: 27 November 2018

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Abstract

Background Non-steroidal anti-inflammatory drugs (NSAIDs) are cornerstone in multimodal analgesia protocols. This point is of great value in morbidly obese patients due to the high prevalence of restrictive pulmonary disease and obstructive sleep apnea. The aim of this study was to test the hypothesis that NSAIDs do not increase acute bariatric surgery complications while optimizing postoperative analgesia.

Methods Databases of two medical centers were retrospectively reviewed to find all patients who underwent bariatric surgery between 1 January 2017 and 31 December 2017. Inclusion criteria were BMI greater than 30 kg/m² and age of 16–75 years old. Patients who suffered from severe organ failure or coagulation disorders were excluded. Patient's demographics, obesity-related diseases (diabetes, hypertension, dyslipidemia), postoperative pain scores, and morphine consumption in PACU, as well as early and late surgical complications, were collected. Patients included from the first institution (where NSAIDs analgesia was prohibited: control group) were compared to patients from the second institution (where NSAIDs analgesia was mandatory: case group).

Results The study population included 270 patients, 134 in the control group, and 136 in the case group. NSAIDs usage produced better analgesia with significant reduction in morphine consumption and PACU length of stay. Also, incidence of surgical complications was the same in the two groups.

Conclusions NSAIDs administration do not increase postoperative complication rate after bariatric surgery. Although NSAID administration provided better analgesia and shorter PACU stay, future prospective studies are needed to confirm these encouraging results and to evaluate their impact on postoperative rehabilitation.

Keywords Bariatric surgery · NSAIDs · Multimodal analgesia · Postoperative complications · Anastomosis leak · Bleeding

Introduction

Obesity is worldwide epidemic causing serious deterioration in global health and leading to many preventable mortalities

[1]. Bariatric surgery remains the only radical treatment for morbid obese patients [2]. However, surgery is not without risks. The two main acute complications that affect prognosis are anastomosis leak and postoperative hemorrhage; they

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occur in around 1–3% of patients [3]. In addition to surgical techniques, morbidity depends largely on anesthetic protocols and pain management [4].

An optimal pain management program shortens hospital stay and improves patient recovery. Analgesia protocols should be based on a multimodal analgesia program, simple to administer and as safe as possible. Non-steroidal anti-inflammatory drugs (NSAIDs) are a cornerstone in postoperative pain management and improve patient's recovery [5, 6]. However, mixed results have emerged from NSAIDs prescription. On one hand, studies have shown that NSAIDs inhibit collagen synthesis and promote intravascular microthrombi formation resulting in reduced oxygen delivery to the anastomosis which delays healing. Those findings have resulted in NSAIDs being avoided in colorectal anastomosis [7]. Also, NSAIDs use was associated with an increased risk of marginal ulcer disease (MU), a complication that occurs in 1–9% of cases between 1 month and 6 years after gastric bypass surgery [8, 9].

On the other hand, newer studies have shown that COX inhibition reduces wound inflammation and postoperative complications [10]. Furthermore, NSAIDs prescription has been shown to reduce morphine consumption and some of morphine-related side effects by 30% (nausea, vomiting, respiratory depression and ileus) [11, 12].

It must be noted that acute kidney injury risk slightly increases among current NSAID users in the general population; this risk will be higher when associated with preexisting chronic renal failure, advanced age (> 65 years old), and chronic NSAID use [13, 14].

With these conflicting data, a question must be addressed: does NSAIDs prescription, in bariatric surgery, increase acute bariatric surgery complications?

Materials and Methods

This retrospective unmatched case-control study was designed to test the hypothesis that NSAIDs do not increase acute bariatric surgery complications. Two groups of patients were included. These groups were chosen from two distinct medical centers experienced in bariatric surgery: Hôtel Dieu de France university hospital where bariatric surgery protocols exclude NSAIDs administration for postoperative analgesia (control group) and the Monseigneur Cortbawi institute hospital where NSAIDs administration, unless medically contraindicated, is mandatory for bariatric surgery postoperative analgesia (case group). All patients who underwent open or laparoscopic bariatric surgery between 1 January 2017 and 31 December 2017, aged between 16 and 75 years, and had a body mass index (BMI) greater than 30 kg/m² were included. Exclusion criteria included patients who suffered from acute or chronic severe organ failure (cardiac, liver, or kidney

dysfunction), coagulation disorders, or patients who were under active anticoagulation or antiaggregation therapy. Patients included from the first institution (control group) were compared to patients from the second institution (case group).

