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Research Article

A Randomized Controlled, Double-Blind Trial Evaluating the Effect of Opioid-Free Versus Opioid General Anaesthesia on Postoperative Pain and Discomfort Measured by the QoR-40

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Abstract

This study measured post-operative opioid consumption and quality of recovery after Opioid-Free Anaesthesia (OFA).

50 Patients undergoing elective laparoscopic bariatric surgery were randomised in two groups. Before induction, the Opioid Anaesthesia (OA) group received 0.5 mcg/kg sufentanil, while the OFA group received 0.5 mcg/kg dexmedetomidine, 0.25 mg/kg ketamine, and 1.5 mg/kg lidocaine. Anaesthesia was induced with propofol and rocuronium and the bispectral index was maintained in both groups between 40% and 60% by adapting end-tidal sevoflurane. Anaesthesia was further maintained with sufentanil or lidocaine and dexmedetomidine. Postoperative analgesia was achieved with 4 g/day paracetamol and with patient-controlled 2-mg morphine. Kalkman and APAIS were measured before anaesthesia. QoR-40, VAS, morphine consumption and cortisol levels were measured postoperatively.

The post-operative opioid consumption was lower in the PACU and quality of recovery was higher next day after OFA versus OA. There were no differences between the two groups regarding age, weight, height, body mass index, gender, information desire, and incidence of obstructive sleep apnoea syndrome, combined anxiety score, and Kalkman points. No differences were found in the number of patients having had one or more intra operative hemodynamic problems. Post-operative major adverse events, like hypertension and bleeding, were significant higher in the OA group.

Postoperative saturation in the post-anaesthesia care unit while giving a 6 l/min O2 mask was lower in the OA group with a higher incidence of hypertension, postoperative nausea and vomiting, shivering or feeling cold and a higher VAS score. The following morning patients in the OFA group had higher QoR-40 scores and lower VAS scores cortisol levels.

Keywords: Opioid free general anaesthesia, Laparoscopic bariatric surgery, Randomized controlled clinical trial, Quality of recovery (QoR-40), Enhanced recovery after surgery (ERAS), Post-operative pain and discomfort

Introduction

Before the introduction of synthetic opioids in the 1960s, sympathetic block was achieved in anaesthesia by giving more hypnotic agents than required to achieve hypnosis. Fluothane and thiopental induced strong hemodynamic suppression creating a hypotension [1,2]. Lidocaine and procaine have been added intravenously at high doses (4.5 mg/kg [3] to 9 mg/kg [4]) to suppress laryngeal reactions with fewer hemodynamic problems. Synthetic opioids that can be given at a high dose, without inducing histamine release, suppress the sympathetic system with less hemodynamic instability [5,6]. Opioids are the strongest analgesics available and therefore assumed to be an essential part of balanced anaesthesia [7].

Sympathetic and parasympathetic suppression can be achieved today with loco-regional anaesthesia or by several non-opioid drugs. Opioid free general anaesthesia can be achieved with 50 mg ketamine given after propofol and before incision in spontaneous breathing patients like for plastic surgery [8]. The alpha-2 agonists [9] suppress better the sympathetic system and can replace opioids for sympathetic stabilization in major surgery [10,11]. A high-dose alpha-2 agonist

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like dexmedetomidine, though it has a shorter half-life than clonidine, has a very long sedative effect, making it difficult to end the anaesthesia phase. A multimodal approach, combining dexmedetomidine with intravenous lidocaine and magnesium, allows for reduction of the dexmedetomidine dose to achieve pain-free rapid awakening [12]. Many studies have shown that lidocaine [13] and magnesium [14] reduce the need for opioids when used as an additive. The combined use of these different non-opioid drugs avoids use of all opioids intra operatively and achieves pain-free awakening [15]. However, what are the advantages to choosing total opioid-free anaesthesia (OFA)?

The aim of this study was to compare total OFA with opioid anaesthesia (OA) for bariatric surgery. When given equal hemodynamic stability intra operatively, will patients have equal recovery comfort and require comparable pain treatment?

Materials and Methods

Our institutional ethics committee approved this study in 2013 with BUN B049201316611 and Eudract 2013-002581-39. Upon granting written informed consent, a total of 59 patients > 18 years old who elected laparoscopic bariatric surgery [16], were enrolled in 2013 - 2014.

