Intraoperative analgesia guided by the Analgesia Nociception Index in bariatric surgery: An unmatched case-control study

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Benefits of intraoperative analgesia guided by the Analgesia Nociception Index (ANI) in bariatric surgery: An unmatched case-control study

Abstract (words count 246)

Introduction Analgesia Nociception Index (ANI) has been proposed for the evaluation of the nociception-antinociception balance in the perioperative period. In obese patient, where the management of analgesia may be rendered difficult by pharmacological changes, we hypothesized that the monitoring of analgesia with ANI would reduce intraoperative opioid consumption during bariatric surgery.

Methods This monocentric, observational, unmatched case-control study aimed to compare perioperative data from obese subjects (body mass index ≥ 35 $kg.m^{-2}$) during bariatric surgery with or without the use of ANI monitoring (ANI+ group versus ANI- group). Intraoperative analgesia was provided by injection of sufentanil, which was performed according to the clinician's assessment in the ANI- group or to the ANI value in the ANI+ group. The primary outcome was the mean hourly intraoperative sufentanil requirement. Secondary outcomes included the need for postoperative morphine titration, incidence of nausea and vomiting, respiratory distress and pain scores in the first 24 hours.

Results Between December 2013 and September 2016, 60 obese patients (i.e. 30 per group) were included. The mean hourly consumption of sufentanil was significantly lower in the ANI+ group (0.15±0.05 $\mu g.kg^{-1}.h^{-1}$ versus 0.17±0.05 $\mu g.kg^{-1}.h^{-1}$, P=0.038). We found no difference between groups regarding the incidence of nausea and vomiting, acute respiratory distress, the need for postoperative morphine titration, or pain scores in the first 24 postoperative hours.

Conclusion The use of ANI monitoring might reduce intraoperative consumption of sufentanil during bariatric surgery but does not appear to be accompanied by a reduction in its side effects.

Introduction

Over the last decade, the number of anaesthesia for bariatric surgery has increased worldwide [1,2]. Obesity, defined as a body mass index (BMI) ≥ 30 $kg.m^{-2}$, induces various pathophysiological changes that affect anaesthetic and perioperative care. Due to the significant obesity-related changes on the respiratory system and the high prevalence of Obstructive Sleep Apnoea Syndrome (OSA) in this population [3,4], obese patients are at risk of increased perioperative respiratory outcomes [5,6]. Furthermore, the pharmacokinetic and pharmacodynamics profile of anaesthetic drug is profoundly modified in morbidly obese population. Indeed, the increase in both lean and fat body mass, and the raise in volume of distribution cause changes in the distribution and elimination of pharmacological agents, particularly the lipophilic ones, such as opioids [7,8]. These pharmacological modifications make it difficult to determine the optimal therapeutic range and expose the patient to a risk of overdose, which may cause serious issues, particularly on the respiratory function. The management of intraoperative analgesia in obese people is still poorly codified and varies according to the opioid used and its method of administration.

During general anaesthesia, there is a balance between the response of the body to a nociceptive stimulus and the antinociceptive component of anaesthesia [9]. Nociceptive stimuli involve the autonomic nervous system and induce vegetative responses such as tachycardia, hypertension, and lacrimation [10,11]. Despite being helpful to assess the nociception—anti-nociception balance and to guide the intra-operative analgesia, these signs are also unspecific [10]. The anaesthetist's aim is to avoid any underdosing of opioid analgesics, which could be responsible for haemodynamic reactions and stress, as well as any overdosing, which is potentially providing hyperalgesia and postoperative respiratory complications [12]. All these considerations complicate the management of intraoperative analgesia in the obese subject.

Recently, special attention has been paid to the monitoring of analgesia through the development of new devices [10]. Among them, the ANI or Analgesia Nociception Index based on the influence of the respiratory cycle on the R-R interval of the electrocardiogram, makes it possible to quantify efficiently the nociception-antinociception balance [13–15]. The ANI is expressed as an index ranging from 0 to 100. An ANI value close to 100 indicates a predominant parasympathetic tone (low stress level, analgesia) while a value close to 0 means a predominant sympathetic tone (high level of stress, nociception).

