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Masterthesis / Original study

Efficacy of a standardized postoperative analgesic protocol in obese patients compared to nonobese and overweight patients: a prospective observational cohort study using visual analogue scale and surgical pleth index

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Abstract

Background: **Obesity alters the pharmacokinetics of drugs, including analgesics. The continuous worldwide increase in obesity puts more and more patients at risk for sub therapeutic analgesic treatment or increased toxicity.**
Objectives: **The aim of this study was to determine the effect of obesity on the efficacy of a standard analgesic regimen consisting of paracetamol, ibuprofen, dexamethasone and piritramide PCIA.**
Design: **An observational prospective study in which included patients were cohorted according to BMI in an obese group or a control group. All patients received the same postoperative pain regimen.**
Setting: Single center, tertiary care hospital, University hospital Ghent Belgium.
Methods: **Patients (18-70 years) undergoing laparoscopic bariatric surgery (obese patients) or laparoscopic procedures similar in duration and intensity as bariatric surgery (non-obese and BMI<30kg m-2) were included. Patients with preexisting liver disease, pregnancy, alcohol or paracetamol intake were excluded from the study. All patients received a standard analgesic regimen consisting of paracetamol, ibuprofen and piritramide. Data were collected at 9 time points during the first 30 hours postoperatively. Statistical analysis was performed using a linear mixed effects model.**
Main outcome measures: **Pain intensity measured with the visual analogue scale (VAS) both at rest and in motion. Simultaneously the surgical pleth index (SPI) at rest and in motion was recorded.**
Results: **41 patients were enrolled, of which 13 were non-obese and 28 obese. Mean VAS at rest over all time points was 15.26mm in non-obese patients, compared to 23.94mm in obese patients with a mean difference of 8.68mm (95% CI 0.02 to 17.34). Three hours after first analgesic administration, obese patients scored 21.06mm (95% CI 8.85 to 33.28) higher compared to non-obese participants. We found no statistically significant difference in SPI between non-obese and obese patients. No correlation between VAS and SPI could be demonstrated.**
Conclusions: **We found a significant effect of obesity on VAS, both at rest as in motion, in the first hours after surgery. SPI showed no correlation with patient reported pain intensity. An analgesic regimen of 4g paracetamol q6hrs might be insufficient in patients with obesity. Further studies on safety and efficacy are needed to elucidate this question.**

Keywords: **Obesity, Analgesia, Nociception, Visual Analogue Scale, Surgical Pleth Index.**

This study took place in the University Hospital Ghent (UZ Gent). Approval by the institutional ethics committee of UZ Ghent (Corneel Heymanslaan 10, 9000 Ghent, Belgium. Chair: Prof. dr. Peleman) was obtained on march 19th 2020.
Patient inclusion took place between September 2020 and December 2023.
Manuscript will be submitted at University Ghent as a MaNaMa thesis.

Introduction

Obesity

Current literature shows distinct changes in the pharmacokinetics of medication leading to the assumption that obese patients are regularly exposed to subtherapeutic plasma levels of analgesics after standard dosing. Nonetheless, there is currently very little literature available on the effect of obesity on postoperative pain and the pharmacodynamics of analgesic compounds. A study from 2020 of 191 chronic shoulder pain patients showed a significant correlation between BMI and VAS where obese patients scored higher[1]. Another study on patients after percutaneous thrombectomy showed a statistically significant higher VAS score in the first hour after surgery in obese patients (24mm versus 30mm; $p = 0.008$)[2]. The clinical significance of this finding however, is debatable. A third study on 850 patients after lumbar fusion showed significantly lower VAS scores in normal weight patients compared to overweight and obese patients[3]. All these studies indicate an effect of a higher BMI towards higher VAS scores. Lastly, a study from 2011 on the association between BMI and pain after scoliosis surgery found no difference in VAS scores between non-obese and obese patients after 2 years postoperative[4]. Despite the evidence of different pharmacokinetics and –dynamics, there is little literature on adequate and safe dosing in obese patients. This puts obese patients at risk of over- or underdosing.

Pain measurement

It is common for patients to experience pain following surgery. Up to 20% of patients reports severe pain in the first 24h following surgery[20]. The following preoperative risk factors for poor postoperative pain control have been identified: smoking, young age, female sex, depression and/or anxiety, disruption of sleep, high BMI, preexisting pain and use of analgesics[21]. The standard postoperative pain assessment utilize subjective rating scales where patients self-report using words, numbers or figures (eg. Numeric Rating scale, NRS; Visual Analogue Scale, VAS). However, these uni-dimensional scales can only be used for awake and cooperative patients[20]. Furthermore, assessing a patients pain this way is complicated by hearing, visual or cognitive impairment[22]. As such, a more reliable objective measurement is useful. The surgical pleth index (SPI, GE Healthcare, Helsinki, Finland) is based on the balance between sympathetic and parasympathetic activity as an indicator of the nociception-antinociception balance. The SPI is derived from the normalized heart beat interval (HBI) and the plethysmographic pulse wave amplitude[23]. A 2009 study showed a weak but significant relation between SPI and NRS in 100 patients[24]. A more recent study of Thee et al. showed only a moderate correlation between SPI and NRS. A ROC analysis showed a moderate sensitivity and specificity of SPI for the discrimination between low-to-moderate and moderate-to-severe postoperative pain[22].

