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Special indications for Opioid Free Anaesthesia and Analgesia, patient and procedure related: Including obesity, sleep apnoea, chronic obstructive pulmonary disease, complex regional pain syndromes, opioid addiction and cancer surgery

Adrian Sultana, MD FRCP FANZCA, Anaesthetist [a, *],
David Torres, MD, MSc, Director of Outcome Research [b],
Roman Schumann, MD, Professor of Anesthesiology and Perioperative Medicine [c]

[a] *Sydney Institute for Obesity Surgery and University of New South Wales, PO BOX 494, Double Bay, NSW, 1360, Australia*
[b] *Clinica Santa Maria, Universidad de Los Andes, Outcome Research, Av. Santa Maria 0500, 6° Piso, Providencia, Santiago, 7520378, Chile*
[c] *Tufts University School of Medicine, Tufts Medical Center, Department of Anesthesiology and Perioperative Medicine, 800 Washington St, Boston, MA, 02111, USA*

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Opioid-free anaesthesia (OFA) is a technique where no intra-operative systemic, neuraxial or intracavitary opioid is administered with the anaesthetic. Opioid-free analgesia similarly avoids opioids in the perioperative period.
There are many compelling reasons to avoid opioids in the surgical population.
A number of case reports and, increasingly, prospective studies from all over the world support its benefits, especially in the morbidly obese population with or without sleep apnoea.
A derivative technique is opioid sparing, where the same techniques are used but some opioid use is allowed.
This chapter is a review of the current knowledge regarding opioid-free or low-dose opioid anaesthetic and analgesic techniques for the following special populations: obesity, sleep apnoea,

* Corresponding author.
E-mail addresses: a.sultana@unsw.edu.au (A. Sultana), dtorres@clinicasantamaria.cl (D. Torres), rschumann@tuftsmedicalcenter.org (R. Schumann).

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chronic obstructive pulmonary disease, complex regional pain syndromes, acute/chronic opioid addiction and cancer surgery.
Practical aspects include sympatholysis, analgesia and Minimum Alveolar Concentration (MAC) reduction with dexmedetomidine; analgesia with low-dose ketamine and co-anaesthesia; and sympatholysis with intravenous lignocaine.
Non-opioid adjuvants such as NSAIDS, paracetamol, magnesium, local anaesthetic infiltration and high-dose steroids are added in the perioperative period to further achieve co-analgesia.
Loco-regional anaesthesia and analgesia are also maximised.
It remains to be seen whether OFA and early postoperative analgesia, which similarly avoids opioids, can prevent the development of hyperalgesia and persistent postoperative pain syndromes.

Definition

Opioid-free anaesthesia (OFA) is a technique where no intraoperative systemic, neuraxial or intracavitary opioid is administered with the anaesthetic. Opioid-free *analgesia* similarly avoids opioids in the perioperative period.

For each component of the technique in Fig. 1, this chapter aims to guide readers to appraise the evidence base regarding OFA and assess its efficacy and safety.

This chapter also provides a clinical protocol to assist those who seek to use OFA in the operating room.

Morbid obesity and breathing-related sleep disorders (OSA)

The goals of avoiding opioids in the obese surgical population include the reduction or prevention of:

- Respiratory depression
- Central muscle rigidity

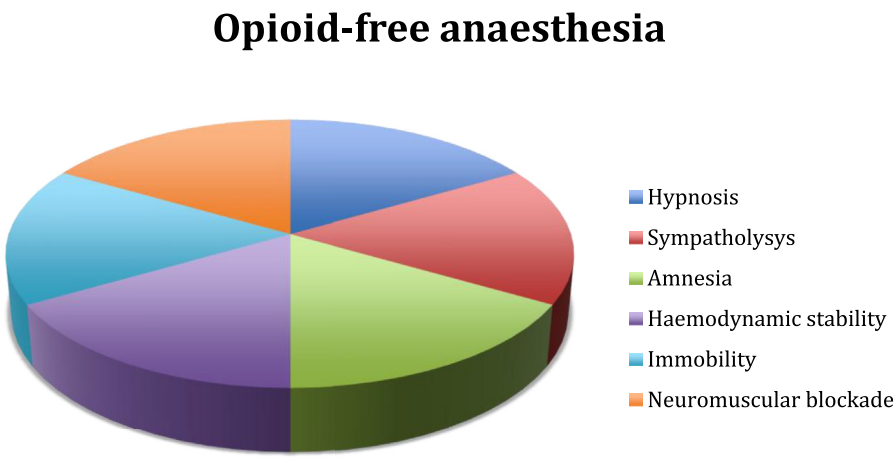

Fig. 1. Components of the OFA technique adapted from Mulier [1].

