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Opioid-sparing strategies in anesthesia for obese patients undergoing laparoscopic sleeve gastrectomy

Dissertation on Doctorate in Medical and Health Sciences in the discipline of Medical Sciences

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I would like to dedicate this work to my wife and children for their patience and continuous support

I am grateful to my mother for her unwavering confidence in me

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LIST OF PUBLICATIONS

The thesis is based on the following papers:

Mieszczański P, Górniewski G, Ziemiański P, Cylke R, Lisik W, Trzebicki J. Comparison between multimodal and intraoperative opioid free anesthesia for laparoscopic sleeve gastrectomy: a prospective, randomized study. Sci Rep. 2023 Aug 4;13(1):12677. **doi:** https://doi.org/10.1038/s41598-023-39856-2.

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Mieszczański P, Janiak M, Ziemiański P, Cylke R, Lisik W, Trzebicki J. Successful Anesthetic Management for Obese Patients with Interstitial Lung Disease Undergoing Laparoscopic Sleeve Gastrectomy: A Bridge to Improved Lung Transplant Eligibility. Am J Case Rep. 2024 Mar 19;25:e942736. **doi:** https://doi.org/10.12659/AJCR.942736.

Impact Factor (2023) = 1.0, MEiN = 70 points

Mieszczański P, Kołacz M, Trzebicki J. Opioid-Free Anesthesia in Bariatric Surgery: Is It the One and Only? A Comprehensive Review of the Current Literature. Healthcare (Basel). 2024 May 27;12(11):1094. **doi:** https://doi.org/10.3390/healthcare12111094.

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Mieszczanski P, Gorniewski G, Janiak M, Trzebicki J. The effect of pre-emptive oral pregabalin on opioid consumption in patients undergoing laparoscopic sleeve gastrectomy with an analysis of intraoperative hemodynamic stability and quality of recovery: study protocol for a randomized, prospective, double-blind study. Trials. 2024 Jun 7;25(1):367. **doi:** https://doi.org/10.1186/s13063-024-08225-3.

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I. LIST OF ABBREVIATIONS

ERABS – Enhanced Recovery After Bariatric Surgery

ERAS – Enhanced Recovery After Surgery

ESP Block – Erector Spinae Plane Block

ESRA – European Society of Regional Anaesthesia and Pain Therapy

LSG – Laparoscopic Sleeve Gastrectomy

FRC – Functional Residual Capacity

ILD – Interstitial Lung Disease

MMA - Multimodal Analgesia

NMDA - N-methyl-D-aspartate Receptor

NRS – Numeric Rating Scale

OFA – Opioid-Free Anesthesia

PONV – Postoperative Nausea and Vomiting

PROSPECT – Procedure-Specific Postoperative Pain Management

QoR-40 - Quality of Recovery-40 Questionnaire

RCT – Randomized Controlled Trial

TAP Block – Transversus Abdominis Plane Block

II. ABSTRACT

Opioids are the most powerful analgesics used in the intra- and postoperative period to ensure pain relief and blunt hemodynamic responses in patients undergoing surgery. Due to their effectiveness and potency, their use seems indispensable in patients undergoing surgical treatment.

However, the disadvantages of opioid administration include serious side effects, such as the risk of causing respiratory failure, excessive sedation, inducing nausea and vomiting, as well as the need to increase doses to achieve a satisfactory analgesic effect. For these reasons, their use may result in a negative impact on the safety and comfort of operated patients and thus delay postoperative recovery, which is in opposition to the Enhanced Recovery After Surgery (ERAS) doctrine.

A population in which early mobilization and avoidance of opioid side effects are important is patients with obesity undergoing bariatric surgery such as the most frequently performed procedure in the world: laparoscopic sleeve gastrectomy (LSG). Taking into account the need to create pneumoperitoneum to perform surgery, positioning the patient in the anti-Trendelenburg position, as well as the specificity of patients with often long-term obesity and its complications, ensuring safety and comfort of anesthetized patients and caring for them in the postoperative period constitutes an additional challenge for the anesthesiologist.

A way to minimize risk and ensure comfort for patients in this group is to use opioid-sparing techniques. They are often part of multimodal analgesia, which involves the use of agents with different mechanisms of action combined with various forms of regional analgesia to keep the required dose of opioids intra- and postoperatively lowest possible.

A specific form of intraoperative multimodal analgesia is opioid-free anesthesia (OFA). It assumes that by combining drugs with different mechanisms of action with or without regional blockade, it is possible to completely eliminate opioid use during surgery and minimize their consumption in the postoperative period. However, OFA is controversial due to insufficient scientific evidence to support its routine use, and there is limited data regarding its potential impact on cardiovascular stability and safety.

Considering great clinical importance of optimal anesthesia techniques in bariatric surgery, this thesis and the presented publications aimed to explore new opioid-sparing techniques and study opioid-free anesthesia as its special form.

In the first manuscript, we report a prospective, randomized study conducted on 59 patients undergoing LSG assigned to two groups. In the first group, OFA was used according to a systematized protocol; in the latter, general anesthesia with multimodal analgesia (MMA) was utilized with the intraoperative use of the short-acting opioid remifentanil. Postoperative care was conducted in a similar manner. The aim of the study was to assess whether the use of OFA and the elimination of intraoperative opioids in favor of coanalgesics such as dexmedetomidine, lidocaine, ketamine, and magnesium sulfate allows for a reduction in the total requirement for opioids during the first postoperative 24 hours. Pain scores on the Numeric Rating Scale (NRS), the occurrence of nausea and vomiting on the Simplified Postoperative Nausea and Vomiting (PONV) Impact scale, the frequency of desaturation and pruritus, and the intraoperative use of vasopressors and fluid therapy as indicators of hemodynamic stability were also examined.

The study did not reveal a reduction in total opioid requirement in the postoperative period. Still, it demonstrated some benefits in the immediate hour after surgery in the form of less frequent occurrence of nausea and vomiting and a statistically significant lower opioid dose. On the other hand, patients in the OFA group required higher intraoperative doses of vasopressors and larger fluid volumes to stabilize hemodynamic parameters. Both techniques allowed for early patient discharge from the hospital that was within 24 hours after surgery.

The second manuscript presents a case report of a 42-year-old patient with interstitial lung disease, on home oxygen therapy that was considered a candidate for lung transplantation on the condition of reducing body weight to improve transplant eligibility. In this patient, OFA was successfully used with a prolonged infusion of coanalgesics in the postoperative period after LSG. Taking into account additional risk factors related to the patient's condition, including severe respiratory failure, lung diffusion disorders, and probability of pulmonary hypertension, this was an extreme-risk patient in the intra- and postoperative period. Implementing OFA and appropriate postoperative care allowed for ensuring the patient’s safety and comfort and the final discharge from the hospital. One year after surgery, the patient significantly reduced his body weight, which led to a spectacular clinical improvement, enabling him to return to professional activity and, at least temporarily, suspend his qualification for lung transplantation.

The third publication in series is a review presenting the contemporary state of knowledge on OFA in bariatric surgery. Summarizing the current literature, the work systematically considers the potential advantages and disadvantages of using such a heterogeneous group of techniques,

its impact on distinct organ systems, clinical aspects of anesthesia and postoperative care. In addition to presenting the most up-to-date literature at the time, the paper also proposes potential indications for administrating OFA and directions for future research.

The last manuscript is a published protocol of an ongoing study that aims to evaluate the administration of pregabalin 150 mg prior to laparoscopic sleeve gastrectomy as a form of preemptive analgesia on total opioid requirements in the postoperative period. The study will also analyze parameters such as pain assessment on NRS, incidence of PONV, visual disturbances, frequency of desaturations, quality of convalescence assessed by completing the Quality of Recovery-40 Questionnaire (QoR - 40) form and hemodynamic stability during surgery. Hemodynamic parameters will be recorded and duration of any hypotension noted. The study is planned as a randomized, double-blind trial enrolling 90 patients. The publication of the study protocol and implementation of reviewer's suggestions allowed for early peer feedback and thus may aid in improving the quality of the main study, increasing transparency and reproducibility, as well as reducing risk of publication bias. The current study may help fill an important gap in knowledge by answering a potential question about the place of pregabalin as one of the coanalgesics in laparoscopic bariatric surgery under the ERAS protocol, which has not been convincingly examined so far.

III. STRESZCZENIE

Techniki ograniczające zużycie opioidów podczas znieczulenia pacjentów z otyłością poddawanych rękawowej resekcji żołądka metodą laparoskopową.

Opioidy są najsilniejszymi środkami analgetycznymi stosowanymi w okresie śród- i pooperacyjnym w celu uśmierzenia bólu i tłumienia reakcji układu współczulnego u chorych poddawanych operacjom chirurgicznym. W związku ze swoją skutecznością i siłą działania ich stosowanie, u pacjentów poddawanych leczeniu operacyjnemu, wydaje się konieczne.

Jednak działania niepożądane opioidów, do których należy m.in. zwiększone ryzyko wystąpienia niewydolności oddechowej, nadmierna sedacja, indukowanie nudności i wymiotów są czynnikami, które mają negatywny wpływ na bezpieczeństwo i komfort operowanych pacjentów. Ryzyko ich wystąpienia jest proporcjonalne do zastosowanej dawki leku. Powyższe niekorzystne działania opioidów mogą wydłużać czas rekonwalescencji pacjentów, co negatywnie wpływa na proces leczenia i jest niezgodne z obecnymi zaleceniami współczesnej kompleksowej formuły opieki okołooperacyjnej dla poprawy wyników leczenia (Enchanced Recovery After Surgery, ERAS).

Populacją, w której szybkie uruchomienie i unikanie działań niepożądanych opioidów jest szczególnie ważne, są osoby otyłe poddawane operacjom bariatrycznym, wśród których najczęściej obecnie wykonywaną na świecie jest rękawowa resekcja żołądka metodą laparoskopową (Laparoscopic Sleeve Gastrectomy, LSG). Biorąc pod uwagę konieczność wytworzenia odmy otrzewnowej w celu przeprowadzenia operacji, ułożenie pacjenta w pozycji anty-Trendelenburga, a także specyfikę pacjentów z często wieloletnią otyłością i jej powikłaniami, zapewnienie bezpieczeństwa i komfortu znieczulanych pacjentów oraz opieka nad nimi w okresie pooperacyjnym stanowią wyzwanie dla anestezjologa.

Jednym ze sposobów, aby zminimalizować ryzyko powikłań i zapewnić komfort chorym w tej grupie, jest zastosowanie technik ograniczających zużycie opioidów, czyli analgezji multimodalnej, która polega na zastosowaniu leków o różnym mechanizmie działania oraz różnych metod analgezji regionalnej. Synergizm działania poszczególnych leków umożliwia redukcję wymaganej dawki opioidów, co ogranicza ryzyko wystąpienia działań niepożądanych.

Szczególną postacią znieczulenia ogólnego jest anestezja bezopioidowa (Opioid-free anesthesia, OFA). W tej metodzie zakłada się, że dzięki odpowiedniemu dawkowaniu

i połączeniu leków o różnym punkcie uchwytu oraz analgezji regionalnej możliwa jest całkowita eliminacja opioidów podczas operacji i minimalizacja ich zużycia w okresie pooperacyjnym. Ta technika znieczulenia jest jednak kontrowersyjna, ze względu na niewystarczającą liczbę dowodów naukowych uzasadniającą jej stosowanie, a także z powodu braku danych odnośnie jej potencjalnego niekorzystnego wpływu na stabilność układu krążenia i innych kwestii związanych z bezpieczeństwem.

Biorąc pod uwagę duże znaczenie kliniczne stosowania optymalnych technik znieczulenia w chirurgii bariatrycznej, celem niniejszej rozprawy doktorskiej i przedstawionego cyklu publikacji było poszukiwanie nowych technik ograniczających zużycie opioidów, a także badanie znieczulenia bezopioidowego jako ich szczególnej postaci.

Pierwsza praca jest badaniem prospektywnym, randomizowanym, które przeprowadzono w grupie 59 pacjentów poddawanych LSG. Zostali oni przydzieleni do dwóch grup. W jednej zastosowano znieczulenie OFA zgodnie z ustalonym protokołem, w drugiej znieczulenie ogólne z analgezją multimodalną ze śródoperacyjnym użyciem krótko działającego opioidu remifentanylu. W obu grupach opiekę pooperacyjną prowadzono w taki sam sposób. Celem badania była ocena, czy użycie OFA i odstąpienie od podawania opioidów śródoperacyjnie na rzecz takich koanalgetyków jak deksmedetomidyna, lidokaina, ketamina czy siarczan magnezu, przekłada się na zmniejszenie całkowitego zapotrzebowania na opioidy w ciągu pierwszych 24 godzin po operacji. Oceniano natężenie bólu w skali NRS (Numeric Rating Scale), występowanie nudności i wymiotów w skali Simplified PONV (Postoperative Nausea and Vomiting) Impact, częstość występowania epizodów desaturacji, świądu i śródoperacyjne zapotrzebowanie na wazopresory i płynoterapię jako wykładniki stabilności hemodynamicznej.

W badaniu nie stwierdzono zmniejszenia całkowitego zapotrzebowania na opioidy w okresie pooperacyjnym, wykazano jednak pewne korzyści w pierwszej godzinie po operacji pod postacią rzadszego występowania nudności i wymiotów oraz statystycznie istotnej mniejszej wymaganej dawki opioidu. Z drugiej jednak strony pacjenci w grupie OFA wymagali śródoperacyjnie większych dawek wazopresorów i większej objętości płynów w celu stabilizacji parametrów hemodynamicznych. Nie stwierdzono różnic w badanych grupach w zakresie możliwości wczesnego wypisu pacjentów ze szpitala w drugiej dobie po operacji.

Druga praca przedstawia opis przypadku 42 letniego pacjenta ze śródmiąższową chorobą płuc, wymagającego przewlekłej tlenoterapii i wstępnie kwalifikowanego do przeszczepienia płuc pod warunkiem redukcji masy ciała, u którego z powodzeniem zastosowano OFA do LSG z

kontynuacją podaży koanalgetyków w okresie pooperacyjnym. Biorąc pod uwagę dodatkowe czynniki ryzyka związane ze stanem pacjenta, w tym wyjściową niewydolność oddechową, zaburzenia dyfuzji gazów w płucach, a także cechy nadciśnienia płucnego, był to pacjent ekstremalnie wysokiego ryzyka wystąpienia powikłań w okresie śród- i pooperacyjnym. Zastosowanie OFA i odpowiednia opieka pooperacyjna pozwoliły na optymalizację stanu ogólnego pacjenta i wypis ze szpitala. Rok po operacji pacjent zredukował istotnie masę ciała, czego wynikiem była znacząca poprawa kliniczna umożliwiająca powrót do aktywności zawodowej i przynajmniej czasowe zawieszenie kwalifikacji do transplantacji płuc.

Trzecia praca z cyklu jest pracą poglądową przedstawiającą współczesny stan wiedzy na temat wykorzystania OFA w bariatrii. W tym opracowaniu, na podstawie aktualnego piśmiennictwa w usystematyzowany sposób, rozważane są potencjalne zalety i wady stosowania tej niejednorodnej grupy technik znieczulenia, z uwzględnieniem wpływu na poszczególne układy narządów czy aspekty kliniczne znieczulenia i opieki pooperacyjnej. Oprócz omówienia aktualnego piśmiennictwa, w pracy zaproponowano też potencjalne wskazania do zastosowania OFA oraz kierunki dalszych badań.

Ostatnia praca jest opublikowanym protokołem badania, które jest w trakcie realizacji, a które ma na celu ocenę zastosowania pregabaliny w dawce 150 mg przed LSG jako formy analgezji z wyprzedzeniem i jej wpływu na całkowite zapotrzebowanie na opioidy w okresie pooperacyjnym. W badaniu analizowane będą też inne parametry takie jak ocena bólu w skali NRS, częstość występowania nudności i wymiotów, zaburzeń widzenia, epizodów desaturacji, a także jakość rekonwalescencji oceniana na podstawie danych z formularza QoR-40. Oceniona zostanie stabilność hemodynamiczna w trakcie operacji poprzez analizę parametrów hemodynamicznych i sumarycznego czasu występowania hipotensji. Badanie zaplanowano jako randomizowane, z podwójnie ślepą próbą, obejmujące 90 pacjentów. Opublikowanie protokołu badania i implementacja uwag po uzyskaniu opinii przedstawicieli społeczności naukowej odnośnie metodologii, może pozwolić na poprawę jakości, transparentności i odtwarzalności badania oraz na zmniejszenie ryzyka wystąpienia tendencyjności publikacyjnej.

Prowadzone badanie wypełnia istotną lukę w wiedzy i pozwoli odpowiedzieć na pytanie o miejsce pregabaliny jako jednego z koanalgetyków w laparoskopowej bariatrii w ramach protokołu ERAS, co nie zostało jak dotychczas w sposób przekonywający zbadane.

Podsumowując, wybór odpowiednich i optymalnych technik znieczulenia ograniczających zużycie opioidów, w tym anestezji bezopioidowej pozostaje dyskusyjny i wymaga dalszych badań. Powyższy cykl czterech prac naukowych, składający się na dysertację doktorską, pozwala na poszerzenie naszej wiedzy w zakresie możliwości i skutków wykorzystania różnych metod zmniejszających zapotrzebowanie na opioidy w okresie okołooperacyjnym u chorych poddawanych laparoskopowym operacjom bariatrycznym.

IV. INTRODUCTION

The primary goal of an anesthesiologist is to facilitate the surgical procedure while ensuring the safety and comfort of the patient not only during the surgery but also in the postoperative period. To perform surgery, traditionally, an anesthetic triad was adapted: anesthesia (unconsciousness), muscle relaxation, and analgesia [1]. After the procedure, crucial factors directly impacting patient comfort and safety in the postoperative period should include effective pain management, prevention of postoperative nausea and vomiting (PONV), facilitation of prompt recovery from anesthesia and avoidance of excessive sedation. Such an approach, adhering to Enhanced Recovery After Surgery (ERAS) guidelines [2], should currently be standard in laparoscopic bariatric procedures, including the most commonly performed in the world, laparoscopic sleeve gastrectomy (LSG) [3]. Complying with ERAS guidelines is crucial as obese patients have increased susceptibility to anesthetic and analgesics' side effects and profit the most from early mobilization and recovery.

To achieve the aforementioned goals, various techniques and drug classes are utilized, including opioids, which have the greatest known analgesic potential. The opioid receptors are located within multiple sites, mostly in the brain and spinal cord. Despite opioids' analgesic potential, they spark a wide range of side effects, such as respiratory failure and oversedation, and they are one of few modifiable factors of PONV. Moreover, their use may be associated with inducing phenomena such as acute tolerance, opioid-induced hyperalgesia, and possible pain chronification [4]. Therefore, the role of opioids in perioperative care is ambiguous, and various methods are utilized to minimize their use and related side effects, among them a wide spectrum of regional analgesia techniques, coanalgesics of different classes, and non-opioid analgesics. In general, the reduction of opioid dosage owing to such methods is described as opioid-sparing anesthesia or anesthesia with multimodal analgesia. Combining multiple methods in selected procedures, complete intraoperative elimination of opioids can be achieved and this is known as opioid-free anesthesia (OFA). Opioid use may be completely eliminated not only during surgery utilizing OFA, but also in the postoperative period, which is referred to as "opioid-free analgesia". Based on the current state of knowledge, opioid-free anesthesia and analgesia with acceptable pain treatment are achievable only in selected procedures and in defined patients. In laparoscopic bariatric surgery, they are reported only as case reports and not a standardized, reliable, fit-for-all protocol.