Gender differences in pharmacokinetics and pharmacodynamics

Most clinical trials exclude women, this leads to absence of information on pharmacokinetics and –dynamics for most drugs. A 2020 study on sex differences in pharmacokinetics show higher plasma concentrations and longer elimination times in women. These differences were strongly correlated with higher incidence of adverse reactions[25]. A 2024 study found a significantly higher VAS score in female patients after scoliosis surgery in the first 48h postoperatively with a higher need for morphine[26].

Methods

Study design

The study was designed as an observational prospective cohort study where patients were included in a study or control group according to BMI. All patients received the same postoperative pain regimen.

Ethical approval

This study took place in the University Hospital Ghent (UZ Gent). Approval by the institutional ethics committee of UZ Ghent (chair Prof. dr. Peleman) was obtained in 2020.

Subjects

The listed surgical procedures were systematically screened for eligible patients between September 2020 and December 2023. In total, 526 patients were screened, of which 351 non-obese and 175 obese patients. Patient inclusion proved difficult due to the COVID-19 pandemic, the researchers and surgeon being regularly unavailable, paracetamol intake before the study which confounded the results of the bloodsamples for the overarching study on paracetamol pharmacokinetics and patients already participating in other studies. Specifically the inclusion of non-obese patients with a BMI <25kg m-2 undergoing laparoscopic surgery proved difficult.

Study patients eligible for participation were adults in the range of 18-70 years with obesity (BMI

>35kg m-2) who underwent elective, laparoscopic Roux-en-Y gastric bypass surgery. The control group consisted of patients between the age of 18 and 70 years with a BMI between 18.5 and 25kg m-2 who underwent elective laparoscopic surgery (Nissen procedures, inguinal hernia, cholecystectomy, …). We looked at laparoscopic surgeries because laparoscopy has an impact on liver perfusion and could thus possibly change the pharmacokinetics of our analgesic regimen. We focused on laparoscopic procedures in non-obese patients with a similar surgical approach and duration in order to match laparoscopic gastric bypass. All procedures were intraperitoneal. Since very few eligible patients had a BMI below 25kg m-2, we increased the BMI threshold for non-obese patients to 30kg m-2 in order to obtain sufficient participants. Patients with an American Society of Anesthesiologists (ASA) of IV or higher were not eligible for participation. Other exclusion criteria were: renal insufficiency (eGFR<30ml min-1), elevated liver enzymes above 3x normal values or documented liver disease, Gilber-Meulengracht-syndrome, pregnancy, chronic alcohol intake or alcohol intake in the last 72 hours, treatment with drugs known to influence CYP2E1 and UDP-glucuronosyltransferase (UGT), chronic malnutrition, known allergy to paracetamol, NSAIDs and/or piritramide, participation in other clinical trials in the last 30 days and refusal to participate.

Patients were screened for eligibility and informed about the study by telephone, information about the visual analogue scale (VAS) and the use of patient controlled intravenous analgesia (PCIA) was given. Patients received a detailed explanation of the study protocol by e-mail. Written informed consent was acquired the day of surgery.

Objective

The objective of this study was to compare efficacy of an analgesic combination of paracetamol, ibuprofen and piritramide in normal and overweight versus obese patients. The primary outcome assessed in the study was the VAS at rest and in motion. Postoperative piritramide consumption and surgical pleth index were considered as secondary outcomes.

General anesthesia

The following protocols for general anesthesia and postoperative analgesia were applied. Every patient was monitored in accordance with ASA standards. Patients were preoxygenated with 80% oxygen and administered remifentanil using the Minto-model to an effect site target of 4ng ml-1. After 2.5 minutes 2mg kg-1 propofol was given and at loss of consciousness 1mg kg-1 rocuronium was administered. Cricoid pressure or ventilation were performed as deemed necessary by the anesthesiologist. 1 minute later, the patient was intubated, after which sevoflurane/air at 2vol% in 6L fresh gas flow (FGF) was started for the first 5 minutes and then switched to 2L FGF. FiO2 in function of saturation. Other medications given were dexamethasone 0.2mg kg-1 and a dose of 2g cefazoline. Patients also received a preload bolus of 10ml kg-1 cristalloids to obtain hemodynamic stability during positioning in the semi-recumbent position.

