CASE STUDY

Ketamine for acute and subacute pain in opioid-tolerant patients

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ABSTRACT

Prolonged acute pain, especially that of oncologic neurological origin, is at times difficult to control; it is seldom entirely alleviated by opioids. We report eight patients with severe pain, three of whom suffered from new onset oncologic metastatic bone pain, others had previous pain syndromes and presented with exacerbation of pain. Pain was associated with hyperalgesia and allodynia phenomena in two patients and with phantom pain in a third one. Tolerance to opioids had developed, and high IV doses of morphine, meperidine or fentanyl, and patient-controlled intravenous and epidural analgesia were insufficient. Several patients became dependent on opioids and could not be weaned from assisted ventilation.

Pain was controlled with decreasing adjunct doses of ketamine. Within 5-10 days of ketamine and opioid protocols, pain was controlled and after an additional 5-7 days, ketamine could be stopped and pain controlled on oral regimens compatible with outpatient care.

Ketamine is an efficient adjuvant analgesic for intractable severe pain, caused by metastasis, trauma, chronic ischemia, or central neuropathic pain. It is effective even when mega doses of IV, epidural, or oral opioids prove ineffective and when signs of tolerance have developed.

Key words: pain, acute, oncologic, breakthrough; ketamine, opioids, tolerance, dependence

INTRODUCTION

Prolonged acute pain, especially that of oncologic origin, is at times difficult to control; it is seldom entirely alleviated by opioids.[1] This is partially because of its complex derivation, ie, its somatic and/or visceral origin, in addition to involvement of neuropathic components that are relatively unresponsive to opioids.[2] It has been suggested that central sensitization plays a major role in this problematic issue.[1,3] Central opioid tolerance may explain the difficulty in controlling pain even when using opioid-containing protocols at progressively increasing doses.[2]

Dorsal horn "wind-up" and central sensitization occur after persistent nociceptive input and are mediated by *N*-methyl-D-Aspartate receptor (NMDAR) activation.[4] These phenomena are clinically apparent as allodynia and hyperalgesia. NMDARs have been shown to play a role in the development of opioid tolerance and the use of NMDA receptor antagonists can reverse established opioid tolerance in animal studies.[4,5] This is especially important in view of the recent documentation of the involvement of morphine in the activation of the NMDAR.[6] Ketamine exerts its analgesic effects by blocking activated (open) NMDAR's, as was shown for dextromethorphan.[7] It has been previously reported[8] that the direct analgesic effect of ketamine as well as its effect on opioid-induced analgesia are not necessarily dose related. Opioid-induced analgesia could be enhanced by the effect of small ketamine doses' action on acute opioid tolerance.[9]

There are several studies, mostly case reports, describing the successful use of ketamine in chronic pain refractory to standard therapies. These include its use in allodynia,[10] chronic ischemic leg pain,[11] and cancer pain.[12] In a model of neuropathic pain, the addition of an NMDAR antagonist restored the ability of morphine to inhibit the transmission of pain.[13] Ketamine given at induction of anesthesia has resulted in reduced postoperative pain scores.[14] When given intraoperatively, it has prevented central sensitization[15] and when administered postoperatively decreased postoperative opioid requirements.[9] The literature is, however, scarce of data regarding treatment of nonsurgical, oncologic and nononcologic, nonterminal patients who experience reactivation of severe pain, resistant to high doses of opioids, or those in whom attempts to wean off opioids have failed.