However, techniques of multimodal analgesia and OFA are characterized by a vast heterogeneity, and the balance of potential benefits and side effects may vary depending on the procedure and even on characteristics of an individual patient. Complete elimination of opioids by supplanting them with other techniques or drug classes may fail to benefit the individual patient given their complexity of comorbidities. Moreover, the choice of particular analgesia technique is procedure-specific, as nociceptive stimulation and tissue damage vary depending on the surgical procedure. On that account, more clinical trials are necessary to explore practical and clinical aspects of various anesthesia and analgesia techniques, with a focus on safety, effectiveness, and utilization in clinical scenarios and, ultimately, long-term sequelae.

Considering the aforementioned aspects, search for the ideal opioid-sparing techniques in LSG remains essential, given potential benefits for the increasing number of patients requiring such surgery, burden in healthcare, global prevalence of obesity, and surging number of bariatric procedures performed [3,5]. On that basis, the scientific focus of this thesis was to study the opioid-sparing techniques in the most commonly performed bariatric surgery, LSG.

IV. 1 A Brief historical background of opioid-sparing anesthesia

The concept of "balanced anesthesia", described as combining two or more agents to alter the level of consciousness and block pain, was introduced by John S. Lundy in 1926 at the Mayo Clinic in Rochester, USA [6]. Originally, the author of this strategy used barbiturates and inhalational agents. In 1946, Cecil Gray and John Halton developed the concept, advocating reduction in the doses of barbiturates and inhalational agents by adding the neuromuscular blocking agent d-tubocurarine and opioid pethidine. The authors emphasized that the use of different types of drugs, each producing one desired effect, allowed use of the lowest possible dose of each agent [7]. In this way, the triad consisting of anesthesia, analgesia, and relaxation has been introduced and is still a basic idea of commonly utilized general anesthesia.

Dating back to 1915, morphine was the primary analgesic agent used in anesthesia and with the development of synthetic opioids, high-dose opioid anesthesia gained popularity. In cardiac anesthesia, the stability of hemodynamics was considered to be an asset of such a technique, in which morphine was largely replaced in the 1970s by fentanyl.

Since the 1980s, advances in agents such as modern volatile and intravenous anesthetics, neuromuscular blocking agents, non-opioid analgesics, and co-analgesics have led to the development of opioid-sparing techniques and, thereby, allowed for potentially faster and smoother emergence from anesthesia [8].

In the 2010s, an opioid-free anesthesia concept was introduced by Belgian anesthesiologist Jan Mulier [9]. Since then, protocols with complete elimination of opioids have been gaining popularity, initially originating in bariatric surgery and spreading to other fields like general, ear-nose-throat, cardiac and neurosurgery.

Despite increasing enthusiasm for opioid-free anesthesia, there are also growing concerns about its safety, in part initiated by an extensive study by Beloil et al. [10]. This pivotal trial, which was interrupted due to cases of cardiac arrest in the OFA group, has cast doubt on safety of the OFA technique. Still, as there were concerns regarding methodology in this study including protocol breaches, no decisive conclusion can be drawn, and the debate on OFA safety and clinical soundness is still open.

IV. 2 Potential benefits of opioid-sparing techniques.

The main reason for the development of opioid-sparing techniques in bariatric anesthesia is the avoidance of opioid-induced respiratory depression [11]. Patients with obesity have numerous factors that contribute to their increased susceptibility to respiratory complications, including reduced lung functional residual capacity (FRC), atelectasis, and coexistence of obstructive sleep apnea or obese hypoventilation syndrome [12]. The increased rate of respiratory complications is common after opioid administration and may be clinically significant even without clear signs of an overdose. In this field, there is ample evidence that adapting opioid-sparing techniques reduces such a risk [13]. Therefore, their use is recommended by both the Enhanced Recovery After Bariatric Surgery (ERABS) and Procedure Specific Postoperative Pain Management (PROSPECT) guidelines [2,14]. On that basis, we successfully utilized not only opioid-sparing but opioid-free anesthesia in a patient with severe comorbidities in the form of interstitial lung disease on oxygen therapy, as demonstrated in manuscript VI.2. In our case report, we demonstrated successful anesthetic management of a high-risk patient in whom general anesthesia considering his comorbidities might have posed a potentially life-threatening risk. Importantly, in our study, we extended the use of coanalgesics throughout the first 24 hours postoperatively, increasing the benefits of opioid avoidance.

One of the most unpleasant side effects for patients that impacts their comfort, hinders their quick mobilization, and may pose a risk of increased blood pressure, wound dehiscence, or bleeding in the perioperative period is PONV [15]. Opioid use is one of the few modifiable factors affecting it, and there is evidence that the relation is dose-dependent [16]. The complete

elimination of opioids could potentially result in the most significant risk reduction [17,18]. Still, there is ongoing debate regarding the duration of this beneficial effect.

In terms of postoperative pain management and opioid requirements after surgery, most randomized controlled trials (RCT) demonstrate improved pain scores and decreased opioid consumption; still, duration of such effects strongly varies and depends on the dosing regimen and utilized techniques [17]. In majority of RCTs, they were demonstrated only in the immediate postoperative period, with no difference in total 24-hour opioid consumption. This leaves open questions of clinical importance and how to prolong over time any potential benefits, which we outlined in our publication VI.3.

Moreover, new evidence demonstrates that high-dose extended opioid use may be associated with negative phenomena such as acute tolerance to opioids requiring increasing doses to achieve an effective analgetic effect or opioid-induced hyperalgesia [19,20]. Opioid side effects may also contribute to development of persistent post-surgical pain, which is estimated to be a problem in up to 30% of patients undergoing bariatric surgery [21]. Proposed mechanisms by which development of the above-mentioned undesired consequences may be hampered are NMDA (N-methyl-D-aspartate) receptor antagonism, alfa-2 receptor agonism, anti-inflammatory profile of local anesthetics and reduction in inadequate pain control during the postoperative period, which constitutes in part opioid-sparing techniques [22,23].

IV. 3 Potential disadvantages and shortcomings of opioid-sparing techniques: why they do not fit all? What future research should be considered?

Although there is a consensus that reducing opioid doses is beneficial for patient care, RCTs have brought about controversies and showed conflicting results, especially regarding benefits of a more far-reaching approach, OFA, compared to a solely opioid-sparing strategy. Such controversies with ambiguous data were examined and presented in synthetic form as a review in manuscript VI.3.

Despite multiple benefits of opioid-sparing or opioid-free anesthesia, such techniques also have their limitations and potential side effects, which may restrict their general use. Moreover, one of the difficulties associated with planning an RCT to evaluate such risks is the vast heterogeneity of applied protocols and interference between distinct agents' side effects.

The serious risks related to use of opioid-sparing co-analgesics is that alfa-2 agonists, lidocaine, magnesium sulfate, and ketamine infusions, may, in various mechanisms, have cardio-

depressive and hypotensive impact on the patient's hemodynamics. Together with steep anti-Trendelenburg positioning of an obese patient undergoing the laparoscopic operation of the stomach, hemodynamical sequelae of the insufflating the peritoneal cavity with carbon dioxide, and a high prevalence of comorbidities with often compromised cardiac function, may lead to hemodynamic instability and organ hypoperfusion, posing a risk of severe complications [24,25]. Surprisingly, this relationship concerning OFA, has not been studied before in patients with obesity undergoing laparoscopic bariatric operations, and our manuscript, VI.1, aims to help bridge this knowledge gap. Our study demonstrated a tendency for hemodynamic instability in patients having OFA, thus resulting in higher doses of vasopressors and fluid volume required to maintain proper hemodynamics. Such shortcoming of the OFA technique compared with relatively short-term benefits demonstrated as seen in our study is important in the discussion on balance of risk and benefit of using OFA in comparison to opioid-sparing strategies.

One possible solution to reduce such a detrimental effect is optimal choice and dosing of co-analgesics; therefore, we planned a study to evaluate a relatively rare co-analgesic in bariatric surgery: pregabalin (VI.4). Pregabalin has anxiolytic, analgesic, and opioid-sparing properties and has been considered a first-line treatment for neuropathic pain [26]. Moreover, it has been effective in preventing opioid-induced hyperalgesia [27] and may be associated with decreased prevalence of PONV [28]. On the other hand, pregabalin has sedative properties which may affect patient recovery after surgery. Our study intends to assess this aspect of clinical practice and provide evidence on the effect of pregabalin administration in a dose of 150 mg, which may contribute to a reassessment of recommendations regarding the use of this drug in patients undergoing LSG.

Further studies on opioid-sparing strategies in laparoscopic bariatric surgery, including LSG, should focus on the practical application and effectiveness of combined administration of different co-analgesics and techniques of regional analgesia, such as infiltration of the surgical site with local anesthetics [29], Transversus Abdominis Plane (TAP) Block [30], Erector Spinae Plane (ESP) Block [31] or the intraperitoneal administration with local anesthetics [32], including a promising blockade of the autonomic innervation of the stomach as a part of the multimodal, opioid-sparing analgesia [33]. Although using neuraxial blockades may impair early mobilization and is currently not recommended for laparoscopic bariatric procedures [2,14], epidural and even thoracic spinal-epidural anesthesia have also been successfully implemented and described [34].

Furthermore, an important topic that requires high-quality RCTs is the question of co-analgesics administration extended into the postoperative period and its influence on the quality of recovery, pain scores, opioid consumption, and patient safety. It is also important to assess whether such measures would shorten or prolong the length of hospital stay.

Finally, as far as further research directions are concerned, no studies evaluate the long-term impact on recovery and postoperative pain chronification, which is an essential issue considering long-term patient comfort and quality of life.

In summary, the emergence of novel methods and techniques used to spare or eliminate perioperative opioid use enables early mobilization with the best possible comfort. The multitude of utilized techniques, their heterogeneity, and the necessity to make allowances for obese patients' specific comorbidities in a personalized approach led to ongoing debate for the most optimal anesthetic strategy. As authors of the manuscripts that are part of this dissertation, we have created RCTs, a case report, a review article, and a study protocol to contribute to the discussion and partially answer the arising doubts and gaps in chosen clinical scenarios.

V. AIM OF THE DISSERTATION

The aim of this dissertation is to identify the optimal methods of opioid-sparing strategies in anesthesia for obese patients undergoing LSG, evaluating their efficacy, limitations, and practical application.

The specific points of studies conducted for this thesis:

1. The efficacy and safety of OFA in patients undergoing LSG.
2. Demonstration of successful utilization of OFA in anesthetic management for LSG in an obese patient with interstitial lung disease.
3. A critical evaluation and review of literature on opioid-free anesthesia in bariatric surgery.
4. Formatting a protocol for an RCT to assess the effect of pregabalin on postoperative opioid consumption, pain intensity, quality of recovery and hemodynamic stability following LSG.

VI. COPIES OF PUBLISHED MATERIALS

VI.1 Comparison between multimodal and intraoperative opioid free anesthesia for laparoscopic sleeve gastrectomy: a prospective, randomized study.

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Comparison between multimodal and intraoperative opioid free anesthesia for laparoscopic sleeve gastrectomy: a prospective, randomized study

Piotr Mieszczański[1,2]✉, Grzegorz Górniewski[1,2], Paweł Ziemiański[2,3], Radosław Cylke[2,3], Wojciech Lisik[2,3] & Janusz Trzebicki[1,2]

Anesthesia for laparoscopic sleeve gastrectomy and perioperative management remains a challenge. Several clinical studies indicate that opioid-free anesthesia (OFA) may be beneficial, but there is no consensus on the most optimal anesthesia technique in clinical practice. The aim of our study was to assess the potential benefits and risks of intraoperative OFA compared to multimodal analgesia (MMA) with remifentanil infusion. In a prospective, randomized study, we analyzed 59 patients' data. Primary outcome measures were oxycodone consumption and reported pain scores (numerical rating scale, NRS) at 1, 6, 12, and 24th hours after surgery. Postoperative sedation on the Ramsay scale, nausea and vomiting on the PONV impact scale, desaturation episodes, pruritus, hemodynamic parameters, and hospital stay duration were also documented and compared. There were no significant differences in NRS scores or total 24-h oxycodone requirements. In the first postoperative hour, OFA group patients needed an average of 4.6 mg of oxycodone while the MMA group 7.72 mg ($p = 0.008$, $p < 0.05$ statistically significant). The PONV impact scale was significantly lower in the OFA group only in the first hour after the operation ($p = 0.006$). Patients in the OFA group required higher doses of ephedrine 23.67 versus 15.69 mg ($p = 0.039$) and more intravenous fluids 1160 versus 925.86 ml ($p = 0.007$). The mode of anesthesia did not affect the pain scores or the total dose of oxycodone in the first 24 postoperative hours. Only in the first postoperative hour were an opioid-sparing effect and reduction of PONV incidence seen in the OFA group when compared with remifentanil-based anesthesia. However, patients in the OFA group showed significantly greater hemodynamic lability necessitating higher vasopressor doses and more fluid volume.

Patients with obesity undergoing bariatric surgery, including the most commonly performed laparoscopic sleeve gastrectomy (LSG), are particularly vulnerable to opioid side effects such as respiratory depression, postoperative nausea, and vomiting (PONV) as well as excessive sedation[1–3]. To reduce opioid use, the Enhanced Recovery After Bariatric Surgery (ERABS) guidelines recommend multimodal analgesia, such as the administration of co-analgesics, regional anesthesia, or non-opioid analgesics[3,4]. These agents in combination make it possible to eliminate the intraoperative use of opioids, which is referred to as opioid-free anesthesia (OFA)[3].

While opioid-free anesthesia (OFA) has shown potential benefits, it is not without risks. In order to address concerns surrounding efficacy and safety following laparoscopic sleeve gastrectomy (LSG) surgery[5,6], a prospective, randomized, single-blind study was conducted. The study aimed to compare anesthetic techniques utilizing multimodal analgesia with remifentanil to intraoperative OFA to provide objective data to assist in decision-making and help balance these techniques' potential risks and benefits.

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Materials/methods

The study was conducted by the 1st Department of Anesthesiology and Intensive Care, Medical University of Warsaw, Poland. Study participants were recruited among patients qualified for elective LSG in the Department of General Surgery and Transplantology between February 2020 and October 2022. Approval for the study was granted by the Bioethics Committee of the Medical University of Warsaw (KR/5/2020), and the study was registered on 07.02.2020 with clinicaltrials.gov (NCT04260659). The study was compliant with the principles outlined in the Declaration of Helsinki, and the manuscript adheres to the applicable CONSORT guidelines.

Study design. The study was designed as a single-blind, randomized, controlled trial. Equal, parallel 1:1 randomization was performed using http://www.randomization.com (Dallal GE). The list was generated on 08.02.2020 and accessed by only one investigator, who informed the anesthesiologist of group eligibility one hour preoperatively.

A sample size of 60 patients was calculated based on the Altman nomogram to obtain a 30% reduction in postoperative opioid consumption with a significance and power of 90%[2].

The patient, the surgical team, and the Post-Anesthesia Care Unit (PACU) staff remained blinded.

Patients scheduled for surgery had a BMI > 40 or > 35 but with comorbidities, were aged 18 to 65, and were LSG-eligible. Informed, written consent was obtained from all participants by one of the investigators. Patients who did not consent to participation in the study, were undergoing revision surgery, had an allergy to any of the drugs used in the protocol, and were unable to cooperate in assessing pain intensity on the numerical rating scale (NRS) scale or use patient-controlled analgesia (PCA) pump were excluded from the study. After the randomization, we excluded from the analysis patients with a change in the extent of surgery.

Patients underwent standardized preoperative preparation. All were instructed preoperatively on how to use a PCA pump and rate pain using the NRS scale.

Anesthesia was conducted according to a protocol based on ESRA Prospect recommendations[7]. One hour before surgery, all patients received paracetamol 1 g i.v., metamizole 2.5 g i.v. and dexamethasone 8 mg i.v. Induction was performed using propofol 2–2.5 mg/kg, while anesthesia was maintained with desflurane. Bispectral Index (BIS) was utilized to monitor awareness with a target value of 40–60. Local infiltration of the trocar insertion sites with 0.25% bupivacaine (40 ml total) was performed by the surgeon intraoperatively.

Before induction, patients in the OFA group received a 10-min infusion of dexmedetomidine (1 mcg/kg ideal body weight—IBW) and lidocaine (1.5 mg/kg IBW). IBW was defined according to Brock formula. In the OFA group, ketamine 0.5 mg/kg IBW i.v. was also administered immediately after propofol. After endotracheal intubation, continuous infusion of dexmedetomidine and lidocaine was started with a dose depending on hemodynamic parameters toa maximum of 1 mcg/kg IBW/h and 3 mg/kg IBW/h, respectively, with a stable solution of dexmedetomidine 100mcg and lidocaine 300 mg with 0.9% NaCl to 20 ml in one syringe[8]. OFA group also received 40–50 mg/kg of magnesium sulfate IBW in balanced fluid solution i.v. If tachycardia above 120/minute with concomitant hypertension above 140/90 mmHg occurred, rescue fentanyl 100 mcg i.v. was to be given.

In the multimodal analgesia (MMA) group, remifentanil in a 2 mg/40 ml solution was dosed using the Target Controlled Infusion (TCI) pump according to the Minto model. The pump was programmed with an IBW set as patient weight and target plasma concentration for induction of anesthesia set to 6 ng/ml[9]. The maintenance dose was adjusted depending on hemodynamic parameters.

In case of bradycardia < 48/min, atropine 0.5 mg was administered and if MAP dropped < 60 mmHg, ephedrine up to a maximum dose of 50 mg in both groups was administered. If, despite that, MAP persisted below 60 mmHg, norepinephrine infusion was started. In our center, after the resection was completed, surgeons asked for a systolic pressure > 120 mmHg to check for hemostasis.

Muscle relaxation was achieved initially by administration of succinylcholine 1–1.5 mg/kg i.v., followed by rocuronium or cis-atracurium to achieve Train of Four (TOF) < 1 during surgery. Residual effects of muscle relaxants were reversed by sugammadex or neostigmine with atropine under TOF control. The decision to choose a muscle relaxant depended on the anesthesiologist's decision and the availability of sugammadex.

Intraoperative heart rate (HR), systolic and diastolic blood pressure (BP) were measured invasively after radial artery cannulation, and pulse oximetry was monitored. Ventilation was managed to achieve an end-tidal carbon dioxide (EtCO2) of 35–45 mmHg and SpO2 > 94%.

After wound closure, dexmedetomidine and lidocaine in the OFA group or remifentanil in the MMA group were discontinued, and oxycodone was administered at a dose of 0.1 mg/kg IBW i.v.

Following extubation, patients were transported to the PACU, where analgesic treatment was administered based on paracetamol 1 g i.v., metamizole 1 g i.v. given every 6 h, and oxycodone (bolus 2 mg, lockout 10 min) administered via a PCA iv pump. All patients in the PACU received 5 l/min oxygen therapy for the first 2 h. In case of nausea, a single dose of ondansetron 4 mg i.v. was administered. Patients remained in the PACU for 24 h after surgery; thereafter they were discharged home.