Ventilator setting were set as following: Tidal volume 6-8ml kg-2 (Ppeak <35cmH2O, driving pressure <12-15cmH2O), PEEP5-10cmH2O, frequency according to EtCO2 (aimed at 35-40mmHg). A recruitment maneuver was carried out before positioning in beach chair or when saturation dropped to <92%.

Peroperatively depth of anesthesia was monitored using entropy and aimed at values between 45-55. At an entropy value >55 for at least 30sec, anesthesiologists were instructed to administer a bolus of sevoflurane by changing FGF to 4L and sevoflurane to 8% for 15sec and return to 2L FGF with 25% increase in Sevoflurane. At an entropy value <45 for at least 30sec, a reduction of 25% in sevoflurane was implemented. TCI remifentanil was adjusted according to assessment of adequacy of anesthesia. Inadequate anesthesia was determined as an increase in systolic blood pressure of >25% or 15mmHg above baseline, heart rate >90bpm in absence of hypovolemia, autonomic signs (sweating, flushing) or somatic signs (movement, swallowing). Excessive anesthesia was determined as a mean blood pressure lower than 60mmHg or a heart rate below 50bpm. The effect site target was adjusted by 25% accordingly and reevaluated after 2.5min. Additional boli of rocuronium were administered as necessary.

Both remifentanil and sevoflurane were stopped at completion of dressings and FGF was set to 6L at 80% oxygen. NMT monitoring was carried out and reversal with suggamadex was performed when necessary.

All doses were calculated using lean body mass (LBM), LBM was calculated using the Janmahasatian formula.

Analgesia protocol

All patients received 600mg ibuprofen at the beginning of surgery followed by 600mg every 8h. Next, 2g of paracetamol were administered followed by 1g every 6h. At the end of surgery, patients received a loading dose of 0.1mg kg-1 piritramide and a patient-controlled intravenous pump with

piritramide for rescue analgesia. Programming of the bolus-only PCA pump was set to 1mg per bolus, 8min lockout and a maximum dose of 25mg every 4 hours.

Pain assessment

The VAS was used to assess pain levels ranging from 0mm (no pain) to 100mm (worst pain imaginable). Pain scores were recorded 9 times in the first 30h following the start of surgery both at rest and in motion. In order to assess pain during movement, patients were asked to cough and sit up straight using abdominal wall muscles. The first 4 evaluations took place at 3, 4, 5 and 6 hours after start of surgery. The following day, 5 additional evaluations were carried out at 24h 24h15min, 25h30min, 27h and 30h. Time points for pain evaluation were determined by the need for blood sampling as part of the overarching study on paracetamol pharmacokinetics. At each time, pain was evaluated using both VAS and SPI. At completion of the study at 30h, the PCA pump was disconnected for a read-out and additional rescue analgesia was prescribed when deemed necessary. All assessments of VAS and SPI where done by the researchers.

Sample size calculation

This study was part of a larger study concerning the pharmacokinetics of paracetamol in obese patients. As such, the performed power analysis was focuses on the determined pharmacokinetic variables.

A power-analysis was performed using G*Power free software[27] to estimate sample size based on the data published by Van Rongen[11]. The sample size was calculated for every individual molecule (Area Under the Curve (AUC) of paracetamol and AUC ratios for paracetamol glucuronide, paracetamol sulphate, paracetamol cysteine and paracetamol mercapturate) using the means: Wilcoxon-Mann- Whitney test (two groups) for a two tailed distribution and a standard alpha error of 0.05, a power of 0.80 and an allocation ratio N2/N1 of 1. For every variable the effect size was calculated based on the simulation of paracetamol concentrations and based on the measured AUCratios for its metabolites by visually deducting means (M) and their standard deviation (SD).

Based on this analysis we aimed to enlist a sample size of 70 patients in total (divided in 15 male and female control patients and 20 male and female obese patients).

Statistical analysis

We consulted the biostatistics department of our hospital before performing any statistical tests. Analysis of the data was done with SPSS statistics 29 (SPSS Inc., Chicago, IL, United states). Categorical variables were presented as percentage and number of cases. Continuous variables were presented as mean ± standard deviation (SD) for variables with a normal distribution and as median and interquartile range for not normally distributed data. Test values are reported with a 95% confidence interval (CI). The Shapiro-Wilk test was used to assess normality of continuous variables. The independent t-test was used to compare the observed differences between groups for normally distributed data. Continuous variables with skewed distribution were compared using the Mann-Whitney U test. Categorical variables were compared using the Chi^2 test or Fisher's exact test as indicated.