Exclusion criteria for this study included patients with allergies to propofol, rocuronium, sugammadex, sufentanil, dexmedetomidine, ketamine, lidocaine, or sevoflurane, patients undergoing emergency laparoscopy, patients having atrioventricular block 2 or 3 or severe bradycardia preoperatively, and patients with hyperthyroidism, thyroid hormone therapy, epilepsy, renal or hepatic failure. Based on the difference seen in daily morphine consumption when using OFA versus OA since 2011 in a factor of 1 to 3 up to 1 to 5 when OFA is continued post-operative we choose 1 to 3 with 90% power and 5% significance and calculated a sample size of minimum 42 patients. 50 patients were randomised in two groups, 5 patients were excluded from analysis due to missing data getting 45 patients just above the calculated 42 (Figure 1).

The following patient characteristics were recorded:

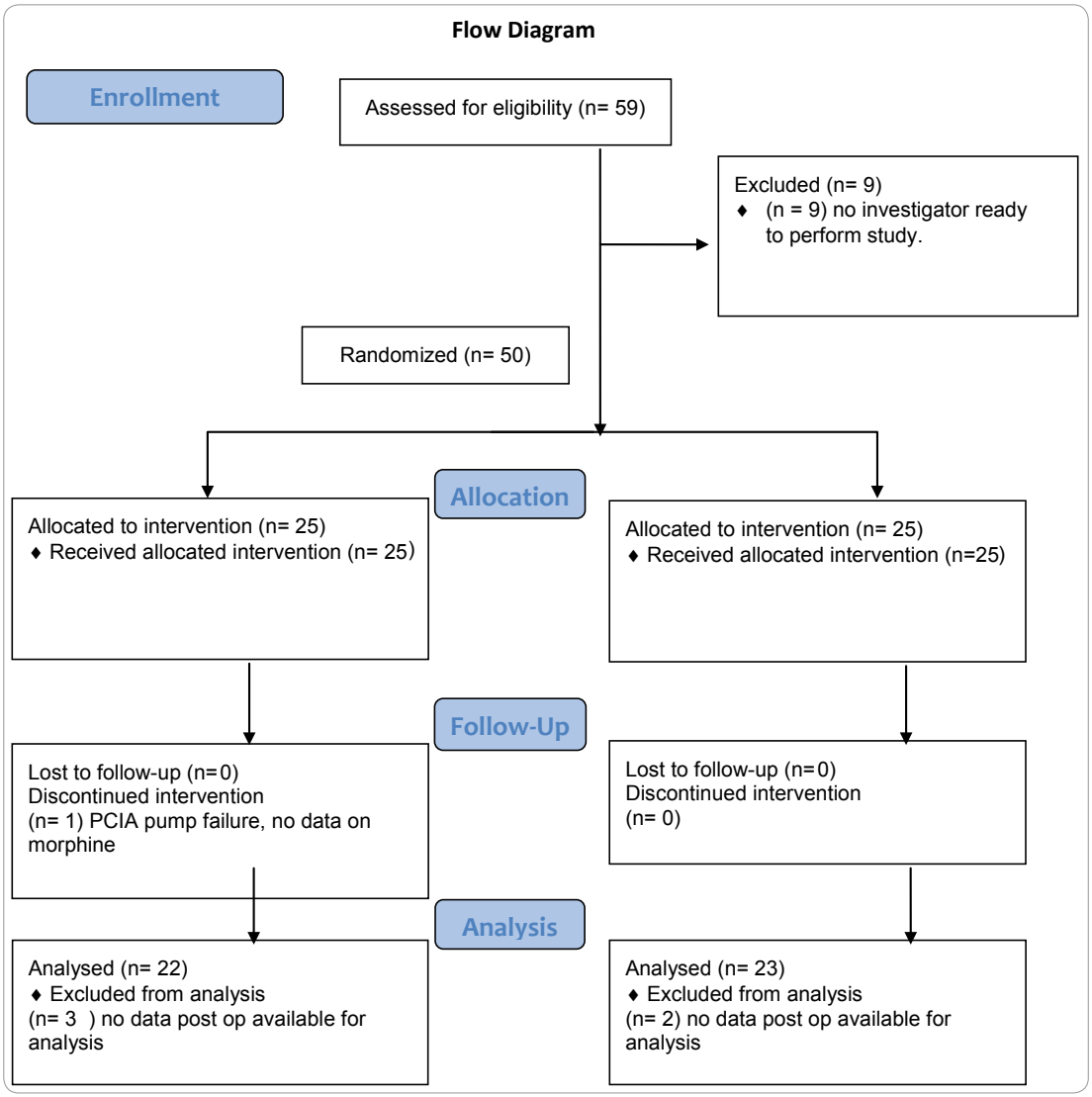

Figure 1: Number of patients enrolled and analysed in this study. 5 patients were excluded from analysis due to insufficient data.

body weight, height, body mass index (BMI), age, and gender. Preoperative desire for information and anxiety scores were measured using the Amsterdam Preoperative Anxiety and Information Scale (APAIS) [17]. Kalkman points that predict the probability of severe pain within the first hour at the Post-Anaesthesia Care Unit (PACU) in surgical patients were calculated preoperatively [18]. Pulse oximetry, electrocardiography, expiratory end-tidal carbon dioxide, bispectral index (Aspect Medical Systems, Inc., Newton, MA), non-invasive blood pressure, and heart rate were monitored in all patients.

Blood samples to measure cortisol levels were obtained from all patients prior to general anaesthesia with intravenous propofol (2.5 mg/kg) and at the ward on the next day. Muscle relaxation was achieved by intravenous rocuronium (1 mg/kg) to facilitate endotracheal intubation and laparoscopy. Home medications taken for hypertension, cardiac and respiratory diseases were continued on the morning of surgery. No sedative premedication was administered.

Patients were randomly assigned to opioid-free anaesthesia (OFA) or opioid anaesthesia (OA) groups using a generated randomisation list. The first 3 patients planned each day for bariatric surgery and eligible for inclusion were chosen for each investigator giving anaesthesia. The OA group received sufentanil (0.5 mg/kg) before induction, while the OFA group received a loading dose of dexmedetomidine (0.5 mg/kg over 10 minutes), ketamine (0.25 mg/kg), and lidocaine (1.5 mg/kg). All drugs are dosed according to ideal body weight (IBW) using the Broca equation [19].