Primary and secondary outcome measures. The primary outcome measures were total oxycodone consumption and pain scores on the NRS scale 1,6,12 and 24 h after surgery. Parameters such as postoperative sedation on the Ramsay scale, PONV impact scale[10], desaturation episodes < 94%, pruritus 1, 6, 12 and 24 h after surgery, highest and lowest intraoperative HR and BP, as well as MAP, were also documented. Further outcome measures were total fluid volume, total ephedrine dose, the need to use norepinephrine infusion or rescue fentanyl in the OFA group, operative and anesthesia time, time to extubation and the ability to discharge the patient home 24 h after surgery.

Statistical analysis was performed using the Statistica 13.1 package (TIBCO Software Inc. (2017). Statistica (data analysis software system), version 13. http://statistica.io.Dell Inc.). Even continuous variables due to low

group sizes and deviating from normal (Shapiro–Wilk test) or asymmetric distributions were analyzed using non-parametric tests (Mann–Whitney U). Nominal and ordinal variables were analyzed using the Chi2 test, with Yates correction when indicated that is for expected counts below 10. *P*-value < 0.05 was considered statistically significant.

Results

Study population. A total of 60 patients were eligible for the study, and one patient was excluded from the analysis due to suspected bowel injury resulting in much-elongated surgery time. Finally, 30 patients were included in the OFA group and 29 in the MMA group (Fig. 1). There were no significant differences between the groups in relation to the distribution of age, sex, BMI, duration of anesthesia, the procedure itself, or time from the end of the surgical procedure to extubation (Table 1). *P*-value < 0.05 was considered significant.

Intraoperative management. There was no significant difference between the groups in the type of drug used to reverse skeletal muscle relaxation (neostigmine, sugammadex). Patients in the MMA group were not

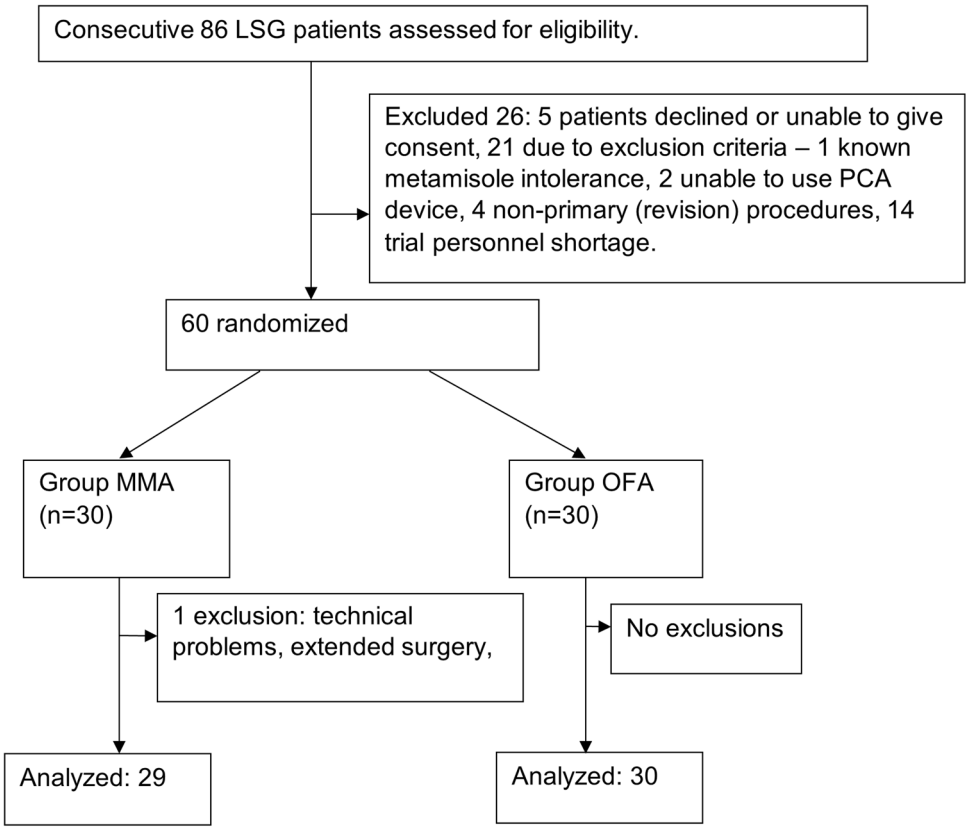

Figure 1. Study chart flow.

Variable	All patients	OFA group	MMA group	*p*-value (Mann–Whitney U test) *p* < 0.05 statistically significant
	Mean (SD)			
Age (y)	43.92 (10)	45.1 (11.6)	42.73 (8.1)	0.13
Weight (kg)	130.75 (23.1)	130.81 (23.6)	130.69 (23)	0.9
Ideal body weight—IBW (kg)	67.10 (12.1)	67.13 (12.6)	67.07 (11.8)	0.83
Height (m)	1.70 (0.1)	1.69 (0.1)	1.71 (0.1)	0.9
BMI	45.16 (7.2)	45.42 (7.9)	44.9 (6.5)	0.85
Anesthesia duration (min)	108.15 (24.5)	108.9 (26.5)	107.38 (22.8)	0.86
Surgery duration (min)	87.81 (26.3)	86.27 (27.4)	89.41 (25.5)	0.5
Time to extubation (min)	8.8 (8.9)	8.77 (3.9)	8.83 (12.2)	0.09

Table 1. Selected characteristics of the study population.

significantly more likely to require atropine to treat bradycardia (3 patients in the OFA group vs. 4 patients in the MMA group, $p = 0.49$, Chi^2).

There was a significant difference in the volume of administered intravenous fluids between the groups—on average, 234.14 ml more fluids were required by patients in the OFA group. They also needed a significantly higher dose of ephedrine. No significant differences were observed regarding minimal and maximal BP and maximal HR values. However, a significantly lower value of the lowest observed HR in the MMA group was measured (Table 2). In 2 patients in the OFA group, a rescue dose of fentanyl was required due to tachycardia/and hypertension, even though the BIS value was below 60. In 2 patients in each group, norepinephrine infusion was necessary.

Opioid consumption and NRS values. There were no significant differences in reported pain (NRS) or total oxycodone requirements between the groups (Table 3). However, at 1 h after the procedure, the dose of oxycodone administered via the PCA pump was significantly lower in the OFA group compared to the MMA group, 4.6 mg of oxycodone (SD 4.34) versus 7.72 mg (SD 4.56) respectively. There were no significant differences at the other assessment intervals (Table 4).

The two patients requiring a rescue dose of fentanyl did not impact our results. Within 24 h after the surgery, they received 40 and 48 mg of oxycodone, respectively, whereas the maximal dose for the whole study population

Variable	All patients Mean(SD)	OFA group Mean (SD)	MMA group Mean (SD)	*p*-value (Mann–Whitney U test) $p < 0.05$ statistically significant
Intraoperative i.v. fluids volume (ml)	1044.91 (345.38)	1160 (32.85)	925.86 (326.95)	0.007
Intraoperative ephedrine dose (mg)	19.75 (14.4)	23.67 (14.2)	15.69 (13.68)	0.039
Max heart rate (1/min)	90.93 (12.27)	91.3 (12.30)	90.55 (12.45)	0.710
Max systolic blood pressure (mmHg)	134.54 (21.18)	135.9 (23.63)	133.13 (18.62)	0.946
Max diastolic blood pressure (mmHg)	78.41 (14.48)	82.03 (15.13)	74.65 (12.97)	0.105
Max mean blood pressure—(mmHg)	97.12 (16.11)	99.99 (17.54)	94.14 (14.17)	0.262
Min heart rate—HR (1/min)	64.90 (11.50)	68.7 (10.95)	60.96 (10.87)	0.019
Min systolic blood pressure—SAP (mmHg)	81.15 (11.15)	79.47 (9.62)	82.89 (12.48)	0.234
Min diastolic blood pressure—DAP (mmHg)	48.88 (7.51)	48.77 (6.73)	49 (8.36)	0.988
Min. mean blood pressure (mmHg)	59.64 (8.25)	59 (7.23)	60.29 (9.28)	0.644

Table 2. Selected intraoperative parameters—values of blood pressure and heart rate, total volume of administered intraoperative i.v. fluids administered and total ephedrine dose.

Variable	All patients Mean (SD)	OFA group	MMA group	*p*-value (Mann–Whitney U test) $p < 0.05$ statistically significant
NRS 1 h	3.81 (2.84)	3.57 (3.05)	4.06 (2.64)	0.524
NRS 6 h	2.37 (1.83)	2.27 (1.87)	2.48 (1.81)	0.666
NRS 12 h	2.46 (1.96)	2.45 (2.28)	2.46 (1.62)	0.632
NRS 24 h	2.68 (2.48)	2.93 (2.70)	2.41 (2.24)	0.601
Oxycodone cumulative PACU dose [mg]	23.62 (14.04)	24.41 (13.64)	22.83 (14.62)	0.405
Oxycodone cumulative total dose [mg]	30.31 (14.07)	31.31 (13.70)	29.31 (14.6)	0.380

Table 3. Comparison of reported pain score values at consecutive time points (NRS scale) and cumulative postoperative oxycodone dose.

Variable	All patients Mean (SD)	OFA group	MMA group	*p*-value (Mann–Whitney U test) $p < 0.05$ statistically significant
Oxycodone 1 h (mg)	6.14 (4.68)	4.6 (4.34)	7.72 (4.56)	0.008
Oxycodone 6 h (mg)	14.0 (9.05)	13.6 (9.63)	14.41 (8.56)	0.603
Oxycodone 12 h (mg)	18.62 (11.71)	18.48 (11.2)	18.76 (12.39)	0.914
Oxycodone 24 h (mg)	23.66 (14.07)	24.48 (13.7)	22.83 (14.62)	0.395

Table 4. Comparison of the cumulative dose of oxycodone administered from the PCA pump at consecutive time points. The difference at 1 h is statistically significant (Mann–Whitney U test, $p = 0.008$).

was 65 mg and 54 mg for the OFA group. These two patients also had no impact on other analyses, including the side effects profile.

Oxycodone side effects and hospital stay duration. The PONV impact scale differed significantly between groups only in the first hour after surgery (Mann–Whitney U test, $p=0.006$). (Table 5). There were no significant differences in the incidence of desaturation < 94% or in the assessment of pruritus between the groups (Table 6.). In the OFA group, 8 patients were not discharged from the hospital the following day after the procedure, compared to 2 patients in the MMA group. However, the difference was not statistically significant. In addition, only in 3 patients (all in the OFA group) was this delay directly related to postoperative pain management. These patients were discharged on the following day.

Discussion

Our prospective, randomized controlled trial found that OFA during the surgery did not affect total postoperative opioid consumption or NRS score. Additionally, the reduction of incidence of PONV and opioid consumption was demonstrated only in the immediate postoperative care setting, and this effect did not persist for six or more hours. Patients in the OFA group were hemodynamically more labile and required more vasopressor support and fluid volume.

There are controversies in the evaluation of the potential benefits of OFA. Our study aligns with previous research[2,11–14] and a bariatric surgery meta-analysis[15], showing no significant difference in total postoperative opioid consumption. Similar to our results, in a study by Mulier 2018[2], the reduction of NRS score and the opioid dose was significant only a few hours after the operation and not later[2]. On the contrary, several trials revealed the superiority of OFA in this aspect. Ubing et al.[16] found less opioid use in 48 h after the operation with significantly lower pain scores. The main difference that could contribute to these results is the continuous administration of the coanalgesics mixture in the recovery room, which may prolong the effects observed in our study only one hour after the operation. Ibrahim et al. demonstrated less morphine use with lower NRS in the first 6 h[17]. Still, in their study, both groups had bilateral subcostal transversus abdominis plane blocks, an essential factor that may impact this result. Reduced total opioid requirement with associated improved pain scores was also seen in recent studies by Ahmed and Soudi et al.[18,19]. The latter trial observed lower pain scores throughout 24 h after the operation. This might result from a relatively higher dose of dexmedetomidine, which was 1 mcg per kilogram of total and not ideal body weight as in our study.

In a broader context, a 2021 meta-analysis by Salome et al. [20] that included 33 studies on patients undergoing different types of surgery confirmed no clinical advantage of OFA in pain control or reduction of opioid consumption. However, a recent meta-analysis, which adopted a more stringent OFA definition and, therefore, inclusion criteria, demonstrated lower opioid requirements in the first 24 h after the operation [21] and lower pain scores only in the first 2 h postoperatively.

Variable	All patients	OFA group	MMA group	*p*-value (Mann–Whitney U test) $p<0.05$ statistically significant
	Median (IQR)	Median (IQR)	Median (IQR)	
PONV Impact 1 h	0 (2)	0 (0)	1 (2)	0.006
PONV Impact 6 h	0 (1)	0.5 (1)	0 (2)	0.66
PONV Impact 12 h	0 (1)	0 (1)	0 (1)	1
PONV Impact 24 h	0 (1)	0 (1)	0 (1)	0.67

Table 5. Comparison of the incidence of nausea and vomiting (PONV Impact score) at 1,6,12 and 24 h after surgery.

Variable	All patients		OFA group		MMA group		*p*-value (Chi^2) $p<0.05$ statistically significant
	No	Yes	No	Yes	No	Yes	
SaO2 < 94% after 1 h	45 (76.27%)	14 (23.73%)	21 (70%)	9 (30%)	24 (82.76%)	5 (17.24%)	0.25
SaO2 < 94% after 6 h	57 (96.61%)	1 (1.69%)	30 (100%)	0	28 (96.55%)	1 (3.45%)	0.99
SaO2 < 94% after 12 h	54 (91.53%)	2 (3.39%)	30 (100%)	0	27 (93.5%)	2 (6.9%)	0.46
SaO2 < 94% after 24 h	58 (98.31%)	0 (0%)	30 (100%)	0	29 (100%)	0	
Pruritus 1 h	55 (93.22%)	2 (3.39%)	30 (100%)	0	27 (93.1%)	2 (6.9%)	0.46
Pruritus 6 h	55 (93.22%)	2 (3.39%)	30 (100%)	0	27 (93.1%)	2 (6.9%)	0.46
Pruritus 12 h	55 (93.22%)	2 (3.39%)	29 (96.67%)	1 (3.33%)	28 (96.55%)	1 (3.45%)	1
Pruritus 24 h	49 (83.05%)	8 (13.56%)	25 (83.33%)	5 (16.67%)	26 (89.66%)	3 (10.34%)	0.74
Hospital discharge within 24 h	10 (16.95%)	49 (83.05%)	8 (26.67%)	22 (73.33%)	2 (6.9%)	27 (93.1%)	0.094

Table 6. Incidence of desaturation < 94% and pruritus at 1,6,12 and 24 h after surgery.

Regarding the PONV rate, our study is in line with most studies[2,6,11,13,16–19] and meta-analysis[15] on OFA to show reduced incidence of PONV, to which opioid administration is the main factor. Avoiding opioids, even strictly intraoperatively, can positively impact the occurrence of PONV. However, there were differences in how long the OFA beneficial effect on PONV lasts. Mulier[2] demonstrated a reduction of PONV rate not only in the close postoperative period as in our study but persisting to 24 h after the operation; a similar effect was described by Zimman-Giemmel et al.[13], but in their study, the result was affected by the fact that only a single assessment was performed, making it difficult to precisely determine the effect of OFA use on the incidence of PONV over time. However, several studies also described a lack of difference in PONV incidence in the OFA group[12,14,18,22].

In an attempt to explain the short-term benefits of the OFA on opioid consumption, NRS score, and PONV incidence in our study, we hypothesize that the observed differences are due to the limited duration of action of the coanalgesics used intraoperatively, such as dexmedetomidine or lidocaine, for which the half-life does not exceed 2 to 3 h, respectively [23,24]. Hence, their effect is too short-lived to significantly affect the entire postoperative day.

To our knowledge, this is the first randomized trial in which patients in the OFA group for bariatric surgery showed significantly greater hemodynamic lability than in the MMA group, manifested by 40% greater ephedrine consumption and 20% greater crystalloid use. It can be expected as obese patients with comorbidities undergo laparoscopy in steep anti-Trendelenburg position, and they receive coanalgesics of which lidocaine, dexmedetomidine, and magnesium sulfate have hypotensive and cardio-depressive effects. Our study showed no significant difference in minimal BP values, but we explain this by immediate treatment of emerging hypotension. In correspondence to our findings, Soudi et al.[18] demonstrated more frequent episodes of hypotension in the OFA group, which the authors explain by defining hypotension as a 20% decrease in BP from basal BP. On the contrary, no difference in BP values was shown in Mulier's 2018 and Mansour's 2013 study[2,20]. Still, the authors of these trials do not report the average dose of vasopressors nor the volume of fluids administered, which are crucial to assess the prevalence of hypotension requiring intervention. In contrast to our results, in a retrospective study performed by Berlier et al., patients in the OFA group with clonidine or dexmedetomidine required vasopressors less frequently than in an opioid-based group, whereas episodes of hypertension occurred more often[25]. However, the authors of the study acknowledge that there were several confounding factors and limitations, such as significant differences in anesthesia mode between the groups[26], as well as methodological limitations in the anesthesia protocols used [27]. In general surgery, aligning with our study, a significantly higher incidence of hypotension while using OFA was described by Helal et al.[28], who demonstrated such a phenomenon in obese patients undergoing laparoscopic cholecystectomy.

There are safety concerns stemming from the study conducted by Beloil et al.[6]. The study had to be terminated after enrolling 312 patients because of significant hemodynamic instability in the OFA group. In a comparative study between OFA and opioid-based anesthesia utilizing remifentanil, five cases of severe bradycardia were observed, including one instance of asystole. On the contrary, in our trial, it was observed that the group receiving MMA treatment exhibited a reduction in their minimal HR. However, this observation did not result in any significant alterations in the administration of atropine. Potential factors contributing to the variance in outcomes may include the administration of higher dosages of dexmedetomidine, averaging 1.2 mcg/kg/hour, during a relatively prolonged anesthesia period, with an average duration of 268 min. It is also important to note that the study did not specifically focus on bariatric surgery.

Based on the research above, the potential for hemodynamic lability in individuals with OFA presents a substantial concern, as hypotension may lead to such consequences as myocardial injury or kidney failure[29]. This is particularly pertinent for those with ischemic heart disease, which is not uncommon in the obese, hypovolemia, or orthostatic hypotension[3,30].

The effects of specific components of multimodal analgesia can vary depending on the procedure and may differ between types of surgeries[31]. The strength of our study is its practical relevance as it investigates the impact of OFA on patients who have undergone one specific type of operation LSG, which according to The International Federation for the Surgery of Obesity and Metabolic Disorders, is the most commonly performed bariatric surgery[32]. We strived for maximum objectivity during our assessment by utilizing PCA and monitoring pain scores, opioid doses, and PONV rates at fixed intervals.

Limitations of our study include the choice of remifentanil in the MMA group, which may increase pain intensity during the first 24 h[33]. In our selection, we adhered to the recommendation from the ERABS guidelines to use drugs with as short a half-life as possible in bariatric anesthesia[4]. Another limitation is the discontinuation of coanalgesic infusion in the OFA group at the end of surgery. The benefit to the patient could be more clinically relevant with the maintenance of these infusions. However, the safety and validity of such treatment require further study.

