Efficacy of ketamine in anesthetic dosage for the treatment of refractory Complex Regional Pain Syndrome (CRPS). An open label Phase II ☐ study.

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Abstract

Objective: Advanced complex regional pain syndrome (CRPS) remains very difficult to treat. While subanesthetic low-dose ketamine has shown promise in early localized CRPS, its use in advanced CRPS has not been as effective. Since ketamine's analgesic potency and duration of effect in neuropathic pain are directly dose-dependant, we investigated the efficacy of ketamine in anesthetic dosage in refractory CRPS patients that had failed available standard therapies.

Methods: Twenty patients (ASA I-III), suffering from refractory CRPS received ketamine in anesthetic dosage over 5 days. Outcome criteria were pain relief, effect on the movement disorder, quality of life, and ability to work at baseline and up to 6 months following treatment.

Results: Significant pain relief was observed at one, three and six months following treatment (93.5 ± 11.1 %, 89.4 ± 17.0 %, 79.3 ± 25.3 %; p<0.001). Complete remission from CRPS was observed at 1 month in all patients, at 3 months in 17, and at 6 months in 16 patients. If relapse occurred, significant pain relief was still attained at 3 and 6 months (59.0 ± 14.7%, p<0.004; 50.2 ± 10.6%, p<0.002). Quality of life, the associated movement disorder, and the ability to work significantly improved in the majority of patients at 3 and 6 months.

Conclusions: Ketamine provided long-term pain relief, remission from associated CRPS-symptoms, improved quality of life and ability to work in previously refractory CRPS patients.

Key words: Complex Regional Pain Syndrome (CRPS), Ketamine, NMDA-Receptor, Reflex Sympathetic Dystrophy (RSD), Pain Therapy, Quality of life

Introduction

Complex regional pain syndrome (CRPS) is a severe neuropathic pain disproportionate to the extent of the primary triggering injury that does not respect a root or nerve territory. Characteristic symptoms include severe unrelenting burning and deep pain, associated with mechano- and thermal allodynia, hyperalgesia and hyperpathia. Swelling, autonomic dysregulation, a movement disorder, atrophy and dystrophy are associated to varying degrees (1). The syndrome may progress with time, and signs and symptoms may spread to sites that were not primarily affected. In some patients it is generalized (2;3). Current standard therapy consists of a variety physical, psychological, behavioral, pharmacological and interventional treatments (4-6). Unfortunately, a subgroup of CRPS patients remains refractory to all standard therapy. For these refractory patients, no effective treatment exists (1).

Ketamine, the currently most potent clinically available NMDA-antagonist, has a well-established role in the treatment of acute and chronic pain (7;8). Its main action is through inhibition of N-methyl-D-aspartate (NMDA) receptors, which are thought to play a crucial role in the generation and maintenance of chronic pain (9;10). In addition to its acute analgesic effects, systemic ketamine modulates correlates of central sensitization in chronic pain states on a long term basis. Wind-up and punctuate hyperalgesia were shown to be significantly reduced up to 7 days after surgery (11). Ketamine administered at higher intraoperative dosage for major abdominal surgery reduced the area of wound hyperalgesia and significantly prevented the initiation and maintenance of chronic pain (12;13). Possible mechanisms are that these effects are mediated through NMDA-receptor inhibition, which may be critical for central sensitization, and anti-inflammatory modulation of the immune system (10;14). Proinflammatory cytokines are involved in the processes of peripheral and central sensitization and are inhibited by ketamine (15). In the management of chronic pain, the use of ketamine at higher dosages has been limited by psychotropic side effects. The incidence and severity of ketamine side effects are dose dependent as are its analgesic potency and duration of action (8).

Several series and case reports have documented reduction of pain intensity, allodynia and associated CRPS signs of autonomic dysregulation and motor dysfunction following the administration of subanesthetic, systemic, epidural and topical ketamine (16-19). A recent case report and larger series demonstrated long term pain relief from subanesthetic ketamine infusions, particularly in early and well localized CRPS (20;21). However, in a subgroup of refractory CRPS with spreading disease, subanesthetic continuous S(+)-ketamine infusions were ineffective (22).

This suggested that ketamine in anesthetic dosages might be effective in this refractory CRPS subgroup. Excellent clinical results were obtained with anesthetic doses of ketamine administered on a compassionate care basis to several refractory CRPS patients (unpublished). Based on this limited clinical experience, a standardized treatment regime was developed, and utilized in the present trial. The therapeutic efficacy of ketamine in anesthetic dosage was studied in a Phase II study in 20 refractory CRPS-patients, who suffered either longstanding or rapidly progressive disease that had failed standard therapy. The primary outcome parameter was acute and long term relief of pain. Other measures included effects on the movement disorder, quality of life, social integration and the ability to work at six months following treatment.

Methods

Patients

The human investigation committees in Tübingen and Saarbrücken, Germany, approved the study. Patients were recruited in the pain clinics of the Department of Neurology of Drexel University College of Medicine (Philadelphia, PA) and pain clinics of the Teaching Hospital University of the Saarland (Saarbrücken, Germany). Informed consent emphasized the experimental nature of this treatment. Special emphasis was placed on the risks associated with the intensive care component of this treatment which includes respiratory and urinary tract infections and other infectious complications such as systemic inflammatory response syndrome (SIRS) and sepsis. Organ failure (single or multi organ failure), cardiovascular complications as well as the associated high morbidity rates of all of these serious complications were stressed. All patients gave their informed written consent.