The bispectral index was maintained in both groups between 40% and 60% by adapting the end-tidal sevoflurane concentration. Deep neuromuscular blockade (NMB) to provide laparoscopic workspace was continued by a rocuronium infusion in both groups to maintain the Train-Of-Four (TOF) at zero and Post Tetanic Count (PTC) below five.

Anaesthesia was further maintained in the OA group with sufentanil (0.25 - 1 mg/kg IBW/h). The OFA group received lidocaine (1.5 - 3 mg/kg/h) and dexmedetomidine (0.25 - 1 mg/kg/h) intra operatively and stopped before end of surgery. Both groups received a Plasmalyte infusion at 100 ml/h. Volume-controlled ventilation with a 6 ml/kg tidal volume was used to achieve end-tidal carbon dioxide of 40 - 50 mmHg by adjusting respiratory rates first and tidal volume second.

Postoperative analgesia was achieved in both groups with the same protocol, 2-g paracetamol loading during surgery followed by 1 g every 6 h and with Patient-Controlled Intravenous Analgesia (PCIA) with 2-mg morphine bolus on demand maximum every 5 minutes without continuous infusion. Neuromuscular block reversal was achieved with 2 or 4 mg/kg sugammadex according to the measured depth at the end of surgery to obtain a minimum TOF of 90%. After surgery, all patients were transferred to a PACU where 6 l/min O2 mask therapy was given until they were ready for a general ward. Patients, anaesthesiologists, surgeons and nurses at the ward and PACU were blinded for the type of anaesthesia given.

Logistic regression analysis was used to describe demographic differences between both groups. Chi-square or t tests were used to determine significant outcome differences between both groups for intraoperative and postoperative variables at the PACU and at the ward. Intraoperatively, the number of patients having one or more moments of bradycardia, hypotension, tachycardia, or hypertension (change of more than 20% from pre-induction value) was compared. In the PACU, the number of patients with low saturation (<94%), obstructive breathing, shivering or feeling cold and the average visual analogue pain score (VAS) score and morphine consumption were compared. The maximum and minimum systolic blood pressure and heart rate during PACU stay were also compared.