In conclusion, the mode of anesthesia did not influence pain scores or opioid administration after the operation. Moreover, the advantages of lessening the incidence and severity of PONV and reducing opioid use were only evident for a limited period following the surgery. Both forms of anesthesia allowed for patient discharge within a day of the procedure. Patients who received OFA required more interventions to maintain their hemodynamic stability, indicating the need for further research to assess its safety and efficacy.

Data availability

The data generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Author contributions

P.M. and J.T. designed the study, P.M. and G.G. analyzed the data, P.Z., R.C. and W.L. acquired the data. All authors reviewed the manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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VI.2 Successful Anesthetic Management for Obese Patients with Interstitial Lung Disease Undergoing Laparoscopic Sleeve Gastrectomy: A Bridge to Improved Transplant Eligibility.

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 42-year-old
Final Diagnosis: Interstitial lung disease • obesity • oxygen dependency
Symptoms: Cough • dyspnoe • poor excersise toleration
Clinical Procedure: Laparoscopic sleeve gastrectomy • opioid-free anesthesia
Specialty: Anesthesiology • Surgery

Objective: Rare disease

Background: Patients with obesity with interstitial lung diseases (ILD) are encouraged to lose weight, as it improves lung function and lung transplant eligibility. As exercise tolerance in these patients is low and weight gain is a common adverse effect of corticosteroids, bariatric surgery can be an effective method for the management of obesity in this patient group. However, perioperative complications in such high-risk patients remain a concern. Therefore, we aimed to demonstrate successful anesthetic management for obese patients with ILD, which may be practically utilized to reduce perioperative pulmonary complications and improve outcomes.

Case Report: Our case report presents a 42-year-old man with ILD who underwent laparoscopic sleeve gastrectomy (LSG). Preoperative studies revealed severe restrictive disease, right ventricular overload with assessed intermediate risk of pulmonary hypertension, and heart failure, with preserved left ventricle fraction but with poor exercise tolerance. Patient had opioid-free anesthesia (OFA) and postoperative multimodal analgesia. Following a 24-h stay in the Post-Anesthesia Care Unit, the patient was transferred to the ward and ultimately discharged home 2 days thereafter. At the 1-year follow-up, the patient reduced his weight by 40 kg and reported a significant improvement in physical capacity.

Conclusions: Our record demonstrates that OFA can be successfully used in high-risk patients with ILD undergoing LSG. In a period of a year, the patient improved so much that he no longer required lung transplantation, which may encourage clinicians to provide bariatric surgery using the OFA technique in the population of patients with obesity and severe respiratory illness.

Keywords: Obesity • Lung Transplantation • Bariatric Surgery • Anesthesia and Analgesia • Idiopathic Pulmonary Fibrosis

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Introduction

Interstitial lung diseases (ILD) are a broad spectrum of disorders characterized by scarring of the lung stromal tissue with restrictive ventilation defects, reduced diffusion capacity of the lungs, and impaired gas exchange [1]. Patients with ILD are characterized by a high prevalence of postoperative respiratory complications in both lung and non-lung surgeries [2]. In addition, obese patients undergoing bariatric surgery, including laparoscopic sleeve gastrectomy (LSG) are at particular risk of respiratory complications involving opioid-induced respiratory depression, atelectasis, and excessive sedation [3,4]. Taking into account the unique anesthetic challenges in this group of patients, the aim of this case report is to demonstrate their successful management using the opioid-free anesthesia (OFA) technique. Despite appropriate treatment, patients with ILD can progress to a life-threatening respiratory failure requiring a lung transplantation.

However, one of the factors that can significantly restrict eligibility and increase the risk of such management is obesity with a body mass index (BMI) of 35 or more [5], which can be associated with post-transplant increase in mortality and primary graft dysfunction [6]. Moreover, it has been proven that weight loss is one of the modifiable factors that improve the results of lung transplantation treatment and increase the chance of successful surgery [7,8]. As these risks diminish with the reduction of BMI values to 30 to 34.9 [7], patients are encouraged to lose weight to improve their pulmonary function tests and post-transplant survival [8,9]. Nevertheless, due to deteriorating exercise tolerance and adverse effects of prednisolone, the prevalence of obesity in patients with ILD is common [9]. For such patients, bariatric surgery can be an effective method of management of obesity and related metabolic derangements, with potential improvement of lung function and transplant eligibility [10].

Although there are reports in the literature on the role of bariatric surgery, including the most commonly performed LSG [11] as a bridging treatment to lung transplantation, the number of publications on this subject is limited [10,12,13] and they do not describe anesthetic management, which is crucial.

The administration of anesthesia and postoperative management poses several challenges, and thus, it is imperative to devise strategies to minimize risks. One such form of anesthetic technique, which can decrease the frequency of pulmonary complications and enhance patients' recovery and safety, is OFA [14]. This article will present a case report of a patient with ILD on oxygen therapy who was successfully anesthetized for LSG as a bridge to lung transplant qualification using the opioid-free technique with multimodal postoperative analgesia.

Case Report

Qualification and Preparation for Surgery

We report our experience concerning a 42-year-old male patient who had LSG. Written informed consent was obtained from the patient for the publication of this case report and accompanying images. The patient reported persistent cough, dyspnea, and deteriorating exercise toleration since 2007. The patient was a smoker, initially suspected of having chronic obstructive pulmonary disease, and ultimately received a diagnosis of respiratory bronchiolitis-associated ILD on the basis of the clinical image, high-resolution computed tomography (**Figures 1, 2**), pulmonary function tests, and lung biopsy. The differential diagnoses considered were non-specific interstitial pneumonia and desquamative interstitial pneumonia, with some of the histopathological features of these entities considerably overlapping. The cessation of smoking and the initiation of treatment with prednisolone and temporarily with azathioprine did not slow the progress of the disease, during which time the patient became oxygen-dependent.

On initial qualification for LSG surgery, our patient had a BMI of 41.6 (height 178 cm, weight 132 kg) and required long-term oxygen therapy, receiving 5 L/min through nasal cannulas. Regarding concomitant diseases, the patient presented with hypertension, heart failure, with preserved ejection fraction and suspected pulmonary hypertension, diabetes treated with insulin, and non-alcoholic fatty liver disease. During preparation for surgery and anesthesia, the patient had arterial blood gas studies (**Table 1**), transthoracic echocardiography, and pulmonary function tests: spirometry, plethysmography, diffusion capacity assessment (**Table 2**), and a 6-min walk test.

Pulmonary function tests revealed a severe, restrictive ventilation defect with a moderate carbon monoxide transfer coefficient reduction. The 6-min walk test had to be stopped after 2 min 5 s due to intolerable dyspnea and leg cramps, with desaturation to 83% on oxygen therapy. In transthoracic echocardiography, right ventricular overload was present. Based on the measurement of the peak velocity of the tricuspid regurgitant wave, the risk of pulmonary hypertension was estimated as intermediate. Left ventricle contractility was preserved, with a left ventricle ejection fraction of 50% and hypokinesis of the lateral wall.

A multidisciplinary team consisting of a cardiologist, pulmonologist, and anesthetist stated that the patient was optimally prepared for bariatric surgery and was subsequently qualified for general anesthesia.

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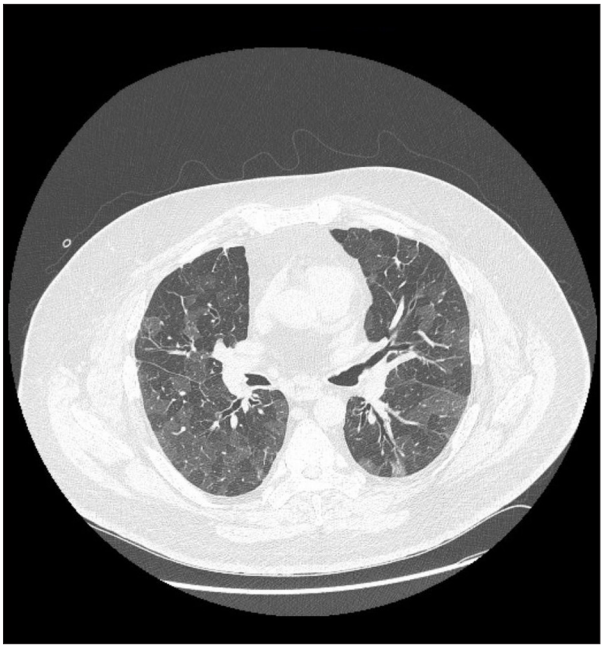

Figure 1. Selected computed tomography scan.

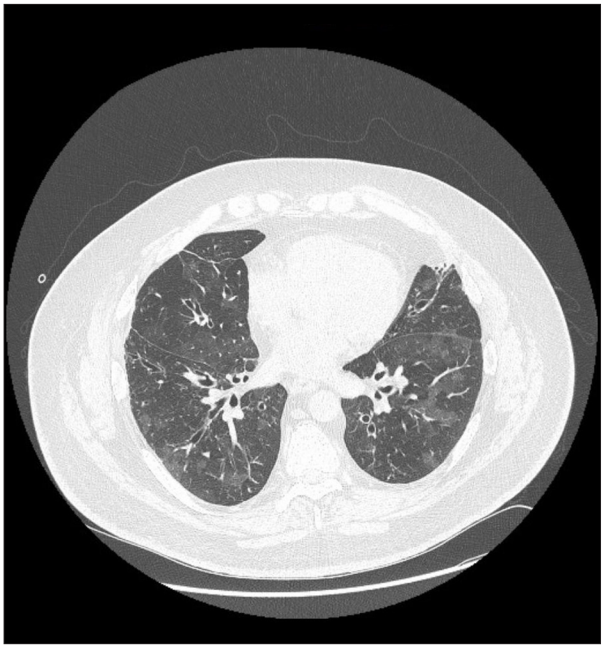

Figure 2. Selected computed tomography scan.

Table 1. Arterial blood gas studies results.

Blood gas analysis	pH	$PaCO_2$ [mmHg]	PaO_2 [mmHg]	HCO_3 [mmol/L]	BE [mmol/L]	Saturation [%]	FiO_2
Preoperative	7.383	51.7	59.8	30.1	5.0	90.2	0.3
Following intubation	7.376	50.2	256	27.3	3.9	99.7	1
1st postoperative hour	7.289	61.4	102	25.4	2.5	97.3	0.6
6th postoperative hour	7.355	54.5	68.1	27.5	4.5	93.7	0.37
24th postoperative hour	7.356	56.1	70.3	28.2	5.4	94.4	0.37

$PaCO_2$ – partial pressure of carbon dioxide in arterial blood; PaO_2 – partial pressure of oxygen in arterial blood; BE – base excess; FiO_2 – fraction of inspired oxygen.

Table 2. Pulmonary function test results.

Parameter	Obtained value	Predicted value	% of predicted value	Lower limit of normal
VC [l]	1.7	5.09	33.4	3.24
FEV1/VC [%]	0.75	0.8	94.12	69.85
TLC [l]	6	7.14	84.01	5.99
RV [l]	71.67	32.29	221.95	2.81
DLCOc (mmol/min/kPa)	6.09	10.64	57.22	8.32

VC – vital capacity; FEV1/VC – ratio of forced expiration in the first second to vital capacity; TLC – total lung capacity; RV – residual volume; DLCOc – diffusing capacity for carbon monoxide corrected for hemoglobin.

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Anesthetic Management Preoperatively

One hour before the surgery, the patient received pre-emptive analgesia with 1 g intravenous (i.v.) paracetamol and 2.5 g i.v. metamizole, adhering to Enhanced Recovery After Bariatric Surgery Society guidelines on LSG anesthesia [15]. We decided against giving dexamethasone, as the patient was already on prednisolone therapy for ILD.

In the operating room, before induction of the anesthesia, dexmedetomidine 70 mcg and 10-min infusion of lidocaine 100 mg i.v. was initiated. After positioning the patient in a benchmark position, preoxygenation with a high-flow nasal cannula (HFNC) was started, with FiO_2 100% at a flow rate of 60 L/min. The anesthesia induction was performed by administering propofol 120 mg and ketamine 40 mg i.v. The ketamine was included as a component of multimodal analgesia due to its NMDA antagonist properties. A video laryngoscope was used, and the intubation was successful at the first attempt, maintaining saturation levels above 96% throughout the intubation procedure.

Conduction of Anesthesia

Anesthesia was maintained using sevoflurane titrated to bispectral index values between 40 and 60. We decided against desflurane to avoid its irritating effect on the airways, and our team discussed using propofol total intravenous anesthesia, which was considered an alternative. Finally, we chose sevoflurane, owing to its potentially beneficial impact on lung mechanics, even though such an effect on patients undergoing LSG is debatable [16]. Following the induction of anesthesia, the radial artery was cannulated to perform arterial blood gas analyses and to monitor blood pressure invasively. Also, continuous infusion of dexmedetomidine 50 mcg and lidocaine 500 mg in 0.9% NaCl up to 50 mL in a single syringe was started, with infusion rates dependent on the hemodynamical parameters. We chose such a strategy to completely avoid opioids intraoperatively and potentially improve the patient's recovery after the operation. During the surgery, magnesium sulfate 4 g i.v. was given, owing to its analgesic properties. To facilitate intubation and provide relaxation of muscles intraoperatively, rocuronium was dosed to keep a train-of-four ratio of 0. Mechanical ventilation was performed in the volume control ventilation mode, with an initial set tidal volume of 500 mL, frequency 16 breaths/min, FiO_2 50%, and positive end-expiratory pressure of 5 cmH_2O.

At the beginning of the operation, the surgeons locally infiltrated the trocar insertion sites, with a total volume of 40 mL 0.25% bupivacaine. The surgical time was 65 min, and its course was uneventful. After placing the last sutures, sevoflurane was discontinued, and muscle relaxation was reversed with sugammadex to reach a train-of-four ratio of 4, with a 90% ratio between the first and fourth responses. We chose sugammadex over neostigmine to avoid muscarinic-related adverse effects and provide a more reliable and complete reversal of neuromuscular blockade. Upon regaining consciousness, the patient was extubated, and HFNC was reintroduced.

Recovery

The infusion of dexmedetomidine and lidocaine was continued after the extubation and throughout the first 24 h of the Postoperative Care Unit (PACU) stay, with a reduced infusion rate of 4 mL/h (dexmedetomidine 4 mcg/h and lidocaine 40 mg/h i.v.). HFNC was continued, with FiO_2 initially at 60%. On admission to PACU, the patient's numeric pain score was 2/10.

After the first hour, the patient was over-sedated and somnolent. Arterial blood gas showed a rise of $PaCO_2$ to 61.4 mmHg, probably due to loss of hypoxic respiratory drive (**Table 1**). We reduced FiO_2 to 37% to reach SpO_2 values of 88% to 90%, which enabled $PaCO_2$ reduction and significantly improved the patient's awareness.

To control the postoperative pain during the first 24 h in the PACU, simple analgesics were used, with fixed administration of metamizole 1g and paracetamol 1g every 6 h, and lidocaine and dexmedetomidine were given as an infusion, to cumulative doses of 1000 mg and 100 mcg, respectively. For any reported numeric pain score >3, oxycodone 2 mg i.v. boluses were given. During his stay in the PACU, the patient required 6 mg of oxycodone in total, whereas the maximal numeric pain score was 6/10.

Following a 24-h stay in the PACU, the patient was subsequently transferred to the ward and ultimately discharged home 2 days thereafter.

In the follow-up visit 1 month after the surgery, a loss of 19 kg in body weight was noted, and the patient was referred to start the procedure of the qualification for lung transplantation. At the 1-year follow-up, the patient reduced his body weight by 40 kg in total, required oxygen therapy only at night, with a decreased flow of 1 L/min, and reported a significant improvement in physical capacity to a level that he could return to professional work. In response to this progress, a multidisciplinary decision was made to suspend the lung transplantation qualification.

Discussion

The presented case study provides evidence of effective anesthetic management, utilizing the combination of OFA and postoperative multimodal analgesia, in a patient with grade III obesity, ILD, and comorbidities who had a significantly increased

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risk for respiratory complications. To the best of our knowledge, the anesthetic technique of such a patient has not been previously published in the literature.

In planning general anesthesia for the described patient, our primary objective was to mitigate the potential for complications arising from anesthesia and the risk of severe hypoxia during the induction and postoperative periods. One of the modifiable factors that significantly affects postoperative respiratory complications is opioid use. Clinically relevant disorders of respiratory mechanics can occur following opioid use, even in the absence of overdose symptoms [17]. To address this issue, the Enhanced Recovery After Bariatric Surgery Society guidelines recommend multimodal analgesia, the administration of co-analgesics, regional anesthesia, and non-opioid analgesics [4,18]. These agents, in combination, make it possible to eliminate the intraoperative use of opioids, which is referred to as OFA [4].

The co-analgesics we used were the alpha-2 agonist dexmedetomidine, lidocaine, and NMDA antagonists ketamine and magnesium sulfate. As these drugs have an independent analgesic effect or potentiate the effect of other analgesics, their administration, especially after surgery, can optimize pain management while reducing opioid use and mitigating the risk of their adverse effects, such as respiratory failure [14,19], postoperative nausea and vomiting [14,20-22], or opioid-induced hyperalgesia [23]. Therefore, this allows for faster convalescence after surgery and anesthesia and early mobilization, an essential element of the Enhanced Recovery After Surgery protocol [14,18]. Nevertheless, the impact of OFA on recovery remains controversial, as in a recent meta-analysis dedicated to bariatric surgery, the improvement in this field was debatable [24]. The paper, however, had significant limitations due to high heterogeneity and did not encompass the most recent study, in which co-analgesics administration was prolonged in the PACU, with a significant improvement in the quality of recovery score [25]. We consider the continuation of co-analgesics infusion as a pivotal element affecting the potential benefits in safety and recovery, as in some studies with repeated pain score assessment, the opioid-reducing effect was diminished immediately after cessation of the co-analgesic infusion [14,20].

When administering co-analgesics in OFA, it is crucial to consider their potential adverse effects, especially their impact on the circulatory system. These medications can induce hypotension [26-28] and escalate the need for vasopressors [20]. Therefore, it is imperative to closely monitor patients receiving these medications and manage any adverse effects promptly. In our case, the co-analgesics that were used may have compromised the hemodynamic condition of the patient that had chronic heart failure and an increased risk of pulmonary hypertension, as assessed by echocardiography [29,30]. However, after discussion, we decided that the potential benefits outweighed the risks, and administering the above-mentioned drugs was carried out under continuous invasive blood pressure measurement, with mean arterial pressure values maintained above 65 mmHg during all stages of anesthesia.

In the presented case, we used a relatively low dose of dexmedetomidine, considering the dose-dependent risk of hypotension, bradycardia, excessive sedation, and increased desaturation rates [26]. In the study by Beloil et al, the dexmedetomidine dose was much higher with prolonged administration, which could have attributed to the reported adverse effects [31]. Moreover, in our presented case, we decided to discontinue the administration of ketamine after induction of anesthesia, as even small doses of this drug can trigger hallucinations [21].

An important factor in improving the patient's safety was the use of HFNC in the pre-oxygenation and postoperative periods. Our case aligns with the evidence that HFNC prolongs the safe apnea time during induction [32], and we demonstrated its practical use. After surgery, HFNC at a flow rate of 60 L/min allowed for a potential for atelectasis reduction and better CO_2 flushing. Nevertheless, we were not able to avoid transient hypercapnia caused by excessive PaO_2, but this was successfully managed by lowering FiO_2, as demonstrated in the arterial blood gas at 6 h and 24 h after surgery (**Table 1**).