- Pharyngeal muscle weakness
- Obstructed breathing
- Negative inotropism
- Nausea, vomiting, ileus and constipation
- Urinary retention
- Tolerance and addiction
- Dizziness and
- Excessive somnolence.

It is highly desirable to avoid respiratory depressants in patients who are diagnosed with or suspected of having sleep-disordered breathing or obstructive sleep apnoea to reduce postoperative complications.

To address the opioid-related adverse events described above, the Sydney Institute of Obesity Surgery (SIOS) has adopted an OFA technique for the bariatric population irrespective of a diagnosis of sleep-disordered breathing. The technique instituted at the SIOS is modelled upon the experiences described by Mulier and De Kock and separately by Zieman–Gimmel [2].

Opioid-free and opioid minimisation techniques have also become a part of enhanced recovery after surgery protocols [3] for bariatric and other surgical interventions (Fig. 2).

The approach that the SIOS has adopted and that is detailed in this chapter is an example of a successful protocol (Fig. 3) that attempts to eliminate the 'opioid step' of the WHO ladder altogether. The OFA concept carries intra- and perioperative pain management beyond any of the steps in the analgesic ladder. It intends to create a new understanding of the physiological response to pain and opioids and includes expectation management to improve the level of safety and efficacy in the delivery of anaesthesia, especially for the morbidly obese and to enhance treatment outcomes.

The first two steps of the WHO analgesic ladder [5] emphasise the use of paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) before starting the use of opioids.

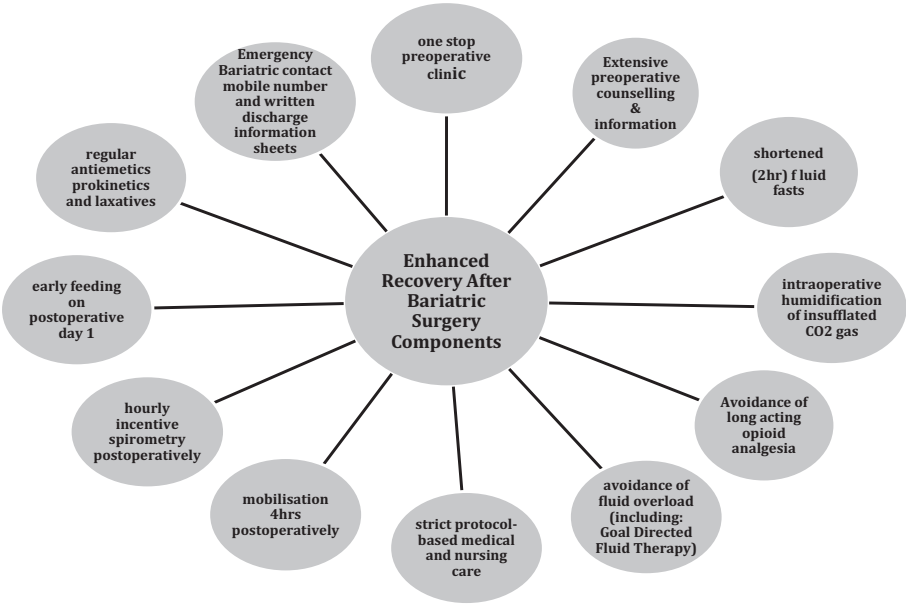

Fig. 2. Adapted from "components of enhanced recovery after bariatric surgery". Obesity Surgery. 2014; 24(5):753–758. https://doi.org/10.1007/s11695-013-1151-4, Awad S, Carter S, Purkayastha S et al. Enhanced Recovery After Bariatric Surgery (ERABS): Clinical Outcomes from a Tertiary Referral Bariatric Centre with open permission [4].

