CHAPTER 5

NSAID USE AFTER BARIATRIC SURGERY: A RANDOMIZED CONTROLLED INTERVENTION STUDY

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Published in:
Obesity Surgery 2016;26:2880-5.
ABSTRACT

Background
Use of nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in bariatric surgery patients. If use of an NSAID is inevitable, a proton pump inhibitor (PPI) should also be used.

Aim
To determine the effect of an, compared to care-as-usual, additional intervention to reduce NSAID use in patients who underwent bariatric surgery, and to determine the use of PPIs in patients who use NSAIDs after bariatric surgery.

Methods
A randomized controlled intervention study in patients after bariatric surgery. Patients were randomized to an intervention or a control group. The intervention consisted of sending a letter to patients and their general practitioners on the risks of use of NSAIDs after bariatric surgery and the importance of avoiding NSAID use. The control group received care-as-usual. Dispensing data of NSAIDs and PPIs were collected from patients’ pharmacies: from a period of 6 months before and from 3 until 9 months after the intervention.

Results
Two hundred forty-eight patients were included (intervention group: 124; control group: 124). The number of users of NSAIDs decreased from 22 to 18 % in the intervention group and increased from 20 to 21 % in the control group (NS). The use of a PPI with an NSAID rose from 52 to 55 % in the intervention group, and from 52 to 69 % in the control group (NS).

Conclusions
Informing patients and their general practitioners by letter, in addition to care-as-usual, is not an effective intervention to reduce the use of NSAIDs after bariatric surgery (trial number NTR3665).
INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications. They are prescribed for arthritic and inflammatory conditions, as well as for acute and chronic pain. Use of NSAIDs is associated with various serious gastrointestinal complications. For patients using an NSAID several strategies are available to reduce the gastrointestinal risks, such as concomitant use of a proton pump inhibitor (PPI) [1].

According to the Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient, NSAIDs should be completely avoided after bariatric surgery, if possible, because they have been implicated in the development of anastomotic ulcerations/perforations, and alternative pain medication should be identified before bariatric surgery [2]. In gastric bypass patients, even a zero-tolerance policy towards use of an NSAID is advocated [3]. Bariatric surgery is the only effective treatment for morbid obesity with enduring weight loss. The total number of bariatric procedures in 2013 performed worldwide was 468,609. Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and adjustable gastric banding were the most commonly performed procedures [4]. Surgical procedures, such as adjustable gastric band and sleeve gastrectomy, do not require an anastomosis. However, with all types of bariatric surgery, the reduced stomach size presents a major problem with NSAID use. NSAIDs may cause serious damage to the stomach pouch by two mechanisms: direct irritation of the mucosa due to their acidic properties, and through systemic effects. The systemic effects arise from inhibition of prostaglandin synthesis, which causes decreased mucous production, increased acid production and decreased mucosal perfusion exposing the pouch to damage of the epithelial layer, erosions, and ulcers [5]. In a systematic review of studies on development of ulcer disease after RYGB, Coblijn et al. found the incidence of marginal ulceration ranging from 0.6 to 25 %. Symptoms of marginal ulceration may vary from epigastric pain and vomiting to perforation or massive bleeding. One of the factors that seems to be associated with increased risk for marginal ulceration is use of an NSAID [6]. In a study on predictors of endoscopic findings after RYGB, Wilson et al. found that NSAID use significantly increased the risk of marginal ulcers (adjusted odds ratio 11.5, 95 % CI 4.8-28) and was associated with staple-line dehiscence (adjusted odds ratio 10.1, 95 % CI 1.1-90.1). Relevant protection against marginal ulceration is achieved when a PPI is simultaneously used with an NSAID [7].

In our local setting of care-as-usual, bariatric surgery patients are verbally informed to avoid NSAIDs by their surgeons. In a study on the influence of bariatric surgery on the use of medication, we found a significant decrease in the use of anti-inflammatory and antirheumatic products, non-steroids (WHO-ATC class M01A), 12 months after bariatric surgery. However, a substantial part of the patients used an NSAID at any moment after bariatric surgery [8].
The aim of the present study was to determine the effect of an, compared to care-as-usual, additional intervention to reduce NSAID use in patients who underwent bariatric surgery, and to determine the use of PPIs in patients who use NSAIDs after bariatric surgery.