Although there was a transient aggravation of respiratory failure in the first hour after surgery, our case outcome was favorable. Afraz et al demonstrated that patients on oxygen therapy had significantly higher mortality and morbidity after bariatric surgery [33]; our report could contribute to the effective management of this increased risk during the perioperative period. The presented approach may also prove valuable in planning the anesthesia of such oxygen-dependent bariatric patients in other centers, as well as encouraging qualifying them for bariatric surgery.

A limitation of this study is that it is a single case report, which, by its nature, restricts the generalizability of our clinical approach. Given the very small number of studies on safe anesthetic techniques such as OFA in obese patients with ILD undergoing bariatric surgery, more high-quality observational and randomized controlled studies are warranted for an evidence-based approach in this patient population.

Conclusions

This case report demonstrates a possible successful anesthesia management in an unusual clinical scenario in a high-risk patient with ILD undergoing LSG as a bridge to lung transplantation. Our record reveals that, due to OFA with multimodal postoperative analgesia and HFNC perioperatively, safe

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performance of bariatric procedure was achievable, which resulted in immense improvement in the patient's condition, including a return to professional activity and avoidance of lung transplantation. We hope that this case report encourages clinicians to provide bariatric surgery in the population of patients with obesity and concomitant severe respiratory illness.

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VI.3 Opioid-Free Anesthesia in Bariatric Surgery: Is It the One and Only? A Comprehensive Review of the Current Literature.

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Review

Opioid-Free Anesthesia in Bariatric Surgery: Is It the One and Only? A Comprehensive Review of the Current Literature

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Abstract: Opioid-free anesthesia (OFA) is a heterogeneous group of general anesthesia techniques in which the intraoperative use of opioids is eliminated. This strategy aims to decrease the risk of complications and improve the patient's safety and comfort. Such potential advantages are particularly beneficial for selected groups of patients, among them obese patients undergoing laparoscopic bariatric surgery. Opioids have been traditionally used as an element of balanced anesthesia, and replacing them requires using a combination of coanalgesics and various types of local and regional anesthesia, which also have their side effects, limitations, and potential disadvantages. Moreover, despite the growing amount of evidence, the empirical data on the superiority of OFA compared to standard anesthesia with multimodal analgesia are contradictory, and potential benefits in many studies are being questioned. Additionally, little is known about the long-term sequelae of such a strategy. Considering the above-mentioned issues, this study aims to present the potential benefits, risks, and difficulties of implementing OFA in bariatric surgery, considering the current state of knowledge and literature.

Keywords: opioid-free anesthesia; bariatric surgery; multimodal analgesia; pain treatment; dexmedetomidine; lidocaine; ketamine; nociception; anesthesiology

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1. Introduction

Currently, approximately 2.5 billion adults in the world are overweight, of which 890 million are obese, and this number is constantly increasing [1]. Approximately 600,000 patients undergo bariatric surgery annually; a much larger group has indications for it [2]. Markedly, it has been reported that almost 75% of patients undergoing laparoscopic bariatric surgery may experience moderate and severe pain [3]. The most potent group of pharmacological substances used to alleviate it and to surpass the nociception intraoperatively during general anesthesia are opioids, and it is estimated they are administered to approximately 99% of patients in the USA perioperatively [4,5]. Their mechanism of action affects the modulation of pain impulses, mainly in the central nervous system, making them highly effective. Unfortunately, despite their high analgesic potency, opioid use is connected with the risk of adverse reactions in the postoperative period, such as oversedation, respiratory depression, postoperative nausea and vomiting (PONV), as well as opioid hyperalgesia. These side effects attributed to opioids complicate the postoperative period, increase costs, and prolong the length of hospital stays [6].

Considering the specificity of patients with obesity undergoing bariatric surgery and their increased risk of complications in the intra- and postoperative period, new methods of anesthesia and analgesia are constantly being searched for, which would allow for greater safety and comfort. One of the techniques used for this purpose is opioid-free anesthesia (OFA), but despite growing evidence, its use remains controversial, and its benefits are questioned.

2. Purpose

This article aims to critically evaluate published material on opioid-free anesthesia in bariatric surgery, providing an integrated and synthesized overview of the current state of knowledge. In our review, we plan to assess whether the opioid-free anesthesia technique has an advantage over anesthesia with multimodal analgesia, including opioid use, which is currently standard in bariatric surgery.

3. Material and Methods

The literature search was conducted using the PubMed, Web of Science, and SCOPUS databases using the keywords "opioid free anesthesia", "opioid free analgesia" and "bariatric surgery anesthesia" in the time period from inception to April 2024. A manual search of the reference lists of the selected publications was also performed to identify additional studies for potential inclusion. The initial data search yielded 1318 papers from PubMed, 2847 from Web of Science, and 2457 from SCOPUS. A total of 6622 articles were identified, and after removing duplicates using Rayyan (Johnson & Phillips, 2018, Newport, UK), the remaining 2040 were screened for eligibility. We have included randomized controlled trials referring to bariatric surgery published in English. Through a title and abstract review, 54 studies were further examined, of which 13 studies were retrieved. We excluded 2 studies as they were referring to open bariatric surgery, i.e., laparotomy, which is currently obsolete. The selection process is depicted in Figure 1. After a full text article assessment, 11 relevant randomized controlled trials were included in this review. The relevant studies are depicted in Table 1.

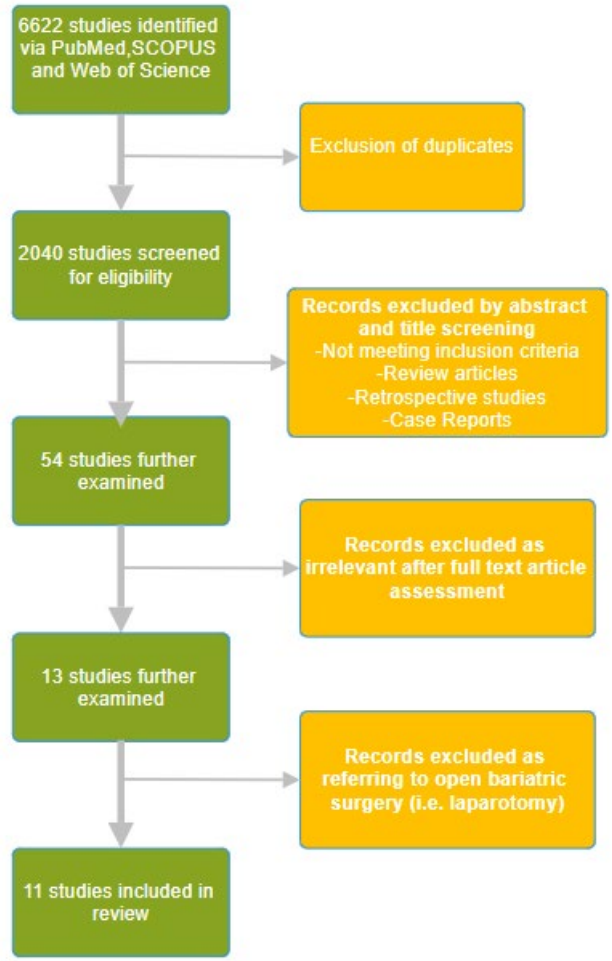

Figure 1. The randomized controlled trials selection flow diagram.

Table 1. OFA randomized controlled trials included in the review. LSG—laparoscopic sleeve gastrectomy, LGB—laparoscopic gastric bypass, SADI-S—single anastomosis dueodeno-ileal bypass.

Author	Year	Number of Patients Enrolled	Type of Surgery	Coanalgesics Used	Primary Outcome Measure	Main Results
Ahmed SA et al. [7]	2022	80	LSG, LGB	Ketamine, Dexmedetomidine, Magnesium sulfate, Lidocaine	Morphine consumption in 24 h	OFA 5.8 vs. 7.2 mg, ($p = 0.003$)
Ibrahim M et al. [8]	2022	103	LSG	Ketamine, Dexmedetomidine, Lidocaine, Dexamethasone	Quality of recovery assessed by QoR-40, at the 6th and the 24th postoperative hour	At the 6th hour, the QoR-40 OFA median [IQR] was 180 [173–195] vs. 185 [173–191], ($p < 0.0001$), but no difference was found at the 24th hour (median values = 191 in both groups)
Mulier JP et al. [9]	2018	45	LSG, LGB	Ketamine, Dexmedetomidine, Lidocaine,	Non-specified	VAS score in the ward OFA group 2.0 vs. 3.3 $p = 0.016$, total morphine consumption 14.7 vs. 18.2 mg $p = 0.33$
Soudi AM et al. [10]	2022	60	Laparoscopic bariatric surgery	Ketamine, Dexmedetomidine, Lidocaine	Non-specified	Nalbuphine consumption in OFA 8.17 $\pm$ 4.8 vs. 23.67 $\pm$ 4.5 mg < 0.001
Ziemann-Gimmel P et al. [11]	2014	119	LSG, LGB, Laparoscopic gastric band	Ketamine, Dexmedetomidine	PONV incidence	OFA group 12 patients (20%) vs. 22 patients (37.3%) [$p = 0.04$; risk 1.27 (1.01–1.61)]
Mansour et al. [12]	2013	28	LSG	Dexamethasone, Ketamine	Heart rate, systolic, diastolic, and mean arterial blood pressure on induction and ½ hourly thereafter	No statistically significant differences between the groups
Clanet et al. [13]	2024	172	LGB	Dexamethasone, Ketamine, Magnesium sulfate, Dexmedetomidine, Lidocaine	Morphine consumption in 24 h	OFA 16 [13–26] vs. 15 [10–24] mg, ($p = 0.183$)
Mieszczański et al. [14]	2023	59	LSG	Dexamethasone, Ketamine, Magnesium Sulfate, Dexmedetomidine, Lidocaine	Oxycodone consumption at 1,6,12 and 24 h, pain scores at 1,6,12 and 24 h	OFA 1 h 4.6 mg vs. 7.72 mg ($p = 0.008$)
Ulbing et al. [15]	2023	99	LGB, LSG, Laparoscopic omega loop bypass, SADI-S	S-ketamine, Dexmedetomidine, Lidocaine, Magnesium Sulfate	Difference in the VAS within the first 24 h after surgery	OFA 2.2 [1–4.4] vs. 4.1 [2–6.5] $p \leq 0.001$

Table 1. *Cont.*

Author	Year	Number of Patients Enrolled	Type of Surgery	Coanalgesics Used	Primary Outcome Measure	Main Results
Campos-Pérez et al. [16]	2022	40	LGB	Ketamine, Dexmedetomidine, Magnesium Sulfate,	Basal and post-surgery cytokine serum levels IL-1β, IL-6, and TNF-α	IL-1β in pre-surgery and post-surgery subjects, significant differences were found (49.58 pg/mL (18.50–112.20) vs. 13 pg/mL (5.43–22), respectively, $p = 0.019$)
Menck et al. [17]	2022	60	LGB	Ketamine, Dexmedetomidine, Lidocaine, Magnesium Sulfate	Pain scores, morphine consumption, delay in discharge from PACU, Rescue morphine	No statistically significant differences between the groups

4. Results

4.1. Opioid-Free Anesthesia—Definition and Assumptions

According to most definitions, OFA is a heterogeneous group of techniques that include general anesthesia without systemic or regional opioid administration [18]. By an alternative definition, OFA involves the use of various methods to eliminate opioids and avoid their side effects without negatively affecting the patient's comfort [19].

Such methods include regional anesthesia (RA) techniques. In the setting of modern laparoscopic bariatric surgery, RA can be used as an element of anesthesia with multimodal analgesia or OFA. The simplest use of RA is the infiltration of the surgical site with local anesthetics [20]. Moreover, interfascial plane blocks, such as Transversus Abdominis Plane (TAP) Block [8,21], Erector Spinae Plane (ESP) Block [22], or the intraperitoneal administration of local anesthetics [23], including a promising blockade of the autonomic innervation of the stomach [24] when used as a part of multimodal analgesia, are also effective in perioperative opioid-sparing. Referring to neuraxial blockades, although epidural and even combined thoracic spinal-epidural anesthesia have been successfully implemented for laparoscopic bariatric procedures [25–27], they are deemed to be too invasive and prevent early mobilization, which has a priority in ERAS strategy [28]. On that basis, there is a consensus that this form of RA can be considered nowadays only in rare cases of open bariatric surgery, but not laparoscopic [28]. Additionally, non-opioid analgesics and coanalgesics (Table 2), including drugs to prevent hyperalgesia and non-pharmacological agents, are also used in OFA.

Table 2. Most frequently used coanalgesics and simple analgesics. NSAID—non-steroidal anti-inflammatory drug.

Agent	Mechanism of Action	Benefits	Potential Side Effects and Risks
Lidocaine i.v.	Blocks voltage-gated sodium channels, hyperpolarization-activated cyclic nucleotide channels, G protein-coupled receptors and potassium receptors, increases intracellular calcium concentration, blocks neutrophil priming	Analgesic, antihyperalgesic and anti-inflammatory properties	Bradycardia, hypotension, risk of toxicity
Ketamine	NMDA receptor antagonist	Analgesic, antihyperalgesic properties	An increase in systemic vascular resistance, tachycardia, hypertension, and risk of hallucinations, may affect bispectral index monitoring
S-Ketamine			
Magnesium Sulfate	NMDA receptor antagonist	Analgesic, antihyperalgesic and antiarrhytmic properties	Prolongation of nodal conduction times, PR, and QRS duration, risk of bradycardia, hypotension, augmenting muscle relaxation
Dexmedetomidine	Alpha 2 adrenergic receptor agonists	Analgesic, inhibiting the sympathetic outflow, antihyperalgesic, decreasing anesthetic requirement, anxiolysis, reduction of shivering threshold	Bradycardia, hypotension, potential vasoconstriction, a sedative effect
Clonidine			
Gabapentin	Calcium channel subunit alpha2-delta, gamma-aminobutyric acid analogs	Analgesic, antihyperalgesic, anxiolysis	A sedative effect, dizziness, blurred vision
Pregabalin			
Dexamethasone	Glucocorticoid	Anti-inflammatory, reducing pain scores after laparoscopy, preventing PONV	Hyperglycemia
Esmolol	Beta 1 adrenergic receptor antagonist	Maintaining hemodynamic stability, short-acting agent	Bradycardia, no analgesic effect
Labetalol	Beta 1,2 and alpha 1 receptor antagonist	Maintaining hemodynamic stability, vasodilatation	Hypotension, bradycardia, asthma exacerbation
Paracetamol	Prostaglandin synthesis inhibitor, possibly other mechanisms	Analgesic, antipyretic	Usually well-tolerated, liver dysfunction requires dose adjustment
NSAID	Inhibition of the cyclooxygenase enzymes	Analgesic, antipyretic, anti-inflammatory	Ulceration or bleeding from the gastrointestinal tract, kidney failure, coagulopathy, drug interactions
Metamizole	The precise mechanism is unknown	Analgesic, antipyretic, spasmolytic	Agranulocytosis, Anaphylaxis, potential for liver toxicity

For practical reasons, a clear distinction should be made between anesthesia without intraoperative opioids and opioid-free postoperative analgesia. Articles reporting the complete elimination of opioids both during and after bariatric surgery [29,30] are based on single case reports and not on routine, reliable practice. In the OFA concept, it is crucial to distinguish between pain and nociception. Pain, according to the definition of IASP

(International Association for the Study of Pain), is an unpleasant sensory and emotional experience that assumes a state of consciousness [31]. Nociception, conversely, refers to a stimulus's reception and excitation transmission in the nervous system [32]. During general anesthesia, the patient's pain perception is disabled, and nociception is based on the response of the sympathetic nervous system, which is mainly the easiest to assess the parameters of the circulatory system, such as heart rate (HR) or blood pressure (BP) [33]. OFA assumes the suppression of the sympathetic nervous system in response to a pain stimulus and the modulation of nociception through the use of methods other than the administration of opioids [34]. Such methods include the use of drugs from the alpha 2 agonists group, lidocaine, ketamine, magnesium sulfate, beta-blockers, or gabapentinoids (Table 2) [35]. Despite its potential benefits, especially for obese patients undergoing bariatric surgery, OFA is controversial and is not currently recommended as a standard treatment. This is due to the limited scientific evidence and frequent reliance on expert opinion [36,37]. This article aims to present the potential benefits, risks, and difficulties associated with this technique.

4.2. Potential Benefits of OFA in Bariatric Surgery

Opioid side effects make it difficult to mobilize the patient early, which is a priority in modern bariatric surgery, in which laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (LGB) are the most frequently performed operations [38]. The use of a comprehensive perioperative care protocol to improve the outcomes of surgical treatment (ERAS, Enhanced Recovery After Surgery), including the reduction or elimination of opioid therapy, is of fundamental importance for patient safety and comfort [28]. Based on its assumptions, the OFA technique should reduce the incidence of respiratory complications, excessive sedation, and postoperative nausea and vomiting (PONV). It should also ensure comparable or better pain control and avoid the risk of opioid-induced hyperalgesia (OIH) [19]. On the other hand, there are concerns about the stability of the circulatory system in patients anesthetized with this technique, as well as whether OFA actually blocks pain conduction or only the stimulation of the sympathetic nervous system in response to a stimulus, and what the long-term consequences of such technique may be [36].

4.3. Respiratory Complications and Oversedation

The avoidance of opioid-induced respiratory depression (OIRD) and oversedation in the postoperative period, and thus an improvement in patient safety, are the main reasons for the interest in OFA in bariatric anesthesia [39–41]. The increased susceptibility to respiratory complications in obese patients involves numerous factors such as reduced functional residual capacity (FRC), atelectasis, air leak, co-occurrence of obstructive sleep apnea (OSA), obese hypoventilation syndrome (OHS) and pulmonary hypertension [42–44]. An increased risk of respiratory complications is common after the administration of opioids and may be clinically significant even without clear signs of overdose [45,46]. In a meta-analysis devoted to the factors of OIRD, one of the conclusions is the possibility of reducing the risk by using opioid-sparing techniques [45]. In line with this recommendation, the Enhanced Recovery After Bariatric Surgery (ERABS) guidelines suggest the standard use of multimodal analgesia involving coanalgesics, regional anesthesia techniques, and non-opioid analgesics [28]. Despite the potentially improved safety due to the complete elimination of opioids, the amount of evidence for the greater safety of OFA in bariatric surgery compared to general anesthesia with multimodal analgesia is minimal. Such evidence is provided by the study of Mulier et al., in which the rate of desaturation < 94% in the postoperative period in patients in the opioid group was 50%, while in only 2 of 23 in the OFA group [9]. However, the issue remains controversial as other trials do not confirm such an effect [13,14,17]. These discrepancies may be explained by the sedative effect of some drugs used in OFA, especially dexmedetomidine, which may have an ambiguous impact on convalescence and the possibility of early mobilization after surgery, presumably dose-dependent. This effect is caused by a presynaptic effect on alpha 2 receptors in the locus coeruleus [47]. As far as the impact of OFA on recovery is concerned, the

trial's results are inconsistent. In a study dedicated to bariatric surgery, dexmedetomidine was associated with meeting the discharge criteria faster in the recovery room; however, it was not associated with a reduction in the length of the hospital stay [48]. Similar results were obtained by Ulbing et al., in whose study patients in the OFA group achieved a statistically higher result in the subjective assessment of recovery using the QoR-40 form 24 and 48 h after surgery, but this was not associated with a shortened hospital stay [15]. On the contrary, in the trial by Clanet et al., no statistically significant difference between the QoR-40 questionnaire results was obtained 24 and 30 days after the surgery [13]. Furthermore, recovery after surgery can also be affected by hallucinations, especially as ketamine is frequently used in OFA protocols. In one study, they were reported in up to 7% of patients; despite this side effect, the satisfaction level of patients during the perioperative period was not affected [12].