Inclusion Criteria

Patients had to fulfill the 1993 IASP–CRPS diagnostic criteria and the 1999 modified research diagnostic CRPS criteria (23;24). The average daily pain intensity had to be 7 points or greater on a numerical rating scale (NRS: endpoints 0: no pain, 10: worse pain imaginable) over a period of at least 6 months while on standard therapy. The CRPS symptomatology had to be either longstanding and spreading, or rapidly progressive. Standard conventional nonmedical (physical therapy, psychological approaches), or pharmacological and interventional treatment modalities had to have failed. Failure of therapy was defined as: 1) no benefit from treatment, or 2) no lasting pain relief (> 2 months). The designation “refractory” included documented failure of: 1.) nonmedical, and 2.) pharmacological mono-, or combined therapy with nonsteroidal antiinflammatory drugs, tricyclic antidepressants, anticonvulsants, low or high potency opioids, and 3) at least three interventional procedures, including selective nerve blocks, epidural analgesia, brachial plexus blocks, sympathetic ganglion blocks, intravenous regional sympathetic blocks (IVRSB), spinal cord stimulation (SCS), surgical sympathectomy, or intrathecal drug delivery systems, and 4) unchanged or progressing state of disease despite these efforts.

Inclusion was limited to ASA class I-III (American Society of Anesthesiologists Physical Status Classification) patients, which apart from their pain related disability, did not suffer from clinically relevant systemic disease. Patients that presented with a history of significant cardiovascular, pulmonary, renal disease or mental disorders were excluded. Further exclusion criteria included known contraindications to ketamine use (severe arterial

hypertension, hyperthyroidism, ischemic heart disease or heart failure), as well as allergies to ketamine or midazolam. Patients with a history of substance or drug abuse, or a suspected somatoform pain disorder were excluded. The inclusion criteria were evaluated by three physicians, a neurologist (RJS) and two anesthesiologists (RTK, PR).

Ketamine treatment protocol

Anesthesia was induced by bolus injection of ketamine (1-1.5 mg/kg) and midazolam (2.5-7.5 mg). Tracheal intubation was facilitated by vecuronium (0.1 mg/kg). Treatment was maintained by infusions of ketamine over 5 days, starting at 3 mg/kg/h, followed by gradual daily titration up to a final dose of 7 mg/kg/h. Midazolam was co-administered and adjusted as clinically required (0.15-0.4 mg/kg/h) to obtain a stable level of deep sedation (Ramsay-Score 4-5), and to attenuate ketamine specific side effects, i.e. agitation (25). The first three patients were not intubated and spontaneous ventilation was allowed. The remaining seventeen patients were electively intubated, to limit the risk of aspiration. These 17 patients were mechanically ventilated. After 5 days, infusions were slowly tapered, first by reducing the ketamine dosage by 20% every four hours, followed by gradual reduction of midazolam in the same manner. Patients were then weaned from mechanical ventilation and extubated once adequate spontaneous ventilation, sufficient gas exchange, and the appropriate level of consciousness together with intact protective reflexes was attained.

Ketamine and norketamine plasma concentrations

Blood samples were drawn into prefabricated EDTA-tubes (S-Monovette®, Sarstedt AG & Co., Nürnbrecht, Germany) from all patients every eight hours to determine ketamine and norketamine levels (the primary ketamine metabolite), plasma concentrations during anesthesia and for 3 days following treatment. Blood samples were centrifuged and plasma aliquots stored until analysis at -80°C. Ketamine and norketamine plasma concentrations were analyzed by simultaneous high-pressure liquid chromatography (26).

Standardized Additional Drugs

Deep Venous Thrombosis and Ulcer Prophylaxis: All patients received intravenous unfractionated low dose heparin 15.000 I.E./d (Liquemin®, Roche, Germany) under regular aPTT monitoring, and the proton pump inhibitor pantoprazole 40 mg/d (Pantozol®, Altana Pharma, Germany).

Clonidine: Clonidine (Catapresan®, Boehringer Ingelheim, Germany) was administered intravenously (0.20-0.85 µg/kg/h) to control cardiovascular stimulation and the psychomimetic and potential neurotoxic side effects of ketamine. It was dosed as clinically required (0.20-0.85 µg/kg/h) to control tachycardia and hypertension. The coadministration of clonidine at a minimum dose of 0.15 µg/kg/h was maintained with midazolam throughout the intensive care treatment.

Alimentation and Glycemic control

Alimentation: The first three unintubated patients received full parenteral nutrition(25 kcal/kg/d) with a ternary mixture of aminoacids (40 g/l), glucose (160 g/l), and fat (40 g/l), containing 1040 kcal/l glucose-fat calories (Oliclinomel® 4.0% GF-E Baxter, Germany). Intubated patients received full enteral nutrition (25 kcal/kg/d) via nasogastral tube (Nutrison Standard®, Nutrisone Multifibre®, Pfrimmer Nutrica, Germany, containing 1.000 kcal/l, proteins 40 g/l, carbohydrates 123 g/l, fat 39 g/l).

Glycemic control: Intensified insulin-therapy (Actrapid®, Novo Nordisk A/S, Denmark) was applied, and insulin dosed as clinically needed to maintain normoglycemia (blood glucose concentrations: 90-150 mg/dl)(27).

Patient safety

Monitoring: Continuous standard intensive care monitoring (arterial blood pressure monitoring, ECG and ST-segment analysis, core temperature, pulse oximetry, capnometry, central venous pressure) was done in all patients. All patients had bladder catheterization.

Blood Gas Analysis and Blood Chemistry: Blood gas analysis was routinely performed every 8 hours and additionally when clinically warranted to adjust mechanical ventilation, insulin therapy, acid-base balance and electrolytes. Detailed blood tests were done before the treatment, daily during treatment, and for the first two weeks

thereafter. Laboratory evaluation included cell counts, electrolytes, coagulation parameters, liver enzymes, C-reactive protein (CRP), creatine phosphokinase (CPK), and CKMB-isoenzyme activity.

Screening for infectious complications: When admitted patients were screened with pharyngeal, nose and rectal swabs for the presence of multiresistant pathogens (methycilline resistant *S*. aureus (MRSA); vancomyxine resitant enterococi (VRE)). During the treatment screening included continuous monitoring of core body temperature, and laboratory parameters (daily leukocyte count, CRP), urine status, and tracheal secretion and urine cultures on the first day of treatment and when respiratory or urinary tract infection was suspected clinically.

Outcome Criteria

The patients' progress during the study, the times and nature of assessments at baseline, 1 week, 1, 3, and 6 months after treatment are summarized in a flow chart shown in figure 1, and the individual responses to treatment are summarized in table 5.