**METHODS**

This randomized controlled intervention study was performed in patients who underwent bariatric surgery in Medical Centre Leeuwarden. The regional research ethics committee (RTPO Leeuwarden) reviewed and approved the study. The study is registered as trial NTR3665.

**Power Analysis**
In patients undergoing bariatric surgery in Medical Centre Leeuwarden between March and December 2011, the prevalence of users of NSAIDs was 28%. We assumed the prevalence of users of NSAIDs in patients included in this intervention study to be the same. The intervention was considered effective with a 50% decrease in users of NSAIDs. Using Fisher’s exact test for 80% power and \( \alpha = 0.05 \) (one-tailed) the required sample size was calculated at 117 per group.

**Study Design**
Patients who underwent bariatric surgery in Medical Centre Leeuwarden between March 2011 and April 2012 were contacted by letter inviting them to participate and return a signed informed consent. If no reply was received within 2 weeks, patients were contacted by telephone. After having obtained written informed consent from all individual participants included in the study, patients were randomized to an intervention or a control group. The intervention consisted of sending a letter to patients and their general practitioners with information on the risks of use of NSAIDs after bariatric surgery, and the importance of avoiding NSAID use, in addition to care-as-usual. Contact information of the general practitioner of each patient was retrieved from electronic medical records. The letter was clearly recognizable as sent by Medical Centre Leeuwarden. The letter included a list of brand and generic names of all NSAIDs available in the Netherlands at the time of the study period. The control group received care-as-usual, consisting of regular medical follow-up after bariatric surgery, as well as usual general practitioner care.
Figure 1 shows the time schedule of the study. For all patients, dispensing data of NSAIDs and PPIs as prescribed by a physician were collected from patients’ pharmacies: from a period of 6 months before and from 3 until 9 months after the intervention. Medication dispensing data included medication dosage formulation, daily dosage, and total number supplied. Dispensing data did not include the counter use of NSAIDs. For use of NSAIDs, salicylates (acetylsalicylic acid, carbasalate calcium) in dosages of more than 100 mg per dosage unit were included. To assess the total number of dispensed NSAIDs for all the patients, defined daily doses (DDDs) of NSAIDs were used. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults [9].

Nine months after the intervention, all the patients underwent a telephone interview. All the patients from the intervention group confirmed that they had received the letter and understood the information. They were all queried through a questionnaire about the indications for use of NSAIDs and the use of NSAIDs purchased over the counter.

All patients’ demographic data (age, gender, type of bariatric surgery, date of surgery) and dispensing data of medication were entered in an Access database (Microsoft®). Patient data were anonymized.

Statistical Analysis
Chi-square test was used for analyzing differences in use of an NSAID and NSAID+PPI between intervention and control group after the intervention. The $p$ values were two-sided, and statistical significance was considered when $p<0.05$. Exact chi-square test was used for analysing differences in distribution between the intervention and control group for using an NSAID and NSAID+PPI. All statistical analyses were performed using SPSS version 19 (IBM Corp., Armonk NY, USA) or SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).
RESULTS

Study Flow
A total of 742 patients undergoing bariatric surgery between March 2011 and April 2012 were assessed for eligibility and were invited to participate. Figure 2 shows the study flow chart of patients and CONSORT diagram. Two hundred and fifty-three patients agreed to participate and returned a signed informed consent form. They were randomized to an intervention or a control group. In total, five patients were lost to follow-up, leaving 124 patients in each group eligible for analysis.

Baseline Characteristics
No significant differences in baseline characteristics between the study groups were detected (Table 1). RYGB was the most frequently performed type of weight loss surgery, followed by omega loop bypass. In the intervention group, 27 patients (22 %) used an NSAID; in the control group, 25 patients (20 %). In the intervention group as well as in the control group, 52 % of the NSAID users also used a PPI.