4.4. Postoperative Nausea and Vomiting

PONV has a multifactorial etiology and significantly contributes to the diminished comfort of patients undergoing laparoscopic bariatric surgery [9] as well as being the most frequent cause of the readmission of patients after bariatric surgery [49]. PONV may also hinder the patient's rapid mobilization and pose a risk of increased blood pressure, wound dehiscence, or bleeding in the perioperative period [50]. Opioid use is one of the few modifiable factors of PONV, especially as its incidence is dose-dependent [51]. There is clear evidence of a reduction in the prevalence of this complication in patients undergoing laparoscopic bariatric surgery, demonstrated in prospective trials [7,9,11,13–15] and in a meta-analysis dedicated to this group of patients in comparison to the anesthesia with multimodal analgesia group [52]. Still, there are discrepancies regarding the duration of the beneficial effect. In a prospective, randomized study by Ziemann-Gimmel et al. [11], researchers demonstrated that Total Intravenous Anesthesia (TIVA) OFA allows for a more significant reduction of the risk of PONV than triple antiemetic prophylaxis and the reference point was the frequency and severity of PONV 24 h after surgery [11]. A similar beneficial effect was maintained in the study by Mulier et al. [9], but in other trials, this effect was shown only in the immediate hours after surgery [13,14]. In the latter trial, in the OFA group, significantly fewer patients required antiemetics, but lower PONV incidence persisted until the 4th postoperative hour. In other studies, however, the observed differences did not reach statistical significance [10,17].

4.5. Pain Control and Reduction of Postoperative Opioid Consumption

Publications supporting multimodal analgesia in patients undergoing bariatric surgery, as included in the ERAS Society guidelines [28], demonstrate a reduction in the doses of opioids required for pain treatment owing to the use of coanalgesics from the alpha 2 agonists group [53–55], lidocaine [56], magnesium sulfate [57] or ketamine [58]. However, there is limited research comparing OFA and anesthesia with multimodal analgesia, including opioid use, for postoperative pain management and opioid dosage, and existing results are inconclusive. In a meta-analysis dedicated to bariatric surgery by Hung et al., a statistically significant reduction in the NRS score was demonstrated in OFA group patients 24 h after surgery; however, considering that this difference did not exceed 1 point on the NRS scale, its clinical significance is questionable [59]. The same study did not reveal a reduction in the total dose of opioids administered postoperatively, only in the initial period in the recovery room [59]. A study by Menck et al. demonstrated no statistically significant differences in both pain scores and opioid requirements at any given time point [17]. Mulier's 2018 prospective, randomized trial stands out as one of the most notable trials highlighting OFA's benefits. The study involved 50 patients who were assigned to either the OFA group or the opioid administration group. The OFA group required significantly less opioids in the recovery room, 4.9 to 15.3 mg of morphine ($p = 0.04$), and had a lower VAS score of 1.7 to 4.9 ($p = 0.01$) [9]. The study presented some limitations in terms of incomplete information regarding the duration of patients' stay in the PACU before their transfer to the ward, where there was no significant difference in opioid consumption, and the OFA

group presented with only a slightly better VAS score of 2.0 compared to 3.3 in the opioid group ($p = 0.016$) [9]. Similar results were obtained by Ahmed et al. in their randomized controlled trial, in which lower pain scores were noted 4 and 6 h after the surgery, whereas the total morphine consumption was statistically but not clinically lower: 5.8 in the OFA group vs. 7.2 mg in the opioid group ($p = 0.003$). [7]. In line with Mulier's trial, a reduction in the dose of opioids only in the initial postoperative period was also demonstrated by Mieszczański et al. [14]. A possible explanation for this difference may be the fact that drugs used in OFA have a half-life of several hours, and their effects subside shortly after the cessation of their infusion [56,60]. One of the few studies with the continuation of the coanalgesics in the postoperative period is the work of Ulbing et al., which demonstrated a lower opioid consumption and a lower VAS pain score in the OFA group [15]. Maintaining the infusion of these drugs may be critical to achieving the clinical significance of the benefits of OFA in bariatric procedures. This has also been demonstrated in a case report of a patient undergoing LSG as a bridge to eligibility for lung transplantation for interstitial disease [61]. In that case, the infusion of coanalgesics was maintained for 24 h after surgery, which resulted in low total opioid consumption and acceptable NRS scores. In conclusion, there is still a lack of unequivocal evidence that OFA is associated with comparable or better-quality pain management. While the beneficial effects of OFA can be prolonged with the continued administration of coanalgesics in the postoperative period, the assessment of the significance of the clinical benefit of this approach requires further research.

4.6. Tolerance, Opioid-Induced Hyperalgesia (OIH), and Long-Term Sequelae

Intraoperative administration of opioids may spark the development of their acute tolerance, which is associated with an increase in total opioid requirements and increases the frequency of side effects [62,63]. Another coexisting problem is the occurrence of OIH, which entails a lower pain threshold and allodynia [64]. This phenomenon has a separate pathophysiology, but the clinical manifestations are similar and, in practice, difficult to differentiate [64]. OIH and the acute development of tolerance are crucial in bariatric surgery, as frequently used remifentanil has the greatest potential in this respect [65], especially at a high dose [66]. This may have an impact on postoperative pain management [55], and the relationship appears to be dose-dependent [65]. When it comes to proven effects in the prevention and treatment of OIH and the development of tolerance to opioids, ketamine or magnesium sulfate (NMDA receptor antagonists), as well as alpha 2 agonists, often included in OFA protocols, are used [67–70]. OFA has a beneficial effect on reducing the doses of opioids used and, therefore, on the prevention of OIH and the development of tolerance to opioids. This is of significant importance, as there exist publications, including a meta-analysis, that indicate the lack of any discernible benefits associated with the administration of opioids prior to the pain stimulus [71]. Another question is the impact of OFA on the incidence of Persistent Postoperative Pain, which is estimated to occur in up to 30% of patients [72], with the incidence ranging in the literature from 5 to 54.4% [73,74]. Considering the potential detrimental effects associated with the use of opioids, the implementation of OFA may serve as a viable solution for mitigating such risks. Additional research is necessary considering the limited availability of only one small study that does not indicate significant differences in chronic pain incidence or intensity among patients who underwent hysterectomy over a six-month duration [75].

4.7. Hemodynamic Stability

Laparoscopic bariatric surgery is associated with the risk of hemodynamic instability, which is caused by the insufflation of the peritoneal cavity with carbon dioxide and an increase in intra-abdominal pressure, positioning a patient in a steep anti-Trendelenburg position, or from co-occurring cardiovascular diseases in obese people [76]. In this respect, there are concerns about the use of OFA in this group of patients, which is due to the depressive effect of the drugs used on the circulatory system. Dexmedetomidine, the most commonly used alpha 2 agonist, has a parasympathomimetic effect on the cardiac

conduction system and inhibits the sympathetic component of the cardiac plexus, resulting in bradycardia and even sinoatrial block. Moreover, this drug causes the relaxation of the vascular tonus and a decrease in systemic vascular resistance (SVR), leading to a decrease in BP (Blood Pressure). On the other hand, with rapid administration, paradoxical vasoconstriction with an increase in BP may occur due to the non-specific stimulation of alpha 1 receptors [60]. With regard to these dose-related adverse effects of dexmedetomidine, the large multicenter POFA study, which compared OFA anesthesia with dexmedetomidine to anesthesia with remifentanil, demonstrated adverse effects of the first technique, such as hemodynamic instability in the form of bradycardia and in one case, asystole, as well as a more frequent occurrence of hypoxia and greater sedation of patients in the postoperative period [77]. The study was interrupted for safety reasons. The article was criticized because the use of high doses of dexmedetomidine (an average of 1.2 mcg/kg/h) with a long anesthesia time (an average of 268 min) raises doubts, and what is more, the limitation is the high heterogeneity of the anesthetic procedures, of which bariatric surgeries consist only a small portion. Nevertheless, POFA is a significant prospective study that questions the safety and soundness of the OFA technique [61]. Lidocaine also has a hypotensive effect through its negative inotropic effect on cardiomyocytes, similar to magnesium sulfate, an NMDA receptor antagonist, or an antagonist of beta 1 receptors, such as esmolol [78–80]. Lidocaine at a dose of 1.5 mg/kg can even be used for controlled hypotension during general anesthesia [78]. The effect of ketamine is ambiguous, although increasing the tension of the sympathetic nervous system causes an increase in HR, BP, and SV (Stroke Volume) while maintaining SVR. Still, in some patients, it may have a negative inotropic effect, causing hypotension and bradycardia [81]. Taking into account the effects mentioned above, hypotension when using OFA may be a problem and require the use of sympathomimetics such as ephedrine or catecholamines more frequently and in higher doses than in conventional anesthesia with multimodal analgesia, as well as more aggressive fluid therapy [14]. This may pose a risk, especially for patients with ischemic heart disease, hypovolemia, or orthostatic hypotension, and OFA is relatively contraindicated in this group [33]. Another problem is the intraoperative, low controllability of some drugs used in OFA, including alpha 2 agonists and lidocaine, the effects of which may be prolonged due to their half-life [60,82]. In the case of hypotension and bradycardia, even after the discontinuation of the administration of these drugs, the disappearance of their effects will be delayed. On the other hand, the data from the clinical trials are inconclusive and contradictory, as in another recent trial, the differences between OFA and remifentanil groups in terms of hemodynamic stability have not reached statistical significance [13], and patients in the opioid group received more fluids than anesthetized without opioids. Similar results, with no significant differences in hemodynamic parameters between OFA and opioid groups, were obtained in a study by Mansour et al. In this particular study, however, ketamine was the only coanalgesic utilized, avoiding the potential hypotension associated with lidocaine, alpha 2 agonists, or magnesium sulfate use [12]. Therefore, further studies are required on the impact of OFA on hemodynamic stability, and the observed differences may result from the heterogeneity of utilized OFA protocols, especially in proportions of particular coanalgesics used.

4.8. Intraoperative Nociception and Monitoring

Repeated nociceptive stimulation reaching higher levels of the nervous system causes central sensitization, defined by IASP as increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold input [31]. This process contributes to the development of acute and persistent postoperative pain [34,83], which, inadequately treated, apart from numerous other unfavorable effects, is one of the main factors in its chronification. The adopted intraoperative opioid dosage is, in most cases, based on the features of sympathetic nervous system stimulation and is considered an indicator of nociception, i.e., based on the assessment of hemodynamic parameters [35]. Drugs used in OFA are weak analgesics (alpha 2 agonists, ketamine, lidocaine) or have no

direct analgesic effect. Therefore, it is unclear whether these drugs provide hemodynamic stability by effectively attenuating nociception or simply blocking the effector, namely the sympathetic nervous system, and what the consequences of this might be. Monitoring intraoperative nociception is challenging and includes the assessment of the vegetative system based on heart rate variation (HRV), the Analgesia Nociception Index (ANI), the NoL Index [84] or the High-Frequency Variability Index (HFVI) [85] as well as the measurement of pupil width [86], and indirectly by determining stress hormones before and after surgery (e.g., cortisol) [9]. Parameters derived from the EEG recording (e.g., bispectral index BIS, entropy) are not suitable for strictly assessing nociception, and their assessment after ketamine administration is unreliable [87]. The amount of research on obese patients anesthetized using the OFA technique is scarce. The literature describes two case reports of such patients with class III obesity and nociception monitoring by ANI assessment [29,88]. In both articles, this technique allowed for maintaining the ANI in the desired range of 50–70, which allows for reasonable control of nociception and minimizing the risk of the patient feeling pain after waking up [29,88]. However, this method, like other techniques based on HRV assessment, is subject to significant limitations, including the use of atropine, sympathomimetics, or other drugs affecting HR used in OFA [89,90]. In the previously cited work, Mulier demonstrated lower cortisol concentration in patients anesthetized for laparoscopic bariatric surgery in the OFA group compared to anesthesia with sufentanil administration. The cortisol concentration was measured before the induction of anesthesia and then in the postoperative department; the increase was statistically significantly lower in the OFA group, which may indirectly indicate lower perioperative stress in this group of subjects [9]. Moreover, a beneficial effect of OFA on reducing immunologically mediated stress response was demonstrated in a study by Campos-Perez et al. [16], in which patients in the OFA group undergoing LGB had lower interleukin 6 (IL6) serum concentrations postoperatively 13 pg/mL (5.43–22) vs. 49.58 pg/mL (18.50–112.20), respectively, $p = 0.019$. IL-6 is considered to be one of the most important pro-inflammatory interleukins and biomarkers of inflammation and immune activation. On the other hand, no differences in other primary outcomes, TNF-α and IL-1β serum concentration, were detected. In this study, no clinical or statistical differences in parameters such as PONV incidence or NRS scale result were observed. Due to observation time being limited to 24 h after the surgery, no conclusions on the clinical significance of IL-6 reduction sequelae can be made [16].

Considering the limited data on blocking nociception and stress response using the OFA technique and the long-term consequences of this method of anesthesia, more research is warranted in this area.

5. Discussion

The literature proves that OFA is feasible and can be successfully implemented as a strategy for bariatric surgery [19]. As far as certainties are concerned, there is unequivocal evidence that OFA decreases the incidence and severity of PONV compared not only to opioid-liberal anesthesia but also to opioid-sparing [11,52]. In other fields, in which OFA is expected to be superior, there is conflicting or scarce evidence, or the evidence is not allowed to be adapted as a standard, and this evidence refers to improving postoperative pain management and decreasing the postoperative opioid requirements [7,9,10,12–15,17], the incidence of opioid-induced respiratory depression or oversedation [9,13,14,17], maintaining hemodynamical stability [12–14] or finally, improving the recovery [8–10,13,15] and long-term outcomes in terms of postoperative chronic pain incidence. One of the main factors contributing to this fact is the vast heterogeneity of OFA protocols and coanalgesics used, and even the adapted dosing regimens—ideal body weight, lean body weight, or adjusted body weight—as well as if and what type of RA techniques were used.

In our experience, OFA is associated with more interventions of the anesthetist intraoperatively, may pose a risk of hemodynamic instability, and does not shorten the length of hospital stays as compared with anesthesia with multimodal analgesia [14]. In our center, we use it in patients with the paramount risk of respiratory complications, for example,

on chronic oxygen treatment [61,91] or with super-obesity (BMI > 50) in an individual risk assessment, and also in cases of severe PONV history. In such cases, to maximize the potential benefits, we maintain coanalgesic administration throughout up to 12–16 h after the surgery.

Future research concerning OFA should compare it with multimodal, low-opioid strategies (not just "opioid-based" anesthesia), assess the optimal dosing regimen and if prolonging coanalgesic administration postoperatively would improve the results, and finally, the long-term impact on the recovery and the postoperative pain chronification.

6. Conclusions

The elimination of opioids during anesthesia is possible, but it poses many difficulties and must be considered in the context of the entire perioperative period, not just the operating room. While, currently, adapting opioid-sparing strategies as an element of anesthesia with multimodal analgesia to minimize the use of opioids is considered a standard in bariatric perioperative care, there are indications that a more radical approach, such as OFA, may have advantages. Based on these assumptions, more and more centers are introducing their use. On the other hand, there is growing evidence that the benefits may be limited, and issues related to safety, long-term effects, and the place of OFA in the Fast Track Surgery doctrine are not resolved. Therefore, considering the meager amount of literature, OFA should not be used as a standard and only as an anesthetic technique in bariatric surgery. The question of the broader application of this method requires further research.

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VI.4 The effect of pre-emptive oral pregabalin on opioid consumption in patients undergoing laparoscopic sleeve gastrectomy with an analysis of intraoperative hemodynamic stability and quality of recovery: study protocol for a randomized, prospective, double-blind study.

Trials

STUDY PROTOCOL

Open Access

The effect of pre-emptive oral pregabalin on opioid consumption in patients undergoing laparoscopic sleeve gastrectomy with an analysis of intraoperative hemodynamic stability and quality of recovery: study protocol for a randomized, prospective, double-blind study

Piotr Mieszczanski[1*], Grzegorz Gorniewski[1], Marek Janiak[1] and Janusz Trzebicki[1]

Abstract

Background Obese patients undergoing laparoscopic sleeve gastrectomy (LSG) are particularly at risk of opioid-related side effects. To reduce patient exposure to opioids, multimodal analgesia, which involves the use of drugs of different classes, may be utilized. One of the drugs under consideration is pregabalin. Despite an opioid-sparing potential, few studies assess the role of pregabalin as an element of multimodal analgesia in LSG. Considering the limited number and inconsistent results of available studies, we decided to conduct a randomized, prospective study on the effect of preemptive pregabalin administration in obese patients on opioid consumption, pain scores, the incidence of opioid side effects, and hemodynamical stability.

Methods The study is designed as a prospective randomized controlled trial with double-blinding. Randomization will be performed in a block with a parallel 1:1 allocation. The intervention will involve receiving a pregabalin 150 mg capsule 1–2 h before the surgery, whereas the control group will receive an identically looking placebo. The primary outcome measure will be total oxycodone consumption in the first 24 h following surgery. Secondary outcome measures will be pain severity assessed using the Numerical Rating Scale (NRS) 1, 6, 12, and 24 h after surgery, postoperative sedation on the Ramsay scale, PONV impact scale, the incidence of desaturation episodes < 94%, and episodes of blurred vision at 1, 6, 12, and 24 h after surgery, intraoperative hemodynamic parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), total fluid volume, and total ephedrine dose. Patient comfort will be additionally assessed using the QoR-40 questionnaire at discharge.

Discussion The study will explore the efficacy and safety of preemptive pregabalin in a dose of 150 mg as a co-analgesic used in multimodal analgesia for LSG. As studies on opioid-sparing regimes concern the safety of obese

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patients, we aim to contribute objective data with a relatively large study sample size. The result of the present clinical trial may support the reassessment of recommendations to use pregabalin in the studied population.

Trial registration ClinicalTrials.gov NCT05804591. Registered on 07.04.2023.