We developed a generalized linear mixed model for the statistical analysis of efficacy. This statistical method considers the repeated measures element of the study design, integrating data from different observations across time within each subject. We created a model for all 4 determinants of pain, VAS and SPI, both at rest and in motion. We selected the following variables as fixed effects: obesity, time and obesity x time interaction.

Correlation was tested using the intraclass correlation coefficient (ICC) based on a consistency, 2-way mixed-effects model.

Results

Patient characteristics

41 patients were enrolled, of which 13 were non-obese and 28 obese. In total 20 men and 21 women were selected. 2 patients dropped out due to intravenous access failure. 6 patients were discharged before conclusion of the 30h follow-up period, however, the collected data was still included. Patient characteristics per patient group and in total are presented in Table I. There was a significant difference in mean age between non-obese and obese group, 54.2 (±12.6) year and 44.4 (±15.6) year respectively. There was a higher percentage males in the obese group in comparison to the non-obese (53.6 vs. 38.5%; p = 0.368). The mean BMI were 26.3kg m-2 ± 2.7 and 41.7kg m-2 ± 4.5 in the non-obese and obese respectively. Mean remifentanil dosing was significantly different between both groups, 0.27µg/kg/min in non-obese patients compared to 0.19µg/kg/min in obese patients (MD 0.08 ; 95% CI 0.01 to 0.17; p = 0.030). We also reported a significant difference in both piritramide usage and demands and deliveries.

Visual analogue scale at rest

There was no difference in mean VAS score at rest over all time points. Figure 1 shows the evolution

Table I. — Patient characteristics.

	Total (41)	Non-obese (13)	Obese (28)	Difference (95% CI)	P value*
Age (years)	47.5 ± 14.6	54.2 ± 12.6	44.4 ± 15.6	9.8 (0.30 to 19.31)	0.044
Sex, n (%) Male Female	 20 (48.8) 21 (51.2)	 5 (38.5) 8 (61.5)	 15 (53.6) 13 (46.4)		0.368
Weight (kg)	109.8 ± 28.1	76.3 ± 12.4	125.4 ± 17.7	-49.1 (-60.11 to -38.01)	<0.001
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.0 (-0.10 to 0.03)	0.313
Lean Body Mass (kg)	62.9 ± 14.6	51.0 ± 11.6	68.5 ± 12.5	-17.5 (-25.80 to -9.22)	<0.001
Body Mass Index (kg m^{-2})	36.8 ± 8.3	26,3. ± 2.7	41.7 ± 4.5	-15.4 (-18.14 to -12.66)	<0.001
ASA classification, n (%) 2 3	 29 (70.7) 12 (29.3)	 13 (100) 0 (0)	 16 (57.1) 12 (42.9)		0.007
Smoker, n (%) Yes No	 8 (19.5) 33 (80.5)	 2 (15.4) 11 (84.6)	 6 (21.4) 22 (78.6)		1.000
Hypertension, n (%) Yes No	 20 (48.8) 21 (51.2)	 5 (38.5) 8 (61.5)	 15 (53.6) 13 (46.4)		0.368
Duration of surgery (min)	116.3 ± 55.2	128.1 ± 76.5	110.9 ± 42.7	17.2 (-31.01 to 65.45)	0.459
Peroperative remifentanil (µg/kg/min)	0.21 ± 0.09	0.27 ± 0.13	0.19 ± 0.06	0.08 (0.01 to 0.17)	0.030
Piritramide usage (mg)	21.3 ± 11.3	12.1 ± 5.7	25.2 ± 10.9	-13.0 (-18.63 to -7.44)	<0.001
Amount of demands of piritramide (n)	17.9 ± 14.8	7.6 ± 6.2	21.6 ± 15.3	-14.0 (-24.84 to -3.25)	0.012
Amount of deliveries of piritramide(n)	13.4 ± 9.1	6.9 ± 5.6	15.7 ± 9.1	-8.8 (-15.43 to -2.16)	0.011

*P-values, non-obese vs obese group.
Numeric variables are presented as mean ± SD. Categorical variables are presented as amount (percentage).
ASA - American Society of Anesthesiologists.

of mean VAS scores at rest for both non-obese and obese patients over time. The only significant difference between the two groups was observed at three and four hours after the first analgesic administration. Results are shown in Table II.

The mean VAS score at rest in all patients was 36.80 (95% CI 30.339 to 43.27); 28.80 (95% CI 22.95 to 34.66); 25.27 (95% CI 19.55 to 30.99); 19.63 (95% CI 13.86 to 25.41); 17.25 (95% CI 11.62 to 22.88) and 14.04 (95% CI 7.92 to 20.16) at three, four, five, six, twenty-four and thirty hours respectively.

