http://dx.doi.org/10.4172/2165-7920.1000186

Clinical Case Reports

Case Report Open Access

Ketamine as Adjunctive Anesthesia in Refractory Complex Regional Pain Syndrome Patients: A Case Series

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Abstract

Complex regional pain syndrome most often follows peripheral soft tissue and nerve injury, fractures, and surgical procedures. The pain is out of proportion to the severity of the injury, spreads beyond a nerve or root territory and increases over time. In general, recommendations for anesthesia for these patients requiring surgery include sympathetic blockade or intravenous regional anesthesia as well as sympathetic blockade in conjunction with lidocaine. Quite often surgery for these patients seriously aggravates their condition.

This is a retrospective evaluation of a case series of the use of ketamine as adjunctive anesthesia in twenty five refractory long standing complex regional pain syndrome patients. All patients met the International Association for the Study of Pain criteria for diagnosis. Ketamine was administered intravenously over four hours from the start of the procedure with midazolam and clonidine in addition to their standard anesthesia. At the end of the procedure, an additional dose of midazolam was administered. Lorazepam was used for restlessness if necessary for three nights after the procedure. All twenty five patients had no exacerbation of their symptoms and signs and no spread of their CRPS. This study supports the effective use of ketamine, midazolam and clonidine as adjunctive anesthesia in severe refractory CRPS patients undergoing a surgical procedure.

Keywords: CRPS; Ketamine; Adjunctive anesthesia; Chronic pain; Refractory pain; Pain syndrome

Abbreviations: CRPS: Complex Regional Pain Syndrome; IASP: International Association for the Study of Pain; IV: Intravenous; EKG: Electrocardiogram; PTSD: Post Traumatic Stress Disorder; NRS: Numeric Rating Scale; ASA Class I-III: American Society Of Anesthesiologists Physical Status Classification; DH: Dorsal Horn; PTNs: Pain Transmission Neurons

Introduction

Complex regional pain syndrome (CRPS) most often follows peripheral soft tissue and nerve injury, fractures, and surgical procedures [1-3]. The pain is out of proportion to the severity of the injury, spreads beyond a nerve or root territory and increases over time [4]. It is characterized as Type I if no specific nerve is injured or Type II if injury to a nerve is demonstrated. There is evidence that Type I patients may have an injury induced small fiber neuropathy [5,6].

Factor analysis reveals that the signs and symptoms cluster into four distinct subgroups: 1) abnormalities in pain processing (allodynia, hyperalgesia and hyperpathia); 2) temperature and skin color changes; 3) edema and sudomotor dysregulation; 4) motor dysfunction and trophic changes [7-9].

In general, recommendations for anesthesia in CRPS patients requiring surgery include sympathetic blockade or intravenous regional anesthesia as well as sympathetic blockade in conjunction with lidocaine [2,10,11]. In an evaluation of 100 patients with upper extremity CRPS that underwent surgery in the affected arm, the recurrence rate was lowered from 72% to 10% in patients receiving postoperative stellate ganglion blocks [11]. Veldman et al. performed surgical procedures after waiting for clinical remission and administration of perioperative intravenous (IV) mannitol. Their recurrence rate was 13% [2]. Although these preemptive anesthetic techniques have often been successful in blocking exacerbation and spread of CRPS following surgical procedures in patients with localized disease, they have often been ineffective in patients with severe refractory CRPS [12]. The purpose of this study was to evaluate ketamine as an adjunctive anesthetic in surgery for severe refractory CRPS patients.

Methods

Following IRB approval from Drexel University College of Medicine, chart reviews were conducted on patients with severe refractory CRPS who underwent surgery and had ketamine as adjunctive anesthesia.

The information obtained included age, gender, inciting injury, CRPS manifestation, duration of disease, spread following surgery, pain intensity pre-operatively and post-operatively and the type of surgery performed. All patients were examined by the same two physicians (RJS and PG) at post surgical visits of 1, 3 and 6 months. They were maintained on their usual pain medication prior to and after surgery.

Inclusion criteria

All patients successfully completed a cardiac evaluation that included a 12-lead electrocardiogram (EKG) and head-up tilt-table testing. They also underwent a psychological clearance. This clearance included a psychological profile and general parameters of intellectual function as well as the Adult Suicide Ideation Questionnaire and the Beck Depression Inventory II. Specific attempts were made to uncover manic depression, schizophrenia, prior drug abuse and severe post traumatic stress disorder (PTSD). Depressed patients were included but the aforementioned psychiatric diagnoses were exclusion criteria. The results of neuropsychological testing in these and other CRPS patients are summarized by Libon et al. [13].