PATIENT DATA

Eight adult patients with acute pain who did not respond to maximal doses of opioids or other pain treatment between January and June 2003 are described in this preliminary report (Table 1). All had disabling, rest pain

Table 1. Demographics, pain origin, and failed drug therapy			
Age/Sex	**Original insult**	**Causes of current acute pain**	**Failed pain management**
35/M	Paraplegia caused by spinal abscess	Bilateral rhizotomy plus DREZ myelotomy	Meperidine 100 mg 5/d IM; fentanyl patch 300 μg/72 h; morphine 1,000 mg/d IV-PCA
65/F	Breast cancer metastasis; paraplegia	Pathologic fracture of tibia, hyperalgesia	Morphine 200 mg/d IM; meperidine 75 mg IM PRN; NSAIDs; COX-2-I; fentanyl patch 100 μg/72 h
23/M	MVA; fracture of maleolus and mandible	Repair of maleolar fracture plus plastic reconstructive surgery; mandibular repair; CVA	Oxycontin 80 mg twice daily; MIR 60 mg 5/d plus 30 mg on demand; carbamazepine 400 mg twice daily, amitriptyline 25 mg twice daily
52/F	Breast cancer metastasis	Bone pain exacerbation, hyperalgesia, dysesthesia	Chlorpromazine 250 mg plus meperidine 250 mg plus promethazine 250 mg/d slowly IV; morphine 1,500 mg/d IV
25/M	Fracture of tibia and fibula	ORIF; later Ilizarov procedure	Oxycodone 20 mg twice daily; MIR 30 mg 4-hourly
54/M	Peripheral vascular disease with lower extremity ischemia	Leg rest pain, allodynia	Epidural ropivacaine 1.6 mg plus fentanyl 4 μg/mL @ 6 mL/h plus 2 mL bolus/15 min; morphine 2 mg IV-PCA/7min
67/M	L_{3-5} laminectomy	Wound infection with spinal abscess, severe sciatic syndrome	Meperidine 100 mg plus promethazine 25 mg plus chlorpromazine 12.5 mg IM 8-hourly
49/M	Leg crush injury	Multiple orthopedic and plastic reconstructive operations; later below knee amputation	Oxycontin 60-80 mg twice daily plus MIR 60-120 mg 5 times/d; clonazepam 0.5 mg twice daily

Abbreviations: IM, intramuscular; MIR, morphine immediate release; MVA, motor vehicle accident; ORIF, open reduction and internal fixation; CVA, cerebral vascular accident; PRN, pro re nata (as needed); COX-2-I, cyclooxygenase type 2 inhibitor; IV-PCA, intravenous patient-controlled analgesia; NSAIDs, non-steroidal anti-inflammatory drugs.

that prevented them from getting out of bed and participating in physiotherapy. Two individuals suffered from malignancy, three had recent trauma, one had vascular pain, and two had central neuropathic pain. The report highlights the initial pain protocols that were prescribed to these patients by the attending ward physician, sometimes in unconventional doses and combinations, or even routes, in the desperate attempt to alleviate refractory pain. It then stresses the usefulness of adjuvant ketamine in decreasing doses by the acute pain service (APS), resulting in complete pain relief on outpatient analgesia regimens.

CASES REPORTS

Case 1

This 35-year-old man suffered from renal insufficiency (treated with peritoneal dialysis), which was complicated by septic ileus due to a pelvic and retro-peritoneal abscess. After drainage of the abscess and colostomy, mycobacterium intradural granuloma developed and he became paretic and subsequently paraplegic. Antibiotic therapy was effective in eliminating infection but the patient became increasingly spastic and developed lower body pain with lower muscle cloniformic contractions. As he showed hypersensitivity to baclofen, he was given oral codeine (40 mg, four times daily) plus paracetamol (1,000 mg, four times daily) and various other NSAIDs, to alleviate pain.

When this treatment became ineffective over a 6-month period, the patient underwent a subtotal (two-thirds) bilateral rhizotomy at levels L_1-S_1 and selective motor resection (dorsal root entry zone [DREZ] myelotomy) at level L_1. Within 24 hours after surgery, pain exacerbated. Seven days of treatment on the ward with meperidine (up to 100 mg IM, five times a day), fentanyl patch (up to 300 μg), and morphine 1,000 mg/d (PCA 10 mg/h continuous infusion plus 10 mg/bolus/7 min), proved ineffective.

Ketamine 500 mg plus morphine 500 mg/24 h by IV-PCA (continuously morphine 10 mg plus ketamine 10 mg/h, and bolus morphine 5 mg plus ketamine 5 mg/7 min) treatment was instituted for 5 days. Despite

drowsiness on days 1-3, the patient reported less pain. Within a week, the original morphine demand decreased by 15 percent. By day 10, the patient was practically pain free. Both morphine and ketamine were weaned off and he was discharged home using only oral oxycontin tablets 20 mg twice daily.

Two months later, a 5-day episode of spinal hyperalgesia occurred. Although total rhizotomy was suggested by the surgeon, a 5-day regimen of IV-PCA morphine 200 mg plus ketamine 100 mg/24 h and bolus morphine 2 mg plus ketamine 5 mg/7 min fully controlled pain. Tapering off both drugs began on day 2 at 25 percent per day and the patient was discharged home free of pain thereafter (13 months follow-up, using oxycontin 20 mg twice daily).

Case 2

This 65-year-old woman had undergone mastectomies followed by chemotherapy 15 and 9 years earlier, due to breast cancer. A recent inoperable pathological fracture in her right proximal tibia superimposed on infant poliomyelitis, resulted in inability to mobilize the patient. Pain was initially controlled by multiple fentanyl patches up to 225 μg: it caused, however, respiratory arrest, followed by CPR, mechanical ventilation that evolved into ventilator dependency, and tracheostomy. Despite a regimen including NSAIDs, COX-2 inhibitors, morphine (200 mg/d), and meperidine boluses (75 mg) IM upon request, pain was still severe, even at rest, and physiotherapy was impossible. Bupivacaine-epidural analgesia was also unsatisfactory.

Intrathecal phenol block to reduce pain and opioid usage in order to enable weaning from the ventilator and implement physiotherapy was dismissed because of pneumonia and sepsis. Fentanyl 100 μg/72 h patch was the only drug to successfully control rest pain. The patient remained drowsy and fully ventilated for another week.

Within 24 hours of starting a ketamine infusion 500 mg/d, combined with the fentanyl patch the patient was able to move out of bed and start physiotherapy. For the first time in weeks, she coughed properly and fever disappeared within 3 days. Phenol (phenoline plus glycerine 0.8 mL) intrathecally was performed at interspace $L_{3\text{-}4}$, which enabled gradual tapering of ketamine to a minimum (50 mg/d) and fentanyl to 25 μg patch/72 h. Three days after the block, both drugs were stopped. Oxycodone syrup (5 mg, four times daily) was started and later reduced to 2 mg twice daily and then stopped.

The patient was discharged to a rehabilitation ward where the tracheostomy was later closed.

Case 3

A 23-year-old victim of a motor vehicle accident that had caused multiple open fractures (mandible, right maleolus, patella, and femur) suffered 10 days later a left occipital-parietal cerebrovascular event, resulting in right hemiplegia. He required 15 days of mechanical ventilation, tracheostomy, and extensive pain treatment (IV morphine 2.5 mg/h plus midazolam for sedation) followed by morphine (10 mg) and meperidine (75 mg) IM upon request, which reached doses of 100 mg and 300 mg/d, respectively. Eight days later, he was still ventilated because of episodes of bradypnea.

Pain was intense only in the hemiplegic part of the body, indicating central sensitization. Oral oxycodone 30 mg twice daily and morphine immediate release (MIR) 30 mg twice daily, in combination with carbamazepine (400 mg twice daily) and amitriptyline (25 mg twice daily) for mood elevation and relief of pain hypersensitization proved ineffective, causing a paradoxical increase in the demand for MIR (60 mg, six times daily!) and oxycontin (80 mg, twice daily). There was also depression and inability to cooperate with the rehabilitation program; apneic episodes prevented disconnection from the ventilator.

All opioids were then stopped by the APS consultant and an IV-PCA regimen consisting of ketamine 500 mg plus morphine 500 mg/d continuously was started, in addition to carbamazepine (400 mg twice daily), amitriptyline (75 mg once daily), and clonazepam (0.5 mg, three times daily). Within 48 hours of the new protocol, the patient was pain free and fully cooperative. Morphine PCA was reduced by 30 percent over 3 days while ketamine dosage remained unchanged for the next 10 days, then reduced by 10 percent per day and then stopped. Carbamazepine, amitriptyline, and clonazepam (600, 50, and 0.5 mg orally, once daily, respectively) were continued and he was transferred to a rehabilitation center. The patient no longer required opioids to relieve pain.

Case 4

A 52-year-old woman, who was suffering for 10 years from bone and lung metastases secondary to breast carcinoma, was referred to the APS due to pain exacerbation. Pain was previously controlled by oxycodone 80 mg twice daily and oxycodone plus paracetamol (10 mg plus 600 mg) as required. The acute exacerbation would not respond to morphine up to 1,000 mg/d by IV-PCA; a 50 percent higher dose led to bradypnea and drowsiness but did not control pain. In addition, there were signs of new onset of centralization of pain, such as hyperalgesia and dysesthesia at the areas of metastasis and she did not allow anyone to touch or move her in bed. A 36-hour additional IV slow administration of chlorpromazine 250 mg, meperidine 250 mg, and promethazine 250 mg daily by the ward staff had no effect and the patient became drowsier but at the same time more painful.

The APS was then consulted; the above regimen was stopped and morphine 1,000 mg plus ketamine

1,000 mg/daily IV was started. There was a dramatic improvement in her condition. Within the first 18 hours of treatment she could get out of bed and walk in her room while fully conscious, although describing a feeling of "light headedness." Within 4 days of the new regimen, the dosages were reduced by 50 percent and were stopped on day 7; she was discharged home a week later with oral nonopioid analgesics.

Case 5

A 25-year-old young male who had fractured his right tibia and fibula underwent internal fixation of the fibula and external fixation of tibia under general anesthesia. Both the pre- and immediate postoperative analgesic ward regimens consisted of meperidine 1 mg/kg IM upon request. Following a pain control protocol, on the 3rd postoperative day the patient could receive oxycodone slow release 30 mg twice daily then 20 mg twice daily for 5 days. Although recovery went unremarkably, 1-week later an Ilizarov procedure was performed under general anesthesia.

Despite perfect bone alignment and lack of infection, and the above analgesia regimen, the patient started to complain of severe pain following the last intervention. Oral morphine immediate release 15 mg for every 4 hour, as a rescue drug did not blunt pain; the dose was doubled. The patient became obtunded but at the same time complained of severe pain.

IV morphine 100 mg plus ketamine 250 mg infusion/24 h plus intermittent boluses of ketamine 5 mg plus morphine 2 mg available every 7 min (PCA) was started by the APS staff. During the first 4 days of treatment (PCA was triggered and delivered the drugs 75 times per day), the patient was still in pain, but was now able to indicate a burning sensation in his leg. The regimen was then changed to the following: (1) oral gabapentine 400 mg once daily plus amitriptyline 50 mg plus clonazepam 0.5 mg twice daily; (2) IV PCA continuous infusion of 100 mg of morphine plus 200 mg ketamine over 24 hours in addition to 2 mg of morphine plus 40 mg ketamine on demand with a lockout interval of 7 min. The morphine amount was halved 3 days later for a 48-hour period, and then discontinued; oral oxycodone 20 mg twice daily replaced it. Ketamine dose remained unchanged for 5 days, pain was bearable but he disliked the "light-headedness": ketamine was then weaned off over a 72-hour period, leaving the patient comfortable on oxycodone 20 mg twice daily.

Pain reappeared 5 days later, requiring repetitive rescue doses of morphine orally (MIR 15 mg, six times daily). Ketamine drip 250 mg/24 h in addition to boluses of 2 mg morphine plus 25 mg ketamine was then restarted. Within 48 hours, pain resubsided and ketamine was satisfactorily reduced by 50 percent per day; oxycontin 20 mg twice a day was continued for 5 additional days. At this point, oxycontin was slowly reduced replacing it with oxycodone immediate release 10 mg twice daily.

Ten days later the patient stopped all opioids. He was also able to reduce carbamazepine to 200 mg daily, clonazepam to 0.25 mg/d, and amitriptyline to 25 mg once at night. The patient was discharged to the rehabilitation ward 1 week later, using the adjuvant therapy only.

Case 6

A 54-year-old male, with history of ischemic heart disease and peripheral vascular disease, was admitted to the vascular surgery department with weeklong intermittent severe rest pain of both legs. He had been treated with alpha-blockers and NSAIDs for the prior 6 months. The new acute pain was associated with allodynia, because of which he would not walk. The patient was initially given oxycodone slow release 40 mg twice daily plus oxycodone syrup upon request, which proved to be insufficient; the patient then became uncooperative. Continuous epidural analgesia ropivacaine plus fentanyl ([1.6 mg plus 4 μg]/mL at 6 mL/h) plus PCEA 2 mL every 15 min did not change pain perception during activity but relieved rest pain only.

The patient underwent aorto-bifemoral bypass grafting under combined general and epidural (bupivacaine and morphine 5 mg) anesthesia 10 days later. Two days after surgery, the epidural catheter was removed because of fever and redness at the site of entry. Morphine was prescribed by IV-PCA 2 mg/bolus with 7 min lockout interval. This did not attenuate pain satisfactorily, and an APS consultant was called. Morphine plus ketamine IV-PCA (0.8 mg morphine plus 5 mg ketamine/bolus at 7 min lockout time) was started. During the first 5 days, the patient consumed a mean of 40 mg morphine plus 250 mg ketamine/24 h: at the end of the second day of treatment, the patient could sit and even step on his feet. To improve cooperation and initiate rehabilitation, this regimen was slowly tapered and was stopped on the 8th day. He was discharged to a rehabilitation ward on oxycodone immediate release 10 mg orally.

Case 7

A 67-year-old male patient was admitted to the orthopedic department because of severe low back pain (VAS 5-7/10) associated with radiation to the left buttock and hip. Five days of acute pain confined him to bed at home. Nine months earlier, he had undergone a L_{3-4} laminectomy and 6 months later discectomy at L_{4-5}. The patient suffered from rheumatoid arthritis as well and was treated with oral methylprednisolone 10 mg daily and methotrexate 17.5 mg IM once weekly.

Hyperalgesia at the sites of the operations was diagnosed upon admission. Initially, the patient was given

rofecoxib 25 mg/d and MIR 15 mg four times daily, but pain intensity (6-8/10) remained almost unchanged. Three days later, MIR was increased to 30 mg upon request plus oxycodone slow release 20 mg once daily, followed the next day by 40 mg twice daily. Neither of these regimens effectively controlled pain and the patient remained in bed essentially immobile.

An abscess was diagnosed around the lumbar spinal cord and vancomycin 1 g plus cefepime 2 g twice daily were initiated. Although the indices of inflammation diminished during the following days, severe pain (8/10) persisted. The patient was then given the ward's analgesic protocol, consisting of meperidine 100 mg, promethazine 25 mg, and chlorpromazine 12.5 mg IM three times daily, with no pain improvement but with rather increased drowsiness.