FIGURE 2. Study flow chart of patients and CONSORT diagram.
TABLE 1. Patient characteristics at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 124 (%):</td>
<td>N = 124 (%)</td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td>104 (84)</td>
<td>97 (78)</td>
<td>0.257¹</td>
</tr>
<tr>
<td>Mean age, year (±SD)</td>
<td>49.8 (9.9)</td>
<td>50.5 (11.2)</td>
<td>0.622²</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>0.506¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roux-en-Y Gastric Bypass</td>
<td>93 (75)</td>
<td>97 (78)</td>
<td></td>
</tr>
<tr>
<td>Omega Loop Bypass</td>
<td>17 (14)</td>
<td>13 (10)</td>
<td></td>
</tr>
<tr>
<td>Sleeve gastrectomy</td>
<td>9 (7)</td>
<td>12 (10)</td>
<td></td>
</tr>
<tr>
<td>Banded bypass</td>
<td>5 (4)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Median number of days between surgery</td>
<td>461 (159)</td>
<td>460 (134)</td>
<td>0.950⁴</td>
</tr>
<tr>
<td>and intervention (IQR³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID users</td>
<td>27 (22)</td>
<td>25 (20)</td>
<td>0.755¹</td>
</tr>
<tr>
<td>Dispensed DDDs of NSAIDs</td>
<td>3444</td>
<td>4142</td>
<td>0.532¹</td>
</tr>
<tr>
<td>NSAID + PPI users</td>
<td>14 (52)</td>
<td>13 (52)</td>
<td>0.991¹</td>
</tr>
</tbody>
</table>

¹ ch-square test; ² unpaired t-test ³IQR = interquartile range; ⁴ Mann-Whitney U test.

TABLE 2. Use of prescription NSAIDs.

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>p-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 124 (%)</td>
<td>N = 124 (%)</td>
<td></td>
</tr>
<tr>
<td>NSAID users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>27 (22)</td>
<td>25 (20)</td>
<td>0.520</td>
</tr>
<tr>
<td>After 9 months</td>
<td>22 (18)</td>
<td>26 (21)</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-5 (-4)</td>
<td>+1 (+1)</td>
<td></td>
</tr>
<tr>
<td>NSAID + PPI user</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>14 (52)</td>
<td>13 (52)</td>
<td>0.295</td>
</tr>
<tr>
<td>After 9 months</td>
<td>12 (55)</td>
<td>18 (69)</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-1 (+6)</td>
<td>+6 (+22)</td>
<td></td>
</tr>
<tr>
<td>Dispensed DDDs of NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>3444</td>
<td>4142</td>
<td>0.455</td>
</tr>
<tr>
<td>After 9 months</td>
<td>2127</td>
<td>3382</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-1317 (-38)</td>
<td>-760 (-18)</td>
<td></td>
</tr>
</tbody>
</table>

¹ chi-square test
**Effect of the Intervention**

In Table 2 the use of NSAIDs as prescribed by a physician and based on dispensing data from patients’ pharmacies is shown. In the period of 3 until 9 months after the intervention, 22 patients (18 %) used an NSAID in the intervention group (difference -4 % compared with baseline) and 26 patients (21 %) in the control group (difference +1 % compared with baseline). The between-group difference was not significant, and the predefined criterion for a successful intervention, a reduction of 50 % in NSAID use compared to the control group, was not reached. In the intervention group, 17 of the 27 users using an NSAID before intervention did not use an NSAID after intervention anymore; in the control group, 13 out of 25. However, after the intervention, 12 patients in the intervention group started using an NSAID, 14 patients in the control group. For using an NSAID, no significant difference in distribution between the intervention and control group before and after the intervention was observed ($p=0.852$).

In both groups, after intervention, more users of NSAIDs also used a PPI. The use of a PPI with an NSAID rose from 52 to 55 % in the intervention group, and from 52 to 69 % in the control group. The difference between the groups was not significant. In the intervention group, 10 of the 14 users using an NSAID+PPI before the intervention did not use an NSAID+PPI after the intervention anymore; in the control group, 6 out of 13. However, after the intervention 8 patients started using an NSAID+PPI, 11 patients in the control group. For using an NSAID+PPI, no significant difference in distribution between the intervention and control group before and after the intervention was observed ($p=0.550$).

In both groups, the total number of dispensed DDDs of NSAIDs decreased after the intervention. However, in the period of 3-9 months after the intervention no significant difference in total number dispensed DDDs of NSAIDs was observed between the groups.