Keywords Pregabalin, Sleeve gastrectomy, Multimodal analgesia, Quality of recovery

Administrative information

Note: the numbers in curly brackets in this protocol refer to the SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	**The effect of pre-emptive oral pregabalin on opioid consumption in patients undergoing laparoscopic sleeve gastrectomy with an analysis of intraoperative hemodynamic stability and quality of recovery: study protocol for a randomized, prospective, double-blind study**
Trial registration {2a and 2b}	ClinicalTrials.gov (NCT05804591) Date of registration 07.04.2023 All items from the WHO Trial Registration Dataset can be found on the ClinicalTrials.gov
Protocol version {3}	7th April 2023 Protocol version 1.0
Funding {4}	This research received no external funding
Author details {5a}	Piotr Mieszczanski, Grzegorz Gorniewski, Marek Janiak, Janusz Trzebicki 1st Department of Anesthesiology and Intensive Care, Medical University of Warsaw, Lindleya 4, 02–005 Warszawa, Poland + 482,250,221,721 klinanest1@wum.edu.pl
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Role of sponsor {5c}	The sponsor has no role in the study design, data collection, or publication

Background and rationale {6a}

Multimodal analgesia is a technique involving different mechanisms of action, owing to which it is possible to reduce or even eliminate the intraoperative use of opioids and significantly decrease their use postoperatively. To achieve this, several co-analgesics, such as alpha-2 agonists, lidocaine, ketamine, magnesium sulfate, and gabapentinoids, are utilized. They are all part of a concept of multimodal analgesia based on addressing different pain mechanisms. The use of multimodal analgesia reduces opioid-induced side effects in the postoperative period, which is especially beneficial for obese patients with a BMI > 35 qualified for laparoscopic bariatric surgery [1, 2]. Such patients are prone to side effects of opioids, primarily respiratory complications, excessive sedation, and a high risk of postoperative nausea and vomiting, which prevent early patient recovery [3].

Pregabalin, one of the drugs used in multimodal analgesia, is a gamma-aminobutyric acid analog. It has anxiolytic, analgesic, and opioid-sparing properties and is commonly used as a first-line treatment for neuropathic pain [4]. Furthermore, it has effectively prevented opioid-induced hyperalgesia [5, 6]. These properties may prove useful in laparoscopic bariatric surgery, during which there is a risk of nerve fiber injury secondary to cutting and coagulation.

The 2018 ESRA procedure-specific postoperative pain management (PROSPECT) recommendations suggest the use of pregabalin in patients who cannot receive simple analgesics [7]. The above statement is based on two trials involving pregabalin perioperatively in patients who underwent LSG. In the study by Schulmeyer et al., a single 150 mg dose of pregabalin 2 h before surgery allowed for a decrease in the total dose of opioids administered in the postoperative period by 50%. What is essential, pregabalin did not increase the rate of experienced side effects such as excessive sedation or dizziness [8]. Nonetheless, this study has significant limitations, as the study did not implement Patient-Controlled Analgesia (PCA) and more importantly, the authors of the PROSPECT recommendations underline the lack of multimodal analgesia in both the study and control groups. In a study performed by Salama et al. [9], a 68% decrease in the total dose of opioids was possible with 75 mg of pregabalin and a dexmedetomidine infusion of 0.4 μg/kg/h. However, in this study, it is impossible to distinguish between the effects of both medications, as dexmedetomidine has also been proven to have analgesic potential. Similar difficulty in assessing the isolated pregabalin effect has been reported in the observational study by Lam et al. In their study, pregabalin, 150 or 300 mg, depending on the patient's weight, was given as an element of multimodal analgesia to reduce or eliminate total postoperative opioid use [10]. In another trial concerning pregabalin, Alimian et al. demonstrated a reduced

incidence of PONV with concomitant lower pain scores throughout the postoperative period in patients undergoing laparoscopic gastric bypass surgery [11]. The limitations of this study include a lack of assessment of sedation and the effects of specific components of multimodal analgesia, which can vary depending on the procedure and may differ between types of surgeries; thus, they are not fully generalizable to patients undergoing LSG [12].

Concerning analgesic management in our study, remifentanil is a basic intraoperative opioid due to its rapid elimination and short time of action, which is in concordance with ERAS guidelines [1]. Moreover, it has been proven that these two drugs have a synergistic effect, which may be beneficial in the perioperative period but, on the other hand, may also cause an increased risk of adverse effects [13, 14]. Pregabalin also has an antihyperalgesic effect, possibly attenuating opioid-induced hyperalgesia sparked by remifentanil [6].

In addition, as pregabalin is a promising element of multimodal analgesia strategy, we plan to measure intraoperative parameters relating to patient hemodynamical stability such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) every 5 min as well as cumulative doses of vasopressors needed, atropine used to treat bradycardia and administered fluid volume. In our study, we hypothesized that pregabalin might have little or no effect on hemodynamical stability in contrast with most commonly used co-analgesics such as lidocaine, dexmedetomidine, or magnesium sulfate [1, 15–18]. Its possibly negligent impact on the circulatory system would be beneficial as obese patients undergoing LSG are particularly prone to hemodynamic disturbances [19, 20], and hypotension may in these patients spark complications like myocardial infarction or kidney failure [21].

To our knowledge, there are no known studies assessing the impact of pregabalin on patient recovery after LSG, with a specific focus on its sedative effects, in isolation from other medications such as dexmedetomidine [10, 11]. As we hypothesized that pregabalin may have a beneficial impact in this field, such an effect will be measured in the postoperative period on both an objective scale and by filling out the Quality of Recovery-40 questionnaire (QoR-40), constructed to measure patient's experience after a broad spectrum of surgeries [22].

In conclusion, considering the limited number and inconsistent results of available studies on the effect of preemptive pregabalin administration in obese patients on opioid consumption, pain scores, the incidence of opioid side effects, and hemodynamical stability, we decided to conduct our randomized, prospective, double-blind study.

Objectives {7}

Our study aims to assess, in the patients with obesity undergoing LSG, what is the difference in total oxycodone consumption (applied by the PCA pump) between preemptive oral pregabalin 150 mg administration compared with placebo, 24 h after the operation. We hypothesized that the investigated intervention would reduce opioid use and improve recovery with potentially fewer opioid side effects, as well as provide similar intraoperative hemodynamical stability.

Trial design {8}

The study is designed as a double-blind, randomized superiority trial. Equal, parallel 1:1 randomization will be performed using http://www.randomization.com (Dallal GE).

Methods: participants, interventions, and outcomes

Study setting {9}

Academic Hospital in Warsaw, Poland.

Eligibility criteria {10}

Eligible patients should have a BMI > 40 or > 35 with comorbidities, be 18 to 65 years old, and be LSG-eligible. Patients aged above 65 years are rarely qualified for LSG, and the elderly have a higher risk of unwanted effects [23]. Patients who did not agree to participate in the study, are undergoing revision surgery, have an allergy to any of the drugs used in the protocol, have end-stage organ failure, are unable to cooperate in assessing pain intensity on the numerical rating scale (NRS) scale or use a PCA pump will be excluded from the study.

Who will take informed consent? {26a}

The consent will be taken by one of the four dedicated investigators, trained before by the principal investigator**.** The approach for consent will be made in the hospital 1 day before the scheduled surgery. One of the investigators will provide the potential participant with a description of the study, potential risks, their rights as a participant, other relevant details and take informed, written consent on a prepared consent form. They will also hand the participant information leaflet. At the time of obtaining the consent for study inclusion, the patient will have a chance to ask questions.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

No blood samples will be obtained in our study. All participants should give informed, written consent to

the research team to share relevant data with researchers taking part in the research, as well as regulatory authorities. This information will be explained to participants and made available on the consent form. All participants should agree to the above.

Interventions

Explanation for the choice of comparators {6b}

Participants will be randomized into two groups: pregabalin and control. They will receive identically looking capsules 1–2 h before the operation. According to Enhanced Recovery After Bariatric Surgery (ERABS) protocols or European Society of Regional Anaesthesia and Pain Therapy (ESRA) guidelines, no pharmacological agent should be compared to the test drug [7]. Therefore, we will choose a placebo as a comparator. As the sedative effect of pregabalin is dose-related, and a dose of 300 mg may produce a clinically relevant level of sedation, we will investigate a lower dose of 150 mg [1, 7, 24].

The intervention and placebo are produced in our hospital pharmacy department by dedicated hospital pharmacists and trained pharmaceutical technicians. The original capsule containing pregabalin is dismantled and the drug is placed in the capsule used for our trial, identically looking for the intervention and placebo group. Lactose is used as a standard excipient in both groups. Therefore, it is not possible to discern the capsules on appearance or taste. The capsules are prepared in a dedicated room, with temperature, humidity, and light conditions complying with the requirements for drug manufacturing and storage**.** To ensure the quality of the capsules during their manufacturing, the weight of the capsule fill is monitored, and a visual inspection is performed.

Intervention description {11a}

The Pregabalin group will receive a capsule containing 150 mg pregabalin as a single dose 1–2 h before the surgery, whereas the control group will receive a same-looking capsule with a placebo. Lactose will be used as a standard excipient in all capsules. The capsule composition does not include dyes, preservatives, or additives, guaranteeing a standard, identical appearance. The capsule has a volume of 0.36 ml, ensuring ease of swallowing. The expiratory date is 1 month after production by our hospital pharmacy.

Criteria for discontinuing or modifying allocated interventions {11b}

Patients will be free to withdraw from the study at request at any time. Theoretically, in rare cases, it is possible that after randomization and receiving the placebo or intervention, the patient would be disqualified from the surgery or anesthesia due to some impossible-to-predict medical factors that would be revealed immediately before the scheduled operation or will not be able to complete the study treatment. In such a case, they would be withdrawn from the "as treated" analysis of the study outcomes.

Strategies to improve adherence to interventions {11c}

The intervention will be administered to the participant only once during the hospital stay, and this fact is noted in their individual medication chart. Therefore, participants' adherence to interventions will be assured.

Relevant concomitant care permitted or prohibited during the trial {11d}

Patients will continue their concomitant treatment due to chronic diseases in the perioperative period unless it is contraindicated in the planned surgery or anesthesia.

Provisions for post-trial care {30}

All study participants stay under medical supervision during the study period. Should any severe drug adverse reaction to pregabalin occur, specialist consultations are available. After the trial period, the patients are provided with standard, usual care.

Outcomes {12}

The primary outcome measure will be total oxycodone consumption 24 h after surgery. Secondary outcome measures will be as follows: pain scores on the NRS scale at 1, 6, 12, and 24 h after surgery, postoperative sedation on the Ramsay scale [25], PONV impact scale [26], the incidence of desaturation episodes < 94% and episodes of blurred vision at 1, 6, 12 and 24 h after surgery, intraoperative heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP): their highest and lowest values, time of MAP < 65 mmHg, > 90 mmHg, HR < 50 and > 90, total fluid volume, total ephedrine dose and patient's comfort assessed in QoR-40 [22] questionnaire at discharge.

Participant timeline {13}

The participant timeline is detailed in Table 1.

Sample size {14}

The primary outcome of the study is 24-h oxycodone consumption. The mean 24-h oxycodone consumption in our previous study was 31.31 mg in patients on multimodal anesthesia [18] and SD was 13.7. In order to calculate sample size, we made the following assumptions: type 1 error (α) was set at 0.05; type 2 error (β) at 0.9 based on two-tailed testing. We considered a difference between groups (δ) greater than 10 mg, this being

Table 1 The participant timeline

	Study period						
	Enrollment	Allocation	Post-allocation				
Timepoint	− 1 day	Day of surgery	Surgery	1 h	6 h	12 h	24 h	Discharge
Enrollment:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
Interventions: pregabalin or placebo		X						
Assessment:								
Baseline variables	X	X						
Total oxycodone				->	->	->	X	
The NRS scores				X	X	X	X	
Ramsay Score				X	X	X	X	
PONV-Impact score				X	X	X	X	
SatO2 < 94%				X	X	X	X	
Blurred vision				X	X	X	X	
Intraoperative SBP, DBP, MBP and HR			X					
Total fluid			X					
Total ephedrine			X					
QoR-40								X

Enrolment — 1 day before the operation, intervention — 1 to 2 h before surgery, assessments — 24 h postoperatively

roughly 30% of the mean dose given above, and a standard maximal single dose of oxycodone in an adult patient, to be clinically significant. Using a sample size formula for two-tailed testing recommended in [27], a sample size of 76 should be enough to detect a substantial difference, as stated above. Taking into account an assumed mean drop-out of 15%, we have adopted a rounded-up sample size of 90 patients.

Recruitment {15}

Patient recruitment starts in April 2023 and is planned to end before April 2025. There will be 4 dedicated investigators responsible for the screening and recruitment of potential participants. All patients qualified for the primary laparoscopic sleeve gastrectomy are identified, screened, and approached if they meet inclusion and do not have exclusion criteria. All patients, prior to study inclusion and signing the consent forms, are reassured that their participation in this trial is entirely voluntary and that refusing to participate or withdrawal at any time during the study would not result in any kind of penalty or negative consequences for the patient.

Assignment of interventions: allocation

Sequence generation {16a}

The randomization sequence is based on http://www.randomization.com (Dallal GE) performed by an investigator not involved in patient clinical assessment before the start of enrollment to the study.

Concealment mechanism {16}

The list is generated and accessed by one investigator, who provides the list to the hospital pharmacy department, where the capsules with drug or placebo are produced. The ward personnel, including the nurse administrating the capsules to the patients, and operating theatre personnel, including anesthesiologists, have no knowledge of patient group allocation.

Implementation {16c}

All subjects who consent to participate and fulfill the inclusion criteria are randomly assigned to pregabalin or placebo groups. The principal investigator will receive the allocation sequence only after the last participant has completed the trial observation period.

Assignment of interventions: blinding

Who will be blinded {17a}

The participants, ward, operating theatre, and postoperative care unit personnel, as well as investigators assessing clinical data of the patients will be blinded to subject allocation.

Procedure for unblinding if needed {17b}

Contact with the investigator responsible for unblinding is possible at all stages of the study. Their mobile telephone number is on the protocols in which the participant's data is collected. If the principal investigator is unavailable, there is an alternative contact to a second, dedicated researcher. In the event of immediate unblinding of the randomization, contact with the trial methodologist (GG), or on-duty staff of the hospital pharmacy is possible even in out-of-hour time. Unblinding is permissible in case of serious complications or suspected severe adverse reactions with a possible relation to the intervention.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data will be collected in 2 protocols: one for the intraoperative evaluation, filled in by the anesthesiologist, and one dedicated for the postoperative period, filled in by the PACU nurse. The nurses note data, such as oxycodone use from the PCA pump and pain scores (NRS) at specified time points, and record these in a dedicated protocol.

Plans to promote participant retention and complete follow-up {18b}

Data will be collected during the hospital stay. At the end of the hospital stay, as a standard 24 h after the surgery, study subjects will be encouraged to fill in the QoR-40 questionnaire.

Data management {19}

The data will be collected in paper form and stored in binders, to which only the principal investigator will have access. After data collection, investigators will check all forms for missing records. The data will be entered manually into an electronic database independently by one investigator, checked for accuracy by a second investigator, and stored on a secure database accessible with a personal login**.** After completion of the study, all data and study documents will be archived and stored by the principal investigator. The data is not public, but upon reasonable request, anonymous data can be made available.

Confidentiality {27}

The data will be treated anonymously and confidentially, and the personal details of participants will not be revealed at any stage of the study. Every participant receives an ID number to anonymize data collection. The identifiable data will be stored separately in paper form in binders, whereas typed-in, anonymized, unidentifiable data will be stored only in electronic form in a secured database.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

No biological specimens will be collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

We set the significance level at $\alpha = 0.05$, consistent with common practice in the biomedical sciences, to minimize the probability of a Type I error, which involves incorrectly rejecting a true null hypothesis. The distribution of numerical variables was evaluated for normality using the Shapiro–Wilk test.

Statistical methods for numerical outcomes with one-time measurement

For numeric outcomes involving a single measurement point (e.g., total oxycodone consumption at 24 h, comparison of lowest and highest BP and HR values, duration of MBP below 65 mmHg or above 90 mmHg, HR below 50/min, and HR above 90/min, total fluid volume administered, total ephedrine usage during surgery, QoR-40 score at discharge), the significance of differences between the study group and the control group will be assessed using the Wilcoxon sum rank test. This non-parametric test is chosen based on the assumption that the distributions of these numerical variables do not conform to a normal distribution. For each outcome variable, the median and interquartile range (IQR) will be reported for both the study and control groups. In addition to the *p*-values, the Wilcoxon effect size (*r*) will be calculated to quantify the magnitude of the difference between the groups. Where possible, 95% confidence intervals for median differences between groups will be reported to provide an estimate of the precision of the observed effects.

Statistical methods for numerical outcomes with multiple measurements

Estimation of the differences between the treatment and control groups for the numerical variables, specifically the NRS score and the PONV-Impact score was conducted using a Repeated Measures Linear Mixed Effects Regression (RLMER) model. This approach was chosen to appropriately handle the intrinsic correlation within patient-level repeated measures data collected at multiple time points. The RLMER model was structured to include fixed effects for the treatment group, time points, and the interaction between the treatment group and time, allowing us to assess how treatment effects vary over time. Additionally, patient-specific random intercepts were incorporated to account for individual

variability in baseline scores, which assumes that each patient has a unique starting point that affects all their measurements. We also controlled for potential confounders (e.g. sex, age, BMI) by including them as fixed effects in the model (see Additional file 1: Appendix A for the RLMER model specification).

The effect sizes (Cohen's *d*) between the treatment and control groups at each specific time point were estimated through contrast analysis, utilizing the estimation of marginal means (EMMs).

Statistical methods for dichotomic outcomes with multiple measurements

For the dichotomous outcomes, specifically for instances of SatO2 falling below 94% and the occurrence of blurred vision, differences between the treatment and control groups at each time point were systematically analyzed using a Generalized Linear Mixed Effects Model (GLMER) with a logit link function. This model was chosen to appropriately handle the binary nature of the data, where the outcomes were coded as 1 for events (i.e., SatO2 below 94% or blurred vision) and 0 otherwise. The differences between groups at each time point were quantified using Odds Ratios (ORs), derived from the estimated marginal means (EMMs) of the fitted GLMER model. Odds Ratios represent the odds of the event occurring in the treatment group relative to the control group, adjusted for other model factors. The ORs, along with their 95% confidence intervals and *p*-values, were presented at each time point to assess the strength and significance of the group differences. These results provide insights into how the likelihood of adverse outcomes (low SatO2 or blurred vision) varies between the treatment and control groups across different time points.

Statistical methods for ordinal outcomes with multiple measurements

For an ordinal outcome, such as the Ramsay score, cumulative link mixed model (CLMM) also known as proportional odds model was used. The response variable, Ramsay score, was modeled using the proportional odds assumption, where the cumulative log-odds of being at or below a certain category are modeled linearly in terms of predictors (see Additional file 3: Appendix C for model specification). The model estimates provided insights into how the probability of achieving a certain level of sedation changes over time and differs between treatment groups while controlling for other covariates.

Characteristics of the statistical tool and external packages

Analyses will be conducted using the R Statistical language (version 4.3.1; R Core Team, 2023) [28] on Windows 10 pro 64 bit (build 19,045), using the packages lme4 (version 1.1. [29]), Matrix (version 1.6.1.1; [30]), robustlmm (version 3.2.3; [31]), emmeans (version 1.8.9; [32]), ggeffects (version 1.3.2; [33]), sjPlot (version 2.8.15; [34]), performance (version 0.10.8; [35]), report (version 0.5.7; [36]) and gtsummary (version 1.7.2; [37]).

As our study is not a high-risk study that uses complex statistical methods, we decided to integrate a statistical analysis plan in this study protocol instead of publishing a separate, detailed statistical analysis plan before the analyses are undertaken [38, 39].

Data collection and monitoring

Clinical data will be entered into protocols in paper form. After each assessment, the identifiers (e.g., name and birth date) will be anonymized, coded, and stored securely. The files will be backed up in a password-protected database. Data will be handled according to EU and local regulations.

Interim analyses {21b}

No interim analyses are planned, and no serious adverse effects are expected to arise during the study, as all therapeutic methods are well-established in many other clinical settings.