Five days passed with no change in his condition. The APS was called to consult and pain management was changed to IV-PCA morphine 2 mg per request with a 7-minute lockout interval. Twenty-four hours after starting this regimen the subjectively-rated rest pain dropped from a score of 9/10 to 7/10; he was less drowsy but would not get out of bed. This PCA regimen was then changed to IV-PCA morphine 1 mg plus ketamine 5 mg/mL 4 mL/h continuous infusion plus boluses of 1 mL/7 min lockout interval. Twenty-four hours later, the patient was able to sit in bed and 8h later he started to walk with a corset without complaints. The pain subsided gradually (<5/10) and by 48 hours the PCA morphine dose was slowly reduced, and completely stopped 4 days later, leaving the patient on only IV-PCA ketamine bolus 5 mg/mL/7 min. Oxycodone 20 mg slow release twice daily replaced morphine satisfactorily.

Five days later ketamine PCA was disconnected; the patient was discharged home uneventfully and without relapse on oxycodone 10 mg twice daily and rofecoxib 25 mg/d, together with antibiotic treatment.

Case 8

A 49-year-old male, victim of a car–train accident was brought to the emergency department (ED) with an open fracture and tissue destruction of his left ankle and foot; only the skin kept together the various parts of the crushed leg. He was bleeding and therefore presented with moderately low blood pressure, but at the same time very painful (9/10 VAS). Tramadol 100 mg IV and meperidine 100 mg IM were administered in the ED after other injuries were excluded and consciousness was verified.

The patient underwent wound debridement and external fixation under general anesthesia a few hours later. During the next 10 days, the patient underwent repeated interventions on his leg due to infection and necrosis of the tissue. During this period, pain was incompletely controlled (VAS >5/10) on the ward by oxycontin 40 mg tablets twice daily and meperidine IM as a rescue drug.

On the 10th posttrauma day, the patient underwent below knee amputation under general anesthesia, after which severe phantom pain (10/10 VAS) occurred. In addition to oxycontin (60 mg twice daily), the patient received clonazepam 0.5 mg orally twice daily, and morphine immediate release 60 mg was added 5 times per day without a satisfactory result. Even increasing oxycontin to 80 mg twice daily and MIR to 120 mg proved ineffective (pain 8/10 VAS).

The APS consultant tested the patient's response to a dose of 25 mg IV ketamine added to 120 mg MIR: pain score briefly dropped from 9-10 to 2-3/10. The patient was then connected to an IV-PCA which delivered 2 mg of morphine plus 10 mg ketamine available every 7 min; MIR was reduced to 90 mg. Mean pain score during the first 48 hours of treatment dropped to 5/10 and on the third day to 3/10. The patient used 400 mg of morphine and 2,000 mg of ketamine during the first 24-hour treatment period. Both ketamine and morphine doses were reduced over the next few days; oxycontin 60 mg twice daily was given on the 4th and 5th day of treatment along with MIR 90 mg three daily: pain score was rated 2-3/10.

The patient was discharged 7 days after amputation to the rehabilitation ward with minimal phantom pain (2/10 VAS), and with a prescription of both oxycodone 40 mg and MIR 60 mg twice daily.

DISCUSSION

The current report demonstrates, presumably for the first time, the role of coadministration of ketamine in promptly and effectively attenuating severe acute pain, as well as hyperalgesia or allodynia, when added to opioids. This effect was evident in patients who had been treated earlier with high doses of opioids, with or without various adjuvant agents in conventional and desperately unconventional combinations which still proved ineffective in controlling pain. Ketamine was effective in weaning patients off opioid dependence. Consequently, patients could be weaned off assisted ventilation and mobilized without suffering from debilitating pain. We assume that ketamine expresses antinociceptive effects, potentiates the analgesic effects of opioids while also reversing tolerance to opioids and interrupting central pain sensitization.