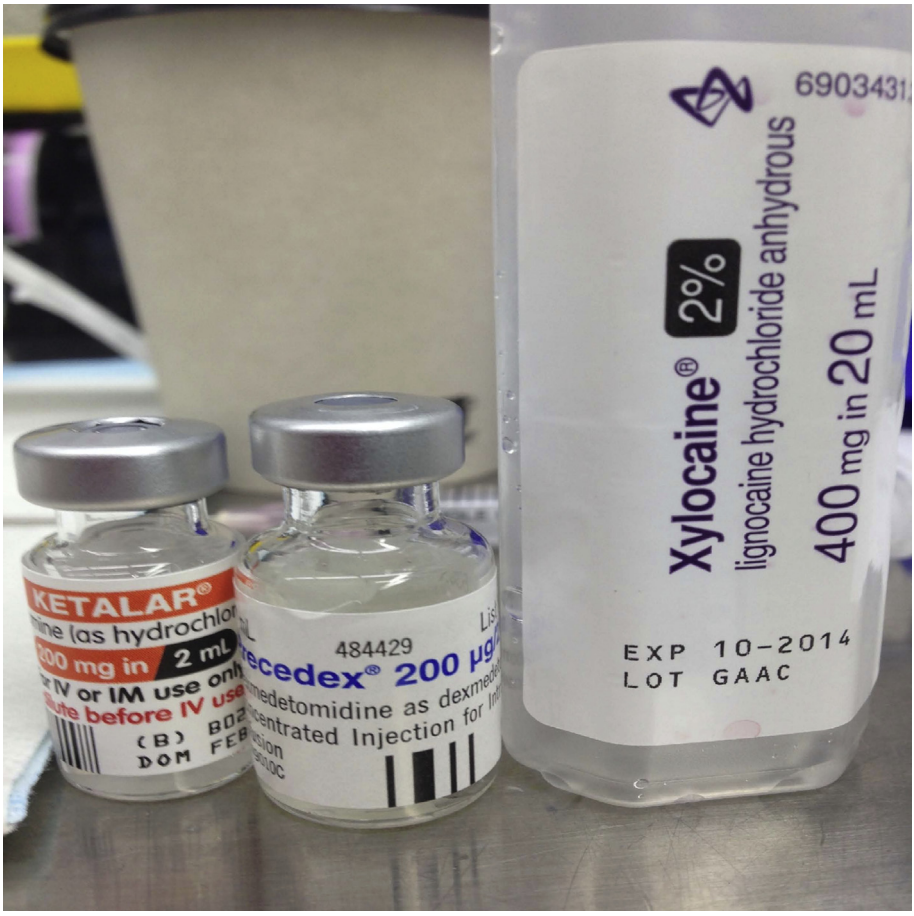

Fig. 3. Multimodal infusion (after Mulier). Dexmedetomidine: 10 μg/ml; Ketamine: 2.5 mg/ml; Lignocaine: 20 mg/ml.

In comparison, an opioid-free technique seeks to maximise the benefits of multiple analgesic adjuncts to achieve synergism of their different mechanisms of action.

Paracetamol (Acetaminophen)

Paracetamol is opioid sparing, effective and safe in the bariatric population [6]

Scheduled intravenous administration of this agent is indicated when the obese bariatric patient is nil by mouth in the early postoperative period rather than on a per-request basis.

NSAIDs

The Cox-2 drug parecoxib is a popular form of NSAID in Australia. It has a low side effect profile [7], particularly regarding gastric adverse events. It is approved by the Therapeutic Goods Administration [8] for use as a one-off dose perioperatively. Parecoxib may be substituted with any other NSAID, provided that the practitioner gives due consideration to bleeding risks and gastric mucosal integrity.

Magnesium

Magnesium acts as a non-competitive antagonist of N-methyl-D-aspartate (NMDA) and has anti-inflammatory effects because it reduces plasma interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha) levels in the postoperative setting [9].

A number of meta-analyses and RCTs within the past 5 years [10,11] have prompted a change regarding the efficacy of magnesium described in the important review of acute pain evidence by Schug and others [12].

While they previously disputed that magnesium had benefits, the 4th edition now reads.

> 'IV magnesium as an adjunct to morphine analgesia has an opioid-sparing effect and improves pain scores'.

Recommended doses included a loading dose of 40–50 mg/kg ideal body weight (IBW), followed by a maintenance infusion of 10 mg/kg/h^2.

Clinicians who integrate magnesium as part of their OFA regime should be mindful of its potentiation of neuromuscular blocking agents and therefore should also pay careful attention to dosing regimens for the latter drugs. Quantitative monitoring of neuromuscular blockade is imperative.

Because of its vasodilating properties as a calcium channel antagonist, magnesium may also act as a hypotensive agent. The use of magnesium may be limited for this reason in a multimodal regimen that employs propofol or inhalational anaesthetic agents, alpha$_2$-agonists and the reverse Trendelenburg position frequently used in bariatric surgery.

Dexamethasone

Dexamethasone is a potent mineralo-glucocorticoid with proven efficacy [13] as an antiemetic for a variety of surgical procedures.

We have incorporated dexamethasone into our multimodal technique on the basis of De Oliveira's work and others where doses of >100 μg/kg in lean adults have clinically significant analgesic properties [14].

We also note that Bartlett [15] and others have cautioned against its routine use in an editorial, and they highlight patients who are diabetic and undergoing procedures (including bariatric) where anastomotic breakdown could be catastrophic.

The editorial generated controversy in subsequent correspondence, and we would await studies in clinical patients that demonstrate harm before we would review our practice.