Female patients reported a mean VAS score at rest of 20.12 compared to 19.08 in men (MD 1.04; 95% CI -7.26 to 9.34; p = 0.801).

Visual analogue scale in motion

Across all time points, we observed no difference in mean VAS score in motion between both groups. Evolution of mean VAS scores in motion for both

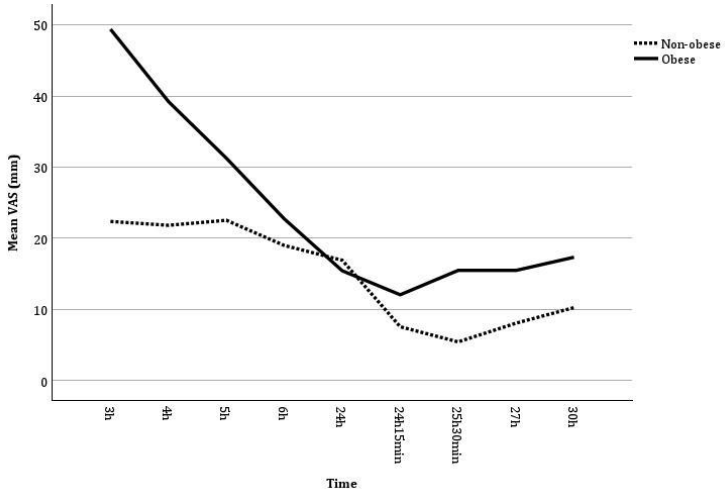

Fig. 1 — Comparison of the visual analogue scale at rest between non-obese and obese patients over time. VAS - Visual analogue scale. VAS is presented as mm. *Statistically significant difference.

Table II. — VAS at rest.

	Non-obese (13)	Obese (28)	Difference (95% CI)	P value*
Overall	15.3	23.9	-8.7 (-17.3 to -0.1)	0.049
3h	26.3	47.3	-21.1 (-33.3 to -8.8)	<0.001
4h	20.8	36.8	-16.0 (-27.4 to -4.5)	0.007
5h	21.3	29.3	-8.0 (-19.3 to 3.4)	0.167
6h	17.9	21.4	-3.5 (-15.1 to 8.0)	0.545
24h	17.3	17.2	0.2 (-11.3 to 11.7)	0.973
24h15min	8.4	13.0	-4.7 (-16.3 to 7.0)	0.429
25h30min	5.8	16.4	-10.5 (-22.5 to 1.4)	0.083
27h	8.6	17.1	-8.6 (-20.5 to 3.4)	0.158
30h	11.1	17.0	-6.0 (-18.1 to 6.1)	0.331
*P-values, non-obese vs obese group. Values are presented as mean.				

non-obese and obese patients over time is depicted in Figure 2. The only significant difference was observed at three hours after the first administration of analgesics. Results are shown in Table III.

At three hours, the mean VAS score over all patients was 45.17 (95% CI 37.05 to 53.29) compared to 36.08 (95% CI 28.74 to 43.43); 32.23 (95% CI 25.05 to 39.41); 28.73 (95% CI 21.52 to 35.95); 30.17 (95% CI 23.11 to 37.23) and 26.71 (95% CI 19.02 to 34.39) at four, five, six, twenty-four and sixty hours respectively.

The mean VAS score in motion was 28.76 and 30.74 in women and men respectively (MD -1.97; 95% CI -12.28 to 8.34; p = 0.700).

Surgical pleth index at rest

Mean SPI considered over all time points was not statistically significantly different between non-obese and obese patients. We only observed a significant difference in SPI at rest at twenty-four hours. Results are shown inTable IV and Figure 3.

The SPI for all patients at three, four, five, six, twenty-four and thirty hours was 38.12 (95% CI 32.19 to 44.04); 33.03 (95% CI 27.79 to 38.26); 30.51 (95% CI 25.33 to 35.70); 31.71 (95% CI 26.58 to 36.83); 49.89 (95% CI 44.80 to 54.99) and 50.63 (95% CI 45.13 to 56.14) respectively.

Women and men showed a mean SPI at rest of 40.06 and 43.43 respectively (MD -3.37; 95% CI -9.45 to 2.71; p = 0.268).