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Received July 13, 2012; **Accepted** August 14, 2012; **Published** August 14, 2012

Citation: Schwartzman RJ, Samudralwar R, Getson P, Alexander GM (2012) Ketamine as Adjunctive Anesthesia in Refractory Complex Regional Pain Syndrome Patients: A Case Series. J Clin Case Rep 2:186. doi:10.4172/2165-7920.1000186

All patients met the International Association for the Study of Pain (IASP) criteria for the diagnosis of CRPS [14] as determined by the same two physicians (RJS & PG). The age range was 17 to 80 years. All patients had to have long standing (greater than 7 years) of active CRPS in at least one extremity that was refractory to treatment. A refractory designation included failure of: 1) non-medical (physical therapy and psychological approaches); 2) pharmacological mono or combined therapy with nonsteroidal anti-inflammatory drugs, various antidepressants, anticonvulsants (gabapentin, carbamazepine), low or high potency opiods; 3) and one of three interventional procedures that included selective nerve blocks, epidural anesthesia, brachial plexus blocks, sympathetic ganglion blocks, intravenous regional sympathetic or sodium channel blocks, spinal cord stimulation, surgical sympathectomy or intrathecal drug delivery systems.

The average daily pain intensity had to be 5 points or greater on a Likert numeric rating scale (NSR) (endpoints: 0–no pain and 10–worst pain imaginable). All patients were in the florid CRPS category by cluster analysis [15]. All patients met ASA class I-III (American Society of Anesthesiologists physical status classification).

Exclusion criteria

Patients were excluded if they suffered significant cardiovascular, pulmonary, renal disease or psychiatric disorders. Depression was not an exclusion factor while manic-depression, schizophrenia, prior drug abuse and severe PTSD were. Further exclusion criteria included contraindications to ketamine use (severe arterial hypertension, hyperthyroidism, ischemic heart disease, heart failure and glaucoma) as well as allergies to ketamine or midazolam. Patients were excluded if: they were unable to complete the pain questionnaire, were unavailable for follow up, or if the record of surgery, medication and status was incomplete.

Infusion protocol (25 patients) as adjunctive anesthesia

Clonidine (0.1 mg) and midazolam (2 mg) were administered intravenously during the induction of anesthesia. Ketamine was infused at the rate of 50 mg/hour. An additional dose of midazolam (2 mg) was given IV at the end of the procedure. Clonidine potentiates NMDA receptor blockade, has pain relieving effects and prevents the neurotoxic side effects noted in rodents [16]. Midazolam (2 mg) is utilized prior to the ketamine infusion for sedation and to block agitation and vivid dreams.

Following the procedure, patients underwent two booster infusions at two weeks, one month and three months (total of six infusions). These consisted of IV ketamine (50 mg/hour to a total of 200 mg) over 4 hours. IV midazolam (2 mg) was given at the start and at the termination of the 4 hours for boosters. The infusion suite for boosters is attended by two nurses who are Advanced Cardiac Life Support certified. The patients' cardiac rhythm (EKG), oxygen saturation, and blood pressure are continuously monitored. Complete blood count, electrolyte profiles and liver enzymes are obtained at the end of the infusion. Ondansetron (4 mg) is administered IV for nausea if necessary. Patients are accompanied to the suite and escorted home by a relative or friend.

Results

Preoperative pain scores revealed intensities ranging from 5 to 9 on the Likert NRS. Twenty four of 25 patients had pain scores above 5/10 and had difficulty with activities of daily living. Seventeen of 25 patients had generalized disease in that CRPS affected all four extremities and the face. All patients returned to their preoperative pain level following surgery. There was no exacerbation or spread of their CRPS at their last evaluation (3 months) in either affected or non-affected areas. This was determined by evaluation of mechanical and thermal allodynia; hyperalgesia to pinprick and evaluation of the wind-up phenomena (2 algesic mechanical stimuli per second to a total of 6 pinpricks) in non-affected or formally affected extremities. Autonomic dysregulation consisting of temperature and color change as well as hyperhidrosis was evaluated clinically in formerly unaffected extremities, face and the torso. Initiation, facility and strength of movement were assessed in all extremities clinically. Neurogenic edema was evaluated clinically in formerly affected and unaffected areas. (Table 1)

One patient with demyelinating disease underwent hip replacement. She was unable to walk prior to surgery but at six months was able to return to work full time as a kindergarten teacher and walk independently for 2 blocks with a walker. Four patients had radiculopathies as the cause of their CRPS which also improved to a clinically significant degree (30%) for approximately 3 months following surgery. The CRPS pain returned to preoperative levels in all patients at 6 months.

Side effects of treatment

Side effects of this protocol (and booster therapy) are headache, nausea, tiredness, difficulty sleeping and dysphoria which occur in approximately 25% of patients and are either self limited or controlled with 2-4 mg of lorazepam once or twice a day for one or two days [17]. At one week the patients had none of the usual adverse effects that may be seen during booster infusion. These include nausea, tiredness, sleep architecture disruption or dysphoria [4]. We ascribe this to careful psychiatric screening, the administration of midazolam and clonidine during the procedure, a quiet controlled atmosphere in the infusion suite and 2-4 mg of midazolam after the procedure. Lorazepam (2 mg) may be used prior to sleep for two or three days after the procedure.

