

## Role and Advantageousness of Ketamine in Obese and Non-Obese Patients: Peri-Interventional Considerations

Avi A Weinbroum\*

Department of Research and Development, Tel Aviv Sourasky Medical Center affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

\*Corresponding author: Avi A Weinbroum, Department of Research and Development, Tel Aviv Sourasky Medical Center affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, Tel: +972-3-5440904; E-mail: draviw@tasmc.health.gov.il

Received date: May 16, 2018; Accepted date: May 25, 2018; Published date: May 29, 2018

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### Abstract

Obese and morbidly obese patients are a growing group of individuals that generates medical, social and economic problems worldwide. They undergo various interventions that require anesthesia and/or analgesia. Despite their healthy look, these individuals are graded at high ASA physical status, mainly because of their impaired respiratory and cardiovascular conditions, and the metabolic changes their body undergoes.

Opioids are the default drugs for perioperative analgesia. Nevertheless, their use has reached a frightening epidemic-like condition worldwide. Multimodal analgesia regimens have been recommended as a perioperative standard of care, particularly for the obese. These regimens employ combinations of opioids and non-opioid compounds that augment the formers' analgesic potencies, thus providing superior pain relief at rest, movement, or on effort, while reducing opioid consumption and their concerned adverse effects. The most important perioperative IV adjuvant currently employed is ketamine that sees resurgence among physicians from diverse medical specialties.

After summarizing obese patients' perioperative drawbacks, this review will illustrate ketamine's neuropharmacology, and will describe its therapeutic usefulness as an analgesic adjuvant. Since data regarding the use of the drug in obese patients is scarce, brief exemplifications of its benefits in non-obese cohorts will be portrayed as well.

**Keywords:** Obesity; Analgesia; Perioperative; Opioids, Adjuvants; Ketamine

### Introduction

Peri-incisional pain is among the main concerns and complaints of patients analgesia are estimated to be insufficient in ~50% of surgical procedures [1]. Inappropriate treatment of acute pain also induces central neural hyperexcitability and persistence [2,3] the build-up of opioid-induced tolerance (OIT) and hyperalgesia (OIH) [4] and prolonged recovery [5].

Multimodal analgesia represents an approach to treating perioperative pain, where the patient is administered with a combination of opioids and non-opioid analgesics that act at specific sites within the central (CNS) and peripheral nervous systems [6]. This leads to minimization of pain, opioid needs, and subsequently, to a decrease in opioid-associated adverse events (AEs), such as nausea, vomiting, sedation, respiratory depression, urinary retention, constipation, and pruritus. Furthermore, reduction of intraoperative opioid use limits the risk of the development of chronic pain and opioid dependency [4,7,8].

Obese and morbidly obese patients grow in their numbers worldwide: one-third of USA adults are obese. Painful interventions, mostly sleeve, Roux-en-Y gastric bypass (RYGB), or other weight reduction operations, even if laparoscopically applied, cause both psychological and physical offsets. Pain complaints are common among obese individuals; they tolerate it to much lower degrees than

the average population [9,10]. Besides surgery itself, stress and pain also deteriorate patients' respiratory, cardiovascular, gastrointestinal, metabolic, and renal functions. Opioids, which are the cornerstone of acute pain management, improve the physical and mental conditions of all patients, also interfering with cognition and behavioral attitudes, and limit physical performances [11,12]. A retrospective analysis of trauma adults of BMI >40 (16,390 patients) unveiled their being at a higher risk for longer hospital and intensive care unit (ICU) stays, and for mortality rate than normal-weight individuals [13]. A >200-patient study of total knee replacement (TKR) reported a twofold increase in procedure-related costs in those with increased preoperative BMI [14].

Uncontrolled pain may initiate changes in both peripheral and the CNS, leading to its amplification and persistence. Peripheral and central sensitizations contribute to the postoperative hypersensitivity state that is responsible for the decrease in pain threshold and for the establishment of aberrant excitatory conditions at the site of injury (primary hyperalgesia) and in its surrounding, uninjured area (secondary hyperalgesia) [4,15]. Opioid-induced hyperalgesia (OIH) also represents a major trigger of acute pain being transformed into the chronic phase, both consequences of the dark side of perioperative excessive opioid therapy [16,17]. These phenomena are further enhanced among obese and morbid obese patients, mainly due to their physical and mental diminished tolerability to nociception [9,18]. Blockade of these sensitizations, is obtainable either via preemptive analgesia (treatment applied before the onset of pain) or preventive analgesia (analgesics administration immediately after pain has been induced) [19,20]. Either regimen results in reduced postoperative pain,

lower incidence or severity of persistent post-surgical pain, and amelioration in postoperative psychological and physical conditions.

Ketamine was proven to best control postoperative- or opioid-induced tolerance and hyperalgesia (POH, OIH, OIT), while producing an acceptable level of antinociception, either if used alone or in association with morphine equivalents (MOEs) [4,16,21,22]. Preemptive ketamine analgesia (IV 0.5 mg/kg bolus followed by 0.25 mg/kg/h), has proved to reduce pain and analgesics consumption or both, even beyond the clinical duration of action of the drug [23].

The present review discusses some of the physio-neuro-metabolic changes occurring in obese patients, and their relationships with anesthesia and analgesia. The pharmacological efficacy of sub-anesthetic doses of ketamine, as a sole drug, or in combination with other analgesics, and its benefits in non-obese patients, vis-à-vis obesity, will also be illustrated.

## Physiology and Pharmacology of the Obese

### Medical diseases in the obese and morbidly obese patient

This review refers to all categories of patients with excessive weight as "obese", unless specifically stated. More than 1.9 billion adults worldwide were reported overweight, of whom >600 million are obese and 41 million children <5 y were informed overweight or obese in 2014. Normal weight ranges between 18.5 and 25 kg/m<sup>2</sup> of the body mass index (BMI). Overweight is defined as a BMI ranging between 25-29.9 kg/m<sup>2</sup> obesity is defined as BMI  $\geq$  30 kg/m<sup>2</sup>, and morbid obesity is defined as a BMI  $\geq$  40 kg/m<sup>2</sup> (or  $\geq$  35 kg/m<sup>2</sup> in the presence of comorbidities).

Most obese individuals depict abdominal (central) obesity, and suffer from metabolic syndrome or type 2 diabetes mellitus [24,25]. There exist respiratory and cardiovascular diseases, kidney dysfunction or diabetic and retinal neuropathy, all of enormous world economic burden. Worth mentioning are also stroke, abdominal or orthopedic disturbances, sleep apnea, cancer, liver disease, obstructive sleep apnea (OSA), and deep venous thrombosis (DVT), or mental illnesses, such as clinical depression or anxiety, body pain, and difficulty with physical functioning [26]. All these influence perioperative outcome [27,28].

### Pediatric obesity

Pediatric obesity represents one of the most problematic public health issues worldwide. In a recent National Health and Nutrition survey, it was suggested that 17% of the children and adolescents in the USA are obese [29]. The WHO defines pediatric overweight and obesity according to standard deviations (BMI Z-scores) from the mean adult BMI values [30,31]. Comparatively, the American definition of childhood obesity describes a BMI  $\geq$  85th percentile as overweight, and a BMI  $\geq$  95th percentile as obesity [32]. Pediatric obesity is a special challenge to the anesthetist (see below) [33]. In fact, most excessive fat is found in the central areas, and less is observed in the legs [34]. Recent clinical trials include a wider range of BMIs, and have indexed pediatric liver volume and function for obesity rather than BMI [35].

### Drug pharmacology in the obese

The overall influence of obesity on drug metabolism (liver function) and elimination (glomerular filtration rate [GFR]) are determining factors, although with large variability. Obesity affects the

pharmacokinetics of many (but not all) IV anesthetic drugs; newer generations of inhalational anesthetics are affected only slightly. Target-controlled infusion (TCI) models, originally established for propofol, remifentanyl and sufentanyl, comprise data (age, gender, weight, and height) that are formula-covariates, thus allowing for safer dose adjustments in obese patients [36-38]. In the absence of a TCI device, anesthesia induction should be slowly, titrating the drugs to the desired clinical effect (regardless of the weight scale). Actually, a drug-by-drug dose decision is necessary for obese and morbidly obese populations. This is since a higher metabolic rate, prevailing in the obese population, would probably lead to a higher rate of toxicity following weight-based dosing, in contrast to body surface area (BSA)-based dosing. At the same time, hepatic metabolism could be a major determinant of drug behavior; this yet unsettled knowledge affects drug absorption, distribution, metabolism and excretion, and more data are still needed, including bioavailability and clearance in children [39]. While obese children require less propofol than normal-weight children, unlike adults there is limited information about the dosing of other anesthetics or opioids in children [40]. Subanesthetic dosing of ketamine is advantageous in these cohorts, especially when administered continuously, because of the low toxic results [41]. Very recent data support the assertions [42] that most anesthetics' dosages would better be based on lean body weight (LBW).

### Pain in the obese patient

Complaints of general and specific musculoskeletal pain are commoner findings among obese than in non-obese individuals [43]. A trivial fall, inducing an immediate, severe pain that may require lengthy check-up and limited ambulation, is exacerbated by overweight [44]. Obesity itself affects pain via several ways, such as the mechanical loading, inflammation, and psychological status [45] thus being a frequent and continuous complaint in this cohort. These contribute to deterioration in physical ability, quality of life, and functional and psychological capabilities [18].

Morbid obesity adversely affects acute and chronic pain conditions via mechanical and structural factors, excessive release of chemical mediators, depression, and sleep deprivation. However, the nature of the relationship among these factors is apparently indirect [9]. The extent of pain interference and the need for medications among obese (BMI  $\geq$  30 kg/m<sup>2</sup>) was compared with normal weight (BMI  $\leq$  25 kg/m<sup>2</sup>) patients, before hip or knee replacement surgery [10]. The former suffered from more intense acute pain, pain-associated impediment of walking distance, and sleep disturbances than the latter. Anxiety and depression scales were similar, but the obese used more frequently strong opioids and NSAIDs. Thus, pain relief was more difficult to obtain, and consequently led to later lower quality of life in the obese. A large retrospective study has concluded that among spine patients presenting to tertiary European centers, obesity, as indicated by BMI, was associated with greater back and leg pain than non-obesity [46].

Although not limited to the obese cohorts, pain catastrophizing, a negative cognitive-emotional response to actual or anticipated pain, which includes rumination about pain, magnification, and feelings of hopelessness about pain, are noteworthy [47]. This may be a primary predictor of the development of chronification of acute pain [48], or persistence of postoperative pain, and therefore warrants preoperative prevention. Finally, a systematic review (7 studies, 380 participants) that evaluated differences in pain thresholds in obese and non-obese subjects [49] revealed a tendency towards a lower pain threshold in the

obese compared to non-obese subjects. Nevertheless, since excessive body weight loss did not change pain thresholds in the former, other factors probably converge towards producing such findings.

### Opioid use in the obese patient

Appropriate drug selection and dosages are important in the obese patients. Besides the problematic increase in opioid abuse worldwide, opioid- and sedative-induced respiratory depression mandate cautious dosing. Unlike remifentanyl, fentanyl's pharmacokinetics has a non-linear relationship to TBW, so that its dosing (mg/kg) decreases as TBW increases [50]. Besides attentive and judicious titration, opioid-induced complications can be further reduced by using multimodal analgesic regimens.

Pre-induction use of ketamine (or clonidine an  $\alpha_2$  agonist) in morbidly obese patients undergoing bariatric surgery was shown to reduce the total doses of intraoperative fentanyl and sevoflurane, time to extubation, postoperative tramadol requests, and pain scores [51,52]. While some assert that opioid dose requirements in the obese would not differ significantly from those among non-obese, they do affect considerably the formers' mood, as well as other vital functions [53]. TCI-fine-tuned-administration of remifentanyl (as during bariatric procedures) may limit opioid AEs' occurrence, shorten time to extubation and quicken the return to spontaneous respiration *vs.* other opioids. However, remifentanyl may induce OIH and PONV in the immediate recovery period, compared to fentanyl [4].

## Ketamine

### Essentials of neuropharmacology of ketamine

Ketamine is a derivative of phencyclidine hydrochloride (PCP) after a long clinical disuse it has recently undergo revival [54]. It maintains stable respiration and blood pressure, analgesia and antidepressant potentials. Ketamine is classified as a Schedule III controlled substance in the USA (i.e., a potential drug for abuse that may lead to moderate-low physical dependence or high psychological dependence, although less than schedule II and I drugs). Compounding material of ketamine has recently become accessible for non-systemic use [55].

Ketamine is a chiral molecule available in a 1:1 mixture of two pharmacological forms: the racemic presentation (R-ketamine) and the esketamine (S-(+)-ketamine). The latter (brand name: Ketanest S) is the (S)-enantiomer of ketamine, which is 3-4 times more receptor-active than the dual mixed/racemic (R/S) compound. S(+)-ketamine is of a higher potency, of faster elimination rate, and its plasma concentrations are accurately measurable compared to the racemate [56]. Nevertheless, the R-form is the most prepared and distributed preparation worldwide, and is the most cited in the literature, as it is in this review. The drug's detailed pharmacology and metabolism are interwoven in the following reviews [4,57,58].

Ketamine is highly bioavailable after IV or IM injections, or rectal deposition [59] oral ketamine undergoes extensive hepatic first-pass metabolism [60]. Like PCP, it interacts with the N-methyl D-aspartate receptor (NMDAR) channels [61], the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), the gamma-aminobutyric acid (GABA) receptors, as well as with muscarinic, nicotinic, cholinergic and opioid receptors. Ketamine has also been found to inhibit the neuronal uptake of norepinephrine, dopamine and serotonin [62] and it antagonizes the HCN1, potassium, calcium, and sodium channels, all of which affecting pain as well.

Parenteral absorption of ketamine is rapid mean  $C_{max}$  is 0.75  $\mu$ g/mL and  $T_{max}$  is 1 h. Ketamine undergoes N-dealkylation, hydroxylation of the cyclohexane ring, conjugation with glucuronic acid, and dehydration of the hydroxylated metabolites, to form the cyclohexene derivative [60]. The beta phase (elimination half-life) of ketamine is ~180 min. Approximately 91% of the metabolites are excreted in the urine and 3% in the feces. The onset effect of IV ketamine is within 30 sec, and 2-4 min for IM administration the duration of (different) effects ranges between 5-10 min (IV) and 12-25 min (after IM injection). Ketamine can be diluted in all physiological solutions, except for lactated ringer.

Ketamine is extensively metabolized to norketamine and dehydronorketamine, with norketamine being the most active metabolite [63]. These two main metabolites are active compounds, permitting analgesia to persist even after the patient has awakened from the sedative effect of the drug [64]. Upon termination of a constant-rate infusion, ketamine concentrations decrease rapidly but norketamine concentrations remain elevated, above ketamine ones for hours. This feature promotes ketamine as a clinically effective drug, especially when used in the currently applied subanesthetic doses instead of the mega doses used in the past. The metabolism of ketamine minimally blocks hepatic enzymes [65] indeed, long-term, low-dose infusions of ketamine in patients with acute kidney dysfunction were not associated with drug accumulation, drug-drug inhibition, or enhanced activity [66] even in hemodialysis-dependent individuals [67]. Ketamine's effects on chronic pain and on depression far outlast the actual drug levels, which are probably due to a secondary structural synaptic connectivity that is mediated by neuronal response to the ketamine-induced glutamatergic blockade. Since ketamine implicates diverse layers of regulation within the CNS (e.g., glial activity, mAChRs, glutamate, or  $\alpha_2$  receptors that are associated with desensitization), and key players in pain pathogenesis (e.g., substance P), its application is highly advantageous over other sedative and analgesic options. It also induces only minimal tolerance compared to other antanalgesics. Finally, it was suggested that ketamine enables 'rebooting' aberrant pronociceptive activity in the CNS, and prevents 'wind-up' (sensitization) of exogenous fear, pain of both peripheral and central origins, and stress-induced endogenous opioid stimulatory activity [68]. Furthermore, the recent acknowledgement of NMDA system being involved in psychiatric disorders, and ketamine's capability of attenuating them, could support ketamine's multi-task usage, so that besides expressing its analgesics properties, it would also improve uncontrolled fears in obese and pain-averse patients [69].

Due to ketamine's age-related pharmacokinetics, children would require higher infusion rates to maintain steady-state sedo-analgesic blood concentrations (~3 mg/L), whereas post infusion half-time effect is shorter than in adults. This leads to a slower return of the former to full consciousness after prolonged infusion. At the same time, lower target concentration of ketamine, when incorporated in multimodal anesthesia or analgesia regimen, would still provide identical effects [70].

It was suggested that after ketamine's injection into the epidural or caudal space, it gains rapid access to the systemic circulation with high bioavailability (level III evidence) [71-73]. While this could explain its prompt (within mins) activity, other researchers assert that the spinal cord-associated pharmacological augmentation is related primarily to its activity at its receptorial sites, as occurring with other drugs [74]. Interestingly, IV ketamine was reported to counteract hypotension occurring following spinal anesthesia [75].

The effective dosage of ketamine, especially in an acute treatment phase, directly reflects its bioavailability. With oral administration, the bioavailability is 17–24%, because of the extensive first-pass metabolism [76]. A study by Brunette et al., in children, showed high bioavailability (45%) [77], whereas Yanagihara et al. found a bioavailability of 20% in adults [78]. In this latter report, the bioavailability of nasal spray was established of approximately 45%. The difference in bioavailability may relate to the higher dose needed in children. Other factors underlying the variability after oral dosing may include the formulation (tablet vs. solution, ketamine concentration), state of the stomach, dietary enzymes induction, entero-enteric grade of circulation, and individual differences in cytochrome phenotype; the latter inter-individual pharmacokinetic variability is common to oral drug administration in general. Intranasal and sublingual ketamine administrations have been reported to yield 45% and 30% bioavailability, respectively [78] but inter-individual variability has been described for these routes as well [79,80]. Ketamine absorption after intramuscular injection has been described as more rapid, with a bioavailability of 93% [81].

### Adverse effects of ketamine

Analgesic effects follow low doses of ketamine, while high doses are amnesic and hypnotic. The most common side effects of IV ketamine are psychotomimetic and dissociative phenomena [82] which correlate with high initial plasma levels. Past reports of out-of-body experiences, visual hallucinations, and lack of coordination or reflex sympathetic activation (brain stem stimulation, which may inhibit noradrenalin reuptake) that may manifest as hypertension, tachycardia and palpitations, are presently very rare even in patients undergoing CABG or OPCAB, since the current usage of ketamine consists of subanesthetic dosings [83]. Respiration may be somewhat affected by the drug, dose dependently; several pediatric studies showed that mild airway and respiratory disturbances occur in 1.4%–6.6% of the patients, and laryngospasm may be detected in <0.4% of adolescents [84,85]. Hypersalivation may occur more frequently in children than in adults [85]. In a large cohort (>8,000) pediatric review, comprising ~50% orthopedic cases [86], high IV ketamine doses (>2.5 mg/kg bolus, or >5.0mg/kg total dose) led to increased incidence of respiratory AEs, including brief but harmless episodes of apnea. Lower loading doses (~1.5mg/kg) did not induce these AEs, and were as effective as the larger doses when evaluating intra-procedural satisfaction. A high rate of AEs was also related to patients' age (>2<14 y). Another review, of >4,000 patients sedated with ketamine in the emergency departments (ED), demonstrated that the odds of severe AEs was >2-fold higher when ketamine was administered intramuscularly (IM), and the risk of laryngospasm was >5-folds vs. IV titrated doses [87]. It was concluded [88] that risks for airway and respiratory AEs, including apnea or laryngospasm, are IM administration, IV abnormally high doses, and ages <2 and ≥13 yoa (peak 12 y.). Importantly, abnormally high pulmonary vascular resistance may contraindicate the use of ketamine in pediatric patients [89]. Interestingly, although ketamine is a sympathomimetic drug, by inhibiting reuptake of catecholamines, ketamine-induced paradoxical hypotension (vasodilation) may take place in children with previously depleted catecholamine stores [90].

While still unconscious and amnesic, minimal catatonic advents may typically occur. Patients' eyes usually remain open and exhibit nystagmus, and patients may later tell of inexplicable dreams they had while under the effects of ketamine. It is wise to advise the staff and

family members that these are normal CNS effects, and that the patient is amnesic and unaware of these occurrences.

Children on long-term ketamine may display sedation, anorexia, urinary retention, and myoclonic movements. A review that summarized 11 RCTs recommended limiting ketamine infusion dosages to 0.05–0.5 mg/kg/h (IV or SC), while the oral advocated dosages are 0.2–0.5 mg/kg/dose bid or tid, up to 50 mg/dose tid [91].

### Clinical Applications of Ketamine

The literature amply documents the use of ketamine by anesthetists and pain specialists. Reports of ketamine usage demonstrate dramatic pain relief that obviates the desire to stop it even when rare psychotomimetic effects do occur.

The currently used “subanesthetic doses”, i.e., 0.2–0.3 mg/kg IV loading dose, and/or infusion rate of <0.5 mg/kg/h or 2–2.5 µg/kg/min [4,92] are optimal and effective analgesic doses. They effectively controls OIH; sedation (lasting <2 min) may, however, occur immediately after drug injection, without psychomimetic events [16,83]. Very low doses (100–250 µg/kg), when given by the London's air ambulance, after unsatisfactory opioid administrations, were demonstrated effective in enhancing analgesia [93], as also proven both during and following orthopedic and general surgery interventions [16,94–98]. Potentiation of opioids analgesia by ketamine is associated with their reduced requirements [83,97,99,100] by 20–45%. Our group has documented that even when given alone, with no adjunct opioids, ketamine modulated pain intensity [22]. Laskowski et al. have reviewed studies encompassing >2,650 ketamine patients. They found that 37.5% of the studies demonstrated decrease in early pain (30 min–4 h), and 25% of late pain (24–72 h), while usage of opioids was reduced. Overall, 78% of the cohorts experienced less pain than placebos, implying improved quality of pain control in addition to decreased opioid consumption [101]. Significant efficacy of ketamine was ascertained in patients undergoing thoracic, upper abdominal, or major orthopedic surgery. However, debate still exists regarding ketamine's efficacy in controlling pain persistence, interrupting long-term pain [16,102,103], or blocking acute-to-chronic pain transition [104].

Patients should be assessed while treated, with an earlier secured venous line and monitoring of heart rate and blood saturation. Ketamine should be injected IV slowly (over ~60sec), since rapid administration may result in brief respiratory depression and possible enhanced sympathomimetic response. A stomach and airways suctioning devices should be at hand and a sedative available in rare cases of agitation. The patient's airways need to be safeguarded despite the drug's safety, while oxygen is used as needed. Because of the rapid–though brief–state of hypnosis that may follow an IV bolus, the patient should be in a supported position during the injection. Ketamine is physically compatible in solutions containing morphine, propofol or barbiturates (Weinbroum AA, unpublished data). The current use of subanesthetic doses of ketamine makes drying agent usage unnecessary. Interestingly, a recently presented abstract [105] has claimed that ketamine's efficacy and safety are devoid of adverse effects that require continuous hemodynamic monitoring. This is further supported by the recent frequent home use of oral ketamine for attenuation of persistent chronic pain or resistant depressive states, where in-hospital safeguards are impractical [106]. Nevertheless, at the author's opinion, the first among such serial administrations should be undertaken under a reliable medical surveillance.

The peripheral neural system is an increasingly appealing target for the use of ketamine. Low dose (0.3%) ketamine combined with bupivacaine (0.5%), when infiltrated locally for inguinal wound repair, proved to prolong the effects of bupivacaine alone [107]. Central and peripheral blocks are potentiated by ketamine as well, as when deposited intrathecally [108-110] and peripherally [111,112]. Similarly, regional IV block [113], topical or subcutaneous infusion [114] and bolus injections at the site of surgery [107] all benefit from antinociception produced by ketamine.

Intra-articular ketamine was proven to attenuate local nociception as well [115,116]. Furthermore, ketamine orally, sublingually, rectally, or topically, also acts at a similar pharmacological pattern, enabling efficacious patient-tailored local pain control [55]. The presence of NMDARs on sensory afferent nerve endings has promoted ketamine's application at somatic cutaneous neural distribution [107] in forms of gel or cream [55], and more recently, as mouthwashes, gargles, swabs, or local oral injections [112]. These latter applications produce oral/throat analgesia in various clinical settings [117]. When given peripherally, ketamine (within an appropriate carrier) can achieve higher local tissue concentrations than when given systemically, producing its pharmacological activity both directly on neurons, as well as on other cell types (keratinocytes, immune cells) [118]. Topical ketamine is at times coadjuvated with different drugs, e.g., amitriptyline, baclofen, lidocaine, ketoprofen, clonidine, gabapentin [55,119]. However, dose levels and appropriate drug ratios are not yet fully established. The mentioned oral or topical applications would suit specific subpopulations, such as obese adults or adolescents scheduled to undergo dental procedures, as appreciated by non-obese [120] or in preparation to painful maneuvers, since sedation by opioids or other sedatives need to be avoided in obese patients. Nevertheless, while IV subanesthetic ketamine doses, administered pre-operatively, and possibly for 48-72 h postoperatively, were proven to reduce MO requirements by ~35% [87,95-97] and allow for faster postoperative rehabilitation, as after TKR [121,122], the effects of local ketamine infiltration in a burn/inflammation model, or intra-articularly, remain inconsistent, being these conditioned by its total dose, time of administration, intra-multimodal regimen ratios, the type of operation, and the physiognomy of the obese patient [116,123]. The recent descriptions by Zur et al. [55] and by others [112] support the efficacy of topical ketamine in many areas and pathologies in the body.

A recent meta-analysis of various postoperative effects of different ketamine regimens combined with 48 h IV-PCA-MO (>1,300 adults and >100 children) for orthopedic, lumbar, abdominal, bone tumor, or gynecological interventions, undertaken under GA or RA, is worth mentioning [124]. This review validated ketamine's 24 h-analgesia efficacy at rest by 32%, the 24 h-MO sparing effect by 28% and the PONV decreased incidence by 44%.

Ketamine efficacy for perioperative pain under any protocol in children and infants was also reviewed, encompassing IV treatment (985 patients), topical (n=225, undergoing tonsillectomy) and ketamine+MO or ketamine+LA deposited caudally (n=714) [125]. The systemic approach of ketamine was efficient during a 2h-PACU stay in reducing postoperative pain scores and analgesics consumption. Ketamine was associated with minimal psychomimetic or PONV rates. The local application during tonsillectomy was associated with 6-24 h decreased postoperative analgesics requirements. The caudal use led to an increase in the duration of the sensory block and improved pain relief at emergence from anesthesia, but not during PACU stay. It can be reliably concluded that ketamine, when administered by any route,

ameliorates most pain-related parameters, with minimal undesired emergence events, and spares other analgesic requests. Psychopharmacological events during recovery from ketamine are rarer in adults than among children [84].

### **Stratification ketamine administration by sites and time-courses**

**Pre-hospital and emergency department sites:** The prehospital use of ketamine is of a growing interest and application worldwide [126]. Pain relief is essential during early handling of traumatized individuals [127] where ~80% of all cohorts suffer from moderate-severe pain after their conditions have been stabilized [128]. IV ketamine is a safe and effective drug during prehospital treatment of patients with bone fractures [128-131], burns [132] even where acute head concussion is suspected or intubation is requested [133]. As a sole analgesic, ketamine equals MO effects in out-of-hospital trauma individuals [134,135] while, if added to MO, the analgesic effects of both drugs result superior to MO-only achievement [136]. Several studies have illustrated the usefulness of intranasal (IN) ketamine, alone or with midazolam, or fentanyl, either in pre-hospital or in the ED settings [137,138]. The need for close patient monitoring and nursing during such scenarios, because of rare, but potential, post-injection agitation or hallucinations, or elevations in heart rate or blood pressure [134,135], is still disputed [138].

Trauma-site first-aid slow IV administration of MO (0.08-0.01 mg/kg LBM), plus ketamine (0.2 mg/kg) top-ups, resulted in ~50% lower pain scores and MO sparing effects that were still appreciated upon arrival to the ED, as compared to the much short-lived effects of a two-fold MO-only dose [139]. In these patients, and more so if obese, ketamine advantageously avoids potential decrease in blood pressure and respiratory depression. In the absence of an IV access [93,140-142], IN S-ketamine (0.2 mg/kg) or rectal (PR) application, were advocated for initial treatment [143]. Finally, ketamine is probably the best drug for rapid sequence induction (RSI) on the field and elsewhere, mainly if hemodynamics and ventilation are unstable [144].

Trauma patients frequently cause concern regarding their neurological condition. In a review encompassing 10 studies (953 patients), 8 studies reported small reductions or no changes in intracranial pressure (ICP) within 10 min of IV ketamine administration. None reported differences in cerebral perfusion pressure, worsening of neurologic outcomes, ICU length of stay (LOS), or mortality. However, the drug should be withheld upon suspicion or the presence of hydrocephalus [145]. When these precautions are kept, no mishaps would occur; rather, ketamine affects ICP similarly to common doses of fentanyl or sufentanil [146]. Especially noteworthy are recent data, originating from combat or rural areas, regarding injured individuals arriving at the ED, where the usefulness of low dose ketamine was recorded, without depicting significant AEs [134,135,147]. Finally, it was concluded [148] that although obese patients sustain fewer head injuries than non-obese, they stay longer in the hospital, and require prolonged mechanical ventilation. Advantageousness of early and continuous ketamine analgesic regimens in this cohort from still awaits RCTs' confirmation.

Ketamine's benefits were recently demonstrated in the ED in an extensive and detailed study [134], where low-dose IV ketamine (0.3 mg/kg) alone resulted as good an analgesic as MO (IV 0.1 mg/kg) given to adults with acute abdominal, flank, low back, or extremity

pain. Rapid reduction (50%) in pain scores was achieved in the ketamine group over time *vs.* a slow, although steady, pain reduction in the MO group. Brief SBP changes followed ketamine administrations, but no meaningful changes in DBP, HR, RR, or SpO<sub>2</sub> occurred. One-tenth of ketamine patients suffered from nausea and hallucinations. The authors highlighted, however, the staff's high satisfaction scores with ketamine's use. Noteworthy, the IV is just one of the routes of ketamine applicability in these settings: ketamine sublingual (SL, 25 mg) or IN (7 mg), helps to calm agitated patients upon their arrival to the ED [149], as well as uncooperative individuals; the few AEs never evolved into critical situations [93].

The combination of ketamine and propofol has become a useful protocol in the ED. An appropriate dose combination produces synergistic pain relief and reduces the frequency and the severity of adverse respiratory events compared to propofol alone, even in children [150], while also minimizing the need for additive opioids or regional anesthesia. The latter may prolong the time to full achievement of analgesia, accomplishment of intervention, and discharge [151]. Nevertheless, prolongation in the time to full awakening from ketamine-propofol combination was noted [130].

Further optimal efficacy of ketamine in children was reported when delivered by TCI (target plasma concentration equals 3 mg/L), or by manual administration (loading dose 1 mg/kg, maintenance infusion rate of 0.1 mg/kg/h that is re-adjustable by 0.2 mg boluses, and its availability for rescue of 1-2 mg/kg), together with MO [70]. It is noteworthy that any patient treated or examined under sedation needs to be escorted at discharge (AA Weinbroum, unpublished data) [152].

A 9 y (30 kg body weight) distressed obese child was reportedly found outdoors suffering from severe pain, shivering, with estimated 3% body surface area burns, but with no visible or palpable peripheral veins [153]. Racemic ketamine 15 mg (=0.5 mg/kg)/0.2 mL was deposited within his nasal mucosa; within 3 min, the patient described resolution of pain and appeared relaxed, alert, and was treated adequately. The authors of an ED study [154] sustained that ketamine IN (mean ~1 mg/kg), as a single agent, is effective in providing appreciable pain relief (>20 mm VAS reduction) in 56% of the investigated adults with severe pain of various origins. Interestingly, those who do not respond to an initial IN dose of ketamine (0.7 or 1 mg/kg), would not benefit from further top-ups (0.5 mg/kg).

The "battlefield analgesia" models are of interest to the military medical community; it also involves use of ketamine. The USA Pain Task Force has established clinical guidelines to ensure provision of adequate analgesia to wounded soldiers on the battlefield [155]. Among other adjuncts, IN ketamine has been utilized safely and successfully, providing rapid and controllable analgesia as early in the course of injury as possible. It also obviates the need for IV access. Judiciously and timely applied ketamine was effective [156] using either 'low-dose' (80-300 µg/kg/h) or 'high-dose' (>300 µg/kg/h) infusions during deployment in severely wounded soldiers. Casualties capable of operating a PCA benefited from ketamine-PCA alone at a rate of 10–20 mg/h plus 5-10 mg bolus/20 min lockout time. Concern about abuse potentials and hallucinatory side effects in high-stress and traumatic pain environment, as is the battlefield, still lack relevant data.

In this regard, the U.S. Critical Care Air Transport Teams (CCATTs) have recently reported a 5-year period of evacuations in combat settings of non-intubated critically ill patients with acute pain [157]. Of 18 (out of 381 cases analyzed) subjects receiving ketamine during

evacuation flight, 14 received it in conjunction with IV opioids, and two received an IV combination of ketamine+opioids and a LA. Two subjects were administered ketamine alone. All in-flight ketamine subjects survived.

Violent and agitated patients pose a serious challenge to the emergency medical services (EMS) personnel as well as to themselves [158] rapid physical control is vital to pre-hospital evaluation as well. While narcotics are unsafe in uncontrollable individuals, especially if obese, BZD are slow to control aberrant behavior and may cause loss of airway control and respiratory depression. Ketamine is the ideal medication, having predictable action and rapid onset. It does not adversely affect airway control, breathing, HR, or BP. A single IM (<4 mg/kg) ketamine injection has thus become part of the specific protocol devised by the EMS during similar circumstances [159]. An IN application, as mentioned above, could be an equally appreciated mode to sedate obese uncontrollable individuals.

## OR and perioperative use

**Preoperatively or preemptive analgesia:** While opiates are meant to preempt analgesia [160,161], they may also evoke preemptive hyperalgesia [4,162]. N-methyl D aspartate receptor antagonists (NMDAR-As) prevent or minimize, the development of pain sensitization, especially if opiate-induced. It is obtainable by low-dose boluses of ketamine *via* diverse routes: IV (<1 mg/kg or ≤ 20 µg/kg/min) [163], epidurally, intrathecally (IT, spinally), IN [153] or IM [22]. They all provide or potentiate analgesia both intra- and post-incidentally and spare opioid usage, and allow for optimal awakening from anesthesia.

**Intraoperative or preventive analgesia:** Ample data reiterate that the ketamine's currently accepted therapeutic regimens consist on pre-incisional boluses followed by intraoperative infusions (e.g., 0.15 mg/kg plus 2 µg/kg/min) [23,57,164]. Most reports found a 33% median reduction in acute postoperative opioid consumption and 20–25% attenuation in pain intensity during the first 48 h after surgery [57,83,96,97,165]. Ketamine loading dose of 0.5 mg/kg, maintenance infusion rate of 5 µg/kg/min, followed by 2 µg/kg/min/48 h postoperatively, all adjusted to target plasma concentrations of 250 ng/mL intraoperatively, and 100 ng/mL postoperatively [166] also proved to efficaciously counteract POH, reduce 2ry allodynia, and lessen MO requirements, while evoking minimal AEs [167,168]. These proven efficacies are of special therapeutic values in cases of thoracotomy by any technique, which is associated with both early and/or persisting pain. This description is more concrete in obese patients due to their body structure and greater technical difficulties. Respiratory recovery and prevention of complications are also of utmost importance in this cohort that would frequently use higher opioid doses or their equivalents, especially during physiotherapy, compared to non-obese [83,96]. Ketamine+MO regimens allowed for a 45% reduction in total MO consumption, while reaching 35% better pain scores compared to those registered among the MO-alone patients, both at 4h and 72 h after surgery.

Overweight patients (BMI<30) were reportedly given PCEA infusion of S (+)-ketamine alone or during fentanyl-based GA for muscle-sparing thoracotomy [169]. Intraoperative cumulative fentanyl consumption was lower (~18%), while postoperative timed median pain VAS scores were also better, and the use of rescue analgesics was lower *vs.* ropivacaine. None complained of psychotomimetic events.

Similar results were documented after cardiac surgery, annulling past fear of meaningful sympathomimetic effects [83,96] while, when using S(+)-ketamine (75 µg/kg bolus followed by 1.25 µg/kg/min/48 h) [170], ketamine satisfactorily provided a 20% reduction in postoperative oxycodone (IV-PCA) use and a 25% longer time until its first use.

Mc Nicol et al. [171] analyzed >1000 patients undergoing various types of surgical procedures known to induce late persistent post-surgical pain (PPSP) (in addition to pre-existing pain). Perioperative ketamine, given by variate regimens IV or epidurally, either by bolus, multiple doses, and/or infusions, pre-, intra- and/or post-operatively, either in combination with opioids (IV-PCA/PCEA) or non-opioids, enabled a 16% postoperative risk reduction of developing PPSP at 3, 6 and 12 mos. Even adults with end-stage kidney dysfunction (ESKD), scheduled for laparoscopic implantation of a peritoneal dialysis catheter, benefitted from ketamine (0.6 mg/kg IV or SC) vs. standardized GA [172]. The SC regimen was of a more stable effect than IV; patients were cooperative during surgery and experienced uneventful recoveries, whereas 5/20 IV patients reported hallucinations.

**Postoperative or preventive analgesia:** Postoperative ketamine administration [23] is habitually applied by IV infusion, combined with PCEA-LA or with IV-PCA-opioid; many protocols are the extension of pre-incisional and/or intraoperative regimens [16,57,83,95-97,173]. All studies showed consistent benefits of IV-PCA-MO plus ketamine or regional analgesia after cardiac, thoracic, abdominal surgery or orthopedic oncological interventions, for up to 72 h. The use of ketamine following general surgery or hip fracture repair [174] under epidural block [175] or IT, intensified preventive analgesia, prolonged LA's duration of both sensory and motor blockades, and spared opiates requirements [16,95,176].

**Post-delivery analgesia:** Pregnancy challenges the anesthetist since obesity inherently develops in all parturients. Higher than normal incidence of hypotension occur when performing epidural or spinal anesthesia in this cohort, or difficulty to place intravenous access and endotracheal intubation (ETT) together with eventual aspiration of the gastric content during GA, all become dangerous reality [177,178]. Ketamine allows for safer airway control in obese patients, also counteracting intra-procedural hypotension [75,179]. Postoperative multimodal drug regimen may include ketamine (0.17 mg/kg/h), which lowers level of sedation and spares IV-PCA-MO usage (~16 mg/patient). The risk of hallucinations was found minimal among parturients [180,181]. Furthermore: besides the maternal dysfunctional and postoperative discomfort or pain, the newborn may be exposed to analgesics as well. Analgesics may interfere with the mother-child relationship and breastfeeding. S-Ketamine (0.5 mg/kg IM bolus 10 min after giving birth, followed by IV 2 µg/kg/min/12 h) proved to reduce MO consumption by 31% within 24 h, suggesting an anti-hyperalgesic action [182]. Subsequent normal ambulation, global wellbeing, and unchanged breastfeeding duration, further underline the safety qualities of ketamine regarding the mother and the newborn. Noteworthy, ketamine crosses the placenta; post C/S newborns may therefore be partially sedated and should be cared for accordingly [183].

### Procedures out of the OR (ED excluded, mostly in children)

The usefulness of ketamine outside the OR merits special mentioning as well. Increasingly larger volumes of interventions take place in clinical suites and on ward; obese patients, particularly

adolescents, are thereby treated for minimal dermal, esthetic or dental interventions. Out of the OR locations and advanced site sedo-analgesia modalities attenuate fear and intimidation, making case handling easier. Indeed, the literature progressively becomes ample with reports of ketamine – alone or as part of multidrug regimens – being used in these settings [184,185].

**Wound care procedures (WCP):** These are short, though painful, procedures (e.g., post burn dressing), requiring quick, reliably safe and profound analgesia, and timely recovery. In an example of ketamine applicability [100] 11 patients, necessitating WCP, were given either IV 0.1 mg/kg MO ( $\leq 8$  mg) or 0.05 mg/kg MO ( $\leq 4$  mg) plus ketamine 0.25 mg/kg in a crossover manner, before each scheduled WCP. Pain intensity after the procedures halved in those receiving ketamine, but 15% reported strange sensations, hallucinations, blurred vision, or uneventful increased DBP. The use of low opioid (MO, fentanyl) doses, or propofol, are applicable in all age populations and for various interventions (Weinbroum AA, unpublished data). Thus, IV ketamine doses (50 µg/kg top-ups every 4-5min) following the first 250 µg/kg bolus plus propofol 10-20 mg/70 kg boluses are suitable. Vital signs monitoring includes HR and SpO<sub>2</sub>; post-procedural monitoring and nursing surveillance are necessary, to tackle potential respiratory, hemodynamic, or cognition changes [138] until full coherence is regained [186]. The present author detected no remarkable AEs in >6,000 patients.

**MRI and sedo-analgesia:** These settings would highly benefit from ketamine, especially in children. Intranasal ketamine (7 mg/kg/instillation) was reported safe and effective in inducing fast moderate conscious sedation [187]. Ketamine bolus is best administered in patients who need to be sedated for <15 min and where interventional pain is expectedly intense but brief, while spontaneous respiration and stable hemodynamics are desired.

**Dentistry:** Premedication with nebulized ketamine (2 mg/kg) in healthy small (3-6-yr) children undergoing dental surgery under GA [120] another area of interest that has grown recently, resulted in 30 min pre-incisional sedation, tolerance to mask induction, augmented post-interventional analgesia, and shortened recovery and discharge times (all better compared to dexmedetomidine 2 µg/kg). A low ketamine-dose protocol also enhanced the effects of LA solutions in adult dentistry [188].

Ketamine also proved beneficial for uncooperative and conventionally unmanageable children requiring dentary interventions [189]. Ketamine IN (5 mg/kg) enabled stable HR and SBP maintenance compared to dexmedetomidine (1 or 1.5 µg/kg), but success rate of the operations was optimal in only 67% of the ketamine treatees. This and other data would support the safe usefulness of ketamine in obese populations during ambulatory and clinical suites dentistry interventions. Indeed, a recently published [190] large scale (>22,000 children, including obese ones, 0-21 y) review described the medical personnel's satisfactory judgment following ketamine's use for procedural sedation or in radiology units. Usage via various routes: IV (n=8,725, mean mg/kg 1.6), IM (n=766, 3.5), PO (n= 102, 5.2), IN (n=5, 2.1), at a total average dose of  $1.8 \pm 1.6$  mg/kg, was advocated optimal. The overall AEs rate was 7.26%; severe such events amounted at 1.77% three children underwent successful cardiac resuscitation following laryngospasm.

Other Various Sites and Procedures of Usage: Ketamine was also proven highly useful in both adults and children who require deep sedation in specific sites [187,191].

- (i) MRI and similar diagnostic sites.
- (ii) Antidepressant electroconvulsive therapy [192,193].
- (iii) Anticonvulsive therapy for status epilepticus [194].
- (iv) Office-based routine procedure [195].
- (v) Cardiac laboratory, where catheterization, interventional cardiology, implantable cardioverter defibrillator (ICD) and radiofrequency ablation (RFA) are performed under sedation, mostly in children [196,197]. In the latter occasions, ketamine was used IV (0.25 mg/kg, up to totals of 50-100 mg) at induction, then continuously, to maintain sedo-analgesia, especially during electrical bursts.

Either alone, or when combined with other drugs, ketamine, as by IN deposition (inducing minimal discomfort in children), has led to anesthetists' satisfaction rates of >90% vs. 21.3% in the sedated population. The former awoke and were discharged home earlier than the latter group [191].

### Proven Usefulness of Ketamine in Obese Patients

Ketamine has an appealing safety profile in obese patients, primarily because they easily develop postoperative respiratory obstruction, hypoxia, and deep sedation, which are ketamine-preventable [198]. The pharmacological effects of ketamine in sparing opioid consumption, as during and after bariatric surgery, are most known (grade B proof); nevertheless, note that dosing scalars of ketamine in obese children still need considerations [199] and pharmacologic elaborations [51,181]. Opioid-free anesthesia and analgesia regimens, which include ketamine, were recently discussed and worth consulting [200].

Obesity represents a risk factor for the development of general and pathophysiological degenerative changes and coxarthrosis [201]. Knee dislocation in morbidly obese patients may induce immediate severe pain and late complications [202,203]. Brief articulation readjustments in the ED would benefit from ketamine, avoiding systemic MOEs usage, and saving the time of arduous attempts to establish an effective local or regional blocks (Weinbroum AA, unpublished data).

Obese patients undergo open or laparoscopic interventions, apparently more frequently than non-obese individuals, perhaps consequently to their background pathologies [204,205] or for bariatric surgery. At the same time, OSA is a safety concern in obese and morbidly obese patients, especially upon using opioid liberally, independently of the technique. The application of total IV anesthesia (TIVA) coadjuvated with ketamine, as during bariatric surgery, is an appropriate choice. The effects of opioid-free+ketamine anesthesia (0.5 mg/kg/h IBW), rather than fentanyl infusion-based GA (0.025-0.25 µg/kg/min IBW), in morbidly obese patients [206] proved effective, safe, and provided lower pain scores compared to the latter. Hofer et al. [207] reported of a super-obese (433 kg) patient, undergoing bariatric surgery, where opioids were omitted intraoperatively and ketamine was used instead. Awake fiberoptic intubation was achieved under the effects of midazolam and ketamine, with the aid of dexmedetomidine. Thus, as in non-obese, quick, reliable and safe sedo-analgesia is obtainable by ketamine in obese patients, while stable respiratory and cardiovascular conditions are also maintained.

Despite the scarce data regarding the question which is the best multimodal opioid-limited regimen in obese, various protocols that include NSAIDs or LAs, consistently comprise ketamine that has

shown to potentiate the former postoperative analgesia, as reported following laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery [204]. Hasanein et al. [208] detailed of the use of propofol-remifentanyl infusion-based GA, when coadjuvated with ketamine (1 µg/kg/min) and followed later by IV-PCA-MO for postoperative analgesia. Reduced intraoperative requirements for remifentanyl and propofol, improved PACU pain scores, and the 24 h reduced PCA-MO requirements, were all assessed in the ketamine-added group. No confusion or hallucinations were recorded in these obese patients.

An exceptional case report described endotracheal intubation under ketamine (plus lidocaine oral spray and dexmedetomidine IV) in a morbidly obese patient (29 y., 150 kg, BMI 51.9) scheduled for discectomy [209] while in the prone position. Dexmedetomidine-ketamine-remifentanyl infusion was used for GA maintenance. The patient awoke painless and clear-minded, and the ETT was removed safely in the same prone position. This report highlights the efficacy of multimodal ketamine regimens in enabling awake, spontaneously breathing, ETT insertion (that recalls emergency cases), and its removal upon awakening, without provoking airway problems. While the combination of ketamine with  $\alpha_2$  drugs seems to have benefited the maneuver, drug doses were neither reported in the English-language abstract, nor were they forwarded at this author's request.

Postoperative poorly-controlled pain, as after THR, TKR, or after a fall, may transform into POH. Heavy opioid analgesia can also delay postoperative mobility, induce venous thromboembolism, impair rehabilitation, and prolong patient's LOS and relative costs. Obese patients are more prone to develop all the above, with undesired late consequences [210,211]. Tukker et al. studied health problems of the lower extremities due to obesity [203]. These researchers concluded that obese individuals after blunt traumatic injury are problematic regarding successful completion of rehabilitation, because of the risk of developing in-hospital complications [13]. Adhikary et al. [202] reported data of 77,785 primary TKA and 49,475 primary THA subjects under various anesthesia regimens. Patients were separated into 7 BMI subgroups (18.5-24.9 kg/m<sup>2</sup>, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0-44.9, 45.0-49.9 and >50.0 kg/m<sup>2</sup>). The authors found that the odds ratio for 4/5 composite complications increased exponentially at BMI  $\geq$  45.0 kg/m<sup>2</sup> among the TKA and in the THA patients. This positive correlation indicated that obese patients develop postoperative pain persistence, which leads to chronic pain conditions that affect negatively their later quality of life [212,213]. Implementation of appropriate, patient-tailored, pre- and postoperative analgesia, minimize these consequences [214]. Ketamine was proven to prevent most of these mishaps in non-obese patients after several orthopedic interventions, e.g., knee arthroscopy [98] anterior cruciate ligament repair [94,116] knee arthroplasty [121,122] oncologic orthopedic limb-sparing surgery [22,97,215] lumbar disk surgery [216] and cervical spine surgery [217]. Indeed, pain control and rehabilitation after TKR improved after as a low bolus dose of ketamine as 0.2 mg/kg, followed by 120 µg/kg/h intraoperatively and continued at 60 µg/kg/h for 2 PODs. IV MO consumption, pain intensity at rest and on mobilization was all reduced steadily by ketamine vs. nefopam for example; ketamine provided improved knee flexion on POD 3, and decreased the time to 90-degree optimal flexion of the knee [121]. A single bolus (0.15 mg/kg IV) of ketamine, administered pre-incisionally, in addition to standardized IV GA, plus bupivacaine+MO intra-articularly at the end of knee arthroscopy, also proved to diminish postoperative IV-PCA-MO by 50%, and intra- and out-of-hospital oral NSAIDs usages. It also lessened postoperative pain at rest and during mobilization (POD 0-2), and lengthened the periods of walking on POD1 [98]. The



above bettered functional scores and long-term survival of the implanted joint those are lower in obese, in which morbidity and mortality are also higher than in normal BMI patients [218].

Finally, as shown above, the use of ketamine is still scarce among various obese subpopulations. This is despite the knowledge that postoperative pain and daily functional interferences are more significant in obese patients than in non-obese ones. Indeed, more NSAIDs and opioids are used in the former, in order to attain satisfactory levels of pain relief [10]. Based on its neuropharmacological potentials, ketamine could benefit obese patients as shown for non-obese ones, and minimize their undesired episodes. These, however, await future clinical confirmations.

### Routes of Administration of Ketamine

Optimal pain control, sedation and anesthesia, are achievable by diverse approaches, including systemic, enteral, or regional, either peripherally, centrally, or locally. These modalities have been tested for ketamine and proven most efficacious when used solely or where coadjuted with opioids or non-opioid drugs. These regimens are seldom applied for other analgesics, making ketamine a unique pertinent drug.

#### Systemic routes of administration

Systemic administration of ketamine is the most frequently used technique. Besides the IV route that is not always achievable in children or in obese patients, the IM route allows for safe and reasonably predictable effects, but is painful, of slower onset and longer recovery times, and induces a higher rate of AEs compared to IV [219]. Ketamine application may benefit from the recently improved intraosseous access technique (bolus dose 0.5-1 mg/kg) that is as efficient as the IV one [220].

The SC route is another modality that circumvents lack or inability to establish an IV line [169,170]. This route pertains obese cohorts [114] mainly adults. Interventional regimens reported the use of ketamine 50 mg bolus+300-500 mg/24 h.

#### Non-systemic routes of administration

The use of ketamine orally, intranasally, transdermally, as well as rectally, topically, and even epidurally or intrathecally, has proven efficient and safe. Most of these routes suit children and those who fear pain in general and needle puncture in particular [221,222]. Since ketamine has been approved by the FDA for the IV and IM administrations only, all other routes are, officially, "off label".

Follow synoptic descriptions of non-IV and non-IM ketamine administrations.

**Inhalational ketamine:** Ketamine by inhalation allows for rapid drug delivery. In a rare report [223] 0.35, 0.5 or 0.7 mg/kg of preservative-free S(+)-ketamine were inhaled for the duration of 20-40 min. Inhalations were tolerable and easily reached completion of treatment. None presented oropharyngeal irritation, hypersalivation, stridor, laryngospasm, cough, dry mouth, hoarseness, dyspnea, tachypnea, aspiration, cardiac dysrhythmia, or blood desaturation, both during and after ketamine administrations. Rare ketamine-related AEs (mild hypertension, nausea, vomiting, and psychodelic effects) were noted. All doses produced the active S-ketamine plasma concentration (>100 ng/mL), making inhalation a valid alternative to other administration routes.

**Oral/oropharyngeal/sublingual ketamine:** Ketamine has recently been marketed as mouthwash, gargle, in form of swab [117] and injectable local oral solution [112]. Orally dissolved ketamine has produced significant postoperative oral/throat analgesia in controlled trials [117]. Intraoral topical applications suit specific subpopulations, such as obese adolescents undergoing dental procedures, as for non-obese ones [120] aiming at avoiding opioids or sedative drugs. Pain relief after tonsillectomy [224] was of better effect after ketamine (20 mg/10 mL artificial saliva or 20 mg/5 mL mixed with in 0.004% MO/5 mL artificial saliva) than placebo, and as efficacious as MO 4% (20 mg/5 mL) (grade II evidence). The solutions were deposited in the tonsillar fossae for 5min. Similarly, local peri-tonsillar infiltration (2 mg/kg), rectal (0.5 mg/kg) or IV (0.5 mg/kg) ketamine employed in children (5-15 y, n=120) [225] when compared to IV tramadol (2 mg/kg) for postoperative pain relief and sedation after adenotonsillectomy, were of similar efficacies. Ketamine IV provided, however, superior analgesia at 6- and 24-postoperative h. Ketamine oral rinse (gargle) applied at the tonsillar fossae (40 mg/30 mL NS) was also found useful to prevent postoperative sore throat (POST) after endotracheal intubation [226].

A recent analysis reviewed sedation modalities for dental procedures [227] applied in 12 different cohorts. Ketamine (0.25 mg/kg, 5, 6, 10, or 50 mg/kg) was used in combination with other drugs, IN (drops or spray) in 4 studies, IV in 2, orally in 5 (of which 1 patient was given as ketamine-laced lollipop), and IM in 1 study. The drug provided highly effective sedation in all these studies, at any dose range; submucosal and aerosol mouth spray also providing analgesia effects [228].

To compare oral dosing regimens across studies, Schoevers et al. [229] computed the daily oral racemate equivalent dose, in mg/kg/day, as follows

- The IV racemate dose was multiplied by 5, to correct for the lower average oral bioavailability
- The S (+)-ketamine dose multiplied by 2, to correct for the double potency relative to racemate
- For IN regimens, the daily oral racemate equivalent dose was multiplied by 2.25 to correct for the lower oral bioavailability.
- For IM dosing, the daily oral racemate equivalent dose was multiplied by 4.65 to correct for the lower oral bioavailability
- The sublingual dose is to be multiplied by 1.5 to obtain their daily oral racemate equivalent dose.

**Intranasal (in) ketamine:** Ketamine has been used IN extensively, as a premedicant, sedative, or pre-incisional analgesic drug, especially where an IV line was unavailable and the IM route was refused. Ketamine was compared to, or co-administered with, dexmedetomidine, or opioids in several studies [187,189,191,230]. While of appreciable results, the combined drug regimens provided obvious superior peri-interventional effects [186], as judged by ratings by both treats and caregivers. From the neuropharmacological and clinical aspects, ketamine is a better choice than dexmedetomidine, mainly since it provides stable hemodynamic conditions.

The sedo-analgesic effectiveness of IN ketamine was also proven optimal when compared with fentanyl in conjunction with moderate-severe painful pediatric (3-13 y, <50 kg bwt) procedures undertaken in the ED due to isolated musculoskeletal limb injuries (lacerations). The subanesthetic IN dose of ketamine (1 mg/kg) was of similar analgesic

effects as was fentanyl (1.5 µg/kg), but with fewer AEs [230]. Given the clinical problems associated with fentanyl in obese pediatric cohorts (sedation, hypoventilation), IN ketamine presents a safer analgesic alternative over fentanyl in this cohort.

**Rectal ketamine:** In a single blinded study [231] 70 children, undergoing elective tonsillectomy, received either rectal ketamine (2 mg/kg) or rectal acetaminophen (20 mg/kg) at the end of surgery. The ketamine group displayed lower pain scores up to 120 min after surgery; dreams or hallucinations were not reported. Systolic blood pressure was slightly higher in the former and 14% displayed nystagmus. A lower ketamine dose (0.5 mg/kg) was still efficient in controlling postoperative pain after the same intervention in a similar cohort [225]. These data prove ketamine PR optimally substitutes acetaminophen. Importantly, rectally deposited drugs bypass the entero-enteric circulation, thus boosting their efficacy and potency.

**Topical (external) use of ketamine:** The dermal mode of use of ketamine (common concentration 50 mg/mL) is popular, providing reduction of mechanical and secondary hyperalgesia. However, distinction between the local antinociceptive from the systemic effects is yet unestablished [232]. Ketamine is combined with gabapentin, clonidine and baclofen, using either transdermal Lipoderm or Lipoderm ActiveMax. This technique can personalize treatment thus embettering focal pain control [233]. Also, topical ketamine cream, compounded in combination with other drugs (amitriptyline, baclofen, lidocaine, ketoprofen, clonidine, gabapentin, pregabalin), was reported by this group with excellent pain control in patients suffering from peripheral neuropathic pain [55]. Similarly, 13 patients had been prescribed topical amitriptyline 1-2% plus ketamine 0.5 for genital, rectal, or perineal pain, which resulted effective. Only 2/13 showed no response. None reported local or systemic AEs, except for local irritation in one patient [234].

Finally, postoperative transdermal ketamine (release rate 25 mg/24 h, i.e., 1.25 mg/h until the 4th h, decaying to ~0.5 mg/h at 5-8 h, then ~0.4 mg/h) was applied at the end of minor abdominal gynecological surgery undertaken under 25 mL 2% lidocaine epidural anesthesia [235]. The time to first request for a rescue analgesic proved >two-times longer among the ketamine users compared to placebos. None of the patients complained of any adverse effect such as nightmare, hallucination, or difficulty in concentrating or answering simple questions (Level II evidence).

### Central (neuraxial) and peripheral (nerve blockade) ketamine analgesia

Ketamine has been tested, and more presently applied, solely or in addition to LAs, for central and peripheral nerve blocks, IV regional blocks, both intra- and postoperatively. Several studies are worth mentioning, describing such use in trauma, ED and orthopedic cases [108,109,236,237].

**Central blocks usage:** Epidural block with deposited ketamine (30 mg) alone was shown to ameliorate postoperative analgesia in females undergoing hysterectomy under GA [238]. Ketamine prolonged the time to first rescue analgesia request, and reduced postoperative PCEA (bupivacaine+fentanyl) consumption. These benefits appeared both when ketamine was administered pre-incisionally (preemptively) and 20 min after skin incision (preventively). The same results were reported after lumbar epidural anesthesia (ropivacaine {10 mg/mL, 10-20 mL} plus S{+}-ketamine {0.25 mg/kg}) was applied 10 min before surgical incision [110]. This regimen resulted in better (time

and potency) postoperative analgesia compared to the effects of the LA alone.

In 90 parturients, undergoing C/S, S (+)-ketamine (0.05 mg/kg) or fentanyl (25 µg) were added to 10 mg plain bupivacaine 0.5% IT [239]. Ketamine's combination was associated with faster onset of sensory and motor blocks, and with a higher maximal dermatomal level of the sensory block; both regimens induced a longer blockade than bupivacaine alone did. The quality of the analgesia was excellent in 93% of fentanyl vs. 90% of the ketamine's, compared to only 77% in the LA-alone group. More minor AEs were recorder among the ketamine vs. the fentanyl patients; no psychological event was reported. Neonatal Apgar scores, after 1- and 5 min, were similar among the experimental groups. Importantly, the ideal dose or concentration of the IT's S (+) ketamine that would induce satisfactory analgesia and longer duration of action during C/S has not yet been established. Most studies base their protocols on Kathirvel's and colleagues' study [240] who indicated a 25 mg of IT S(+) ketamine as efficacious to spare the effects of bupivacaine, while >1 mg/kg would induce AEs.

The benefits of ketamine were further highlighted in a review [241] that analyzed 13 RCTs (n=584 ambulatory children) where ketamine (0.25-0.5 mg/kg) was coadjuvated with caudal-based single dose (bupivacaine or ropivacaine) blocks. The combined-drug regimen improved analgesic efficacy, and prolonged the postoperative analgesia time compared to the LAs alone (mean difference 5.6 h), also reducing the need for rescue doses; no worrisome AEs were reported. Importantly, uncertainties still reign ketamine's clinical neurotoxicity, regarding dosing, single vs. repeated dose regimens, and the pediatric age ranges, are all to be established.

**Peripheral nerve root s and ketamine:** Ketamine addition to peripheral blocks not only hastens the onset of sensory and the motor blockades, but it potentiates them as well. Continuous peripheral nerve block (CPNB) has gained popularity in recent years, especially where US guidance is available. Peripheral blocks are recommended for many grounds, especially for respiratory reasons in obese individuals. Ketamine was reportedly adjuvated to lignocaine and bupivacaine boluses for stellate ganglion block (STGB) in patients suffering from peripheral vascular disease (PVD) of the upper limbs [242]. The addition of ketamine (0.5 mg/kg) provided a 14 h-longer pain relief compared to the LA alone, and 12 mos. duration of no pain after the procedure, together with complete healing of gangrenous fingers in 17/19 patients.

The combination of ketamine with lidocaine, for perioperative intravenous regional anesthesia (IVRA) for hand or forearm surgery, is also worth mentioning [243] mainly because it may take the place of GA in obese patients. Lidocaine (3 mg/kg/40 mL) alone allowed for the completion of interventions as did the same when coadjuvated with ketamine (50 mg). Nevertheless, the latter provided less tourniquet postoperative pain, 4-time-prolongation of the time to first request for postoperative rescue analgesics, and their 62% lower consumption than the former. Postoperative pain scores were also lower whereas AEs rates were similar.

### Conclusion

Pain is one of the main perioperative issues that need prompt assessment and adequate control, especially since persistent acute pain may stimulate hyperalgesia and transform acute into chronic pain. Obese patients suffer more than non-obese individuals from pain, and handle it worse. Opioids are disadvantageous in obese individuals, due

to their negative effects on vital functions, and more so when previous pathologies and chronic pain are involved. Opioids occasionally become pro-nociceptive as well. The application of drugs that induce safe and predictable analgesia is thus essential, and ketamine is such a drug. Its neuropharmacological potentials and ease of application, starting from the trauma site, throughout the emergency department, and OR, as well as outside it, have improved pain control in almost all occasions, at all population ages, and interventions. The pharmacokinetics of the drug and its dosing scalars are still to be accurately established in the obese pediatric subgroup. Nevertheless, adhering to the current subanesthetic dose regimens and adjusting them to patient's LBW, ketamine best provides obese individuals with optimal and sustained analgesia via all existing routes of administration (oral, intranasal, inhalational, topical, rectal, and regional). Due to its ability to spare opioids' needs, reduce their AEs, and be of limited untoward respiratory and cardiovascular effects of its own, ketamine could benefit obese patients, as shown for non-obese ones, and minimize complications obese patients undergo when in pain.

## Acknowledgements

The author wishes to thank Ms. Esther Eshkol for proof editing the manuscript potential conflicts of interest and Mr. Eitan Noyman for technical assistance.

## Conflicts of Interest

The author declares no conflicts of interests.

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