All patients in the NSAIDs group (case group) received prophylactic LMWH (Low-Molecular-Weight Heparin) prior to the procedure whereas only patients who did not undergo laparoscopic procedure in the control group received such prophylaxis.

Both groups followed this anesthesia protocol:

Induction was achieved using propofol, lidocaine, and fentanyl/sufentanyl and a muscle relaxant (succinylcholine, rocuronium, or cisatracurium). Maintenance of anesthesia was assured with sevoflurane or isoflurane and a gas mix of O₂/N₂O (0.5). Analgesia protocol included 1 g of paracetamol and 0.05–0.1 mg/kg (ideal body weight) of morphine given in both groups at the end of the surgical time, but only patients in the case group received also IV ketoprofen 100 mg as part of the analgesic protocol. Antiemetic prophylaxis (ondansetron 8 mg given 30 min before end of surgery) was systematic. Antagonization of myorelaxant agent was a must and extubation was achieved after full upper respiratory reflex recovery. Patients were transferred to the post anesthesia care unit (PACU) for recovery and for postoperative pain control using morphine titration.

IV Ketoprofen was continued in the case group for 48 h postoperatively at the dose of 100 mg/12 h.

Two surgeons performed surgeries, one in each hospital: they were graduated from the same medical school and have identical surgical techniques. Patients in both hospitals were discharged 48 h after surgery unless postoperative complications occurred.

Data were collected from patient's records: anesthesia and PACU records, follow up, and hospital discharge notes. Surgeon's outpatient follow-up records were also reviewed to detect long-term postoperative complications up to the end of May 2018 (5 to 17 months postoperatively).

Primary outcomes included incidence of acute bariatric surgery complications: anastomosis leakage and bleeding.

Secondary outcomes included opioid consumption (dose of morphine titration in mg needed to achieve a VAS score less than 4/10), PACU length of stay (minutes), and pain control (VAS scores on arrival to the PACU and directly before discharge). After PACU discharge, postoperative VAS pain scores were not collected: pain evaluation was not performed on regular basis during the postoperative period, and this data was lacking in patients records. Given the retrospective aspect of this study, it was not possible to retrieve this kind of data even if we planned to interview patients by phone.

The normal distribution of the collected data in each group was verified using the Shapiro-Wilk test. The chi square test with fisher correction was used as needed to compare qualitative variables; the student *T* test was used for mean comparison. Visual analog scale scores (VAS) were compared using

the Mann Whitney and Kruskal-Wallis tests. Two-way ANOVA models were used to assess the effect of baseline factors and their interaction with study groups. A *p* value of less than 0.05 was considered statistically significant. All analyses were conducted using SPSS version 21.

Results

The final study population included 270 patients (330 files were studied and 60 patients were excluded) who underwent bariatric surgery: 134 patients did not receive NSAID drugs (control group) and 136 patients received NSAIDs (case group).

Patients’ demographics, patients’ comorbidities are summarized in Table 1.

Three comorbidity parameters are significantly prevalent in the control group (hypertension (HTN), asthma, and obstructive sleep apnea (OSA)). In this understanding, post hoc two-way ANOVA was performed, studying the effect and the interaction of each of the previously mentioned factors with NSAIDs administration on post-operative pain. None of the interactions was statistically significant. The effect of these factors on postoperative complication incidence could not also be assessed for there are too few cases (two complications in each group) to conduct a meaningful statistical analysis.

Also, we must notice that 2.9% of patients in the control group vs. 0% in the case group suffered from chronic renal failure without statistical significance. Chronic renal failure

and/or age more than 65 years would have constituted exclusions criteria in a prospective randomized study comparing NSAIDs to placebo. With all patients aged less than 65 years [case group (mean ± SD) 35.64 years ± 9.80; (min = 20 years-max = 56 years) vs. control group (mean ± SD) 38.31 years ± 12.81; (min = 16 years-max = 63 years)] and 0 patients suffering from chronic renal failure, the use of NSAIDs was safe in the case group. Furthermore, no acute kidney injuries were identified when hospital discharge notes and surgeon’s outpatient follow-up records were reviewed. However, serum creatinine levels were not routinely tested in the postoperative period; therefore, this kind of data was not collected.