The review evaluated 25 females and 2 males. The usual female to male ratio in CRPS is 4:1 [18]. The average age of the patients was 46.2 ranging from 21 to 67 years. They suffered with CRPS for at least 7 years and had failed standard therapy as defined above. All patients underwent an operative procedure unrelated to the treatment of CRPS. All patients were evaluated for pre and post operative pain scores and for spread of their CRPS to initially unaffected body parts.

Discussion

The major findings of this study are that ketamine used as adjunctive anesthesia in refractory CRPS patients undergoing surgery was successful in reducing pain and blocking spread in severely affected long-standing patients. Ketamine, the currently most potent clinically available NMDA-antagonist, has a well established role in the treatment of acute and chronic pain including the pain seen in CRPS [19-22]. It has been shown to reduce wind-up and punctate hyperalgesia for 7 days following surgery (Table 2) [23]. Its usage in higher intraoperative dosage for major abdominal surgery reduced the area of wound hyperalgesia and prevented the initiation and maintenance of chronic pain [24]. It has also been effectively used in patients undergoing spinal fusion and other orthopedic procedures [25, 26]. Recently it has been utilized during elective coronary artery bypass graft surgery and has been demonstrated to attenuate the usual proinflammatory cytokine response during and after this procedure [27].

The primary cause of persistent post surgical pain is neuropathic

Patient #	Age/ Gender	CRPS Duration (Years)	Inciting Injury	Status of Spread Baseline
1	21 F	10	Trauma: Right Wrist Ruptured Tendon	RUE
2	67 F	11	Brachial Plexus Traction Injury, Cervical Plexus Injury: Trapezius Ridge, Lower Back, Bilateral UE	Lateral LLE, Shoulders, Neck, and Back
3	28 F	12	Surgery and Lymph Node Removal of Left Breast	Bilateral UE, Chest, Neck, and Back
4	62 F	24	MVA: Back and All Limbs	Face
5	62 F	23	Brachial plexus Traction Injury: Bilateral Upper Extremities	Bilateral Lower Extremities and Face
6	53 F	9	Disc Herniation: RUE	RLE
7	29 F	14	Cholecystectomy: Midepigastric Region	All Limbs, lower back, right Lower Face
8	30 F	11	MVA: Brachial Plexus Traction Injury/RUE	RLE and Lower Back
9	63 F	10	Trauma: Lifting/ Neck and Upper Back	Bilateral UE
10	41 F	15	Trauma: Torn Ligament/RUE	LUE, Bilateral LE
11	45 F	9	Trauma: Brachial Plexus Traction Injury/Neck and RUE	RUE and Bilateral LE
12	54 F	22	Trauma + Cellulitis /LUE, LLE	RUE,RLE, Back
13	26 F	14	Trauma: Right Thumb and Right Ankle	All Limbs and Back
14	60 M	13	Thoracic Outlet Surgery: Upper Body	4 Limbs, Central, Hearing Loss
15	38 F	15	Brachial Plexus Injury: RUE ; MVA: LUE +Bilateral LLE/Central Annular Tear at C5-6 + C6-7	All Limbs and Face
16	47 F	13	MVA	All Limbs and Face
17	34 F	9	MVA: LUE	All Limbs and Face
18	50 M	7	MVA: Herniated Cervical C6-7 with Discogenic Disease at C5-6 + C7-T1	All Limbs
19	24 F	7	Foot Surgery: Full Body, Dystonic, R>L	All Limbs and Face
20	54 F	8	MVA: Cervical, Thoracic, Lumbar, L Knee Problems Cervical Plexus Injury: RUE, LLE Sympathetic	
21	52 F	15	MVA	All Limbs and Face
22	58 F	8	Unknown	All Limbs and Face
23	41 F	8	MVA-Brachial Plexus Injury/LUE	All Limbs and Face
24	59 F	8	Brachial Plexus Traction Injury	All Limbs
25	44 F	8	MVA: RUE	RUE, RLE

Table 1: Demographics.