Total quality of recovery (QoR-40) [20] and its subgroups, VAS score and morphine consumption for the first 24 hours after leaving the PACU were measured. The changes in cortisol levels [21] between preoperative and postoperative levels within 24 hours of leaving the PACU were measured. Pain was measured by classical VAS scores and by pain scores included in the QoR-40.

Linear regression analysis was used to determine if the total QoR-40 score, the mean VAS score, and morphine consumption at the PACU and the following day in the ward were significantly different between groups. Age, BMI, gender, Obstructive sleep apnoea syndrome (OSAS), desire for information, anxiety, and Kalkman points were used as control variables.

Results

There were no differences in the multivariate logistic regression analysis between the two groups regarding age, weight, height, BMI, gender, the incidence of preoperative OSAS, hypertension, and combined anxiety scores (Table 1). Patients in the OFA group had more sleeve and conversion procedures. No differences between the two groups were found intra operatively, using the multivariate logistic regression analysis, in the number of patients having one or more hemodynamic problems, such as bradycardia, hypotension, tachycardia, or hypertension defined as a change of 20% from the pre-induction values with or without required treatment (Table 2).

Multivariate logistic regression analyses identified significant differences between the two groups postoperatively at the PACU

Table 1: Demographic comparison.

Demographic comparison	OA (22)	OFA (23)	p-value *
Mean (SD)			
age (years)	44.32 (11.06)	41.87 (11.21)	0.552
weigth (Kg)	113.2 (13.6)	108.9 (19.9)	0.491
height (m)	1.68 (0.08)	1.69 (0.09)	0.684
body mass index (Kg/m2)	38.33 (9.09)	38.01 (5.06)	0.350
gender (M/W)	10/12	7/16	0.894
pre op OSAS yes/no	6/16	4/19	0.349
pre op hypertension yes/no	7/15	8/15	0.307
known PONV yes/no	1/21	2/22	0.832
prev surgery yes/no	20/2	20/3	0.396
prev abdominal surgery yes/no	10/12	10/13	0.123
lap RNY/lap Sleeve/Lap bar conversion	20/1/0	16/3/4	
information desire	4.59 (0.91)	5.87 (0.98)	0.025 *
anxiety score	7.64 (1.20)	8.69 (11.96)	0.074
Kalkman points	24.75 (1.56)	27.69 (3.13)	0.052

Multivariate logistic regression analysis *

OA, opioid anaesthesia; OFA, opioid-free anaesthesia; OSAS, obstructive sleep apnoea syndrome; PONV, postoperative nausea & vomiting; RNY, Roux &Y gastric bypass.

Table 2: Number of patients with intra operative hemodynamic instability.

	OA (22)	OFA (23)	p-value *	Test
Bradycardia (yes/no)	4/18	4/19	0.88	Chi-square
Hypotension (yes/no)	8/14	12/11	0.34	Chi-square
Tachycardia (yes/no)	13/9	11/12	0.34	Chi-square
Hypertension (yes/no)	10/12	7/16	0.24	Chi-square

OA, opioid anaesthesia; OFA, opioid-free anaesthesia. No differences were found intra operatively in the number of patients having one or more hemodynamic problems.

Table 3: Postoperatively in the post-anaesthesia care unit (PACU).

yes/no mean (SD)	OA(22)	OFA(23)	p-value *	test
lowest saturation < 94% with 6 l/min oxygen mask yes/no	11/11	2/21	0.002 *	chi-square
obstructive breathing yes/no	3/18	0/23	0.067	chi-square
PONV yes/no	14/7	3/20	<0.001 *	chi-square
shivering or having cold yes/no	5/16	0/23	0.013 *	chi-square
mean VAS score	4.9 (0.8)	1.7 (0.9)	<0.001 *	t-test
Morphine used (mg)	15.3 (7.1)	4.9 (2.1)	0.004 *	t-test
highest SAP (mmHg)	166.4 (12.4)	123.6 (5.5)	<0.001 *	t-test
highest heart rate (beats/min)	92.0 (6.8)	79.5 (5.4)	0.004 *	t-test
lowest SAP (mmHg)	135.2 (7.6)	111.8 (4.8)	<0.001 *	t-test
lowest heart rate (beats/min)	73.5 (7.1)	68.9 (5.4)	0.284	t-test
major adverse events yes/no	6/14	0/23	0.007 *	chi-square