We demonstrate here the effectiveness of ketamine in a diverse group of patients (Table 1). Causes and duration of pain as well as the clinical manifestations of opioid-induced dependence or tolerance range from acute cancer pain to central neuropathic pain, phantom limb pain and trauma-induced orthopedic pain. The common denominators in all patients were (1) acute intractable pain associated (in 5/8 patients) with abnormal pain perception; (2) extremely high opioid usage (up to 1,000 mg/d of morphine) in most patients; (3) development of both

Table 2. Individuals' effective therapeutic protocols	
Age/Sex	**Therapeutic protocol**
35/M	Ketamine 500 mg plus MO 500 mg/d for 5 d by IV-PCA. The patient was initially drowsy but less painful. By day 10, both drugs were stopped and substituted by oral NSAIDs with no pain.
65/F	Ketamine 500 mg plus fentanyl patch 100 μg/24 h enabled the patient to get out of bed, cough, and undergo physiotherapy. Both drugs were tapered within7 d; the patient remained with only oral oxycodone.
23/M	IV-PCA ketamine 500 mg plus MO 500 mg/d. Within 48 h, the patient was pain free and fully cooperative. MO was reduced first, then ketamine. Minimal doses of mood elevators allowed rehabilitation.
52/F	18 h after MO1,000 mg plus ketamine 1,000 mg/d by IV-PCA, the patient walked in the room; the dosages were reduced by 50 percent by day 4 and stopped by day 7. The patient was discharged home without opioids.
25/M	MO 200 mg plus ketamine 500 mg/d by IV-PCA. MO reduced by 50 percent within 3 d, then stopped; ketamine reduced and stopped 72 h later. The patient remained with pain controlled.
54/M	MO 40 mg plus ketamine 250 mg/d for 2 d allowed for free ambulation; by day 5 dose reduction enabled rehabilitation. The drugs were stopped on day 8.
67/M	IV-PCA MO 1 mg plus ketamine 5 mg/mL/7 min bolus plus 1 mL/h infusion enabled the patient to sit in bed within 8 h of treatment; he later walked with corset for 2 h/d comfortably. MO was reduced and stopped by day 4; ketamine reduced and stopped 5 days later. The patient was discharge home with oxycodone and rofecoxib.
49/M	MO 400 mg plus ketamine 2,000 mg/24 h by PCA reduced pain score by 50 percent. Both drugs tapered over 5 d; the patient was discharged to rehabilitation center with MIR 180 mg without pain.
Abbreviations: MO, morphine; d, day; h, hours; IV-PCA, intravenous patient-controlled analgesia; MIR, morphine immediate release.	

dependence and tolerance to morphine/fentanyl/meperidine, which also required the addition of adjuvants and assisted mechanical ventilation (eg, cases 2 and 3); (4) their being obtunded and uncooperative for various periods of time. While similar opioid-related occurrences have been described in the presence of neuropathic pain,[13] the doses used in such patients have never reached the magnitude reported here, probably because of the presence of acute, subacute and past history of pain in most of these patients (Table 2).

It is generally acknowledged that damage to tissue associated with surgery often produces hyperalgesia (exaggerated nociceptive response to noxious stimulation), allodynia (nociceptive response to innocuous stimulation), and persistent spontaneous pain. These enhanced responses to noxious or non-noxious stimuli result from nociceptor sensitization in peripheral tissues or centrally.[16,17] Once established, central sensitization may become substantially independent of the precipitating event[18] and then constitute a pathophysiologic mechanism underlying pain hypersensitivity states, as found in this case series and elsewhere.[16,19] It is well recognized that hyperalgesia and allodynia associated with central sensitization after tissue injury and inflammation partly stem from activation of NMDAR.[18,20,21] According to this scenario, it was reported that NMDAR antagonists are particularly effective in reducing persistent pain associated with central sensitization in various experimental models.[3,7,15,22-24] We and others, indeed, showed that even sub-anesthetic doses of a clinically available NMDAR antagonist, such as ketamine, decrease postoperative pain if added to general anesthesia before or after a surgical procedure.[9,14,15,25] One case in our series suffered from acute stroke; ketamine was used and found to be effective and safe. Nevertheless, caution should be exercised in patients where there is a suspicion of high intra-cranial pressure.

We have previously discussed the possibility that neural plasticity is modified by past central sensitization. These events involve acute, subacute, or chronic peripheral stimuli. This complex phenomenon may, however, remain silent after an initial injury or continuous painful state, until an additional pain sensation generates a new or superimposed stimulus, which reignites the silent and abnormally sensitized pathway (as occurs, for example, with hyperalgesia in persistent or intermittent phantom pain).[26] The mechanism of dorsal horn "wind-up" and central sensitization that occur after past persistent nociceptive input is mediated by NMDAR activation.[4] This might explain the described clinical picture of increasing doses of opioids that do not succeed in reducing pain, opioid-generated tolerance and the associated abnormally

perceived pain (cases 2, 4, and 6). The trigger of central sensitization in our patients was pain that they had suffered from for weeks or years but that had disappeared or became subtle, before the current episode reignited the pain and generated centrally mediated, overwhelming pain. All kinds of opioids appeared ineffective in reducing the new superimposed intolerable pain until ketamine was given, initially in high doses to "override" the aberrant NMDAR function.

It has been demonstrated that morphine itself may induce acute (postoperative) and chronic pain tolerance via the facilitation of the NMDAR activation system.[21,27] Tolerance to opiates is defined as a progressive reduction in their effect[28] and is generally thought to occur over a period of days or weeks with repeated administration of opioids. However, several authors have reported a more rapid onset of tolerance[29] observed with a wide range of opiates, including morphine, fentanyl and their derivatives, as is demonstrated in the present report and in animal models of analgesia.[30]

Several of our patients (cases 1, 4, 7, and 8) also suffered from hyperalgesia and allodynia. There is considerable evidence that these two phenomena associated with nerve injury or inflammation stem from activation of NMDAR.[31] The administration of NMDAR antagonists such as dizocilpine maleate (MK-801), ketamine or memantine, strongly reduces hyperalgesia or allodynia in both animals[32-34] and man.[9,35,36] Phantom pain was also relieved by dextromethorphan.[26] Finally, Célèrier and colleagues have clearly demonstrated that[37] the antinociceptive effects of morphine and fentanyl, two opiate analgesics widely used in humans in the management of pain are blunted by concomitant NMDAR-dependent opposing effects, which are only revealed when the predominant antinociceptive effect is sharply blocked by naloxone. This study provided the rationale for the beneficial combination of NMDAR antagonists with opiates for relieving pain by preventing pain facilitatory processes triggered by opiate treatment per se. Taken together, these findings point to a role for NMDAR in opiate-activated pain facilitatory systems, opposing the expression of analgesia in an enduring manner, ie, leading to tolerance. They thus support the use of ketamine to override the facilitatory effects of the opioids on NMDAR and interrupt the path to abnormal pain sensation.

Noteworthy, the data presented are limited in that they report a limited number of rare occurrences. They also describe pain regimens used on the ward prior to the APS intervention that are unconventional in their doses, combinations and routes, and sometimes extreme, because of the severity of the pain syndromes and the lack of suitability of the ward routine pain protocols. The APS used ketamine, at times in very high doses, to control pain in patients who were ventilated (3 of 8) and/or with severe opioid tolerance. Such ketamine doses would be considered "anesthetic" in naïve patients; however, they resulted in analgesia, seldom sedation, in the described individuals, who were resistant to opioids while in severe pain.

CONCLUSIONS

It may be concluded that ketamine interrupted a vicious cycle of posttrauma, infectious, and malignancy-associated acute exacerbation of pain in patients who had previously (weeks to years) suffered from various pain syndromes. It also blocked pain that was opioid-resistant, associated in some cases with hyperalgesia and allodynia. Thus, whenever pain worsens despite increasing doses of opioids with or without adjuvant agents, analgesia may be satisfactorily managed by the addition of ketamine (at an initially high dose) followed first by tapering of opioids and finally by tapering of ketamine as well.

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