Ketamine

Ketamine is another non-competitive antagonist of the n-methyl-D-aspartate receptor and is commonly used either as a small bolus of 0.25–0.5 mg/kg IBW or in a low-dose continuous infusion at 2–2.5 μg/kg/min.

Schug and others have summarised its benefits in APMSE4 [10] (Table 1) in both the general acute pain [16] population and bariatric patients [17].

Table 1
'Ketamine in acute pain' according to Schug [10].

- Reduces the incidence of chronic postsurgical pain
- Reduces opioid consumption
- Reduces time to first analgesic request
- Reduces postoperative nausea and vomiting compared to placebo
- Improves analgesia when combined with opioids
- Reduces the development of acute tolerance/opioid-induced hyperalgesia associated with remifentanil use
- Reduces postoperative pain in opioid-tolerant patients
- Is especially useful when combined with magnesium

Table 2
Clonidine vs Dexmedetomidine.

Clonidine	Dexmedetomidine
Alpha 2 > Alpha 1	Alpha 2 > Alpha 1
220:1	1620:1
Partial agonist	Full agonist
Mildly lipophilic	Highly lipophilic
Reduces MAC by 50%	Reduces MAC by 90%
Plasma T1/2: 9–12 h	Plasma T1/2: 2–2.5 h
PB 50%	PB 94%
Elimination half-life: 8 h	Elimination half-life: 2 h
Distribution half-life: >10 min	Distribution half-life: 5 min
Inactivation at the locus coeruleus 'similar to normal sleep'	

Alpha-2 agonists Dexmedetomidine and Clonidine

The alpha$_2$-adrenoreceptor agonists represent a historical anomaly. They were pre-eminent in veterinary anaesthesia long before they became commonly used in human anaesthesia [18]. These drugs become difficult to use or unsuitable in the context of cardiovascular compromise. Noting the importance of accounting for interspecies variability known from veterinarian medicine, it is also important to appreciate the possibility of inter-patient variability. When using alpha$_2$-agonist-based techniques, careful haemodynamic and anaesthetic depth monitoring should be employed.

Over-sedation and haemodynamic compromise, specifically bradycardia and hypotension, are the main risks. Over-sedation can be avoided by timely cessation or tapering of maintenance infusions; bradycardia and hypotension often need to be treated with anticholinergic and vasoactive agents including ephedrine [19].

In the context of OFA, Schug and others in APMSE4 [10] conclude that:

Systemic alpha$_2$-agonists **reduce**
- Postoperative pain intensity
- Opioid consumption and
- Nausea

without prolonging recovery times [10].

The role of dexmedetomidine during opioid-free or opioid-sparing regimes in general surgical patients, the morbidly obese and, particularly, in sleep-disordered breathing patients is supported by a number of papers [20–24].

This has led to its inclusion in opioid-free regimens [25].

It is also worth noting the utility of dexmedetomidine in chronic obstructive pulmonary disease [20] patients.

Dexmedetomidine also preserves both sleep architecture [26] and airway patency [21].

Table 3
According to Palmer [47].

CRPS Prevention strategies and the anaesthetist
- Regional, sympathetic or epidural block or infusion
- Corticosteroids
- Non-steroidal anti-inflammatory drugs (NSAIDS) including COX-2 inhibitors
- Clonidine, ketamine or lignocaine infusions

(Reprinted from Aust Prescr 2015; 38:82–61 Jun 2015 https://doi.org/10.18773/austprescr.2015.029 with the permission from the author Ass Prof. Greta Palmer).

The pharmacokinetics of dexmedetomidine in the morbidly obese are believed to support its dosing under a LBM or IBW protocol [27,28].

At SIOS, we set the syringe driver at 100 kg for the simplicity of dosing.

A TCI program for dexmedetomidine has been published [29], but a 'smart' pump manufacturer has not yet adopted it.

Clonidine is also useful. However, its pharmacodynamic/pharmacokinetic profile may be undesirable [30] in the anaesthesia context because of its roller coaster effect on haemodynamics and prolonged sedation. Accordingly, we only recommend its use to top-up an inadequate sympatholytic state (Table 2).

Lignocaine (Lidocaine)

Lignocaine is a short-acting amide local anaesthetic agent. It is potent as a sodium channel blocker and has been shown to provide excellent analgesia when administered intravenously [31]. The evidence base supports lignocaine as an analgesic agent, an opioid-sparing agent, an anti-inflammatory and a co-anaesthetic [32]. It has particular benefit in the preservation and restoration of gastrointestinal function [33] and reduces the incidence of postoperative nausea and vomiting [34].

Just 3 years after it was synthesised and described for use as a local anaesthetic, the innovative use of lignocaine as a potent intravenous analgesic for labour pain, postoperative and cancer pain [35] was reported. Its use as a mainstay for the inpatient treatment of acute migraine was pioneered in Sydney, Australia, as early as the 1970s [36].

Grassi [37] has commented that the widespread use of systemic lignocaine for acute pain management is off-label but that it would be almost criminal to deny critical groups of patients (respiratory cripples, for example) its benefits.

Esmolol

This ultra short-acting cardio-selective beta 1 adrenergic blocker may be useful in attenuating unwanted sympathetic response during OFA [38].

Practicalities of OFA for bariatric surgery

Our own use of the multimodal mixture pioneered by Mulier [39] has been previously described [40].

We utilise a loading and maintenance intraoperative dose of dexmedetomidine/lignocaine/ketamine.

More recently, we combine this technique with TCI propofol (Schnider protocol) and have found that only moderate effect site target concentration (Cet) targets of 2.5–4.0 μg/ml are required if TBW is programmed as the weight scalar for the TCI [41].

Prior to induction of anaesthesia, a loading multimodal infusion based on 100 kg IBW is started at 20 ml/h equivalent to

- 2 μg/kg/h of dexmedetomidine
- 0.5 mg/kg/h of ketamine and
- 4 mg/kg/h of lignocaine

Patients are then induced with 2 mg/kg IBW of propofol and intubated with the aid of 1 mg/kg IBW rocuronium, after which maintenance with propofol TCI at 2.5–4 μg/ml effect site target concentration (Cet) is continued and neuromuscular blockade is maintained with 0.5 mg/kg/h (IBW) of rocuronium for the duration of pneumoperitoneum.

Routine antiemetic prophylaxis is administered with ondansetron, and dexamethasone is given in high dose both as an antiemetic and an adjunctive analgesic.

The loading multimodal infusion is continued until head-up position, peritoneal insufflation and placement of abdominal ports are complete.

The multimodal infusion is then progressively stepped down to 10 and 5 ml/h, equivalent to 1 and 0.5 μg/kg/h of dexmedetomidine, respectively.

To avoid delayed awakening and over-sedation, we interrupt the multimodal infusion 10–20 min prior to cessation of surgery [41]. Additional analgesia is provided with 1–2 g of intravenous paracetamol and 40 mg of parecoxib, together with intraperitoneal local anaesthetic and wound infiltration. At the end of surgery, complete reversal of neuromuscular blockade is performed, often using sugammadex as the preferred reversal agent.

The multimodal infusion is restarted upon arrival in the postanaesthesia care unit (PACU) at the lower rate, equivalent to 0.5 μg/kg/h of dexmedetomidine, where it is frequently the only analgesia required. In suitable patients, it may be used as a bridge to fentanyl PCA prior to ward transfer.

We are awaiting the evolution of nursing protocols prior to continuing an opioid-free technique for extended analgesia on the ward or high dependency unit.

Chronic postsurgical pain

Katz et al. [42] at Toronto General Hospital have introduced the concept of a Transitional Pain Service with the aim of preventing chronic postsurgical pain.

They describe how 'a multidisciplinary perioperative pain management plan is created prior to surgery'. In addition to surgical, logistic and behavioural components, the plan involves extended acute pain relief using all the non-opioid adjuncts discussed in this chapter including ketamine, alpha$_2$-agonists and lignocaine.

It is anticipated that if other groups follow the lead from Toronto, data collection from multicentre trials will unearth the outcome data that are necessary to select the interventions, which prevent the development of chronic postsurgical pain (Fig. 4).

Cancer surgery

Hontoir and Saxena et al. have shown statistically significant improvement in patient comfort after oncologic breast surgery prospectively with rigorous blinding and statistical analysis and using a clonidine/lignocaine/ketamine combination in the opioid-free group [43].

We therefore conclude that a well-conducted opioid-free technique such as the one we have described offers a clinical benefit to this group of patients, some of whom may suffer from obesity and sleep-disordered breathing.

As to the wide-ranging discussion on whether anaesthetic technique affects long-term outcome or recurrence after cancer surgery, there appears to be limited evidence.

Surgery, the processes of anaesthesia and individual anaesthetic agents have a complex effect on immunity, and each component may eventually prove to affect cancer outcome in its own way [44].

Basic cancer cell biology suggests that opioid analgesics inhibit both cellular and humoural immune function. It is conceivable that opioid avoidance therefore may improve cancer outcomes. However, definitive prospective data are not yet available.

Complex regional pain syndrome

Complex regional pain syndrome (CRPS) is a painful debilitating condition in a limb. It is associated with abnormalities in skin; bone; and the autonomic, sensory and motor nerves [45]. The condition, once established, is extremely difficult to treat and causes severe disability.

Anaesthetists may therefore play a role in the primary or secondary prevention of CRPS. All the multimodal techniques described here under OFA may have a role; however, only limited evidence is available in the literature [46] (see Table 3).

Role of opioid-free/multimodal analgesia in the opioid-tolerant patient

As a consequence of the worldwide epidemic of substance use disorders, chronic non-cancer opioid therapies and the recognition of dependence as a result of opioids for acute pain in some patients,

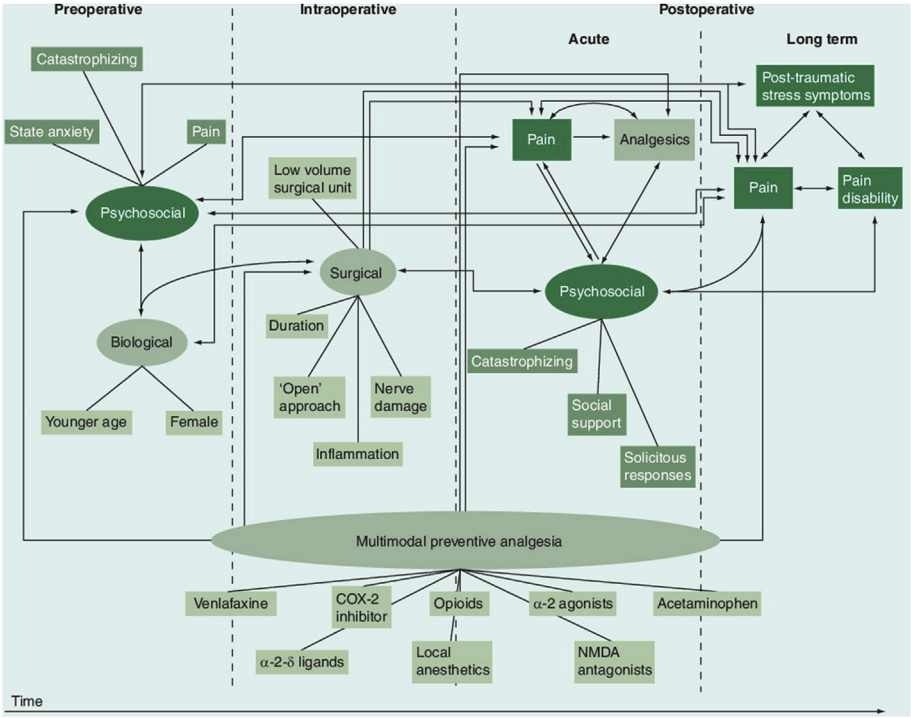

Fig. 4. Reprinted from J Pain Res. 2015 Oct 12; 8:695–702. https://doi.org/10.2147/JPR.S91924. eCollection 2015, 'The Toronto General Hospital Transitional Pain Service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain' with permission from Katz et al.).

anaesthetists will encounter opioid-tolerant patients presenting for surgical procedures on a regular basis. Management of the acute pain in opioid-tolerant patients includes their opioid maintenance dose and providing analgesia by opioid-reduced or opioid-free multimodal analgesia. Huxtable et al. have reviewed this topic [48] in detail, and their plan is reproduced with permission (Table 4).

In this group of patients, opioids will still form a substantial part of the inpatient management; however, buprenorphine maintenance therapy is fraught with problems and may need to be substituted with methadone.

Every possible component of the multimodal armamentarium should be introduced early during the patient's admission. However, success in preventing the escalation of opioid doses is not guaranteed, and the evidence for this approach is nascent.

Alpha$_2$-agonists offer added advantages in this special patient population because of their beneficial effects in preventing opioid withdrawal symptoms while doses are being adjusted or opioids are being rotated.

Case report

We present a case report of an opioid-tolerant patient who presented for sleeve gastrectomy. Her acute pain was managed with OFA as follows:

A 36-year-old woman with a body mass index of 40 kg/m^2 presented for elective sleeve gastrectomy *18 months after a sequential anterior and posterior lumbar intervertebral fusion. S*he was suffering from severe back pain and anxiety/depression.

Her maintenance drug regimen included long-term treatment with codeine 300 mg/day, citalopram and prednisolone. She was intolerant to

Table 4
Principles of acute pain management in opioid-tolerant patients.

Acute pain management in opioid-tolerant patients Table 4	
Preoperatively	
1. Preoperative planning	Assessment Patient education including management plan (admission to discharge) Ensure usual prescribed opioid (including buprenorphine) is taken on the day of surgery In MMT or BMT, consider arranging a 'take away' dose for self-administration on day of surgery Liaise with other healthcare professionals as indicated
Inpatient management	
2. Intraoperative analgesia	Replace usual opioid Titrate additional opioid to effect Consider risk of awareness Use non-opioid and adjuvant drugs
3. Postoperative analgesia	
a. Give adequate doses of opioid in addition to usual opioid	Incremental doses that are higher than the age-based doses usually prescribed for opioid-naive patients may be needed (including higher PCA bolus dose) Much higher than expected total daily opioid doses may be required Titration to effect for each patient remains important Monitor pain, functional activity scores and sedation Expect the need for more frequent review and adjustment of dosing
b. Strategies that may help to attenuate tolerance or OIH	Opioid rotation Ketamine
c. Use of non-opioid and adjuvant analgesic drugs	Limited or no evidence of benefit in opioid-tolerant patients but may be useful: Paracetamol and/or NSAIDs Gabanoids Lignocaine
d. Regional analgesia	Central neuraxial or other regional blockade (consider a catheter technique) Useful as part of a multimodal regimen Neuraxially administered opioids may not prevent opioid withdrawal
4. Prevention and treatment of withdrawal syndromes	Maintain usual opioid dose equivalent Give usual opioid (including buprenorphine) or give equivalent dose of another opioid or same opioid by a different route Monitor for drug withdrawal (opioids and other drugs) Drug replacement or symptom management (e.g. clonidine, benzodiazepines)
5. Close liaison with other treating clinicians and specialist teams	In-hospital and post-discharge pain management Related social, psychiatric and behavioural issues
Management after discharge	Liaison with community providers Discharge management plans Consider legislative restrictions for opioid prescribing Consider early follow-up or relevant new referral

(Reprinted from Anaesthesia and Intensive Care 2011; 39:804–23, 'Acute pain management in opioid-tolerant patients: a growing challenge' with permission from Huxtable CA, Roberts LJ, Somogyi AA, MacIntyre PE.)

- NSAIDs
- Fentanyl
- Oxycodone
- Morphine
- Tramadol

However, she could tolerate pethidine, which unfortunately was no longer available at the hospital where she was treated.

Intraoperatively, she received an opioid-free anaesthetic using the modified Mulimix technique supplemented by desflurane and neuromuscular blockade. Sixteen milligrams of dexamethasone, paracetamol and intraperitoneal infiltration with ropivacaine 0.75% were also administered.

The surgical course was uneventful (Fig. 5, jpeg attached), and her immediate PACU stay was initially complicated by over sedation (chin lift needed) and nausea (droperidol 0.5 mg).

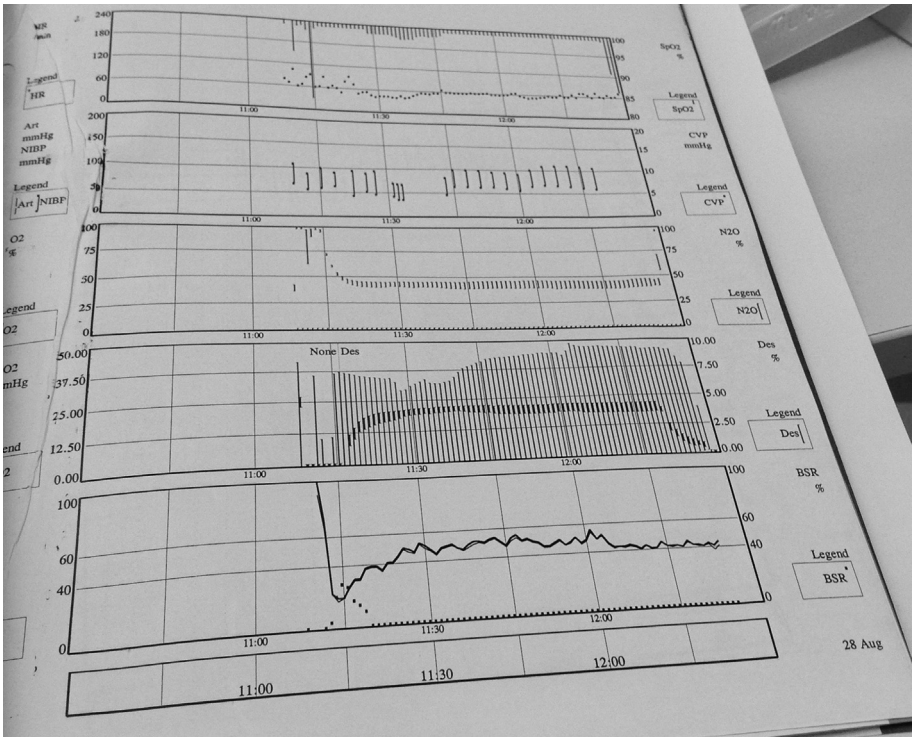

Fig. 5. Opioid tolerant Intraop data.