Different types of surgeries were performed in this population. Laparoscopic sleeve gastrectomy was the most frequent procedure performed with 78.4% in the case group and 57.4% in the control group. No open sleeve gastrectomy was performed in the case group (Fig. 1). However, no statistical difference was detected in secondary outcomes when analysis was performed according to surgery type.

Patients in both groups were discharged 48 h after surgery except for the three patients who suffered from bleeding, whom had a delayed hospital discharge.

Primary Outcomes

We did not find any statistically significant difference in complication rates between the two groups (Fig. 2) with only two complications reported in each group (*p* = 0.99 Fisher test two sided).

In the case group, one patient had surgical site bleeding and one patient suffered from peritoneal fistulae. In the control group, both patients had surgical site bleeding. All detected

Table 1 Patients’ characteristics

Patients’ characteristics	Case (n = 136)	Control n = (134)	<i>p</i> value
Age (years)	35.64 ± 9.80	38.31 ± 12.81	0.56
Females	63.43%	53.67%	0.11
BMI	41.64 ± 5.34	42.31 ± 7.43	0.40
ASA 2 status	98.5%	94.85%	0.17
Arterial hypertension*	17.16%	38.97%	< 0.01*
Diabetes mellitus	14.18%	16.18%	0.54
Dyslipidemia	19.4%	29.4%	0.07
Smoking history	55.22%	50.73%	0.47
Asthma*	3%	9.56%	0.04*
Obstructive sleep apnea*	5.97%	30.88%	< 0.01*
COPD	7.22%	4.41%	0.78
Arrhythmias	1.47%	0%	0.62
Chronic renal failure	0%	2.94%	0.12
Hepatic failure	0%	2.21%	0.25
Hypothyroidism	4.48%	2.94%	0.54
Coagulopathies	1.47%	0.74%	0.62
GERD	7.46%	8.09%	1.00
Previous bariatric surgery	2.23%	5.88%	0.22

*Distribution between the two groups was statistically different (*p*<0.05)

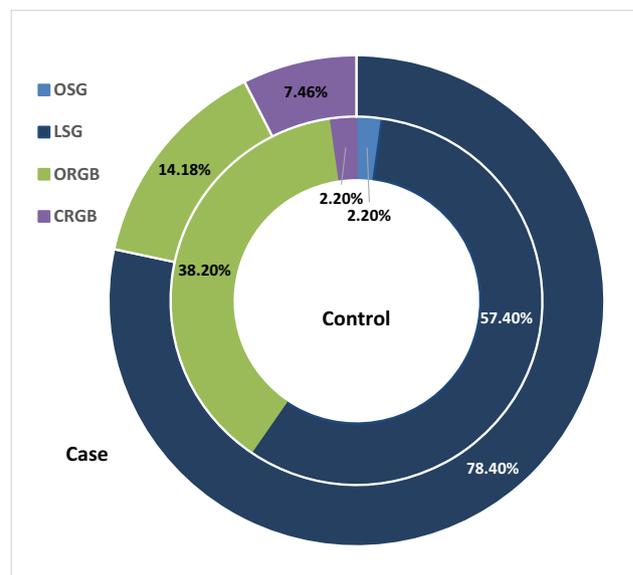
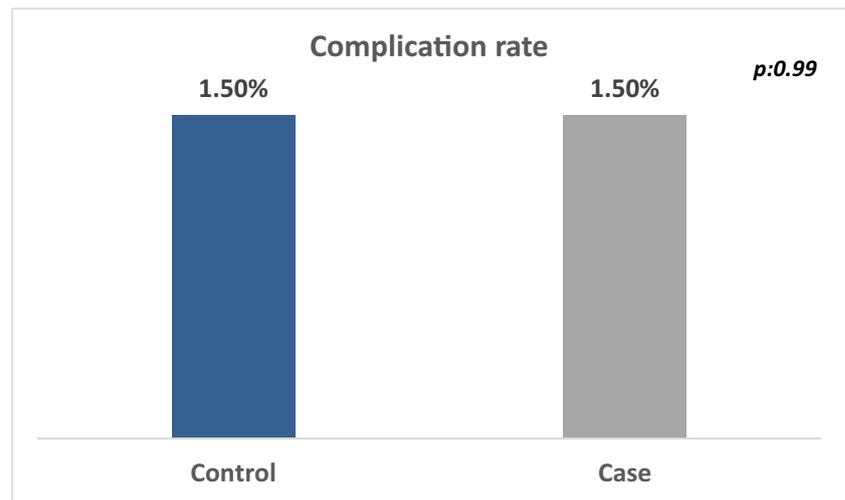


Fig. 1 Performed surgery types: OSG (open sleeve gastrectomy), LSG (laparoscopic sleeve gastrectomy), ORGB (open roux-en-Y gastric bypass), CRGB (celioscopy roux-en-Y gastric bypass)

Fig. 2 Postoperative complications

complications required surgical management. No patient suffered from anastomotic leakage.

Secondary Outcomes

Adequate pain control was achieved, VAS values less than 3/10 at PACU discharge in both groups. However, the control group had higher morphine consumption (Table 2) and required more time to achieve pain control thus longer length of stay in the recovery room (Fig. 3). VAS values were not affected by the type of surgery; a non-parametric ANOVA (Kruskal-Wallis) showed no difference in pain control when analysis was done according to surgery type (*p* value = 0.130).

Discussion

This study aimed to support the hypothesis that NSAIDs used for analgesia after bariatric surgery do not increase major postoperative complication rate such as anastomosis leak and bleeding. The incidence of these complications was very low and comparable between the two study groups. Some comorbidities were prevalent in the control group (namely: HTN, OSA, and asthma); however, prevalence of major risk factors for bariatric surgery complications such as diabetes, smoking, prior bariatric surgery, and reflux [15–17] were

comparable in both groups. These results support our study hypothesis and are consistent with published data [18, 19]. Also, NSAIDs were administered for only 48 h in the case group: a recent meta-analysis of six RCTs (480 patients) of patients receiving at least one dose of NSAIDs or COX-2 inhibitors within 48 h of surgery showed that the risk of anastomotic leakage after bowel surgery was not significantly increased (Peto OR 2.16 [95% CI 0.85–5.53, *P* = 0.11] [20]. Furthermore, the risk varies with duration of the treatment, and it is higher after 3 days or more of NSAIDs than after 1 or 2 days only [21]. In this perspective, the limited time of NSAIDs' usage (48 h postoperatively) along with the absence of chronic renal failure and patients' age less than 65 years had been protective factors against development of acute kidney injuries in the case group [13, 14]. However, in future prospective randomized studies comparing NSAIDs to placebo: age more than 65 years old and existence of chronic renal failure should be exclusions criteria. On the other hand, it should be acknowledged that achieving a sufficient statistical power to compare leakage and bleeding rate between the two groups requires a sample size with at least 1500 patients per group. Although, this study is retrospective and reflects real-world settings for use of NSAIDs in bariatric surgery; however, for the given sample size, the rates are quite similar, albeit with low statistical power (< 10%), thus generalizing the study results is far from guaranteed.

Table 2 Opioid usage and pain management

	Case	Control	<i>p</i> value
Intraoperative fentanyl consumption (μg)	298.58 ± 88.38	317.68 ± 106.68	NS
End of Surgery morphine administration (mg)*	1.63 ± 2.46	3.27 ± 3.15	< 0.001*
PACU morphine requirement (mg)*	3.49 ± 3.38	7.96 ± 5.00	< 0.001*
VAS at PACU entry	3.87 ± 2.16	3.46 ± 2.80	NS
VAS at PACU discharge	2.31 ± 1.35	1.54 ± 1.04	NS

*Mean values were statistically different between the two groups (T test, *p*<0.05)

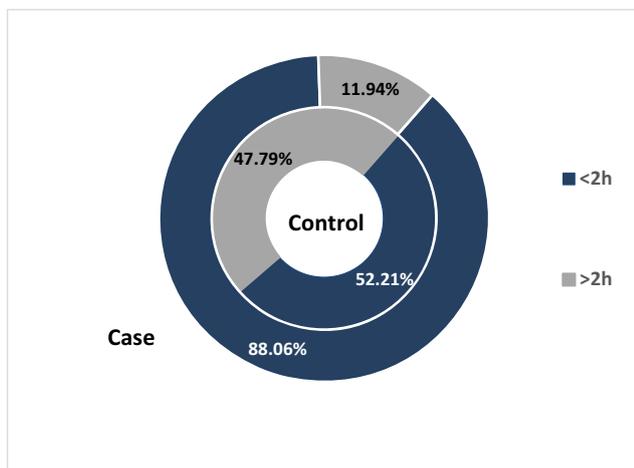


Fig. 3 Post anesthesia care unit (PACU) length of stay ($p < 0.01$)