Here, we tested the hypothesis that the ANI monitoring of analgesia in obese patients during bariatric surgery could reduce intraoperative opioid consumption. Therefore, we conducted an unmatched case-control study on bariatric surgery patients before and after the introduction of the ANI monitor in our institution.

Material and methods

Study design

This monocentric, observational, unmatched case-control study was conducted in patients who underwent bariatric surgery (gastric bypass, sleeve-gastrectomy or gastric band removal) from December 2013 to September 2016 and was approved by the Institutional Review Board (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III, protocol n° DC 2015/112). Patients operated on between December 2013 and May 2015, i.e. prior to the introduction of the ANI monitor, were retrospectively included (ANI- group), while patients operated on between June 2015 and September 2016 were included prospectively (ANI+ group). Inclusion criteria were: BMI $\geq$ 35 $kg.m^{-2}$, age $\geq$ 18 years and the intraoperative use of sufentanil as opioid agent. Exclusion criteria included situations where the ANI measurement was not interpretable, in accordance with the manufacturer's recommendations, such as rhythm disorders, presence of a pacemaker, use of beta-blockers drugs, pathology of the autonomous system, and patient with chronic pain treated with opioid drugs.

Protocol

All patients received standard intraoperative monitoring by included electrocardiogram, pulse oximetry and non-invasive blood pressure measurement. In the ANI+ group, patients were monitored by ANI device and Bispectral Index (BIS) for depth analgesia and anaesthesia, respectively. Anaesthesia was induced by using propofol, sufentanil and succinylcholine. The doses were left to the clinician's discretion. Anaesthetic maintenance was ensured by halogenated anaesthetic (sevoflurane) or target-controlled infusion (TCI) of propofol and was titrated to maintain BIS values between 40 and 60 throughout the intraoperative period. As expected, intraoperative analgesia based on sufentanil differed between groups. In the ANI- group, sufentanil injections were performed according to the attending clinician’s assessment

based on clinical signs, pharmacology and his experience. In the ANI+ group, sufentanil injections followed a pre-established protocol achieving an optimal level of analgesia, with an ANI index between 50 and 70, according to the manufacturer's recommendations. An injection of 5 µg of sufentanil was indicated when the ANI was less than 50 and greater than 30, and an injection of 10 µg was indicated when the ANI was less than 30. Protocol deviations were allowed when the hemodynamic status contraindicated the injection or when the intuition of the clinician was strong and opposed to ANI data. In both groups, the postoperative prescriptions were left to the clinician's discretion.

Outcomes

The primary outcome was the mean intraoperative hourly sufentanil requirement, based on the patient's weight and expressed in micrograms per kilograms per hour ($\mu g.kg^{-1}.h^{-1}$). We performed a subgroup analysis on the primary outcome according to the type of surgery (gastric bypass, sleeve-gastrectomy or gastric band removal). Secondary outcomes included the need for morphine titration in the Post-Anaesthesia Care Unit (PACU), the prevalence of nausea and vomiting in PACU, adverse respiratory event in PACU defined by the need for invasive or non-invasive ventilation (NIV), the maximum pain in the first 24 hours after being discharged from PACU and returning to the conventional ward, evaluated by the Numerical Rating Scale for pain (NRS) ranging from 0 to 10, and the consumption of opioid analgesic and non-opioid analgesic within the first 24 hours after being discharged from PACU.

Statistical analysis

Continuous variables are expressed as mean ± SD or median (interquartile range, 25th to 75^{th} percentile) according to the type of variable distribution. Categorical variables are presented as number (percentage of patients). The sample size was determined from preliminary

retrospective analysis including 10 patients no receiving the ANI monitoring. In these patients the mean hourly intraoperative consumption of sufentanil was 0.16± 0.05 $\mu g.kg^{-1}.h^{-1}$. Considering a 25% decrease in patients with ANI as clinical relevant, a sample size of 30 per group provided 85% power with a two-sided type I error of 0.05 to show this difference. Two-sided Student's t-tests were used for normally distributed data, after testing normality of the distribution using a Shapiro–Wilk test. Mann-Whitney U-test was used to compare non-normally distributed data and Fischer's exact test was used to compare categorical data. As a sensibility analysis, the primary outcome was also analysed using an analysis of covariance adjusted for imbalanced baseline covariates. A *P*-value < 0.05 was considered statistically significant. For the subgroup analysis, a *P*-value <0.025 was considered to indicate statistical significance, with the use of Bonferroni adjustment.

Results

Between December 2013 and September 2016, a total of 60 patients were included (30 patients in the retrospective ANI- group and 30 patients in the prospective ANI+ group) (Fig. 1). The patient's characteristics are summarised in Table 1. Patients were globally comparable except for OSA prevalence significantly more frequent in the ANI- group and age significantly lower in ANI+ group. The number of patients undergoing sleeve-gastrectomy, gastric bypass and gastric band removal was respectively 29 (48%), 25 (42%) and 6 (10%). The duration of interventions was comparable between both groups for gastric bypass (192 [168-216] min versus 216 [156-308] min, P = 0.93), for sleeve-gastrectomy (157 [133-183] min versus 164 [130-178] min, P = 0.84) and for gastric band removals (162 [118-181] min versus 82 [76-99] min, P = 0.40).

The mean dose of propofol use for induction was significant lower in ANI- group (1.8± 0.5 $mg.kg^{-1}$ versus 2.2± 0.7 $mg.kg^{-1}$, P=0.03). Conversely, the mean dose of succinylcholine used for the induction was comparable in both groups (0.96±0.15 $mg.kg^{-1}$ versus 0.94±0.16 $mg.kg^{-1}$, P=0.80). The mean hourly consumption of sufentanil was significantly reduced in the ANI+ group (0.15 ± 0.05 $\mu g.kg^{-1}.h^{-1}$ versus 0.17 ± 0.05 $\mu g.kg^{-1}.h^{-1}$, P=0.038) (Fig. 2). A subgroup analysis showed that the difference in mean hourly consumption of sufentanil was mainly observed in gastric bypass surgery (0.15 ± 0.04 in the ANI- group versus 0.11 ± 0.03 $\mu g.kg^{-1}.h^{-1}$ in the ANI+ group, P=0.01) (Fig. 3). These significant differences still remain after adjusting for imbalanced baseline covariates (i.e. age and obstructive sleep apnoea syndrome) within overall population (P=0.022) as well as subgroup analysis (P=0.019).

Profile of perioperative analgesia is summarized in Table 2. Treatments used for preventive analgesia initiated in operating room were similar in both groups. In PACU, the proportion of patients requiring morphine trends to be higher in ANI+ without reaching significance (43% versus 20%, P=0.09). The prevalence of nausea and vomiting was similar in both groups. In

the ANI- group, one patient experienced alveolar hypoventilation requiring the use of NIV, compared to none in the ANI+ group. After discharging from PACU, the median maximum NRS score in the first 24 hours was 3.5 [3.0-5.0] in the ANI- group versus 3.5 [2.3-5.0] in the group ANI+. Twelve patients (40%) in the ANI- group and nine (30%) in the ANI+ group had an NRS> 4 score in the first 24 hours after discharge from PACU, P=0.59. The proportion of patients requiring opioid analgesic within the first 24 hours after discharge from PACU was similar.

Discussion

The main finding of our study is that a strategy of anaesthesia management using ANI monitoring significantly reduces opioid consumption without increasing pain scores in the first 24 postoperative hours, compared to a strategy without analgesia monitoring. However, this sparing effect of opioids does not seem to decrease adverse effects of these drugs.

The opioids used in perioperative are incriminated for their side effects especially respiratory depression and induced nausea and vomiting. Recent studies show that they are also providers of healing failure [16], immunosuppression disorders [17] and secondary hyperalgesia phenomena [12,18]. Current international recommendations on enhanced bariatric surgery programs include the use of multimodal analgesia to reduce opioid use and side effects [19]. This strategy is particularly relevant in the obese patient population, where the use of opioid-agent is associated with an increased risk of hypoventilation and hypoxemia due to respiratory compliance disorders and the high incidence of OSA [3,20,21]. Nevertheless, minimising intraoperative doses of opioid-agent should not lead to underdosing which exposes to the risk of nociception, stress and autonomic and haemodynamic reactions. The challenging objective for the attending anaesthetist is therefore to maintain a level of analgesia included in this narrow therapeutic window.

The management of intraoperative analgesia in the obese subject must take into account the pharmacological changes induced by morbidly obesity. Indeed, several parameters could modify the pharmacokinetics of anaesthetic agents: an increase in fat mass, a lesser extent lean body mass or an increase in cardiac output and thus circulating blood volume [7]. Lipophilic agents, such as sufentanil, are more stored in the adipose tissue [7], resulting in a lower concentration peak and later concentration equilibrium. Moreover, the apparent volume of distribution and the half-life elimination of sufentanil is increased in obese patients [22]. Consequently, there is a risk of an accumulation, a prolonged residual effect of the molecule

and therefore a risk of postoperative respiratory depression [8]. However, for some authors, the volume of distribution related to the total body weight is comparable between obese subjects and people with normal weight, indicating that the drug is similarly distributed in the excess body mass and lean tissues [23]. Then they recommend to administer sufentanil as a loading dose based on total weight and to reduce maintenance doses. Other authors, such as Slepchenko, find that sufentanil pharmacokinetic models developed for non-obese subjects are adapted to moderate obese subjects (i.e. BMI <40), but that in severe obese subjects, sufentanil concentrations are overestimated [24].

All these considerations make difficult the management of intraoperative analgesia in obese patient, hence the particular interest of monitoring analgesia in this population. Among the various monitoring systems, the ANI provided by the MDoloris® monitor is based on the heart rate respiratory variability principle. It offers a view on the autonomic nervous system and is a reflection of the balance nociception-antinociception. Several studies have reported ANI monitor's reliability and its ability to detect a nociceptive stimulus during general anaesthesia [25–27]. Recently, Daccache et al. studied the feasibility and safety of a remifentanil administration protocol, based on the ANI index during vascular surgery on 180 patients [28]. The authors showed good feasibility and safety of ANI use, and also reported the use of low doses of remifentanil and the existence of low pain scores in the first 24 hours postoperatively.

In our study, sufentanil injections were protocolised in the ANI+ group and performed according to the ANI index, whereas in the ANI- group they were performed according to the clinician's opinion. We demonstrated that the management of intraoperative analgesia based on ANI monitoring is associated with a reduction in the consumption of sufentanil in bariatric surgery. This reduction was more pronounced in the subset of patients who underwent bypass surgery. This surgery has the particularity to last longer than procedure for sleeve gastrectomy

or gastric band removal. It also has longer periods with few nociceptive stimuli (realisation of digestive sutures for example). This result could reflect a practice of systematic injection, not adapted to these low pain-operating times. ANI's use highlights the possible over dosage during these weak nociceptive stimulation periods where the administration of opioid-agents is not necessary.

Furthermore, more patients in the ANI+ group than in the ANI- group required morphine titration in PACU, although this difference was not statistically significant. This can be explained by the absence of a standardised postoperative analgesia protocol. Indeed, in the ANI- group, 3 patients had benefited from a morphine administration at the end of the intervention. All patients from the ANI- group who received a morphine titration in PACU had not received intraoperative NSAIDs, well known for being powerful analgesics [29]. In the ANI+ group, 13 patients had received a morphine titration in PACU, 9 out of them had not received intraoperative NSAIDs, whereas among those who did not receive morphine titration, 70 % (12 out of 17 patients) received intraoperative NSAIDs.

Some limitations should be noted in this study. First, we used sufentanil as opioid agent for induction and maintenance of intraoperative analgesia, due to local habits. Remifentanil could have been a good alternative in the obese population because of its pharmacological advantages, including a short elimination half-life and a high clearance and therefore a lower risk of accumulation. Secondly, data from the control group were collected retrospectively. Unfortunately, there are some missing data especially in PACU, that's why it was not possible to reliably compare pain score in PACU and length of extubation between the 2 groups. Finally, we could observe statistical difference in hourly sufentanil requirement. However, we must recognize that the observed difference is clinically few relevant.

Conclusion

The use of ANI monitoring might reduce intra-operative sufentanil consumption in bariatric surgery. However, this benefit does not seem to be accompanied by a reduction in its side effects. Our results need to be confirmed by a randomised controlled prospective study to encourage the use of ANI monitoring in bariatric surgery or any other surgery performed in obese patients.

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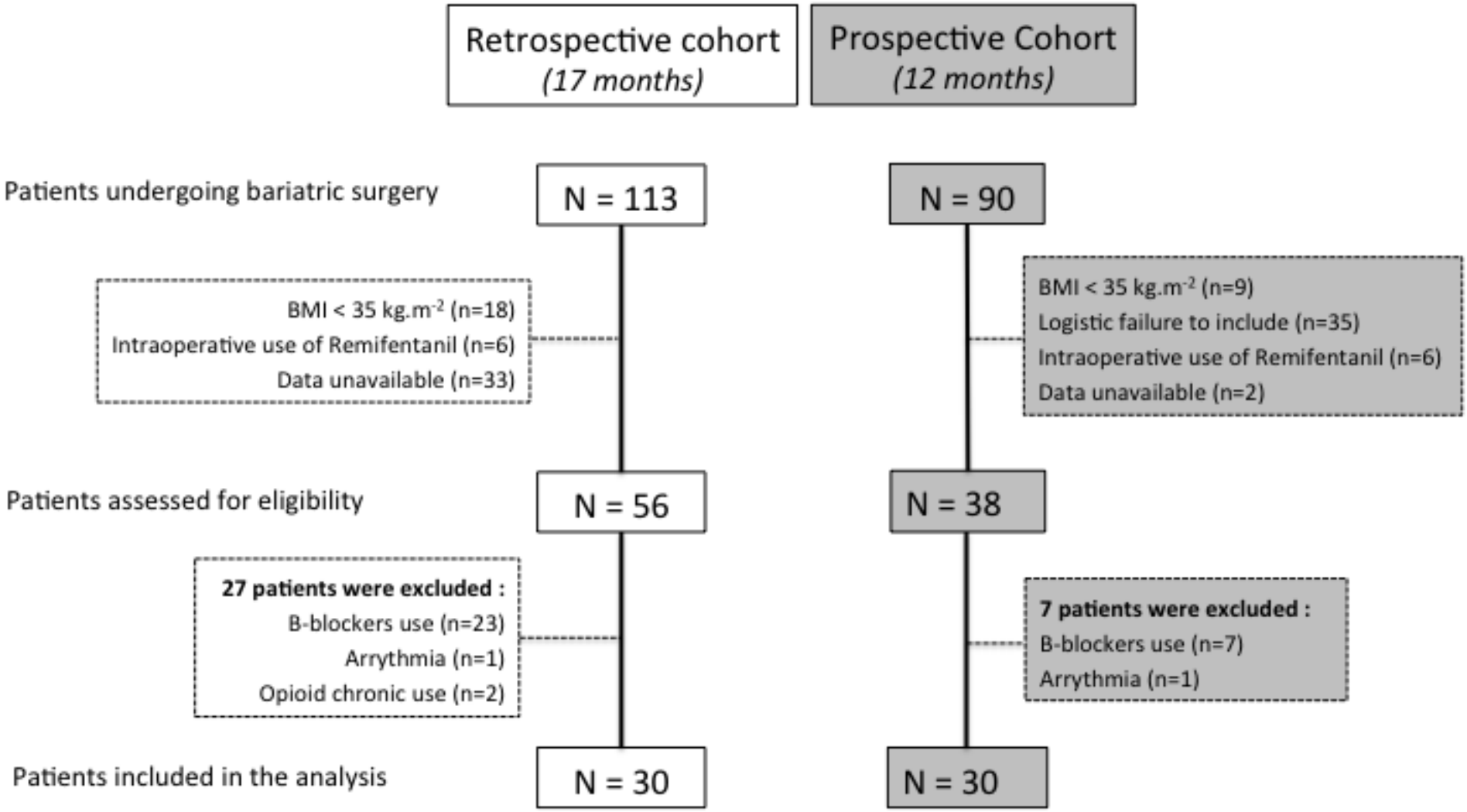
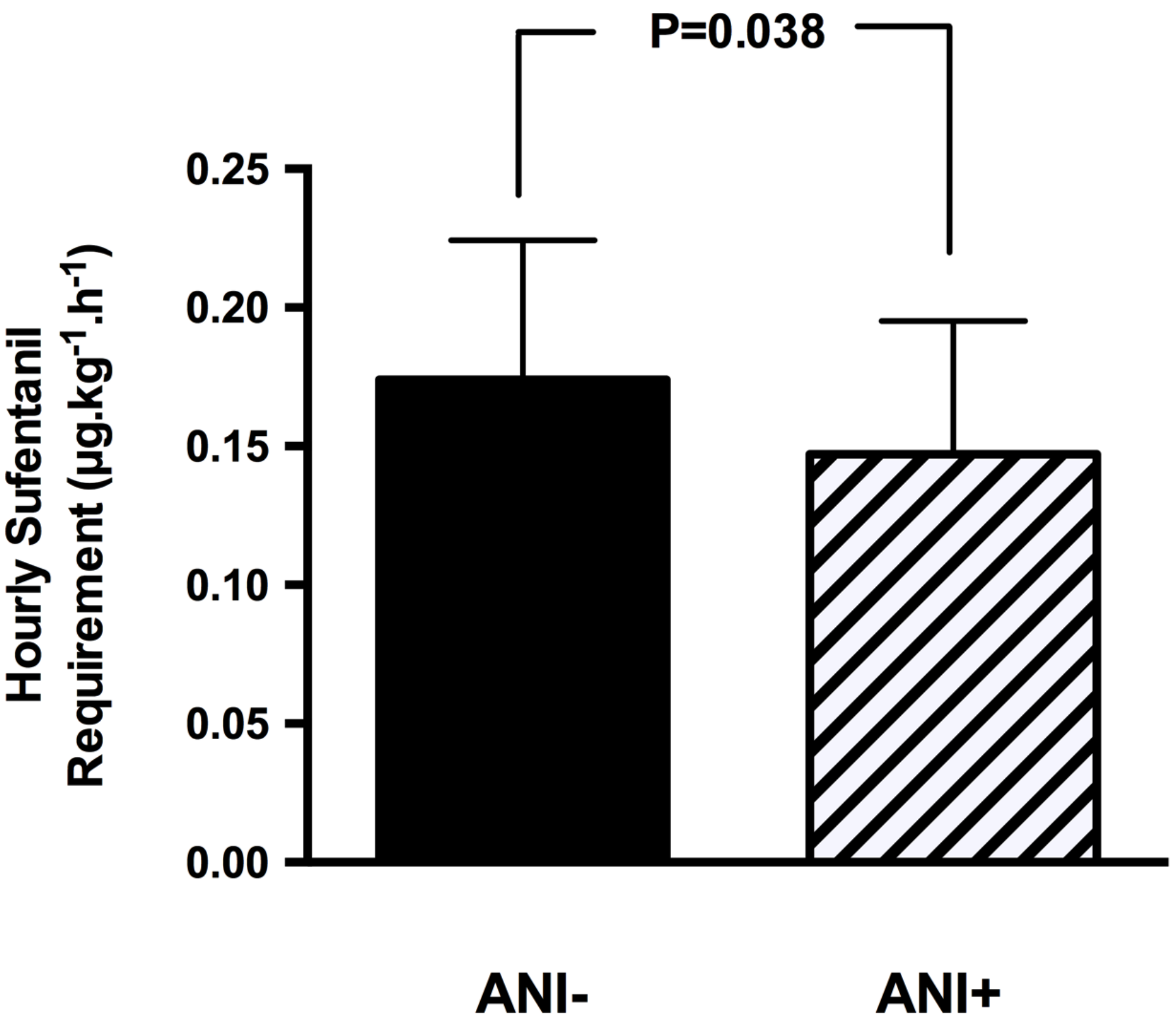

Retrospective cohort
(17 months)
Prospective Cohort
(12 months)
Patients undergoing bariatric surgery
N = 113
N = 90
BMI < 35 kg.m-2 (n=18)
Intraoperative use of Remifentanil (n=6)
Data unavailable (n=33)
BMI < 35 kg.m-2 (n=9)
Logistic failure to include (n=35)
Intraoperative use of Remifentanil (n=6)
Data unavailable (n=2)
Patients assessed for eligibility
N = 56
N = 38
27 patients were excluded :
B-blockers use (n=23)
Arrythmia (n=1)
Opioid chronic use (n=2)
7 patients were excluded :
B-blockers use (n=7)
Arrythmia (n=1)
Patients included in the analysis
N = 30
N = 30


P=0.038
0.25
0.20
0.15
0.10
0.05
0.00
Hourly Sufentanil Requirement (µg.kg-1.h-1)
ANI-
ANI+

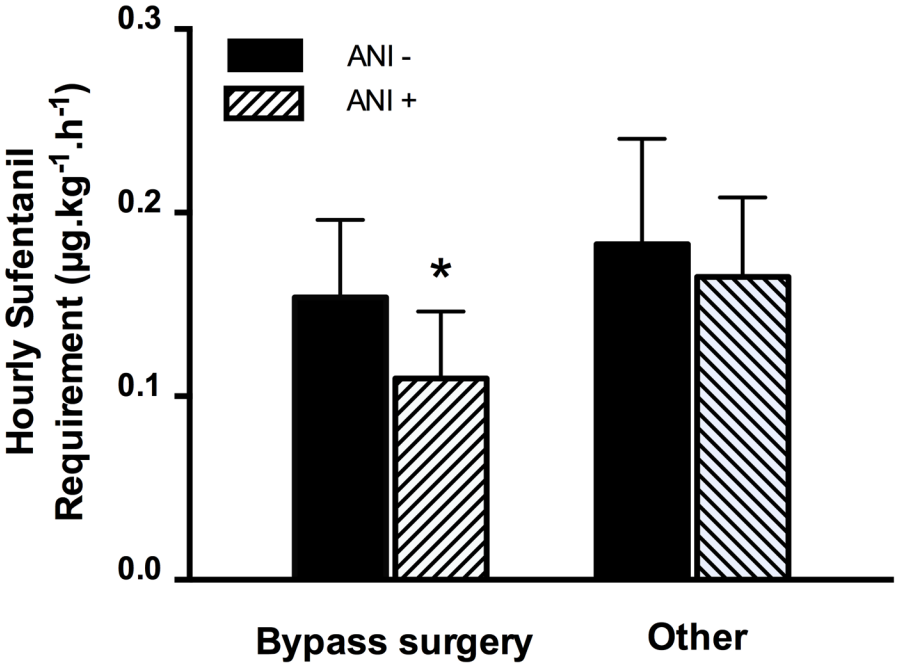

0.3
0.2
0.1
0.0
ANI -
ANI +
Hourly Sufentanil Requirement (µg.kg-1.h-1)
*
Bypass surgery
Other

Table 1 Patients baseline characteristics of patients (n=60)

Variables	ANI- (n=30)	ANI+ (N=30)
Age (years)	50 (39-56)	40 (34-50)*
Female	27 (90)	26 (87)
Body Mass Index ($kg.m^{-2}$)	43 (41-45)	47 (41-48)
Body Mass Index severity		
Obesity class II †	3 (10)	6 (20)
Obesity class III ‡	27 (90)	24 (80)
Weight (kg)	115 (107-126)	122 (110-142)
ASA status		
ASA II	6 (20)	3 (10)
ASA III	24 (80)	27 (90)
Comorbidities		
Obstructive Sleep Apnea Syndrome	13 (43)	5 (17)*
Diabetes mellitus	8 (27)	7 (23)
Type of surgery		
Sleeve gastrectomy	12 (40)	17 (57)
Gastric bypass	15 (50)	10 (33)
Gastric band removal	3 (10)	3 (10)

Data are expressed as median (25-75th percentile) or n (% of patient). ANI= Analgesia Nociception Index; Obesity Class 2 † (moderate) : $35 \leq BMI < 40$ and class 3 ‡ (severe): $BMI \geq 40$. *: P value < 0.05 ANI-

Table 2 Post-operative analgesia profile

	ANI- (n=30)	ANI+ (n=30)
Preventive analgesia drug started in the operative room		
- Paracetamol	28 (93)	30 (100)
- Nefopam	11 (37)	16 (53)
- Tramadol	23 (77)	19 (63)
- Ketoprofen	12 (40)	16 (53)
- Chirocaine infiltration	2 (6)	6 (20)
Post-operative analgesia within 24 first hour		
- Paracetamol	30 (100)	30 (100)
- Nefopam	13 (43)	14 (47)
- Tramadol	24 (80)	20 (67)
- Ketoprofen	16 (53)	14 (47)
- Morphine	3 (10)	3 (10)
Maximal NRS in the first 24h after recovery room (NRS>4)	12 (40)	9 (30)

Data are expressed as n (% of patient). ANI= Analgesia Nociception Index; NRS = Numerical Rating scale. No significant difference between groups.