**Results from Telephone Questionnaire**

In Figure 3, the self-reported indications for use of NSAIDs, as obtained by telephone questionnaire 9 months after the intervention, are shown. Ten patients from the intervention group reported over the counter use of an NSAID; two of these patients also used an over the counter PPI. Seventeen patients from the control group reported over the counter use of an NSAID. None of these patients also reported use of an over the counter PPI.
In this study, an intervention consisting of sending a letter to patients and their general practitioners with information on the risks of use of NSAIDs after bariatric surgery, and the importance of avoiding NSAID-use, was not effective in reducing the use of NSAIDs. Moreover, after the intervention, no difference in concomitant use of a PPI and an NSAID between the intervention and control group was observed.

Although scarce, high-quality studies on patient- and physician-directed interventions have been shown effective in reduction of use of various medications. In a systematic review to identify effective methods for stopping pre-existing prescribing in situations where continued prescribing may no longer be clinically warranted, Ostini et al. concluded that in the most effective interventions, patients were included in the stopping process, either by their prescriber or with the cooperation of the prescriber [10]. For long-term users of benzodiazepines, a simple letter intervention from general practitioners demonstrated to be an effective method to decrease or stop their medication [11]. Sending a simple information leaflet by general practitioners to long-term users of dyspepsia medication has been shown effective in reduction of prescriptions of PPIs [12].

Although the intervention of this study was patient- as well as general practitioner-oriented, it was not successful. Joint disorders were an important group in the self-reported indications for an NSAID by the patients. For this indication, NSAIDs are difficult to substitute. This might partly explain the failure of the intervention of this study.
The intervention in this study might have had an effect in the over the counter use of NSAIDs and PPIs. The self-reported over the counter use of NSAIDs was lower in the intervention group than in the control group. Results from the telephone questionnaire also indicate that the over the counter use of PPIs was slightly higher in the intervention group compared with that in the control group.

Before surgery, bariatric surgeons inform their patients about the risks of using an NSAID. In this study, at baseline, often more than 1 year after surgery, 22 % of the patients in the intervention and 20 % in the control group used an NSAID. In both groups, only 52 % of those patients also used a PPI. A successful policy to decrease the use of NSAIDs after bariatric surgery and lower the risk of development of anastomotic ulcerations/perforations has yet to be found. Community pharmacists might have an active role, as pharmacist-led interventions have demonstrated to improve safe use of nonselective NSAIDs in patients at increased risk of gastrointestinal side effects [13].

To our knowledge, this is the first study to investigate an intervention on the NSAID use after bariatric surgery, which involved patients and their general practitioners in the intervention. Changes in use of NSAIDs and PPIs were based upon original complete and detailed dispensing data from patient’s pharmacies. The study achieved its expected sample size, and patient follow-up rates were high.

This study has several limitations. To explore the use of NSAIDs and PPIs, dispensing data from patient’s pharmacies has been utilized. However, there may be a discrepancy between the patient’s actual use of medication and the use assessed by dispensing information. Nevertheless, to determine the change in medication use over time, before and after the intervention, dispensing data should be an adequate substitute for the actual use of medication. Detailed use of over the counter medication was not recorded in this study.

In the written informed consent, no information on the intervention to reduce use of NSAIDs was included. Patients from the control group might get information on the intervention from patients from the intervention group. In our local setting until 1 year after bariatric surgery, group meetings for patients are scheduled for follow-up. However, for the majority of patients the intervention was carried out more than 1 year after surgery. Moreover, as yet in the Netherlands pharmacies do not register bariatric surgeries of their patients, so information on not using an NSAID after bariatric surgery by a pharmacy is not likely.

Around 80 % of the patient population was female; thus, it is difficult to apply our results to men. However, this 80-20 distribution is an accurate representation of the population undergoing bariatric surgery.
CONCLUSION

In spite of guidelines to avoid NSAIDs after surgery, their use by bariatric surgery patients is considerable. Moreover, many NSAID users do not use a PPI. However, informing patients and their general practitioners by letter, in addition to care-as-usual, is not an effective intervention to reduce the use of NSAIDs after bariatric surgery. The most effective way to lower the use of NSAIDs after bariatric surgery, and to promote simultaneous use of a PPI if an NSAID is still necessary, has yet to be determined.

ACKNOWLEDGMENTS

We thank NJGM Veeger, PhD, clinical epidemiologist, Medical Centre Leeuwarden, for his statistical help.


SECTION IV

BIOAVAILABILITY OF METOPROLOL