All patients who developed bleeding had a “roux en y” bypass surgery (RYGB), a BMI of more than 40 kg/m², and had received prophylactic low-molecular-weight heparin (LMWH). It must be noted that all the 134 patients in the NSAIDs group received prophylactic LMWH prior to the procedure whereas patients going through laparoscopic procedure in the control group did not receive any thrombotic prophylaxis. This is due to difference in management protocols between the two medical centers. This difference may represent a methodological weakness in our study; however, the surgical techniques and anesthesia protocols used in both institutions were identical. This being stated, few (one in the NSAIDs group and two in the control group) bleeding events occurred in order to conduct any meaningful statistical analysis, but at least we may assume that administering NSAIDs in association with prophylactic LMWH do not seem to increase the risk for bleeding.

The fourth complicating patient who developed peritoneal fistulae had undergone a laparoscopic sleeve gastrectomy.

Patients who developed complications had a surgery time of more than 2 h, which might suggest technical difficulties. However, we did not find any proof of surgical difficulties in the surgery records.

Pain control in the PACU was evaluated using VAS scores. Both groups had good pain control with comparable fentanyl consumption during surgery and VAS scores at PACU discharge. Patients in the control group received double the morphine dose at end of surgery for comparable VAS scores at PACU entry. Also, they received double the morphine titration dose in order to achieve adequate pain control and needed to stay two times longer in the PACU before they reached discharge criteria. We might suggest that NSAIDs administration was able to reduce morphine consumption and shorten PACU stay. This can result in less opioid-related side effects (nausea, vomiting, paralytic ileus, respiratory, and sedation or neurological depression leading to hypoxia and hypercarbia) [22]. This point is of great value in morbidly obese patients mainly due to the associated restrictive pulmonary disease and the

high prevalence of obstructive sleep apnea [23]. In our study, patients who received NSAIDs had effectively shorter PACU stay suggesting faster pain control and recovery of neurologic status and airway protection reflex. Furthermore, it has been shown that shorter PACU stay reduces postoperative morbidity and mortality [4].

Other factors such as early ambulation and optimal cooperation in respiratory physiotherapy are also predictors of better outcome [4]. Unfortunately, the impact of this shorter PACU stay and lesser morphine consumption on postoperative rehabilitation was not addressed in this study, e.g., length of stay (LOS) was not compared between the two groups for it was virtually similar for all the patients except for three patients who suffered from bleeding. Lacking variability of LOS precluded any meaningful statistical analysis. One might hypothesize that NSAID administration, by reducing opioid consumption and improving pain management, may have positive impact on postoperative rehabilitation.

The retrospective aspect of this study did not allow for randomization or any prevention of confounding factors (surgery types, LMWH administration, etc.). VAS values were not affected by the type of surgery (Kruskal-Wallis, p value = 0.130), and bleeding risk does not seem to be increased by LMWH and NSAIDs coadministration; however, the observed low rate of complications may highlight the need for further prospective randomized controlled studies with bigger sample size in order to support our conclusions regarding the safety of NSAIDs for analgesia after bariatric surgery.

Finally, this study did not include postoperative follow up to evaluate the direct impact of NSAIDs on pain management and early rehabilitation. It would have been interesting to evaluate the impact of this better analgesia on patient satisfaction and/or quality of life (QoL): while salutary per se, QoL questionnaires were not feasible given the study was retrospective. A QoL dimension should be adopted in future prospective protocols on the subject.

Conclusion

This study was able to support the hypothesis that NSAIDs do not increase postoperative complication rate after bariatric surgery, even when administered in association with prophylactic LMWH. Although, NSAIDs administration was found to reduce opioid consumption and PACU stay. These encouraging results motivated the use of NSAIDs for analgesia after bariatric surgery at the “control group” hospital: surgeons whom were reluctant to their use in this setting are now convinced to enroll their patients in future prospective randomized studies comparing NSAIDs to placebo, where confounding factors can be controlled (e.g., diversity in bariatric procedures, techniques, surgeons, hospitals; existence of chronic renal failure; age etc.). This kind of studies is needed to confirm

these encouraging results and to evaluate their impact on postoperative rehabilitation.

Compliance with Ethical Standards

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

Ethical Approval For this type of study formal consent is not required.

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

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