Patient #	Amt Ketamine Utilized	Surgery Performed w/Ketamine
1	200mg	Denervation of trapezium, lower right wrist implantation of palmer cutaneous branch of the median nerve into the pronator quadratus muscle
2	200mg	Left Knee Replacement
3	200mg	Laparoscopic sigmoid resection with coloproctostomy and suture rectopexy of rectum to the sacral promontory
4	200mg	Knee Replacement
5	200mg	Left Total Knee Replacement
6	200mg	Total Hip Replacement
7	200mg	Placement of Dental Implants
8	200mg	Tracheal Reconstruction
9	200mg	Lumbar spine surgery
10	200mg	Cervical spinal cord stimulator insertions
11	200mg	Sinus surgery
12	200mg	Colonoscopy and bladder stones
13	200mg	Wisdom teeth removal
14	100mg	Arthroscopic Repair of Left Rotator Cuff
15	100mg	Cervical Discectomy
16	90mg	Full Mouth Dental Extraction
17	100mg	Cervical Discectomy + Multilevel Fusion
18	100mg	Cervical Discectomy
19	150mg	Surgical Resection of Sup. Peroneal Nerve
20	80mg	Arthroscopic Resection of Plica from Left Knee
21	60mg	Full Mouth Dental Extraction
22	80mg	Needle Biopsy of Breast
23	100 - 125mg	Breast Reduction
24	80mg	Laparoscopic Cholecystectomy, Hernia Repair
25	100mg	Gastroparesis/ Laparoscopic Fundal Plycation, Arthroscopic Meniscectomy

Table 2: Surgical Procedures with Adjunctive Ketamine.

from damage to the nerves in the operative field or C-δ and A-δ nociceptors in soft tissue [28-30]. Recent studies in rodent models of post surgical pain have elucidated its different components emanating from the skin incision and that from deep fascia muscle and tendon [31,32]. Endothelin-1 (ET-1) is endogenous peptides whose effects are mediated by the

G-protein-coupled receptors ET_A and ET_B [33] and is found in the epidermis, dermis and subcutaneous vasculature [34]. It appears to be pivotal in the mechanism that induces post-incision primary allodynia and contributes to central sensitization and secondary hyperesthesia [31,35]. There is also evidence that post-incision primary mechanical hyperalgesia is due to hydrogen ion sensitive channels rather than activation of ET_A receptors [36-38].

In a series of behavioral and electrophysiological experiments following incision of the glabrum skin of rodents, Brennan and colleagues demonstrated: 1) spontaneous activity of C-δ and A-δ nociceptor afferents; 2) behavioral guarding and spontaneous activity in nociceptive afferents and pain transmission neurons of the Dorsal Horn (DH) following deep tissue trauma while 3) decreased heat and mechanical withdrawal latency were associated only with skin incision [32,39-44]. Clinical studies support this experimental work in that deep tissue injury is correlated with both post surgical pain and opiods consumption [45-48].

All of the patients in this study had severe long standing disease of at least 7 years duration and a Likert NRS ≥ 5/10. It would be expected from both clinical and experimental evidence that they had ectopic activity in injured axons [49], activation of spinal microglia and astrocytes [50-54] that in concert with changes in MAP kinases are a major component of central sensitization and the induction and maintenance of neuropathic pain [29,53,55]. They also would be expected to have modifications in pain circuitry as a consequence of altered gene expression and the death of inhibitory DH interneurons [54,56,57].

A great majority of these patients were on significant doses of opiods at the time of surgery and maintained their usage afterwards. Recent experimental work has demonstrated that chronic morphine consumption enhances both p38 and extracellular receptor kinase phosphorylation in pain transmission neurons (PTNs) of the DH (the latter a marker of central sensitization) and in microglia. This data was correlated with decreased resolution of postoperative allodynia [58]. Chronic morphine consumption also enhances MAPK signaling that increases the expression of membrane receptors for ATP, cytokines and chemokines-all important for the maintenance of chronic pain [53]. Recently phosphokinase C epsilon, expressed in PTNs, has also been suggested as a mechanism that enhances the nociceptive response to a second injury [59]. All of these patients suffered an original injury, a second surgical injury and most were morphine dependant and tolerant at the time of the surgery. Experimentally and clinically blockade of the NMDA receptor has been shown to reduce pain under these circumstances [60,61]. This study demonstrated the effectiveness of ketamine, midazolam and clonidine in small doses as an adjunct in anesthesia in blocking pain exacerbation and spread of CRPS from a variety of surgical procedures.

The limitations of the study are those inherent in a retrospective non-randomized uncontrolled case series. The CRPS patient population studied is not representative of that seen in most pain centers (more severe and of longer duration). No quantification of static and dynamic mechano allodynia, thermal allodynia or deep muscle sensitization at the site of surgery and at a distance was obtained. The role of clonidine and midazolam in preventing the spread of pain following surgical procedures could not be ascertained. A complete double blind randomized controlled trial would be necessary to determine ketamine's effectiveness as an adjunctive anesthetic in refractory CRPS patients. The trial would be difficult to design due to ethical concerns as ketamine adjunctive anesthesia appears to be more effective than past procedures in severely affected patients.

Acknowledgement

The author would like to thank the Emily Sunstein Foundation for the Study of Neuropathic Pain and the Mark and Amy Tilly Foundation for the Study of Complex Regional Pain Syndrome for their generous support.

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