Pain Assessment and Degree of Pain Relief

The degree of a patient's subjective pain intensities was rated by a numeric scale (NRS, endpoints: 0-no pain, 10-worst pain imaginable) at baseline and at follow-up examinations. The degree of pain relief following treatment was calculated as: Percent pain relief = $(NRS_{baseline} - NRS_{follow\ up}) / NRS_{baseline} \times 100$

Movement Disorder

Data was obtained at baseline and 1, 3 and six months after treatment for both upper and lower extremities.

Upper extremity motor evaluation: Assessment of active range of motion was based on norms described by Kendall et al.(28). Arm movement was quantified by utilizing a combination of the performance of specific motor tasks (placing a book in a shelf above shoulder level, ability to comb one's hair, putting on a sweater, tying an apron) in addition to the results of the range of motion evaluation. Hand movement assessment combined grip function (gripping and holding a cup) and pinch grip ability (gripping, holding and use of a key, pencil and writing). Based on the observed range of movement combined with performance in the described functional tasks, the movement disorder was quantified utilizing a 4 point rating scale: 0: normal movement; 1: moderate disability (moderately reduced active range of motion, muscular strength, initiation and completion of motor tasks); 2: severe

disability (severely restricted active range of motion, weakness, poor initiation and completion of motor tasks); 3: total disability (only residual movement, severe weakness and inability to perform motor tasks).

Lower extremity motor evaluation: The assessment of motor function of the lower extremity was based on the ability to walk and was scored on a 4 point rating scale: 0: normal movement (unimpaired walking); 1: moderate disability (inability to walk 500 meters); 2: severe disability (inability to walk 200 meters); 3: total disability (ability to walk < 50 meters or inability to walk).

Quality of Life

The assessments to estimate disease related impairments in activities of daily living, social integration, and the ability to work represent recognized aspects of quality of life. The assessments were performed at baseline and at 3, and 6 months following therapy.

Activities of Daily Living: Patients were asked to rate their performance of typical activities of daily living. The representative tasks of everyday life were based on selected key items contained in valid questionnaires, such as the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) and the Stanford Health Assessment Questionnaire (HAQ) (29;30). Patients were instructed to rate their ability to independently perform the following tasks self care (preparing meals and eating (cutting food), drinking, dressing, washing, drying, and combing), and household activities (house cleaning, grocery shopping, washing dishes, and gardening). The degree of impairment was rated using a 4 point numeric scale: 0: no impairment (all tasks can be performed independently), 1: moderate impairment (tasks can be accomplished but with difficulty), 2: severe impairment (<50% of activities can be performed independently); 3: total impairment (majority of tasks cannot be performed; dependent on the help of others)

Social Integration: Patients were queried in regard to their ability to function socially and rated their overall impairment. Representative activities were chosen from the aforementioned validated questionnaires (WHYMPI, HAQ). Patients were asked to rate their ability to perform recreational activities (pursuing hobbies, playing sports, taking trips, seeing friends/relatives, reading, going out), cultural activities (attending concerts, movies, theatre). The degree of impairment was rated using a 4 point numeric rating scale: 0: no impairment, 1: moderate impairment (all activities can be performed, but with difficulty), 2: severe impairment (<50% of activities can be performed

independently); 3: total impairment (majority of activities cannot be performed and the patient is dependent on the help of others)

Ability to Work: The ability to work was rated on a 4 point scale: 0: no impairment, 1: moderate impairment (able to work more than 4h/d but less than 8h/d), 2: severe disability (able to work up to 4h/d), 3: total impairment (able to work only 2 h/d or totally unable to work)

Side Effects of treatment

Ketamine specific side effects: Psychotomimetic side effects: The occurrence, duration, and severity of ketamine specific psychotomimetic side effects were documented following treatment. These included: anxiety, hallucinations, restlessness, difficulty in concentration, disruption of sleep, dizziness, dysphoria, euphoria, and disorientation.

Other adverse treatment effects: These included all potential adverse effects associated with the intensive care nature of the treatment, such as respiratory, urinary tract or systemic infection, and cardiovascular and pulmonary complications. The occurrence of these complications, their treatment and resolution were documented.

Statistics

Data were analyzed using the statistical software package JMP IN (Version 5.1.2, SAS Institute, Cary, NC, USA). The Kolmogorov-Smirnov test was used to assess normality. Non parametric paired t-tests on ranks were used to analyze differences between baseline and those obtained during and following therapy for not normally distributed data. Normally distributed data were analyzed by paired t-tests. Alpha was set at 0.05. For multiple comparisons the alpha correction of Bonferroni was performed.

Results

Patient demographics: Twenty ASA-physical status class I-III patients were enrolled and completed the study (18 female and 2 male; mean age 30.4 ± 10.4 years, range: 14-48 years). The mean duration of CRPS was 49.4 ± 25.0 months (range: 6-84 months). All patients suffered from severe or spreading CRPS. Two had rapid contiguous spread affecting the entire extremity, two suffered from mirror spread, and 16 had generalized CRPS. (table 1) All patients had been unresponsive to multiple conventional treatments and had failed standard pharmacological therapy and numerous invasive procedures. (table 2 and 3)

Pain Intensities and Pain relief

Pain Intensities: Pain intensities were analyzed for the entire group, as well as for the subgroup of patients with recurring initiating or maintaining pain (nociceptive or neuropathic, but without associated CRPS signs or symptoms) and the subgroup with relapsing CRPS (neuropathic pain and associated CRPS signs and symptoms).

At baseline, pain intensity of the entire group (*N*= 20), and of the subgroups with later recurring pain, and relapsing CRPS were NRS 8.9 ± 0.3, 8,8 ± 0.2, and 9.2 ± 0.2 (mean ± SD) respectively, and no statistically significant differences between the groups were detected.

Following ketamine treatment a significant reduction of pain intensity was observed at one week and one month for the entire group (NRS 0.5 ± 0.8, and 0.6 ± 1.0), and the subgroup with recurring pain (1.4 ± 0.7, and 1.7 ± 1.1, *N*= 7) ($p<0.001$). At three months pain intensity was significantly ($p<0.001$) reduced compared to baseline in the entire group (NRS 0.9 ± 1.6) and the subgroup with recurring pain (2.0 ± 0.9, *N*= 4). Three patients had a CRPS relapse, but had significantly reduced pain compared to baseline (NRS 3.8 ± 1.4, $p<0.004$). Pain intensity at 6 months was significantly reduced for the entire group of patients (2.0 ± 2.4, $p<0.001$), the subgroups with recurring pain (3.6 ± 2.0, $p<0.001$, *N*= 6), and those with a CRPS relapse (4.6 ± 1.1, $p<0.002$, *N*= 4). The results are summarized in figure 2.

Pain Relief: The calculated percentage of pain relief was significant following ketamine treatment at one week (mean ± SD: 94.5 % ± 8.9, and at 1, 3 and 6 months (93.5 % ± 11.1, 89.4 % ± 17.0, 79.3 % ± 25.3) in the entire group of patients ($p<0.001$). Analyses for the subgroup with recurring pain showed significant pain relief at one week (84.4 % ± 8.22, *N*= 7, $p<0.001$), and 1, 3, and 6 months (81.4 % ± 11.5, 77.8 % ± 10.1, and 64.32 % ± 23.8, *N*= 7, 4, and 6, $p<0.001$ in all), respectively.

Pain relief in the subgroup of CRPS patient with relapse was maintained at 3, and 6 months (59% ± 14.7, *N*= 3, p<0.004, and 50.21% ± 10.6, *N*= 4, p<0.002). Figure 2 summarizes the results.

Movement Disorders

Upper Extremity: For statistical analyses, the separately assessed scores the impairment of movement in the arm and hand of each side of the body was added to a total score for hands and arms. Thus, the minimal sum score was 0 (normal bilateral movement) and maximal 6 (total bilateral impairment). All patients (*N*= 20) showed impaired movement in the upper extremities.

At baseline a sum score of 3.2 ± 1.2 (mean ± SD) for movement in the arms, and 3.7 ± 1.2 for movement in the hands was documented (*N*= 20). At 1, 3, and 6 months, a significant (p<0.001) reduction of the sum score was noted for the movement impairment in the arms (1.4 ± 0.83, 0.5 ± 0.8, and 0.4 ± 0.8), and hands (1.6 ± 0.8, 0.5 ± 0.9, and 0.5 ± 0.8), respectively.

Lower Extremity: Statistical analyses of scores for decreased movement in the lower extremities were based on the direct scores of the aforementioned 4-point based numeric rating scale. Of the entire group, only those with a movement disorder in the lower extremity were included for statistical analyses. At baseline, patients with movement disorder of the lower extremity (*N*= 15), had a score of 2.3 ± 0.7 (mean ± SD). Following treatment, their impairment was significantly reduced at 1, 3 and 6 months (1.3 ± 0.9, 0.6 ± 0.7, and 0.6 ± 0.6; *N*= 15, p< 0.001). Figure 3 summarizes the results.

Quality of life

Activities of Daily Living: At baseline, the ability to independently accomplish activities of daily living was rated as severely impaired by 7, and as totally impaired by 13 patients, with a mean score of 2.35 ± 0.4 (mean ± SD) for the entire group. At 3 months, the impairment was rated as severe by 1, as moderate by 12, and as not impaired by 7 patients, with a mean score of 0.7 ± 0.6, and a significant difference compared to baseline (p<0.001). At 6 months, there was a significant difference in the ability to perform activities of daily living compared to baseline. One patient rated total impairment, 3 severe impairment, 6 moderate impairment, and 10 patients no impairment for a mean score of 0.7 ± 0.9 (p<0.001). Results are shown in figure 4.

Social Integration: The impairment in social integration prior to treatment was rated as complete by 11 patients and severe by 9. Their mean impairment score was 2.5 ± 0.5. At 3 months, their impairment was rated as severe by 1, as moderate by 10, and 9 were unimpaired. Their mean score of 0.6 ± 0.6, was significantly improved compared to their pretreatment baseline ($p<0.001$). At 6 months, there was significant improvement in the group with 1 patient rating total impairment, 2 severe impairment, 6 moderate impairment, and 11 patients no impairment (mean score of 0.6 ± 0.8 ($p<0.001$). Results are shown in figure 4.

Ability to Work: The impairment in the ability to work prior to treatment was rated as complete by 11, severe by 5, and as moderate by 4 patients (mean impairment score of 2.3 ± 0.8). At 3 months, the impairment in ability to work was rated as complete and severe by 1 patient in each category, as moderate by 8, and as not impaired by 10 patients (mean score of 0.6 ± 0.8), which was significantly improved compared to their baseline ($p<0.001$). At 6 months, there was significant improvement in the ability to work as only 2 patients in the cohort were unable to work, 4 had moderate impairment, and 14 patients had no impairment (mean score of 0.5 ± 0.9) ($p<0.001$). Results are shown in figure 4.

Ketamine and Norketamine plasma concentrations

HPLC analysis of ketamine and norketamine plasma levels was in 18 patients. The sampling and analysis of two patients was incomplete, because of initial technical difficulties and therefore were not included in the analyses. Figure 5 summarizes the plasma concentrations for ketamine and norketamine.

Side effects

Ketamine specific side effects

Psychotropic ketamine side effects: Psychotropic side effects that included anxiety, dysphoria, nightmares and difficulties with sleep were observed in the majority of patients upon emergence from ketamine anesthesia. The intensity of these ketamine specific side effects was most severe in the initial days following emergence from anesthesia and resembled an acute withdrawal. These symptoms were successfully treated with small doses of clonidine and/or benzodiazepines. The psychotropic side effects faded within the first week following treatment in the majority of patients. However, 5 patients reported difficulties with sleeping and recurring nightmares for a

month following treatment. Muscular weakness was reported in all patients for as long as 4-6 weeks following treatment.

Adverse treatment effects

Infectious complications: No major or life threatening complications were observed. The majority of complications were infections associated with the intensive care nature of treatment. Seven patients had respiratory infections, tracheobronchitis in 5, and pneumonia in 3 patients. Fever was observed early (within 24-48h) following the initiation of anesthetic doses of ketamine, with concomitant leucocytosis (12,000-16,000/µl) and elevation of the CRP (6-25 mg/dl). Culture of tracheal secretions revealed *S*.aureus (multisensibe *S*. aureus (MSSA), *N*=6), Klebsiella pneumoniae (*N*= 2), and Proteus mirabilis (*N*= 1), as the pathogens in these cases. Lower urinary tract infections were seen in six patients, and urine cultures revealed Enterococcus species (E. coli, E. faecalis) as the pathogens. These infectious complications were successfully treated with antibiotic therapy.

Laboratory Evaluation: During treatment, transient rises in liver enzymes, CK and CKMB were observed. Blood tests prior to the start of therapy revealed elevated liver enzymes (γ-GT: 20-60 U/l in 5 patients, and GOT: 20-38 U/l in 5 patients) all of whom had been taking combinations of analgesics, antidepressants and seizure medications. Under anesthesia, elevations of liver enzymes were noted in 16 patients for γ-GT (range: 30-94 U/l), GOT (range 30-98 U/l), and GPT (20-94U/l), the maximal elevations occurred on day 5-6 of treatment. Elevations in CPK (range: 20-800 U/l) were observed in 16 patients, all of whom had normal ratios for CPK/CKMB which where below 10%. Both the elevation of liver enzymes and CPK decreased following treatment and returned to reference values within 10-14 days.

Discussion

This study demonstrates an impressive effect of anesthetic ketamine in advanced and refractory CRPS patients. Pain scores were significantly improved and long term complete pain relief was observed in 50% of patients. Patients that suffered recurring pain alone and recurring pain in conjunction with a CRPS relapse also maintained significant relief during the course of the study. In addition, there was significant improvement of the movement disorder, ability to perform activities of daily living and the ability to work in concert with the decrement in pain.

There are many possible mechanisms that underlie the marked and long lasting effects of anesthetic ketamine in these severely affected CRPS patients. Because this is an open label phase II study with lack of controls, the results may not be completely attributable to ketamine. Anesthetic doses of ketamine have not been studied in the therapy of chronic pain states. Existing evidence for the efficacy of ketamine in chronic pain disorders was obtained by utilizing low subanesthetic dose protocols primarily for neuropathic pain states other than CRPS. The first data on the beneficial effects of ketamine for CRPS was obtained from case reports and small case series (16-19;21). In these studies, subanesthetic ketamine was administered via systemic, epidural or topical routes and provided dramatic relief from pain and associated CRPS symptoms in some patients. However, these studies differ in the routes of ketamine administration, dosage, treatment time, patient clinical profiles, and the duration of observation following treatment. The main limitations in determining the benefit of ketamine in these studies are sample size, lack of a control population and standardization of the treatment and measurement protocols. Long term pain relief for 8 months was observed following a 10 day course of epidural ketamine (0.25µg/kg/h) in a patient with lower extremity CRPS (16). Harbut utilized continuous subanesthetic ketamine for 6 days in a patient that had suffered 9 years of CRPS and achieved pain relief for 5 months (21). Recently, a larger scale retrospective case series described long term relief from pain following continuous low dose ketamine (20). In this series, the best response to ketamine was observed in patients with early CRPS whose symptoms and signs were well localized to the distal aspects of one extremity. In a subgroup of refractory CRPS patients, we recently showed subanesthetic continuous S(+)-ketamine (500 mg/d) administered over 10 days (exceeding the equianalgesic ketamine dosages used by Correll) was ineffective in relieving pain or attenuating severe thermal and mechanical allodynia (22). To our knowledge, there are no randomized controlled trials on the efficacy of ketamine in the treatment of CRPS.

CRPS is generally thought to be a subset of neuropathic pain (31;32). The exact pathophysiology is unknown but strides have been made in the understanding of possible mechanisms that underlie the generation and maintenance of this neuropathic pain (1;10). A critical role for NMDA-receptors that contribute to central sensitization in chronic neuropathic pain is well established (9;10). Consequently, the efficacy of several NMDA-receptor antagonists has been investigated in various neuropathic pain conditions. In human and animal studies, ketamine was shown to have a dose-dependent effect on neuropathic pain features, such as secondary hyperalgesia, allodynia, long term potentiation and wind-up (33-37). Several clinical trials in neuropathic pain conditions have confirmed beneficial effects of ketamine in the therapy of chronic pain. In a randomized controlled trial of post herpetic neuralgia, iv ketamine significantly reduced pain, allodynia and hyperpathia (38). Similarly, intravenous ketamine has been shown to produce significant pain relief and reduction of wind-up pain in a randomized controlled trial of chronic phantom pain (39). A randomized trial of intramuscular ketamine provided 24 hours of significant pain relief in patients with facial neuralgia(40). Several trials have noted long term affects of ketamine that outlast its pharmacological profile (11-13;40). In addition, animal and clinical studies have demonstrated that the efficacy of ketamine is dose-dependent (12;34;35;41). Since the incidence and degree of ketamine side effects also depends on dosage, most trials in pain medicine have been done with low doses (7). This trial of anesthetic dosage of ketamine in refractory CRPS demonstrated long term significant pain relief that outlasts its pharmacological profile.

Many aspects of the pathophysiology of CRPS remain unclear. Recently, CRPS has been posited to be a disease of the central nervous system (CNS) (42). The molecular mechanisms underlying CRPS are hindered by lack of an exact animal model that is completely valid for this complex clinical entity (43). Its characteristic signs and symptoms may occur as a consequence of dysregulated efferent central control of several systems (i.e. somatosensory, motor and sympathetic) and appears to be maintained from a peripheral sensitizing afferent nociceptive barrage. The molecular mechanisms responsible for inducing and maintaining these lasting and self maintaining neuroplastic changes in CRPS are not known but there is evidence for NMDA-receptor mediated neuronal plasticity and facilitation of central pain processing (1). Another potential mechanism underlying the syndrome is injury induced activation of central microglia that secrete inflammatory cytokines which activate central pain projecting neurons (44). The relative importance of mechanisms for central sensitization mediated by the NMDA receptor and subsequent calcium cascades or effects of inflammatory cytokines on pain transmission neurons or both in concert is not known (10;14). Recent evidence in a rat model of neuropathic pain demonstrated a

comparable long term suppression of allodynia by ketamine that outlasted the duration of its NMDA blockade (41). Thus, downregulation of central sensitization mediated by NMDA-receptor blockade might explain in part long term effects of ketamine in neuropathic pain.

Other relevant mechanisms mediated by ketamine that contribute to pain relief in these patients must be considered. These include potential modulation of peripheral NMDA- and non-NMDA-receptors. Ketamine inhibits peripheral glutamate receptors which play a role in both peripheral and subsequent central sensitization (45). In addition, ketamine interacts with various receptors involved in nociception that include AMPA and kainate glutamate receptors, voltage-dependent ion channels, sodium and L-type calcium channels, opioid receptors (μ, κ, and δ-opioid receptors), $GABA_A$-receptors and nicotinic and muscarinic acetylcholine receptors (8). Ketamine induced inhibition of nitric-oxide synthase might also contribute to its analgesic effects (8). As noted above, proinflammatory mediators are known to play an essential role in the processes of peripheral and central sensitization (46). Ketamine induces a profound inhibition of proinflammatory cytokines and other inflammatory mediators, both in experimental and clinical studies (8;15). A recent study demonstrated significant increases in proinflammatory cytokines in the cerebrospinal fluid of CRPS patients, which suggests a potential role of neuroimmune activation in CRPS (47). The anti-inflammatory effects of ketamine administered in anesthetic doses may also play a role in its effects on these patients. Alternatively or in addition to ketamine, midazolam and clonidine may also contribute to the effectiveness of this treatment. Clonidine, a central α_2-adrenergic agonist, has analgesic properties (48). Its analgesic potency is weak but has effect when administered by epidural, intrathecal or a transdermal route. Although the analgesic effects of intravenous clonidine are controversial, a synergistic interaction with ketamine in our patients is possible (48). Another synergistic effect of this treatment may be due to midazolam, a short acting $GABA_A$ agonist. In the course of central sensitization, GABA-ergic inhibitory transmission is depressed by NMDA-dependent mechanisms which leads to prolonged depression of inhibitory transmission and thus potentiation of central pain projecting neuron hyperexcitability (10;49). The large doses of midazolam administered during treatment would be expected to enhance GABA-ergic induced inhibition during this treatment while its role as an analgesic is unclear (10;49). The possible contributions of the placebo effect and or resetting of pain processing mechanisms due to 5 days of anesthesia in the beneficial effects of this treatment are unknown.

A most relevant concern of this invasive procedure is patient safety. Modern intensive care medicine standards achieve a high level of patient safety. Ketamine has been safely used for over 30 years in clinical anesthesia and also in intensive care. However, a potential concern is NMDAR-antagonist induced neurotoxicity that has been demonstrated in animal experimental work in the developing and adult rat brain (50). Neurotoxic effects are prevented by administration of clonidine and $GABA_A$-agonists (51;52). To the best of our knowledge, neurotoxicity of ketamine to date has not been demonstrated in humans(53). Initial studies investigating ketamine sedation in brain injured patients in the intensive care setting were not associated with significant morbidity or mortality (54;55). However, these studies were not powered for a valid assessment of safety. The reported duration of ketamine sedation (6.1 ± 3.2 days) and the dosage of ketamine (maximal dose: 94 ± 23µg/kg/min) are comparable to our study (5 days of sedation; maximal dose: ~ 84 µg/kg/min) (54).

Nonetheless, it must be emphasized that this protocol is associated with serious risks. The major complications observed in this study were respiratory and urinary tract infections, representing typical infections in intensive care. Although, in this series, infections resolved under antibiotic treatment, it must be emphasized that infectious complications still represent the main source of morbidity and mortality in modern intensive care medicine. Transient ketamine specific psychotropic side effects occurred on emergence from ketamine anesthesia and were successfully controlled by benzodiazepines and clonidine. There were no long-term psychiatric or cognitive impairments in any patient (56). Moderate muscle weakness persisted for a month to six weeks.

Conclusion

The lack of a control group and the small sample size of this phase II study limits interpretation of our results but suggests that ketamine in anesthetic dosage is an effective last line option for severe, advanced CRPS patients that have failed all available standard therapies. The results of this study should be confirmed by larger, and ideally randomized clinical trials.

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Legends

Figure 1: Flow chart summarizing patients' progress through the study. The left side of the diagram shows the timing of the assessment of patients and the investigated treatment with anesthetic ketamine. The right side of the diagram shows he investigated outcome parameters at the different assessment times throughout the study.

Figure 2: Summarizes the pain intensities (A.) and the degree of pain relief (B.) before and following the treatment. A) Shows the pain intensities (NRS: 0-10, data presented as mean ± SD) of the entire treatment group (N=20) for baseline, at 1 week, and 1, 3, and six months following treatment and significant differences compared to baseline (*: $p<0.001$), and the results of the subgroup analyses for patients with recurring pain (N=7 at 1 week, and 1 month, N=4 at 3, and N=6 at 6 months) and significant differences compared to baseline, as well as results for the subgroup with relapsing CRPS (N=3 at 3 months, N=4 at 6 months) and significant differences compared to baseline (+: $p<0.004$, #: $p<0.0029$).

B) Summarizes the percentage of pain relief following the treatment. Data are presented as means ± SD for the entire group and the subgroups with recurring pain, and relapsing pain respectively. Significant degrees in the percentage of pain relief are indicated (*: $p<0.001$; +: $p<0.004$; #: $p<0.002$).

Figure 3: Summarizes the changes for the movement disability score (4-point rating scale: 0: normal movement, 3: total impairment) of the different assessment times. Data are presented as means ± SD for baseline, and the follow-ups at1, 3, and 6 months. A.) Upper extremity: Data show the results of a sum-score (movement disability scores of both body sides were added, thus a minimal score of 0 (normal bilateral movement), and 6 (total impaired bilateral movement) for impairment of movement in arms and hands, and significant differences compared with baseline (*: $p<0.001$). B) Lower extremity: Results and significant differences in the movement disability score for the lower extremity at baseline and the follow up assessments ($p<0.001$)

Figure 4: Summarizes the results for the assessments of quality of life: the impairment in activities of daily living, the impairment in social integration, and the ability to work. Patients rated their impairment on a 4-point rating scale (0: no impairment, 3: total impairment). A) Shows the absolute number (*N*) of patients in each category of impairment at baseline and the follow-ups, and significant differences compared to baseline (*$p<0.001$). B.) Severity of Impairment: Summarizes the impairment scores for the entire group for impairment of activities of daily living, social integration, and the ability to work at baseline, 3, and 6 months and significant differences compared to baseline (*$p<0.001$).

Figure 5: Ketamine and norketamine plasma concentrations. Summarizes the by HPLC determined plasma concentrations for racemic ketamine and the primary active metabolite norketamine [µg/ml] over the 5 treatment days with anesthetic days and subsiding in the 3 consecutive days after anesthetic ketamine treatment.

Table 1: Demographics: Summarizes statistic data of patients' demographics for the entire group of patients, and the analyzed subgroups: recurring pain (all patients with recurring pain, either neuropathic, nociceptive, or both at one of the follow ups), CRPS-relapse (all patients with a CRPS-relapse), and results of the statistical comparison of differences between the entire group and the subgroups (exact p-values).

Table 2: Characterization of CRPS-status at baseline: Summarizes patients' age, gender, ASA-class (American Society of Anesthesiologists Physical Status Classification), and CRPS related characteristics at baseline: triggering injuries, sites of primary CRPS manifestation, duration of disease (months), the type of spread, the status of disease spread at baseline, and the pain intensity at baseline (NRS: 0: no pain, to 10: worst pain imaginable.

Table 3: Failed Physiotherapy and pharmacotherapy: Summarizes the individual patients' failed physiotherapeutic and pharmacotherapeutic approaches at baseline. The "+" indicates, which treatments have been performed and failed, defined as being without primary effect, or no lasting (> 2 months) on pain relief. (NSAID: non steroidal anti-inflammatory drugs, DMSO: dimethylsulfoxid containing ointment)

Table 4: Failed Interventional therapies: Summarizes for the individual patients' failed interventional treatments at baseline. The performed interventions, which had failed, are indicated by a number, indicating the frequency of failed interventions, or by a "+". Failure was defined as being without primary effect on pain, or no lasting effect (> 2 months) on pain relief.

Table 5: Individual outcome following anesthetic ketamine: Summarizes the individual patients' outcome for: Pain response (data shown for the follow ups at 1, 3, an 6 months; FR: full remission, RP: recurring pain, CRPS: CRPS-relapse), Movement disorder (data shown for baseline, 3, 6 months; numbers given indicate: sum score movement disability in the arms (0: bilateral normal movement - 6: bilateral total impairment) / sum score movement disability in the hands (0: bilateral normal movement - 6: bilateral total impairment) / movement

disability score for the lower extremities (0: normal walking – 3: total impairment), and the impairment in the assessed aspects of quality of life: Every day activities, Social Life activities, and Working capacity (NI: no impairment, MI: moderate impairment, SI: severe impairment, TI: total impairment).

Table 1.

		Entire Group	Subgroup: Recurring Pain from Initial Injury	Subgroup: CRPS-Relaspse
	N	20	9	4
age [years]	(mean ± SD)	30.4 ± 10.7	30.7 ± 8.2	33.7 ± 11.9
	range (min-max)	34 (14 – 38)	23 (19 - 42)	26 (20 - 46)
	p-value		0.95	0.58
weigth [kg]	(mean ± SD)	68,4 ± 18,7	68,6 ± 15,9	68,7 ± 31,6
	range (min-max)	67,3(48,5 -115,8)	49 (48,5 – 97,5)	66,0 (49,8-115,8)
	p-value		0,99	0,98
heigth [cm]	(mean ± SD)	167,6 ± 10,7	168,9 ± 12,6	168,0 ± 12,6
	range (min-max)	42,0 (152 -194)	42,0 (152 – 194)	29,0 (154 – 183)
	p-value		0,78	0,95
Duration of CRPS [months]	(mean ± SD)	49,4 ± 25,6	49,7 ± 22,8	60,0 ± 19,6
	range (min-max)	78 (6-84)	60 (24 -84)	48 (36 – 84)
	p-value		1,0	0,59

Table 2

Patient #	Age	Gender	ASA-Class	Triggering injury / Site of primary CRPS manifestation	CRPS duration (months)	Type of Spread	Status of Spread baseline	Pain Intensity (NRS: 0-10) baseline
1	16	f	I	sprain injury / right wrist and hand	8	contiguous	entire right arm	9
2	26	f	I	brachial plexus traction injury / right shoulder	12	mirror	shoulders and arms bilaterally	9
3	25	m	II	Hodgkin's disease, compression of brachial plexi by lymphoma / shoulders	24	mirror	shoulders and arms bilaterally	9
4	46	f	II	brachial plexus traction injury / right arm	60	generalized	generalized	9.5
5	29	f	II	electrical shock / right arm	30	contiguous	right arm, shoulder, face	8.5
6	46	f	III	crush injury right ankle and foot, operative osteosynthesis / right foot	72	generalized	generalized	8.5
7	28	f	III	trauma to lower back / right leg	60	generalized	generalized	9.5
8	42	f	II	cruciate ligament tear, tibial impression fracture / right knee	30	generalized	generalized	8.5
9	22	f	II	tendon rupture digit IV, operative repair / right hand	72	generalized	generalized	9
10	19	f	II	fracture metatarsal-V / right foot	60	generalized	generalized	9
11	20	f	II	trauma to right shoulder and lower back / right arm	36	generalized	generalized	9
12	35	f	III	trauma to right shoulder and lower back / right arm	72	generalized	generalized	9
13	38	f	III	crush injury digit-III right hand, infection and amputation / right hand	24	generalized	generalized	9
14	19	m	II	sprain injury wrist / right hand	84	generalized	generalized	9
15	36	f	II	para-venous i.v.-line / left hand, left forearm	60	generalized	generalized	9
16	25	f	II	Arnold Chiari repair operation / left shoulder, arm	25	generalized	generalized	9
17	48	f	II	extension/distension trauma / right hand	72	generalized	generalized	8.5
18	41	f	II	car accident, whiplash injury / right arm	84	generalized	generalized	9
19	14	f	III	brown reclude spider bite inner right thight / right thigh and leg	7	generalized	generalized	9.5
20	33	f	II	tibial torsion fracture, osteosynthetic operation / left lower leg	63	generalized	generalized	9