Methods for additional analyses (e.g., subgroup analyses) {20b}

As yet, there is no plan to perform subgroup statistical analysis.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Analyses will be performed for the groups as randomized, primarily with an "as treated" approach. Participants withdrawing from the trial will be followed up, according to the routine clinical practices, but not analyzed further from the point of withdrawal unless they consent using the selected data.

In this type of clinical study, with a very short observation time of clinical data, which is monitored in the PACU, the possibility of missing values will be very low, especially in the primary outcome measure, as the data on oxycodone consumption will be collected using electronic PCA log. Overall, we expect missing outcome data to be minimal and only due to human error or equipment malfunction and, therefore, completely at random. In such a case, missing data will not be replaced.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

Data associated with published work will be available upon reasonable request. Should this occur, only

anonymous data will be made available to protect participant confidentiality.

Composition of the coordinating center and trial steering committee {5d}

The study will be coordinated by the principal investigator and one dedicated researcher, who will coordinate all phases, including randomization and data storage.

Composition of the data monitoring committee, its role and reporting structure {21a}

The study includes no interim analysis; the patients involved have non-critical conditions and will undergo treatment for a relatively brief period. Furthermore, pregabalin has a well-established safety profile with a very low probability of harm to the patient. Therefore, apart from the supervision of the Medical University of Warsaw, no external data monitoring is planned.

Adverse event reporting and harms {22}

Most reported adverse effects caused by pregabalin were mild to moderate intensity, dose-dependent, and occurred within the first 2 weeks of initiating treatment. The most common adverse reactions reported across all patient populations in premarketing controlled trials, which occurred in greater than or equal to 5% of patients taking pregabalin and twice the rate reported by patients receiving placebo, were: somnolence, dizziness, blurred vision, difficulty with concentration/attention, dry mouth, edema, and weight gain [40].

In our trial, participants will be advised to contact ward personnel as soon as possible in case of unexpected or adverse effects or any discomfort supposedly associated with the capsule intake. All the patients will be supervised during their hospital stay, and all possible adverse events or reactions will be observed, recorded, and reported in the study.

Frequency and plans for auditing trial conduct {23}

The research team will discuss trial conduct during a meeting every 3 months or more frequently if necessary. If there are any changes in the study, the Bioethics Committee, the journal, and Clinical Trials will be notified as soon as possible.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

This study has been approved by the Bioethics Committee of the Medical University of Warsaw (KB/17/2023), and the study was registered on 07.04.2023 in Clinical Trials (NCT05804591). The study was compliant with the principles outlined in the Declaration of Helsinki and adhered to the applicable CONSORT guidelines.

Patients eligible for recruitment will obtain detailed information about the trial, including potential risks, and subsequently, informed, written consent will be obtained. The consent form was approved by the Bioethics Committee.

Any deviation from the protocol will be documented in a report. All significant protocol modifications have to be reviewed by the Bioethics Committee, then registered in Clinical Trials, and communicated among the researchers. If the participant information changes, updated consent forms and patient leaflets have to be used.

Dissemination plans {31a}

The trial team will disseminate the results. The team will meet every month to discuss the progress of the study. The results obtained from this study will be disseminated at conferences. A full study report will be submitted for publication in a peer-reviewed journal. We do not plan to notify the participants of the results of the study as a standard, but we can do so upon request.

Discussion

We describe the protocol of a clinical trial to evaluate the effect of preemptive oral pregabalin administration as an element of multimodal analgesia strategy in patients undergoing LSG, which is most commonly performed in bariatric surgery [41]. Given the limited number of clinical trials and methodological restrictions in existing publications [8–11], which demonstrate varying but significant opioid use reduction in the postoperative period as well as the scarce amount or absence of studies focusing on other significant aspects, additional evidence is required before incorporating pregabalin into a multimodal regimen in the perioperative management of LSG [42].

Our study's possible limitation may be the use of a *z*-test for the primary outcome to estimate the sample size, while we expect the use of a non-parametric test in the analysis. Therefore, the non-parametric analysis may not reach 90% power. However, as we applied a 15% larger sample size, it may compensate for using a non-parametric test.

In conclusion, the results of the trial based on our protocol will aim at filling this gap and provide us with evidence on the effect of pregabalin administration in a dose of 150 mg on opioid consumption, pain scores, quality of recovery, and hemodynamic stability, which may contribute to a reassessment of recommendations to use this drug in the patients undergoing LSG.

Trial status

The current protocol version 1.0 is dated 07.04.2023. The recruitment start date is 24th April 2023 and it is planned to be completed by April 2025. Our study is currently enrolling participants.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08225-3.

Additional file 1: Appendix A – The RLMER model specification.

Additional file 2: Appendix B – The GLMER model specification.

Additional file 3: Appendix C – The CLMM model specification.

Acknowledgements
Not applicable.

Authors' contributions {31b}
PM is the Principal Investigator; he conceived the study, led the proposal and protocol development, and wrote the original draft of this manuscript. GG was the lead trial methodologist. MJ reviewed and edited the manuscript. JT contributed to the study design and reviewed the manuscript. All authors read and approved the final version of the manuscript.

Funding {4}
This research received no external funding.

Availability of data and materials{29}
The anonymized data generated and analyzed during the current study, including the statistical code, will be available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate {24}
This study was approved by the Bioethics Committee of the Medical University of Warsaw (KB/17/2023) on January 16, 2023, under the reference number KB17/2023. Written informed consent will be obtained from all participants. The study is compliant with the principles outlined in the Declaration of Helsinki and adheres to the applicable CONSORT guidelines.

Consent for publication {32}
Not applicable.

Competing interests {28}
The authors declare they have no competing interests.

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Publisher's Note

VII. RESULTS AND SUMMARY

The dissertation comprises of four distinct papers: a randomized control trial, case report, review and a published study protocol. The focus of the presented manuscripts was placed on patient safety and comfort with regards to opioid-sparing anesthetic techniques for laparoscopic bariatric surgery.

In the first presented manuscript (VI.1), a novel technique of OFA was assessed in the most commonly performed bariatric procedure, that is, LSG [3], when compared with standard anesthesia using multimodal analgesia in adherence to ERABS and PROSPECT guidelines [2,14]. There is an ongoing debate on OFA in bariatric surgery due to limited research and conflicting results. Despite assumptions that such an anesthetic technique would improve safety, comfort, and recovery speed of obese patients, there is a report of potential harm [10] and lack of benefits of such management. In our study, by adapting the OFA protocol from a publication by Mauermann et al. [35] we demonstrated only a limited advantage of OFA, restricted to the first postoperative hour, when opioid requirements and PONV prevalence were significantly lower. In contrast to our expectations, OFA did not affect crucial clinical parameters such as total oxycodone consumption, pain scores, or incidence of desaturations or sedation level. Also, both techniques allowed early hospital discharge the day after surgery, which is of paramount importance in the ERAS strategy. On the other hand, participants allocated to the OFA group experienced more hemodynamic instability, required higher vasopressor doses and fluid infusions, which is clinically a serious drawback, questioning the balance of gains and risk. However, the significant limitation of our study lies in restricting co-analgesics only to the time of surgery. It is possible that continuing their administration into the postoperative period could extend clinical benefits and make them more prominent.

A practical application of OFA, combined with an extended administration of co-analgesics up to 24 hours is described in our second manuscript (VI.2). In the publication, we present a case report of an obese patient with co-existing interstitial lung disease (ILD) requiring home oxygen therapy who has been considered for bariatric surgery as part of a bridge to lung transplantation eligibility. In such high-risk patients perioperative complications remain a concern. We successfully adapted OFA with multimodal, opioid-sparing postoperative analgesia as a strategy, which helped reduce the perioperative risk of this individual patient. Our findings, despite limitations of being a case report, indicate that techniques such as OFA may be

effectively utilized in the anesthetic management of obese patients with severe lung comorbidities who are on oxygen therapy.

Our third paper is a narrative review synthesizing contemporary state of knowledge on OFA in bariatric surgery (VI.3). It covers major clinical issues, including its impact on respiratory complications, pain scores, and pain management, prevalence of oversedation, PONV, late and persistent sequelae, opioid-induced hyperalgesia, opioid tolerance, intraoperative nociception, and stress response. In our study, we presented a broad spectrum of RCTs and attempted to interpret conflicting and ambiguous study results. As one of the difficulties in describing an OFA technique stems from vast heterogeneity of utilized protocols and varying nomenclature, our intention in the review article was to shed light on complicated issues and discuss clinical scenarios in which its application may be beneficial for patients.

Finally, considering that clinical advantages of OFA technique may be limited and potentially associated with hemodynamic instability, we decided to plan and conduct a new RCT to investigate the effect of pre-emptive pregabalin administration on opioid consumption, pain scores, intraoperative hemodynamic stability, and quality of recovery. Our fourth paper comprises a structured study protocol of a randomized, double-blinded clinical trial in which we describe our current research in detail (VI.4). Pregabalin is a promising drug that has analgesic, opioid-sparing, and anxiolytic properties [36]. Moreover, it has efficiently prevented opioid-induced hyperalgesia [37,38]. Taking into account a scant amount of research, pregabalin may be considered an under-investigated co-analgesic in bariatric surgery, and those few studies that have examined it have serious methodological limitations [39,40,41]. As a result, according to PROSPECT guidelines, pregabalin currently can be considered only in cases of inability to administer simple analgesics, which are extremely rare clinical scenarios [14]. We hope that results of our study based on the published protocol will help fill a gap in our knowledge on the effectiveness and possible harm of pregabalin use in patients undergoing LSG, with future ramifications on perioperative recommendations.

Conclusions:

1) Although there is a general consensus that opioid-sparing strategies improve the safety and comfort of obese patients undergoing laparoscopic sleeve gastrectomy, it is not resolved how such a strategy should be optimally implemented.
2) Opioid-free anesthesia may have potential advantages, but due to safety concerns and efficiency, it is currently not deemed a standard strategy. As the benefits of this strategy

are limited if applied only at the time of surgery, its optimal mode of administration requires further studies.

3) The novel opioid-sparing strategies like pre-emptive pregabalin administration are promising, but their impact on safety and comfort requires more research to identify its place in clinical practice.

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IX. BIOETHICAL COMMITTEE APPROVALS OF STUDIES CONSTITUTING THE DISSERTATION

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
Fax: 022/ 57 - 20 -165

ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

KB/.....5...../2020

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 13 stycznia 2019 r. po zapoznaniu się z wnioskiem:

Lek Piotr Mieszczański,
I Klinika Anestezjologii i Intensywnej Terapii ,
ul. Lindleya 4, 02-005 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt.: „Znieczulenie bezopioidowe w bariatrii. Badanie randomizowane."

wyraża następującą
opinię

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

*niepotrzebne skreślić

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

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02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

KB/17...../2023

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 16 stycznia 2023 r. po zapoznaniu się z wnioskiem

Lek. Piotr Mieszczański
I Klinika Anestezjologii i Intensywnej Terapii ,
ul. Lindleya 4, 02-005 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt."Zastosowanie pregabaliny u pacjentów poddawanych laparoskopowej resekcji żołądka.Badanie randomizowane podwójnie zaślepione z grupą placebo."

- Badanie może być prowadzone wyłącznie w okresie obowiązywania polisy ubezpieczeniowej.

wyraża następującą
opinię

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

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Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

*niepotrzebne skreślić

X. MANUSCRIPT CO-AUTHORS' DECLARATIONS

Warszawa, 23.07.2024
(miejscowość, data)

Dr n. med. i n. o zdr. Radosław Cylke
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Comparison between multimodal and intraoperative opioid free anesthesia for laparoscopic sleeve gastrectomy: a prospective, randomized study. Sci Rep. 2023 Aug 4;13(1):12677** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

zbieranie danych, czynny udział w badaniu, akceptacja wersji do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

Wkład lek. Piotra Mieszczańskiego w powstawanie publikacji określam jako 70 %,

(imię i nazwisko kandydata do stopnia)

obejmował on: *koncepcję i projekt badania, czynny udział w badaniu, analizę i interpretację wyników, napisanie artykułu, krytyczną ocenę, akceptację wersję do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Piotra Mieszczańskiego

(imię i nazwisko kandydata do stopnia)

dr n. med. i n. o zdr.
Radosław Cylke
specjalista chirurgii ogólnej
3168980

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 23.07.2024
(miejscowość, data)

Dr hab. n. med. Janusz Trzebicki
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Comparison between multimodal and intraoperative opioid free anesthesia for laparoscopic sleeve gastrectomy: a prospective, randomized study. Sci Rep. 2023 Aug 4;13(1):12677** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

koncepcja i projekt badania, nadzór merytoryczny, krytyczna ocena i akceptacja wersji do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 10 %.

Wkład lek. Piotra Mieszczańskiego w powstawanie publikacji określam jako 70 %,

(imię i nazwisko kandydata do stopnia)

obejmował on: *koncepcję i projekt badania, czynny udział w badaniu, analizę i interpretację wyników, napisanie artykułu, krytyczną ocenę, akceptację wersję do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Piotra Mieszczańskiego

(imię i nazwisko kandydata do stopnia)

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(podpis oświadczającego)

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Warszawa, 23.07.2024
(miejscowość, data)

Prof. dr hab. n. med. Wojciech Lisik
(imię i nazwisko)

OŚWIADCZENIE

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Warszawa, 23.07.2024
(miejscowość, data)

Dr n. med. Paweł Ziemiański
(imię i nazwisko)

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(imię i nazwisko kandydata do stopnia)

Dr n. med. i n. o zdr.
Paweł Ziemiański
specjalista chirurgii ogólnej
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2452670

.....
(podpis oświadczającego)

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Warszawa, 23.07.2024
(miejscowość, data)

Dr n. med i n. o zdr. Radosław Cylke
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Successful Anesthetic Management for Obese Patients with Interstitial Lung Disease Undergoing Laparoscopic Sleeve Gastrectomy: A Bridge to Improved Lung Transplant Eligibility. Am J Case Rep. 2024 Mar 19;25:e942736** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
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dr n. med i n. o zdr.
Radosław Cylke
specjalista chirurgii ogólnej
3168980

.....
(podpis oświadczającego)

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Warszawa, 23.07.2024
(miejscowość, data)

Dr hab. n. med. Janusz Trzebicki
(imię i nazwisko)

OŚWIADCZENIE

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(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Piotra Mieszczańskiego

(imię i nazwisko kandydata do stopnia)

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Warszawa, 23.07.2024
(miejscowość, data)

Dr n. med. i o zdr. Marek Janiak
(imię i nazwisko)

OŚWIADCZENIE

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Wkład lek. Piotra Mieszczańskiego w powstawanie publikacji określam jako 70 %,

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(imię i nazwisko kandydata do stopnia)

Marek Janiak
.....
(podpis oświadczającego)

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Warszawa, 23.07.2024
(miejscowość, data)

Prof. dr hab. n. med Wojciech Lisik
(imię i nazwisko)

OŚWIADCZENIE

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Warszawa, 23.07.2024
(miejscowość, data)

Dr n. med Paweł Ziemiański
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Successful Anesthetic Management for Obese Patients with Interstitial Lung Disease Undergoing Laparoscopic Sleeve Gastrectomy: A Bridge to Improved Lung Transplant Eligibility. Am J Case Rep. 2024 Mar 19;25:e942736** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
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(imię i nazwisko kandydata do stopnia)

Dr n. med. i n. o zdr.
Paweł Ziemiański
specjalista chirurgii ogólnej
i transplantologii klinicznej
2452670

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Warszawa, 23.07.2024
(miejscowość, data)

Dr hab. n. med. Janusz Trzebicki
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Opioid-Free Anesthesia in Bariatric Surgery: Is It the One and Only? A Comprehensive Review of the Current Literature. Healthcare (Basel). 2024 May 27;12(11):1094** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

koncepcja i projekt badania, nadzór merytoryczny, analiza i interpretacja wyników, krytyczna ocena i akceptacja wersji do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 20 %.

Wkład lek. Piotra Mieszczańskiego w powstawanie publikacji określam jako 70 %,

(imię i nazwisko kandydata do stopnia)

obejmował on: *koncepcję i projekt badania, analizę i interpretację wyników, napisanie artykułu, krytyczną ocenę, akceptację wersję do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Piotra Mieszczańskiego

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 23.07.2024
(miejscowość, data)

Dr n. med. Marcin Kołacz
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **Opioid-Free Anesthesia in Bariatric Surgery: Is It the One and Only? A Comprehensive Review of the Current Literature. Healthcare (Basel). 2024 May 27;12(11):1094** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

analiza i interpretacja wyników, krytyczna ocena i akceptacja wersji do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 10 %.

Wkład lek. Piotra Mieszczańskiego w powstawanie publikacji określam jako 70 %,

(imię i nazwisko kandydata do stopnia)

obejmował on: *koncepcję i projekt badania, analizę i interpretację wyników, napisanie artykułu, krytyczną ocenę, akceptację wersję do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Piotra Mieszczańskiego

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 23.07.2024
(miejscowość, data)

Dr hab. n. med. Janusz Trzebicki
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **The effect of pre-emptive oral pregabalin on opioid consumption in patients undergoing laparoscopic sleeve gastrectomy with an analysis of intraoperative hemodynamic stability and quality of recovery: study protocol for a randomized, prospective, double-blind study. Trials. 2024 Jun 7;25(1):367.** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

koncepcja i projekt badania, nadzór merytoryczny, krytyczna ocena i akceptacja wersji do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 5 %.

Wkład lek. Piotra Mieszczańskiego w powstawanie publikacji określam jako 70 %,

(imię i nazwisko kandydata do stopnia)

obejmował on: *koncepcję i projekt badania, napisanie artykułu, krytyczną ocenę, akceptację wersję do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Piotra Mieszczańskiego

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 23.07.2024
(miejscowość, data)

Dr n. med. i o zdr. Marek Janiak
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **The effect of pre-emptive oral pregabalin on opioid consumption in patients undergoing laparoscopic sleeve gastrectomy with an analysis of intraoperative hemodynamic stability and quality of recovery: study protocol for a randomized, prospective, double-blind study. Trials. 2024 Jun 7;25(1):367.** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

napisanie artykułu, krytyczna ocena, i akceptacja wersji do druku

Mój udział procentowy w przygotowaniu publikacji określam jako 20 %.

Wkład lek. Piotra Mieszczańskiego w powstawanie publikacji określam jako 70 %,

(imię i nazwisko kandydata do stopnia)

obejmował on: *koncepcję i projekt badania, napisanie artykułu, krytyczną ocenę, akceptację wersję do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Piotra Mieszczańskiego

(imię i nazwisko kandydata do stopnia)

Marek Janiak
.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 23.07.2024
(miejscowość, data)

Dr n. med. Grzegorz Górniewski
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. **The effect of pre-emptive oral pregabalin on opioid consumption in patients undergoing laparoscopic sleeve gastrectomy with an analysis of intraoperative hemodynamic stability and quality of recovery: study protocol for a randomized, prospective, double-blind study. Trials. 2024 Jun 7;25(1):367.** oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

koncepcja i projekt badania, krytyczna ocena i akceptacja wersji do druku

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(imię i nazwisko kandydata do stopnia)

obejmował on: *koncepcję i projekt badania, napisanie artykułu, krytyczną ocenę, akceptację wersję do druku.*

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Piotra Mieszczańskiego

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników