REVIEW / DERLEME

A NEW GOAL IN OPIOID MANAGEMENT IN OBESE PATIENTS: OPIOID-FREE ANAESTHESIA

OBEZİTE HASTALARINDA OPİOİD YÖNETİMİNDE YENİ AMAÇ: OPİOİDSİZ ANESTEZİ

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SUMMARY

Opioids have unique features that facilitate premedication, smooth induction, ease the maintenance of anaesthesia and improve postoperative pain relief. However, they also have side effects such as respiratory depression, nausea and vomiting. Obesity is one of the most frequent disorders that require attentive opioids management. The physiological and pathophysiological consequences of opioids in obese population lead clinicians avoid or limit these drugs during anaesthetic management. The drugs used for an opioid-free anaesthesia plan include, but are not limited to, α-2 adrenergic receptor agonists, ketamine, lidocaine, gabapentinoids and magnesium, separately or in combinations. For opioid-free anaesthesia, clinicians should have thorough knowledge of pharmacokinetic and pharmacodynamic properties of substitute drugs used instead of opioids. Anaesthesia depth should be monitored. Minimally invasive surgery, experienced surgery and anaesthesia team help ensuring the success of this technique. Opioid-free anaesthesia is a new horizon for anaesthetists who try to perfect their practice in overweight patients. In this regard, opioid-free anaesthesia for obese population should be reserved for cautiously-selected patients and interventions.

KEY WORDS: *Obesity, Opioid, Opioid-free anaesthesia*

ÖZET

Opioidler premedikasyonda, intraoperatif dönemde indüksiyon ve idamede ve postoperatif dönemde etkin analjezi uygulamalarında kendine yer bulan, ancak respiratuvar depresyon, bulantı kusma gibi yan etkileri de bulunan özellikli ilaçlardır. Obezite ise opioidlerinin yan etki profillerinin belirginleştiği bir yandaş hastalık olup, opioidlerin bu popülasyondaki fizyolojik ve patofizyolojik profilleri, klinisyenlerin anaestezi yönetimi sırasında opioidlerden kısmen veya tamamen uzaklaşmasına neden olmaktadır. Opioidsiz anestezi uygulamasında kullanılan ilaçlar bunlarla sınırlı olmamakla beraber, sıklıkla α-2 adrenerjik reseptör agonistleri, ketamin, lidokain, gabapentinoidler, magnezyum ve kombinasyonlarını içermektedir. Opioidsiz anestezi uygulaması için anaestezistlerin opioidlerin yerine geçecek ilaçların obez hasta grubundaki farmakokinetik ve farmakodinamik özelliklerini iyi bilmeleri ve anestezi derinliğini monitorize etmeleri gerekmektedir. Minimal invazif cerrahi teknikleri, deneyimli cerrahi ve anestezi ekipleri tekniğin başarısına katkı sağlayacaktır. Bu bağlamda, opoidsiz anestezi dikkatle seçilmiş hasta ve cerrahilerde tercih edilmelidir.

ANAHTAR KELİMELER: *Obezite, opioid, opioidsiz anestezi*

Current perioperative anaesthesia practice highly depends on opioids in modern clinics. Opioids have unique features that facilitate premedication, smooth induction, ease the maintenance of anaesthesia and improve postoperative pain relief. The competence of efficient analgesia and haemodynamic stability makes opioids eligible and, sometimes, indispensable in anaesthetic management. However, as every rose has its thorn, opioids are not also free from side and adverse effects such as respiratory depression, nausea and vomiting. The advantages and disadvantages of opioids require a true equilibrium and judgement when administering these drugs. But the characteristics of the patients and the surgical interventions may change the balance towards undesirable conditions from the start. Obesity is one of the most frequent disorders that complicates whole anaesthetic management as well as opioid use. Co-existence of the obstructive sleep apnoea with obesity even worsens the consequences of opioids during anaesthetic management (1,2).

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Impact of obesity on opioid pharmacology

Obesity is characterised by huge amount of adipose tissue that acts like an organ itself. This organ has hormonal and inflammatory functions, and, sometimes extraordinarily and excessively (3). Adipocytes induce macrophages to produce and react to TNF-α, IL-1, IL-2, IL-6, IL-8, IL-18, plasminogen activator inhibitor, monocyte chemotactic protein which provoke an ongoing inflammatory state and impaired fibrinolysis. Leptin, osteopontin and angiotensinogen are adipokines secreted by adipocyte/inflammatory cell complex. Leptin induces sympathetic over-activity, ventricular hypertrophy, platelet aggregation. Angiotensinogen nourishes sympathetic over-activity as well as vasoconstriction. Osteopontin contributes to vascular remodelling. Adinopectin which is also a product of adipose tissue causes nitric oxide release, insulin sensitization and anti-inflammatory activity (3). In addition to metabolic involvement, pharmacologic behaviours of the drugs are also altered in obese patients. When opioids are considered, both pharmacokinetic and pharmacodynamic alterations should be taken into account while administering to obese patients.

Pharmacokinetics of opioids in obese patients

The current knowledge about correct dosing and clinical assessment of opioids is limited in obese patients, since these patients usually aren't included to clinical studies during drug development (4,5). The clinician using opioids in obese population is expected to be fore-sighted and have an ability to interpret the present data in this specific group of patients. However, obesity affects all four phases of pharmacokinetics. The quantity and quality of transport glycopeptides needed for absorption to all tissues haven't been evaluated in obese patients and absorption phase can be affected due to previous bariatric surgery. Cardiac output volume is relatively higher and blood flow to adipose tissue is lower in obese population. Distribution volume (V_d) which is an indicator for drug dosing should be adjusted wisely to avoid insufficient or over –dosing of opioids. However, there is no consensus on which body weight should be used for drug dosing in obese population, but recommendations for each opioid exist. Total body weight, ideal body weight, adjusted body weight, corrected body weight, lean body mass and expected body weight have all been used for estimating a body weight that should be used for drug dosing in overweight patients (6). These indirect indicators of distribution volume are all calculated by formulas. Shortly, the rise in total body weight correlates with the increase in fat mass, but the increase in lean body weight reaches to a plateau between body mass index (BMI) values of 30 and 40 and doesn't rise even though total body weight increases.

When calculating opioid dose for obese patients, it is recommended to use specific body weight calculations for each opioid. It is suggested to use lean body mass or adjusted body weight for remifentanil (7). V_d and $t_{1/2}$ for sufentanil and alfentanil are increased in obese population but V_d/kg is similar to non-obese patients. Initial induction dose according to total body weight and lessened doses for maintenance are advocated for sufentanil and alfentanil for overweight patients with BMI up-to 40 and lean body weight for BMI>40 (8). Morphine dose is calculated according to ideal or adjusted body weight (9,10). Lean body weight or pharmacokinetic mass should be used for fentanyl dosing in obese patients, however various PK/PD models exist and these models frequently over-calculate the effective plasma concentrations of fentanyl in overweight patients (11).

Opioid metabolism depends on glucuronidation which is increased in obese patients (12). This means a fast metabolism leading to a fast rise in effective drug concentration in blood. If renal function of the patient is well-preserved, effective drug concentration decreases rapidly, but if renal functions are impaired, high and long- lasting effect of opioids are observed. Excretion of the drugs in obese patients altered due to increased blood volume, higher glomerular filtration rate and clearance. However, renal morbidities which are very frequent in obese population may also impair opioid metabolism.

Pharmacodynamics of opioids in obese patients

Nociception and opioid potency have also been suggested to vary in obese population. Animal studies claimed that pain sensitivity is higher but opioid potency is lower in obese objects in comparison to lean ones. This information confirmed by human studies variedly (13). The variations in the studies may be explained by altered number and function of opioid receptors due to several gene polymorphisms involving in opioid pharmacodynamics in obese population (14,15). Obesity is associated with decreased μ-opioid receptor availability in the brain whereas bariatric surgery has a normalizing effect on brain opioid receptors (16,17).

How will we plan opioid- free anaesthesia in obese patients?

Opioids provide the advantages of haemodynamic stability, sympathetic blockade, efficient analgesia and decreasing the need for hypnotic agents. However, physiological and pathophysiological consequences of

opioids in obese population lead clinicians avoid these drugs during anaesthetic management, partially or totally. Regional techniques or drugs which have similar efficiency but different adverse effects have been used to replace opioids (18). The drugs used for an opioid-free anaesthesia plan include, but are not limited to, α-2 adrenergic receptor agonists, ketamine, lidocaine, gabapentinoids and magnesium.

Dexmedetomidine and clonidine (α-2 adrenergic receptor agonists) replace opioids in terms of blunting sympathetic activation, intraoperative anti-nociceptive and sedative effect, postoperative analgesia, minimal respiratory depression, less postoperative nausea and vomiting (19-23). Dexmedetomidine infusion (0.2- 0.8 mcg kg^{-1} h^{-1}) has been suggested to decrease the need for volatile anaesthetics and the haemodynamic parameters in comparison to fentanyl intraoperatively and postoperative pain scores and morphine or fentanyl consumption during bariatric surgery (24–27). Also for extremely obese patients, dexmedetomidine has been used instead of opioids to ensure uneventful recovery and postoperative analgesia with less opioids (22,28). Ketamine (up to 1 mg kg^{-1}) has been reported to provide better recovery profile, better postoperative pain scores and less opioid consumption without a benefit in hypnotic use after bariatric surgery (23,29). Lidocaine (bolus 1.5 mg kg^{-1}, infusion of 2 mg kg^{-1} h^{-1}) improves the quality of recovery and decreases postoperative use of anti-emetics and opioids during bariatric surgery (30,31). Gabapentin and pregabalin were reported to improve postoperative nausea and vomiting, pain scores when used in obese population (32-34).

Combinations of the drugs have also been used for opioid-free anaesthesia plan. A combination of clonidine, lidocaine, ketamine, magnesium, methylprednisolone and ketorolac has been reported to successfully replace fentanyl in terms of analgesia with less sedation in obese population (35). Some other papers also suggested that opioids might be avoided by various combinations of these drugs at various doses (Table I) (21,36,37). Lavender aromatherapy and hypnosis are other non-medical alternatives described for opioid-free anaesthesia in obese population (38-40).

Disadvantages of opioid-free anaesthesia

Disadvantages of opioid-free anaesthesia are actually related to the side or adverse effects of the substitute drugs. Cardiovascular depression requiring vasopressor support and cutaneous vasoconstriction have been associated with α-2 adrenergic receptor agonists. Risk

Table I. Drug combinations with various dose regimens for opioid free anaesthesia

Drugs	Doses
Dexmedetomidine	0.6 µg kg^{-1} bolus, 0.3 µg kg^{-1} h^{-1} infusion
Lidocaine	1.5 mg kg^{-1} bolus, 2 mg kg^{-1} h^{-1} infusion
Dexmedetomidine	0..2-0.6 µg kg^{-1} h^{-1}
Ketamine	100 mg h^{-1}
Dexmedetomidine	1 µg kg^{-1} bolus, i 0.7 µg kg^{-1} h^{-1} infusion
Ketamine	1 mg kg^{-1} bolus
Dexmedetomidine	0..5 µg kg^{-1} bolus, 0.1-0.3 µg kg^{-1} h^{-1} infusion
Ketamine	0..5 mg kg^{-1} bolus
Clonidine	0.75-1.5 µg kg^{-1} bolus, 0.75-1.5 µg kg^{-1} h^{-1} infusion
Ketamine	0..125-0.25 mg kg^{-1} bolus, 0.125-0.25 mg kg^{-1} h^{-1} infusion
Lidocaine	1.5 mg kg^{-1} bolus, 1.5-3 mg kg^{-1} h^{-1} infusion
Magnesium	40 mg kg^{-1} bolus, 40 mg kg^{-1} h^{-1} infusion
Dexmedetomidine	bolus 0.5^{-1} µg kg^{-1}, 0.5^{-1} µg kg^{-1} h^{-1} infusion
Ketamine	0..125-0.25 mg kg^{-1} bolus, 0.125-0.25 mg kg^{-1} h^{-1} infusion
Lidocaine	1.5 mg kg^{-1} bolus, 1.5-3 mg kg^{-1} h^{-1} infusion
Magnesium	40 mg kg^{-1} bolus, 40 mg kg^{-1} h^{-1} infusion
Clonidine	150 µg kg^{-1} bolus
Ketamine	25 mg bolus
Lidocaine	1 mg kg^{-1} bolus
Esmolol	40 mg kg^{-1} bolus, 40 mg kg^{-1} st^{-1} infusion

of awareness without opioids is another possible outcome. Ketamine has been reported to affect EEG-based or similar monitoring and deteriorates the parameters that may help evaluate anaesthesia depth. Furthermore, optimization of intubation conditions may be failed without opioids.

Requirements of opioid-free anaesthesia

As every clinical skill, opioid-free anaesthesia needs a time to develop a learning and practice curve. During this period, limited opioid use should be employed without immediate transition to opioid-free anaesthesia (41). Clinicians should have thorough knowledge of pharmacokinetic and pharmacodynamic properties of substitute drugs used instead of opioids. Anaesthesia depth should be monitored. Furthermore, minimally invasive surgery, experienced surgery and anaesthesia team might help ensuring the success of this technique.

Conclusion

Opioid-free anaesthesia is a new horizon for anaesthetists who try to perfect their practice in overweight patients. This may be verified by use of many drugs and their combinations and tailored according to the requirements of the intervention and the patients. While discussing options and strategies for opioid-free anaesthesia for obese population, it should be kept in mind that almost all of the studies on this subject have been done in bariatric surgery which is almost always elective. This elective surgery brings its own advantageous circumstances such as a patient with optimised comorbidities, optimal timing and experienced operation team. However, opioid- free anaesthetic plans or regimen may not be eligible for a very possible scenario of a morbidly obese patient with diabetes, hypertension and heart failure undergoing emergency laparotomy after a car accident. In this regard, opioid-free anaesthesia for obese patient should be reserved for cautiously selected patients and interventions.

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