The opioid-free mixture of dexmedetomidine, lignocaine and ketamine was continued with a low-dose continuous infusion (equivalent to 0.5 μg/kg/h of dexmedetomidine, 0.125 mg/kg/h of ketamine and 1 mg/kg/h of lignocaine).

In the PACU, she was transitioned to a patient-controlled analgesia device programmed with the same mixture, whereby she would receive dexmedetomidine 10 μg, lignocaine 20 mg and ketamine 2.5 mg per bolus locked out for 5 min. Intravenous paracetamol at 1 g every 6 h for 24 h was part of the regimen.

The patient self-administered 7 doses of PCA overnight and was able to return to her routine oral medication the next day. No further opioid or non-opioid analgesia was required during her 2-day inpatient stay.

This case study suggests that multimodal OFA and analgesia play a role in the acute pain management of the opioid-tolerant patient presenting for incidental surgery. Further research is indicated.

Summary

Opioid-free anaesthesia has come of age as an alternative to standard opioid-based techniques in the management of morbidly obese patients for bariatric surgery.

Evidence-based techniques employing core analgesics and adjuvant drugs such as magnesium, ketamine, alpha$_2$-agonists and systemic lignocaine are effective in avoiding large doses of opioids and avoiding the use of remifentanil.

Hypnosis, analgesia, amnesia, sympatholysis and haemodynamic stability are achieved during pneumoperitoneum for upper gastrointestinal surgery, while immobile surgical conditions are maintained with accurate neuromuscular blockade.

Similar agents are used postoperatively to maintain opioid-free or opioid-sparing analgesia.

Opioid-induced hyperalgesia and the perioperative ill effects of opioids are thereby avoided. The technique may also be applied to

- Patients with respiratory compromise
- OSA without obesity
- Patients with opioid dependence and certain chronic pain syndromes and
- Oncology patients with clear benefits for ERAS protocols after colorectal and breast cancer surgery.

While groups of clinicians have embraced these concepts and techniques enthusiastically, large prospective studies from independent units worldwide are awaited. Such studies would cement the evidence base for obesity anaesthesia and the other special indications described in this study.

Conflict of interest

Dr. Adrian Sultana: None.
Dr. David Torres: None.
Professor Roman Schumann: None.

Practice points

- OFA techniques have been increasingly accepted, most frequently for morbidly obese patients undergoing bariatric surgery and especially in the context of sleep-disordered breathing.
- We have provided a specific example of a technique for a bariatric population that provides safe and effective OFA at SIOS.
- Multimodal techniques should include paracetamol and NSAIDs

Together with:

- Ketamine
- Dexmedetomidine
- Lignocaine
- Magnesium.

The level of evidence for magnesium is in support of its use in the context of OFA in clinical practice.

- Other sub-populations of patients may benefit from this technique including those with respiratory impairment, with chronic pain syndromes and opioid-tolerant patients.
- Basic science would suggest that patients having surgery for primary cancers may benefit from avoiding the immuno-depressant effects of opioids, and this technique has been clinically successful in breast and colorectal oncological surgery for reducing acute surgical pain.
- Avoiding opioids in high doses and remifentanil in particular would seem to be a clear method of avoiding opioid-induced hyperalgesia, and there is evidence for attenuation of hyperalgesic syndromes with the adjunctive use of ketamine and magnesium in adults.
- Opioid-tolerant patients presenting for acute painful interventions require expert care and planning. It is suggested that adding a multimodal opioid-free or opioid-sparing technique to their baseline opioid status may be of benefit for this challenging group of patients.

Research agenda

- Mulier's group has accumulated enormous data both prospectively and retrospectively with regard to OFA as applied to their practice for Roux-En = Y Laparoscopic Bypass [49].
- However, large outcome studies comparing standard opioid-based techniques with protocol-driven OFA are evolving from bariatric centres around the world.
- Patient population and procedure-specific regimen are awaiting clinical validation.
- The role of opioid-free adjuvants in preventing CRPS remains to be subjected to the same rigorous analysis for the management of this difficult condition.
- Despite difficulties, enrolment units with special experience in opioid-tolerant patients should investigate multimodal strategies in prospective clinical trials to assess the role of this pharmacological technique in the comprehensive management of their patients during acute pain episodes.
- The oncology community requires answers to the following questions: Are the immunogenic effects of opioids on cancer cells merely a study in cell biology or do they have relevance in the planning of anaesthetic techniques for cancer patients?"
- If avoiding opioids is ideal in surgical oncology, which cancers are most amenable to these techniques?

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