Surgical pleth index in motion

We observed no statistically significant difference in mean SPI in motion between the two groups. Figure 4 illustrates the mean SPI in motion in function of time for both non-obese and obese patients. Results are shown in Table V.The mean SPI in all patients was 49.38 (95% CI 43.45 to 55.31); 51.73 (95% CI 46.51 to 56.95); 55.94 (95% CI 50.89 to 61.00); 52.40 (95% CI 47.29 to 57.51);

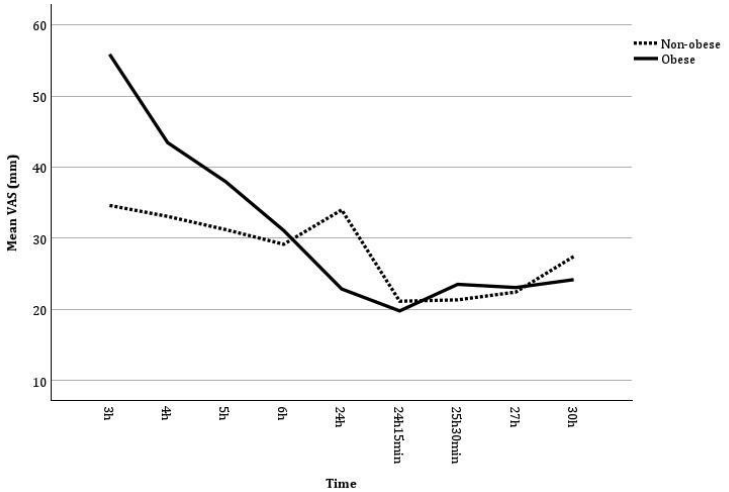

Fig. 2 — Comparison of visual analogue scale in motion between non-obese and obese patients over time. VAS - Visual analogue scale. VAS is presented as mm. *Statistically significant difference.

Table III. — VAS in motion.

	Non-obese (13)	Obese (28)	Difference (95% CI)	P value*
Overall	27.9	31.6	-3.8 (-14.5 to 7.0)	0.486
3h	37.0	53.4	-13.4 (-31.7 to -1.0)	0.037
4h	31.2	40.9	-9.7 (-24.1 to 4.6)	0.183
5h	28.8	35.7	-6.9 (-21.1 to 7.3)	0.338
6h	27.5	29.9	-2.4 (-16.9 to 12.0)	0.741
24h	34.5	25.8	8.7 (-5.7 to 23.1)	0.233
24h15min	21.7	21.9	-0.2 (-14.8 to 14.4)	0.977
25h30min	20.7	25.3	-4.6 (-19.6 to 10.3)	0.541
27h	21.9	25.8	-3.8 (-18.9 to 11.2)	0.613
30h	27.5	25.9	1.6 (13.6 to 16.8)	0.834
*P-values, non-obese vs obese group. Values are presented as mean.				

Table IV. — SPI at rest.

	Non-obese (13)	Obese (28)	Difference (95% CI)	P value*
Overall	39.8	43.6	-3.8 (-10.3 to 2.7)	0.243
3h	41.6	34.6	7.0 (-4.2 to 18.3)	0.220
4h	35.0	31.0	4.0 (-6.2 to 14.3)	0.438
5h	30.4	30.6	-0.3 (-10.6 to 10.1)	0.960
6h	31.0	32.4	-1.5 (-11.8 to 8.8)	0.777
24h	45.5	54.2	-8.7 (-19.1 to 1.7)	0.101
24h15min	38.8	47.0	-8.2 (-18.6 to 2.3)	0.124
25h30min	48.2	50.3	-2.1 (-12.9 to 8.7)	0.704
27h	42.0	57.3	-15.3 (-26.0 to -4.5)	0.006
30h	45.9	55.4	-9.4 (-20.4 to 1.5)	0.090
*P-values, non-obese vs obese group. Values are presented as mean.				

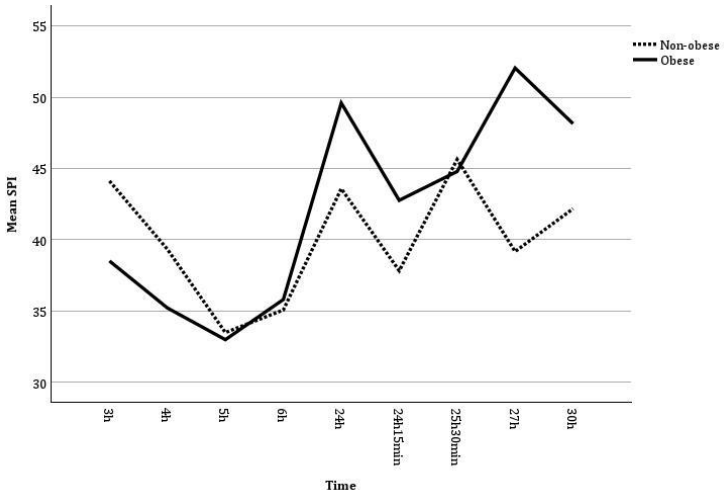

Fig. 3 — Comparison of the surgical pleth index at rest between non-obese and obese patients over time. *Statistically significant difference.