chi-square or t test for each parameter *

OA, opioid anaesthesia; OFA, opioid-free anaesthesia; PONV, postoperative nausea and vomiting; VAS, visual analogue scale; SAP, systolic arterial pressure. Multivariate logistic regression analyses identified significant differences between the two groups postoperatively at the PACU for the lowest saturation below 94%, PONV, shivering or feeling cold, VAS scores, highest and lowest SAP, highest heart rate, total morphine consumption and number of major adverse events.

for the lowest saturation below 94% (p = 0.002), Post-operative nausea and vomiting (PONV) ($p < 0.001$), shivering or feeling cold ($p = 0.013$), VAS scores ($p < 0.001$), highest ($p < 0.001$) and lowest ($p < 0.001$) Systolic Blood Pressure (SAP), highest heart rate (p = 0.004), total morphine consumption ($p = 0.004$) and number of major adverse events ($p = 0.007$) (Table 3). The incidence of bradycardia and obstructive breathing was not significantly different.

Significant differences between the OA and OFA groups were found the morning after surgery in the ward for QoR-40 scores ($p < 0.001$) and some of its subgroups. Changes in cortisol levels ($p = 0.029$), and VAS scores ($p = 0.016$) (Table 4) were although significant lower probably clinical not important. Total morphine consumption after the PACU, via a PCIA pump, was not significantly different. A linear regression model showed that the OFA group had significant ($p < 0.001$). Increases in total QoR-40 score, with no impact of BMI, gender, OSAS, desire for information, anxiety, or kalkman points. (Table 5)..

Linear regression analysis found that OFA induced a lower VAS score at the PACU and 24 hours postoperatively at the ward, with no impact of age, BMI, gender, OSAS, information desire, anxiety, or Kalkman points (Table 6). Linear regression analysis also showed that OFA reduced morphine consumption at the PACU, but not at the ward the following day (Table 7).

6 patients in the OA group developed a serious adverse event in the PACU. Severe hypertension required an anti-hypertensive treatment and two of them developed post-operative haemorrhagic problems. The first got an intra-abdominal bleeding

Table 4: Postoperatively in the ward.

mean (SD)	OA (22)	OFA (23)	p-value *	test
emotional state	7.2 (0.8)	8.1 (0.5)	0.051	chi-square
physical comfort	7.9 (1.0)	10.4 (0.5)	<0.001*	chi-square
psyche support	6.6 (0.3)	6.7 (0.4)	0.62	chi-square
physical independence	3.8 (0.6)	4.7 (0.4)	0.007*	chi-square
pain score	4.5 (0.6)	6.1 (0.4)	<0.001*	chi-square
sleep score	0.5 (0.3)	0.8 (0.2)	0.040*	chi-square
total Qo40 score %	74 (6)	89 (3)	<0.001*	chi-square
cortisol change	10.5 (5.0)	3.6 (4.4)	0.029*	t-test
VAS score	3.3 (0.7)	2.0 (0.7)	0.016*	t-test
Morfine need (mg)	18.2 (5.6)	14.7 (4.7)	0.330	t-test
LOS (days)	3.68 (0.40)	3.30 (0.36)	0.147	t test

chi-square or t-test for each parameter *

QoR-40, quality of recovery-40; OA, opioid anaesthesia; OFA, opioid-free anaesthesia; VAS, visual analogue scale, LOS; length of stay. Significant differences between the OA and OFA groups were found the morning after surgery in the ward for QoR-40 scores, cortisol levels and VAS scores.

Table 5: Factors influencing QoR-40 scores.

