Chapter

Role of Ketamine as Part of the Anti-Hyperalgesic Approach in Opioid-Free Anesthesia (OFA) and Postoperative Analgesia (OFAA)

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Abstract

There is increasing evidence of the close relationship between persistent activation of the glutaminergic pathway, central sensitization, hyperalgesia and chronic pain. Opioids have long been the standard analgesics used in the perioperative. However, their side effects, namely opioid-induced hyperalgesia, opioid tolerance and post-operative dependence in patients with chronic pain that are to undergo aggressive surgeries have motivated anesthesiologists to develop alternative anesthetic techniques. They include analgesic and anti-inflammatory drugs that act by modulating the nociceptive pathways with an opioid-sparing effect and even opioid-free anesthesia (OFA). In OFA plus postoperative analgesia (OFAA) techniques, ketamine plays a fundamental role as an analgesic with its antagonist action on the N-Methyl-D-Aspartate-receptors (NMDAr). However, ketamine is limited to use at sub-anesthetic doses ("low-doses") due to its dose-dependent side effects. Consequently, other analgesic drugs with anti-NMDAr effects like magnesium sulfate and other non-opioid analgesics such as lidocaine and alpha-2-adrenergic agonists are often used in OFAA techniques. The aim of this text is to present a summary of the importance of the use of ketamine in OFA based on nociceptive pathophysiology. Additionally, the perioperative protocol (OFAA) with the anti-hyperalgesic approach of ketamine, lidocaine and dexmedetomidine co-administration in our center will be described. Some of the main indications for the OFAA protocol will be mentioned.

Keywords: Opioid-free anesthesia, OFA, Opioid-free anesthesia and analgesia, OFAA, minimizing-opioid-use, NMDA-receptors antagonists, ketamine-magnesium-lidocaine-dexmedetomidine-methadone, anti-hyperalgesia, central sensitization, opioid intolerance, opioid-induced hyperalgesia, craneocervical/thoracic fixation, complex spine surgery

1. Introduction

Nociceptive phenomena associated with surgical trauma involve local and systemic inflammatory processes, activation of cellular and humoral immune mechanisms, and adrenergic and neuroendocrine activation. The activation of the glutaminergic pathway plays a determining role in secondary sensitization at the level of the central nervous system, which is responsible for nociceptive amplification, persistence of postoperative pain, and hyperalgesia.

Strategies to reduce perioperative opioid consumption and its consequent side effects have been based on the use of multimodal analgesia schemes. The development of opioid-free anesthesia (OFA) techniques, indicated for particular patient populations in which opioids may be harmful, requires the use of drug mixtures in which NMDA receptors (NMDAr) antagonists are integral. The most clinically used NMDAr inhibitors in anesthesia are ketamine and magnesium sulfate. Their co-administration in OFA techniques has synergistic analgesic effects. The concomitant use of intravenous lidocaine and dexmedetomidine provides additional benefits to the use of NMDAr antagonists to reduce the central sensitization phenomenon (SC), hyperalgesia and opioid-induced hyperalgesia (OIH).

2. NMDAr are involved in nociception even from the beginning of tissue trauma: peripheral hyperalgesia is an event modulated by a glutamatergic system in the dorsal root ganglia (DRG)

The nociceptive pathway undergoes important functional changes and modulation under surgical trauma (tissue damage and inflammation). This plasticity is mediated by many mechanisms, including peripheral and central sensitization. The paramount element for these modificationsis the result of release of many chemical mediators peripherally as well as neurotransmitters in the spinal cord and the brain [1].

Peripheral sensitization contributes to increased afferent stimulation of the spinal cord. It is mediated by many processes in which nerve tissues and immune cells act under a complex barrage of pain-mediating substances. The nociceptive impulse generated by an inflammatory event in peripheral tissue is regulated in the dorsal root ganglia (DRG) by a system that involves satellite glial cells and glutamatergic NMDA receptors (NMDAr) [2].

Mechanical inflammatory nociceptor sensitization is dependent on glutamate release in the DRG and subsequent NMDAr activation in satellite glial cells. That fact supports the idea that peripheral hyperalgesia is an event modulated by a glutamatergic system in the DRG. Moreover, retrograde sensitization of the primary sensory neuron has been proposed as an essential mechanism for induction and maintenance of peripheral inflammatory hyperalgesia. It has been suggested that this phenomenon is due to the release of glutamate in the spinal cord, which acts retrogradely on NMDARs present at the presynaptic terminals of the primary sensory neuron [3–5].

In summary, numerous receptors and ion channels are involved. Continued increased input to the spinal cord results in further central sensitizing changes.

3. What is the importance of glutaminergic pathway in the nociceptive process and secondary sensitization during surgical trauma?

The glutamate receptor NMDAr is the starting pointof secondary sensitization and the amplification of pain. Hence, the NMDAr may be a potential target

for analgesic therapy in the context of opioid-free anesthesia and postoperative analgesia (OFAA).

The primary sensitization resulting from local inflammation of the tissue under surgical trauma activates the "asleep afferent" thereby increasing the total nociceptive afferent signals to the spinal cord, which is the beginning of the development of the central sensitization. The excitatory amino acid glutamate plays a central role both via the α-amino-3-hydroxy-5- methyl-4-isoxazolepropionate (AMPA) ion-channel linked receptor in acute pain transmission and via the N-methyl-d-aspartate (NMDA) receptor to mediate sensitizing effects. In the acute state, the NMDAr are limited by a voltage-dependent magnesium ion block of the channel. Increased afferent input from primary sensitization releases the magnesium ions and activates theNMDA receptors. NMDAr activation increases intracellular calcium flux and enhances the activation of the second-order neuron. The increase in intracellular calcium also stimulates cyclooxygenase, lipoxygenase and protein-kinases [2, 6].

Surgical stimulus activates C fibers and generatesa progressive build-up in the amplitude of response in dorsal horn neurons andbrings onthe Wind-up phenomenon, which is a specific initiator of central sensitization [1].

4. How does the glutaminergic pathway mediate the persistence of pain after surgery and chronic pain?

Neuropeptides like substance P and the calcitonin gene-related peptide (CGRP), released from primary afferent neurons, contribute to the activation of the NMDAr in pain states. Neuropeptides such as neurokinin A and B act on NK receptors and activate the NMDAr directly by inducing decreased potassium ion conductance and phosphorylation-induced increases of intracellular calcium, facilitating central sensitization and hyperalgesia. Brain-derived neurotrophic factor (BDNF) is produced by nerve growth factor (NGF)-dependent nociceptors and increases the glial inflammation. Moreover, BDNF augments spinal neuron excitability by phosphorylation-mediated stimulation of the NMDAr.

Finally, longer-term changes of central sensitization may be explained by transcriptional changes.

Hence, the significance ofthe spinal cord as a location for an anti-hyperalgesic approach leads us consider the important role the NMDA receptors have in central sensitization and their potential usefulness as a focus of analgesic therapeutics [7, 8].

Ketamine and magnesium sulfate are the most frequently used NMDAr antagonist drugs in anesthesia. Ketamine in association with lidocaine and dexmedetomidine infusions have led to the development of opioid-free anesthetic techniques (OFA). Moreover, the combination of low doses of ketamine with these adjuvant medications have shown an important opioid-sparing effect on postoperative pain control and has an additional anti-hyperalgesic effect [8].

5. Why should opioid use be minimized during the perioperative period?

Intravenous opioids are the commonly used analgesics during general anesthesia along with hypnotic drugs. Opioids provide potent analgesia, attenuate the neuroendocrine response triggered by surgery, and provide hemodynamic stability. However, these drugs have side effects like nausea, vomiting, decreased intestinal peristalsis, respiratory depression, histamine release and opioid-induced hyperalgesia mediated by NMDAr stimulation [6].

Multimodal postoperative analgesia has been the gold standard for more than 20 years. It makes for opioid-sparing and better outcomes than with drugs like morphine that are administered as a sole analgesic agent after surgery. OFA is based on the association of drugs and/or techniques that makes for good quality general anesthesia with no need for opioids. The association can combine NMDAr antagonists (ketamine, lidocaine, magnesium sulfate), sodium channel blockers (local anesthetics), anti-inflammatory drugs (NSAID, dexamethasone, lidocaine) and alpha-2 agonists (dexmedetomidine, clonidine) [9].

There is a group of patients in whom opioid use is relatively contraindicated. It is comprised of those with gastrointestinal intolerance susceptible to developing intestinal ileus, functional bladder disorders, a history of severe nausea and vomiting, sleep apnea syndrome, morbid obese, patients with mast cell activation syndrome (MCAS), autonomic symptoms like postural orthostatic tachycardia syndrome (POTS), patients with chronic pain, chronic fatigue syndrome and myalgic encephalomyelitis, patients with high-dose opioid use, opioid tolerance, opioid-induced hyperalgesia (OIH) and patients who are prone to drug dependence [9–13].

The above patients benefit from OFAA techniques. When feasible, the use of regional anesthesia is helpful. Then again, the substitution of opioids for analgesic drugs with different mechanisms of action is desirable when general anesthesia is indicated [14, 15].

6. Ketamine, magnesium, lidocaine and dexmedetomidine: an anti-hyperalgesic combination

Ketamine plays a fundamental role in OFA techniques since it is a potent NMDAr inhibitor that provides an excellent analgesic effect at sub-anesthetic doses. Since ketamine can cause dose-dependent side effects (cardiovascular excitation, hallucinations, psychomimetic events, nausea and vomiting as well as hyper-salivation), it is advisable to associate it with other NMDAr antagonists like magnesium sulfate or dextromethorphan to enhance its analgesic effect with lower doses.

Ketamine and magnesium have been widely described as improving postopera- pain control. The literature has consistently reported that both drugs provide effective postoperative analgesia and a reduction in opioid consumption. A meta-analysis that aggregated data from 2482 patients showed that intravenous ketamine reduces postoperative opioid use by 40% [16]. Similar results have been shown with the administration of intravenous magnesium [17–19].

Furthermore, experiments on the association of ketamine and magnesium may give us an important clue as to the useful of the association. In fact, pretreatment with ketamine has been demonstrated to improve the anti-nociceptive effect of magnesium [20]. Interestingly, myocardial and endothelial cells express NMDA receptor. Thus, a synergistic effect can be expected on the NMDA receptor in the cardiovascular system with the resulting cardiovascular stability by the competitive blocking actions of drugs [21, 22].

On the other hand, there are many publications that describe the use of intravenous lidocaine as a systemic analgesic with particular attenuating effects on the intraoperative inflammatory reaction at multiple levels (i.e., reduction of inflammatory biomarkers by direct action on cell membrane of monocytes, neutrophils and mast cell, PKC-mediated reduction of Ca^{++} intracellular influx and K^{+}_{A}-channels, action over cholinergic, adrenergic, GABAergic, NMDAr, and NK-1r pathways, etc.). Lidocaine has a non-relevant analgesic effect mediated by Na^{+}-channel blocks at therapeutic plasmatic concentrations [10, 23, 24].

Additionally, lidocaine modulates the immune response to surgical trauma with benefits in term of cancer recurrence. So, it is advisable to associate the intravenous infusion of lidocaine along with dexamethasone plus non-steroidal anti-inflammatory drugs (NSAIDs) to complement the analgesic effect of NMDA antagonists through the reduction of inflammation due to surgical trauma. Moreover, it has been shown that the intravenous lidocaine reduces the requirements for hypnotic drugs (propofol or sevoflurane) and has a dose-dependent anti-NMDAr effect [25–31].

Dexmedetomidine is an alpha-2 adrenergic agonist which acts at different levels of the nociceptive pathway like on the peripheral nerves, pre-synaptic receptors at the dorsal horn of the spinal cord and at the supraspinal level (Locus Coeruleus). The association of dexmedetomidine with OFA may provide additional benefits. They encompass the attenuation of the sympathetic nervous system, a reduction in intraoperative catecholamines release, a decrease in the requirements for hypnotics (propofol or inhalation anesthetics) due to its sedative effects, decreases in the post-operative psychomimetic side-effects of ketamine, the prevention of postoperative delirium and shivering [32, 33].

Meta-analyses have shown that clonidine and dexmedetomidine provide analgesia with an added opioid-sparing effect and PONV reduction [34, 35].

The authors has been using the OFAA protocol on patients with a medical history of postoperative nausea and vomiting, ERAS protocols in complex laparoscopic surgery that include bariatric surgery and patients with chronic pain, opioid treatment and OIH who are to undergo extensive/complex spinal surgery. The outcomes of our patients have undergone complex gastro-intestinal surgery have been consistent with the published literature. An important reduction in nausea and vomiting (20%), a faster recovery from intestinal peristalsis, adecrease in ileus and acute gastric remnant dilatation, and a reduction in the post-operative use of opioid rescue (30%) have been recorded in our case-series [36–38].

7. Is it feasible to provide a perioperative management focusing on anti-hyperalgesia and central sensitization for patient with chronic pain who are to undergo major spinal surgery?

Patients with severe spinal deformities like scoliosis, and cranio-cervical-thoracic instability due to connective tissue defects and Joint Hypermobility Syndrome often suffer from widespread chronic pain and hyperalgesia. In patients with Joint Hypermobility Syndrome (JHS) who developed cranio-cervical instability (CCI), both severe craniocervical pain and widespread pain (i.e., somatic/neuropathic/visceral), have multi-factorial causes, that are strongly related to chronic nociceptive neuro-inflammation, glial activation and neuronal plasticity in the spinal cordas well as in the brainstem and brain that lead to a common final pathway, which is the Central Sensitization phenomena (CS) [7, 10].

Furthermore, many patients with CCI, JHS, chronic fatigue and severe chronic pain receive different types of opioids, which further complicates pain due to OIH. Sometimes, these patients may suffer from a category of pain known as central intractable pain. It is a painful condition that does not respond to opioids and their use may even be detrimental to the patient [6, 7].

Therefore, considering the probable mechanisms of the chronic pain (CS and OIH) that affect patients with JHS and CCI as well as their frequent association with MCAS and POTS, the use of opioids in total intravenous anesthesia (TIVA) during occipitocervical~thoracic fixation (OCF) was halted in our practice. Intra-operative opioid-based analgesia has been replaced by infusions of lidocaine, ketamine,

magnesium, dexmedetomidine and propofol as hypnotic [10, 39]. As stated before, they are coadjuvants with known anti-hyperalgesic properties. This OFAA protocol aims at improving postoperative pain control, minimizing postoperative opioid rescues and reducing preoperative opioid doses in those patients who have been prescribed those drugs over a long period (**Figure 1**).

Infusions of lidocaine, ketamine and dexmedetomidine are continued at lower doses during the post-operative period (for a maximum of one week) as part of a multimodal analgesia plan [10, 39]. The continued perioperative use of a lidocaine, ketamine and dexmedetomidine infusion and the gradual reduction of the doses over one week might overcome the peak of the inflammatory surgical-response. Therefore, its effect on pain and Central Sensitizationis to minimize opioid exposure and result in a reduction of VAS [8, 39–43].

In a case-series study of 42 patients with JHS that have undergone OCF [39], the authors found a lower VAS in the OFA group in the postoperative time ($p < 0.001$). The reduction in the VAS was more significanton the 1st postoperative day in the OFA group 5.35 (4.83–5.86) vs. the Opioid group (OP) 7.89 (7.56–8.23) ($p < 0.001$), meaning up to 32% decrease in the VAS of the OFA group. TheVAS at hospital-discharge was lower in the OFA group: 4.96 (4.54–5.37) vs. OP group: 6.39 (6.07–6.71) ($p < 0.001$). The methadone requirement was lower in the OFAgroup ($p < 0.001$). No methadone rescue was needed with 78% (IC 95%)of patients in OFA group. On the contrary, 95% (IC95%) in the OP group needed methadone rescue at high doses. The OFA group showed decreased ileus, nausea and vomiting ($p < 0.001$). Compared with preoperative values, there were decreased opioid

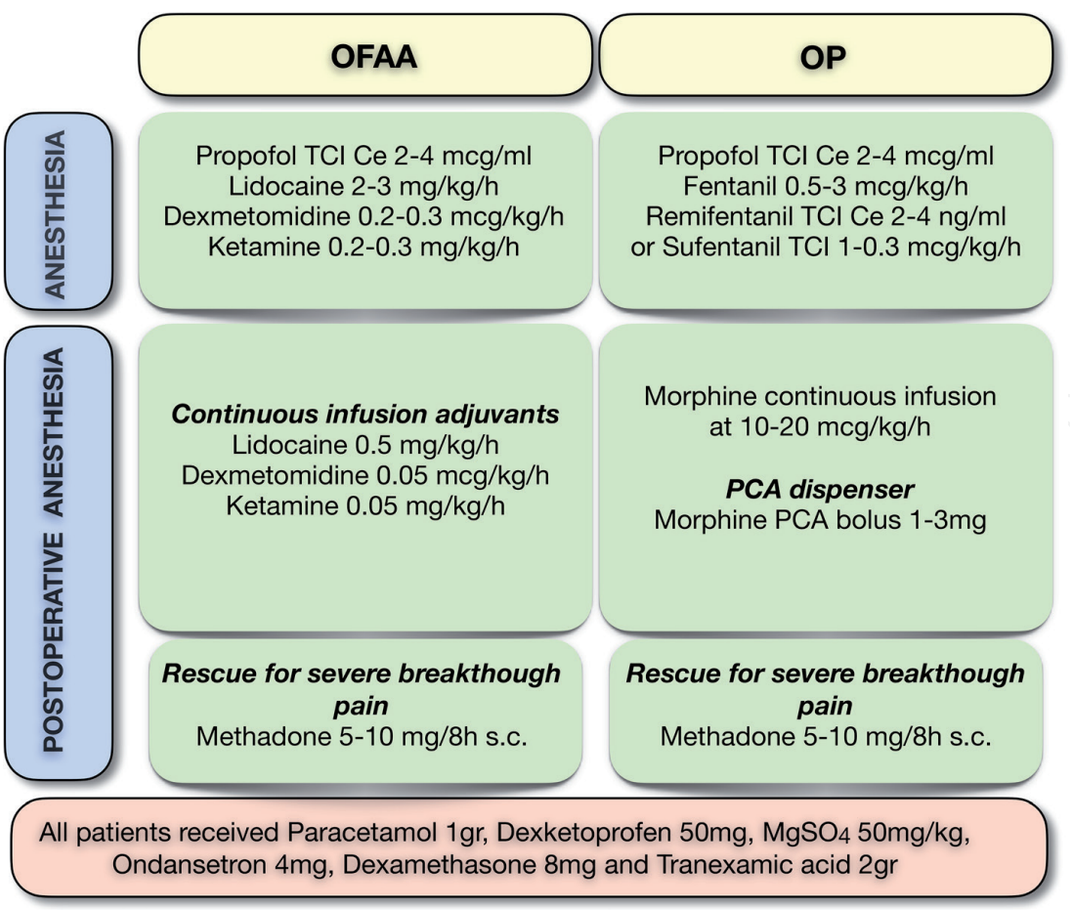

Figure 1.
Opioid-free anesthesia and analgesia (OFAA) vs. opioid based anesthesia and analgesia (OP) protocols for patients with joint hypermobility syndrome undergoing craneo-cervical fixation. Adapted from Ramírez-Paesano C., et al. [39].

requirements for 60.9% in the OFA group at hospital-discharge. A 77% reduction of anxiolytics requirements was also seen. In the OFA group, 17.4% (n = 4) of patients had visual hallucinations. Haloperidol was used in two patients [39].

The doses of lidocaine, ketamine, magnesium and dexmedetomidine proposed in the author's protocol seems to be a combination with balanced anti-nociceptive synergism. It coincides with recent publications that describe lidocaine, ketamine, dexmedetomidine and MgSO4 as the best options in both obese patients and complex spine surgery [23, 44].

According to the literature, there is more consensus on the benefits of OFA use in bariatric surgery or complex laparoscopy surgery. In term of the reduction of postoperative opioid requirements and a better recovery, the controversies that surround the benefits of OFA in major spinal surgery may be due to the diversity of surgical-procedures, the varying degrees of complexity of the cases and the exceptionally varied use of coadjuvants for post-operative multi-modal analgesia. However, there is strong evidence that opioid-inclusive anesthesia does not reduce postoperative pain but is associated with more side effects in comparison with the opioid minimizing approach. OFA management should be evaluated on a case-by-case basis.

With the current evidence, OFA management could not be confirmed as an independent factor in reducing postoperative pain in all the surgical settings in which it has been used. However, OFA management plus postoperative use of lidocaine, ketamine, and dexmedetomidine infusions (OFAA) as part of robust multimodal analgesia may explain the results seen in patients with extensive chronic pain, hyperalgesia and Central Sensitization phenomena [10, 39, 45, 46].

8. Is it possible to use some opioid as postoperative rescue in OFAA?

Many times patients undergoing extensive surgery require postoperative opioids as rescue for breakthrough pain control. The OFAA protocol used in our hospital includes methadone as rescue for severe postoperative pain [10, 39]. We believe that methadone is the most suitable opioid to use as rescue analgesic for severe pain due to its anti-MNDAr effect. Methadone decreases OIH and attenuates the central sensitization phenomenon. It also has a reducing effect on the reuptake of serotonin and norepinephrine. All these mechanisms of action make methadone a suitable opioid for use in OFAA protocols. In addition, the use of methadone with ketamine (both anti-NMDAr) shows a "boosting" and synergistic effect that enhances the opioid-sparing effect [47].

Recent publications have recommended the use of methadone (0.15–0.2 mg/kg bolus) at the start of anesthetic induction in complex spinal surgery [48]. Methadone has been shown to provide a postoperative opioid-sparing effect and improved pain control. These benefits appear to persist for months after surgery compared to other opioids such as morphine or hydromorphone [49].

A recent meta-analysis confirms the benefits of methadone use at the onset of anesthesia in extensive and painful surgeries [50, 51].

9. Are there some contraindications to the use of OFAA?

We should be noted that OFAA is no applicable to all patients. OFAA is relatively contraindicated in patients with node blocks, autonomous nervous system disfunctions including orthostatic hypotension as seen in patients with multiple systemic atrophy disease. Furthermore, OFAA should not be administered to patients with coronary stenosis or acute coronary isquemia as well as patients with hemodynamic instability, increased intracranial pressure or polytrauma. The peripheral vasodilation caused by

OFAA which could limit the perfusion of vital organs [52]. Finally, OFAA should not be administered to patients who have known allergies to some of its components.

10. What can be found in the literature on the risks and benefits of OFAA?

There is uncertainty in the literature on the balance between OFA benefits and risks. Some systematic reviews have shown an improvement in the incidence of postoperative pain, nausea and vomiting [53]. However, alpha-2-receptor agonists such as Dexmedetomidine or clonidine may be responsible of some side effects such as hypotension, bradycardia and sedation. Therefore, the safety of OFAA has been questioned [53–55]. The authors have not observed the aforementioned complications with the use of dexmedetomidine, probably because we did not administer starting boluses, and the maintenance doses used were limited to 0.2–0.3 mcg/kg/h.

A Meta-Analysis of randomized controlled trials including 2209 participants comparing OFAA to opioid based anesthesia (OBA) found no clinically significant effect of OFA on acute pain and opioid use after surgery in a large sample of studies. However, it found clinically important reductions in postoperative nausea, vomiting, shivering and sedation incidence showing a beneficial impact on postoperative patient comfort [56]. Definitive evidence-based conclusions related to the use of OFAA are still lacking. For this reason, it is important to continue exploring how to prevent its side effects as well as possible alternatives.

11. Conclusion

The activation of the glutaminergic pathway plays a determining role in secondary sensitization at the level of the central nervous system, which is responsible for nociceptive amplification, persistence of postoperative pain, and hyperalgesia.

The development of opioid-free anesthesia techniques, indicated for particular patient populations in which opioids may be harmful, requires the use of drug mixtures in which NMDAr antagonists are essential.

The most clinically used NMDA receptor inhibitors in anesthesia are ketamine and magnesium sulfate. They are the cornerstone to reduce or avoid the SC phenomenon, hyperalgesia and OIH in the surgical setting. Their co-administration in OFA techniques has synergistic analgesic and anti-hyperalgesic effects. The concomitant use of intravenous lidocaine and dexmedetomidine provides additional benefits to the use of NMDAr antagonists.

The authors consider that OFA has precise indications. However, the use of regional anesthetic techniques (whenever possible) or the use of intravenous mixtures with anti-hyperalgesic and opioid-sparing effects should be used, ifpossible, in patients with a history of chronic pain or with central sensitization phenomena and hyperalgesia who are to undergo extensive and very painful surgeries. Finally, methadone is a suitable opioid for use in modified OFAA protocols because its anti-NMDAr action and opioid-sparing effect.

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Conflict of interest

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