64.70 (95% CI 59.74 to 69.66) and 65.20 (95% CI 59.54 to 70.86) at three, four, five, six, twenty-four and thirty hours respectively.

The mean SPI in motion was 56.75 in female patients and 61.06 in male patients (MD -4.31; 95% CI -10.09 to 1.47; p = 0.139).

Correlation between VAS and SPI

To look for a possible correlation between VAS scores and SPI an ICC was calculated. At three hours we found an ICC of 0.06 (95% CI -0.27 to 0.37) and -0.06 (95% CI -0.37 to 0.27) at rest and

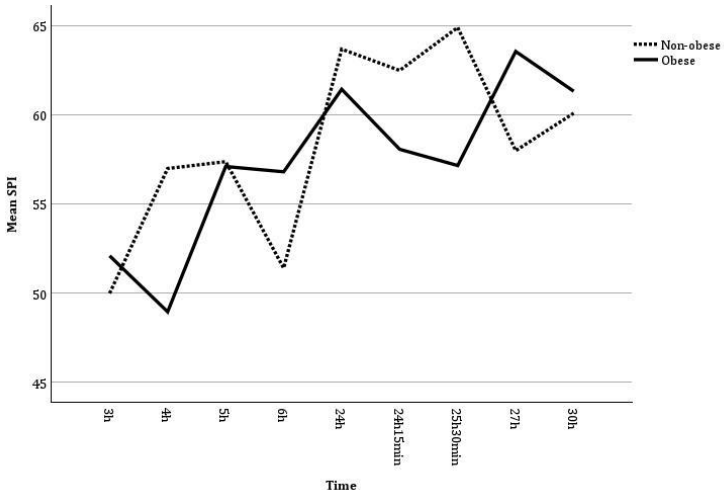

Fig. 4 — Comparison of the surgical pleth index in motion between non-obese and obese patients over time. *Statistically significant difference.

Table V. — SPI in motion.

	Non-obese (13)	Obese (28)	Difference (95% CI)	P value*
Overall	59.1	58.7	0.4 (-5.8 to 6.6)	0.904
3h	49.8	49.0	0.8 (-10.5 to 12.1)	0.894
4h	55.2	48.3	6.9 (-3.3 to 17.1)	0.183
5h	55.7	56.2	-0.4 (-10.5 to 9.6)	0.933
6h	49.5	55.2	-5.7 (-16.0 to 4.6)	0.274
24h	64.8	64.6	0.1 (-10.0 to 10.3)	0.982
24h15min	64.1	60.2	3.9 (-6.5 to 14.3)	0.466
25h30min	67.7	61.2	6.5 (-4.3 to 17.2)	0.239
27h	60.9	67.5	-6.6 (-17.3 to 4.2)	0.229
30h	64.2	66.2	-2.1 (-13.3 to 9.1)	0.715
*P-values, non-obese vs obese group. Values are presented as mean.				

in motion respectively. At six, twenty-four and thirty hours the ICC were 0.10 (95% CI -0.23 to 0.40) and 0.05 (95% CI -0.26 to 0.36), 0.01 (95% CI -0.31 to 0.32) and -0.08 (95% CI -0.38 to 0.24), 0,08 (95% CI -0.28 to 0.42) and 0.05 (95% CI -0.31 to 0.39) at rest and in motion respectively.

Discussion

The aim of this study was to determine the effect of obesity on the efficacy of a standard dosing regimen of ibuprofen 600mg every 8h, a loading dose of 2g of paracetamol in combination with a maintenance dose of 1g four times daily and PCA using piritramide. Our results suggest a significant effect of obesity on postoperative pain measured using VAS at rest and in motion. We observed a statistically significant difference in overall VAS score between both groups, but without clinical significance since these values are within the clinical target of VAS score below 30 and is indicative of a qualitative postoperative analgesia. Obese patients scored 21.1 and 13.4mm higher on VAS at rest and in motion respectively compared to non-obese patients three hours after the first administration of analgesics. This difference in mean VAS seems to gradually disappear in the first hours following surgery, with only the VAS at rest at 4h being statistically significantly different as visualized in Figures 1 and 2. At no point in time was there a difference in SPI both at rest and in motion between the two groups, except for SPI at rest at twenty-seven hours (MD 15.26; 95% CI 4.50 to 26.02; p = 0.006). The need for rescue analgesia with Piritramide was significantly higher in the obese group compared to the non-obese group, 25.2mg vs 12.1mg respectively (MD 13.0mg; 95% CI 7.44 to 18.63; p <0.001). This difference could be explained by the higher loading dose based on LBM included in the total Piritramide consumption. However, obese patients also requested Piritramide 3 times more frequently compared to non-obese patients, 21.6 vs 7.6 times (p = 0.012). The intraoperative remifentanil

dosing was 0.08µg/kg/min higher in non-obese patients (95% CI 0.01 to 0.17; p = 0.030) possibly indicating a higher pain intensity in surgeries of non-obese patients.

A study done in 2019 on the performance of the SPI in 189 conscious postoperative patients showed a significant difference in SPI before and after surgery. Analysis showed a cut-off value of 44 (sensitivity: 84%, specificity: 53%) for prediction of postoperative pain[28]. Another study reported a cut-off value of 29 as the optimal target to predict moderate-to-severe postoperative pain (sensitivity: 68%, specificity: 57%)[29]. This heterogeneity could be linked to the anesthetic technique used[29]. SPI values are significantly affected by age and volume status. Due to lower wall stress and higher extensibility combined with a higher baseline heartrate, younger patients have an underestimation of SPI[30]. The current study showed a significant difference in mean age between the non-obese and obese group (54.2 vs 44.4). This could lead to an underestimation of the SPI in the obese group. In 2018, a study in 89 patients, showed a correlation between the peripheral perfusion index and patient reported VAS score[31]. Several studies showed that SPI could be used to differentiate between no or mild postoperative pain and moderate-to-severe pain[32,33].

In the present study, there was no correlation between VAS and SPI as illustrated by figures 5-8. This suggests SPI is not a suitable measure for postoperative pain.

We aimed for equal gender distribution in both study groups to minimize the effect of sex differences in pharmacokinetics and pharmacodynamics. Our study failed to show a sex-related difference both in patient-reported pain measures using VAS and objective pain measures using SPI.

In the current study there was a mean difference of 9.8 years (95% CI 0.30 to 19.31; p = 0.044) between non-obese and obese patients. The literature shows no consensus on the effect of age on pain perception. A 2015 study on pain levels after acute whiplash injury showed no influence of age on pain levels[34]. Other studies showed a lower pain sensation in primarily elderly patients[35,36] .This makes it difficult to predict the effect of the observed age gap on patient reported pain levels in the current study.

There was also a significant difference in ASA classification distribution between both groups. This is to be expected as obese patients have a higher risk for co-morbidities than non-obese patients. A study from 2017 of ASA classification on pain management in total knee arthroplasty patients receiving adductor canal blockade showed a higher opioid consumption in ASA 3 patients compared to ASA 2 patients despite equal pain scores[37]. This could mean that the difference in ASA classification is a possible confounder in the current study.

A major limitation of the present study is the fact that it was part of a larger research project concerning the pharmacokinetic effects of obesity on paracetamol. As such, power analysis was done for paracetamol and its metabolites rather than the VAS scores and SPI. Furthermore, we performed our statistical analysis on an incomplete dataset due to difficulties with patient inclusion. As such we had only 13 non-obese and 28 obese patients. We conducted a post-hoc power analysis for VAS score on day 0 to calculate sample size, based on data from Majchrzak et al. on pain intensity in obese and non-obese patients after lung surgery. They found on day 0 a VAS score of 34 (10) mm in non-obese patients versus 45 (12) mm in the obese group. Based on these data, statistical difference between groups could be predicted with a β risk of 80% at a α level of 0.05 when including 13 patients per group[38]. We also did not register a baseline VAS at the beginning of surgery. Lastly, we compared laparoscopic gastric bypass surgery in obese patients with laparoscopic intraperitoneal surgery in non-obese patients. We aimed at including surgeries similar in approach and duration in order to minimize the effect on postoperative pain. However, this remains a source of heterogeneity between non-obese and obese patients as well as between non-obese patients. All these factors make it difficult to draw reliable conclusions.

Patients received a standardized postoperative pain protocol consisting of paracetamol, but also received ibuprofen 600mg three times daily and a patient controlled analgesic pump with piritramide for rescue analgesia and dexamethasone 0.2mg. kg-1. The cumulative piritramide dose was taken into account in our statistical model, however, the use of ibuprofen is a possible cofounder. We also did not standardize the use of neuromuscular blocking agents. Some studies suggest deep neuromuscular blockade results in lower VAS scores[39-41].

Conclusion

Obese patients are known to have altered pharmacokinetics and as such, the efficacy of standard dosing of postoperative analgesia can be questioned. Our study indicates a difference in pain sensation measured using VAS scores between non-obese and obese patients only in the

first hours postoperatively. This seems to be in line with the available literature on pharmacokinetics and -dynamics. SPI as a measure of postoperative pain did not show a correlation to patient reported VAS scores. Further research focused on pharmacodynamic differences between non-obese and obese patients with larger study populations is needed in order to support our findings.

Consent: The research was conducted in accordance with the World Medical Association Declaration of Helsinki. All participants have given written informed consent on admission for their data to be recorded in our database.

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