Age (years)	coefficient	std. error	t-statistic	p-value *
	-0.003	**0.002**	**-2.051**	**0.050***
Body mass index (Kg/m2)	-0.001	0.002	-0.575	0.570
Gender (male=1)	-0.049	0.04	-1.214	0.235
OSAS (yes=1)	-0.085	0.049	-1.714	0.098
information desire component	-0.003	0.01	-0.304	0.764
combined anxiety component	-0.008	0.006	-1.301	0.204
Kalkman points	-0.002	0.004	-0.373	0.712
OFA/OA (OFA=1)	0.166	0.034	4.855	<0.001*

linear regresion analysis *

QoR-40, quality of recovery-40; OA, opioid anaesthesia; OFA, opioid-free anaesthesia; OSAS, obstructive sleep apnoea syndrome; only OFA improves quality of recovery.

Table 6: Linear regression analysis evaluating the factors having impact on the VAS scores at PACU and next day.

	At PACU		Following day in ward	
	Coefficient	p-value *	Coefficient	p-value *
Age (years)	-0.029	0.402	0.01	0.727
Body mass index (Kg/m^2)	0.001	0.977	-0.039	0.305
Gender (male=1)	0.175	0.833	0.715	0.283
OSAS (yes=1)	0.418	0.637	-0.301	0.670
Information desire Component	-0.1	0.613	-0.056	0.725
Combined anxiety component	0.114	0.357	0.147	0.143
Kalkman points	-0.077	0.425	-0.088	0.265
OFA or OA (OFA=1)	-3.045	0.000*	-1.195	0.043*

Linear regression analysis *

OA, opioid anaesthesia; OFA, opioid-free anaesthesia; OSAS, obstructive sleep apnoea syndrome. No factors except OFA has impact on VAS score next day.

requiring admission on intensive care for one day. Patient could leave hospital after 5 days without further complications. This patient was known with hypertension. To prevent postoperative bleeding, we try always to increase the systolic blood pressure above 140 mmHg to find the bleeding spots and put some extra clips [22]. In this patient, the intra operative systolic blood pressure rose only to 125 mmHg during bleeding control at end of laparoscopy and the patient developed a maximum blood pressure in the recovery of 156/97 mmHg while losing 75 ml from his drain. Anti-hypertensive drugs were given but during the night the patient developed tachycardia with more blood loss requiring blood transfusion and a laparoscopic intervention to

Table 7: Linear regression analysis evaluating the factors having impact on the morphine consumption at PACU and next day.

	At PACU		Following day in ward	
	Coefficient	p-value *	Coefficient	p-value *
Age (years)	-0.177	0.337	0.064	0.736
Body mass index (Kg/m^2)	0.279	0.268	-0.365	0.177
Gender (male=1)	2.132	0.626	-6.263	0.176
OSAS (yes=1)	1.369	0.769	2.081	0.707
Information desire component	-0.383	0.717	-1.01	0.355
Combined anxiety component	0.806	0.225	0.187	0.790
Kalkman points	-0.551	0.291	-0.159	0.766
OFA or OA (OFA=1)	-9.848	0.014*	-0.124	0.975

Linear regression analysis *

OA, opioid anaesthesia; OFA, opioid-free anaesthesia; OSAS, obstructive sleep apnoea syndrome. No factors except OFA reduced morphine consumption on the PACU.

stop a bleeding on the omentus. This complication might have been prevented if blood pressure rise intra operative and blood pressure control post-operative was done better. The second patient developed an abdominal wall hematoma requiring blood transfusion without surgical intervention. He was not known with hypertension and blood pressure rose to 140 mmHg systolic intra operative during bleeding control. Postoperative pain control with PCIA morphine was insufficient with VAS between 4 and 10 requiring a total amount of 40 mg morphine during the first 24 hours and having postoperative blood pressure between 120/65 and 165/100 mmHg. It is not clear if this pain and hypertension affected the hematoma formation or was a result of the hematoma development. The other 4 patients in the OA group required also anti-hypertensive medications and could leave the PACU without further problems.

Discussion

In this study, a combination of drugs was given to allow for total opioid-free anaesthesia with the same hemodynamic stability and rapid recovery as opioid anaesthesia. The drugs lidocaine [9] and dexmedetomidine [8] used to replace opioids during anaesthesia were previously shown to reduce intraoperative opioids and to reduce the adverse effects associated with opioid use.

No premedication and full muscle reversal was achieved in every patient. Nevertheless, low saturation with an O_2 mask and obstructive breathing was lower in the OFA group. PONV and shivering or feeling cold was also significantly lower in the OFA group, likely due to the reduced level of opioids required postoperatively or by the alpha 2 agonists preventing direct shivering. No bradycardia or hypotension post-operative was found in the OFA group, hypertension however was a problem in the OA group. That is the reason why alpha 2 agonists like clonidine are already frequently added intra and post-operative in opioid anaesthesia but was not allowed in this study.

In 2011 no studies existed showing a reduced post-operative opioid consumption with less pain, but today some studies have been published showing comparable results [10,13,23]. Samuels [10] found in a retrospective analysis that opioid free anaesthesia needed 50 % less opioids post-operative while opioid sparing anaesthesia did not make any difference. His observation suggests that exposure to even marginal amounts of opioids intra operatively increases the need for opioids in the post-operative course. We found after starting a morphine PCIA pump that the difference in opioid consumption was not significant anymore on the second day. This shows the importance of avoiding all opioids intra operative instead of only reducing the amounts by adding additives.

Samuels [10] found also that, patients on opioid-sparing and opioid-free anaesthesia, were more promptly waking up from their surgery with pain well-controlled, and had “clearer heads.” This is comparable to our lower VAS scores on the first day and better QoR-40 scores on the second day showing an enhanced recovery.

Bakan [13] found comparable only an initial reduction in postoperative fentanyl consumption from 120 mcg to 75 mcg, respectively, while it became comparable at postoperative 6th hour. He found on the contrary a higher recovery time in OFA but also lower pain scores, rescue analgesic and ondansetron need.

Ziemann-Gimmel [21] found no difference in opioid consumption post-operative for the same VAS scores but did not explain what post-operative period was compared. This study found a significant reduction in PONV in the OFA group even when triple PONV prophylaxis was given to both groups.

The OFA patients in our study had fewer PONV, shivering, and OSAS problems in the PACU and had an improved recovery score. The aim of this study was to look to opioid consumption and QoR-40 and therefore yes or no was recorded and no extra classification for PONV, shivering and obstructive breathing was made during the observations. No clinical difference in cortisol levels shows a comparable stress-free anaesthesia. The risk of masking nociceptive reactions like tachycardia by using alpha2agonist is not a problem, it are the sympathetic reactions that have to be block during general anaesthesia.

The Kalkman pain-prediction score did not predict postoperative pain, probably by the strong opioid reduction in the OFA group only. When giving opioids as analgesics in a PCIA mode, the opioid sparing effect of OFA decreases the following day. The positive effects of OFA on recovery parameters and pain scores like VAS score and QoR-40 remain. No information exists on the relation between VAS scores and the pain scores included in the QoR-40, but it was not the aim to compare it in this study. QoR-40 was measured only the next day and on that moment both pain scores showed a significant difference that is however not clinical important for the VAS score. (< 2 points difference)

We had 6 major adverse events in the opioid group with 2 haemorrhagic complications. This is exceptional high as our haemorrhagic complications in lap RNY dropped from 3.5 % to 1 % in 2013. [13] A surgical bleeding could be related to insufficient pain treatment and insufficient blood pressure control post-operative next to surgical aspects. Paracetamol 2 gram, diclofenac 75 mg and PCIA with 2 mg morphine maximum every 5 minutes was insufficient to block all hypertensive reactions post-operative. 50 % of the patients in both groups had known hypertension treated at home and opioid free anaesthesia uses more vasodilating drugs facilitating hemodynamic stability postoperative.

This study has some limitations. The study group was too small to evaluate less frequent adverse events. A large, retrospective follow-up study is needed, with focus on complications and adverse events, before stating that the OFA method is safer with fewer complications than the current opioid anaesthesia in bariatric surgery.

Conclusion

The findings of this study suggest that OFA in bariatric surgery gives an equal hemodynamic stability intra-operatively, while patients getting OFA require fewer analgesics, have an improved quality of recovery after surgery and less serious adverse events in the PACU. OFA reduces the need for postoperative opioids in the PACU, reduces postoperative hypertension and desaturation and improves VAS scores and the quality of recovery as measured by QoR-40 scores on the following day.

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