Table 3

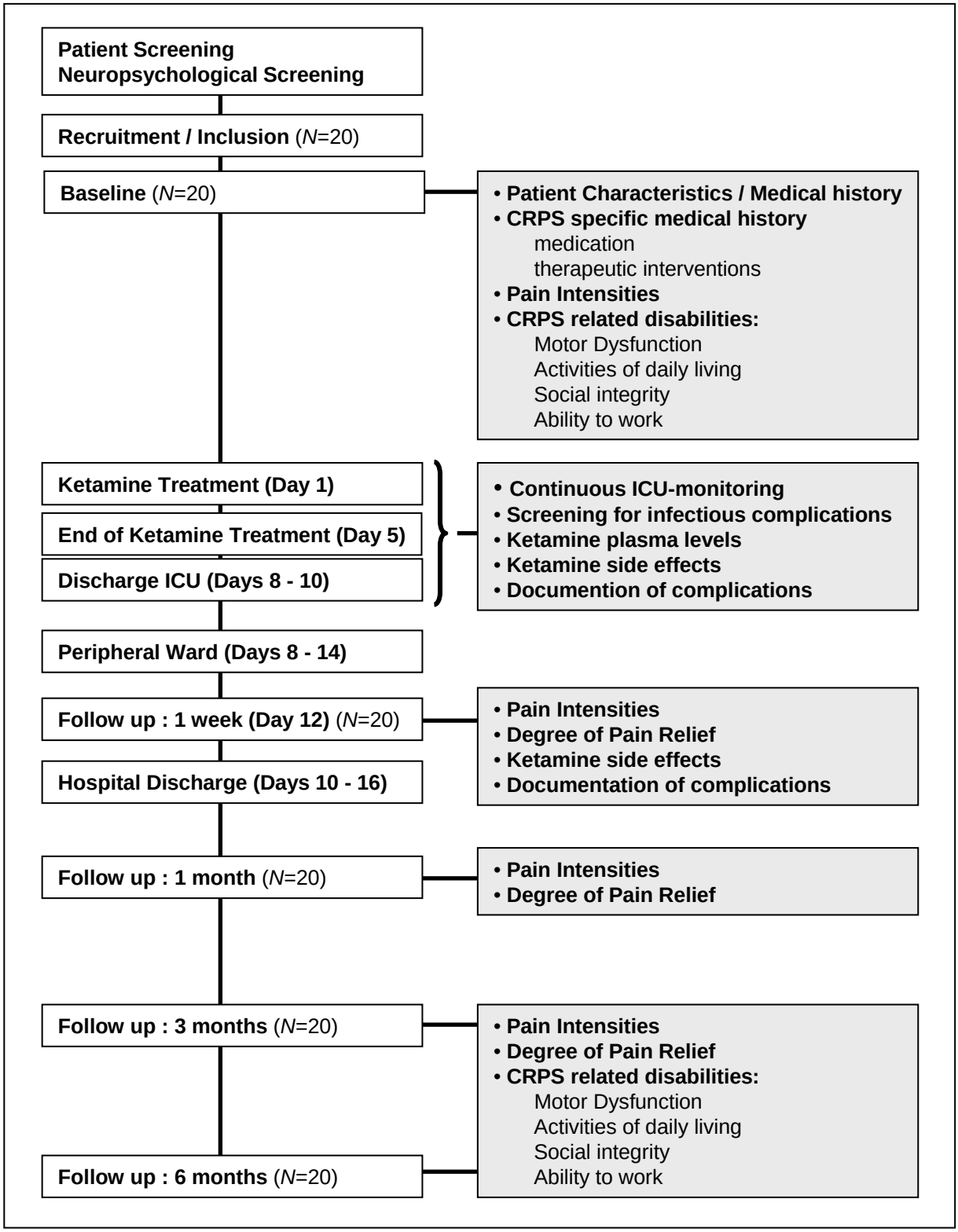
Patient #	Physiotherapy	Pharmacotherapy							Topical Pharmca	
		NSAID	Antidepressants	Anticonvulsants	Spasmolytics	Sodium-Channel-Blocker	Low-Potent Opioids	High-Potent Opioids	Lidocaine	DMSO
1	+	+	+				+	+		
2	+	+	+	+	+	+		+		+
3	+	+	+	+	+			+		
4	+	+	+	+	+	+	+	+		+
5	+	+	+	+	+		+	+		+
6	+	+	+	+	+		+	+		+
7	+	+	+	+	+		+	+		
8	+	+	+	+	+	+	+	+	+	
9	+		+	+	+			+		
10	+	+	+	+	+			+		
11	+	+	+	+	+			+		
12	+	+	+	+	+			+		
13	+	+	+	+	+			+		
14	+	+	+	+			+	+		
15	+		+	+	+		+	+		
16	+		+	+	+			+		
17	+	+	+	+			+	+	+	+
18	+	+	+		+		+	+		
19	+	+	+	+	+			+		
20	+	+	+	+	+		+	+		+

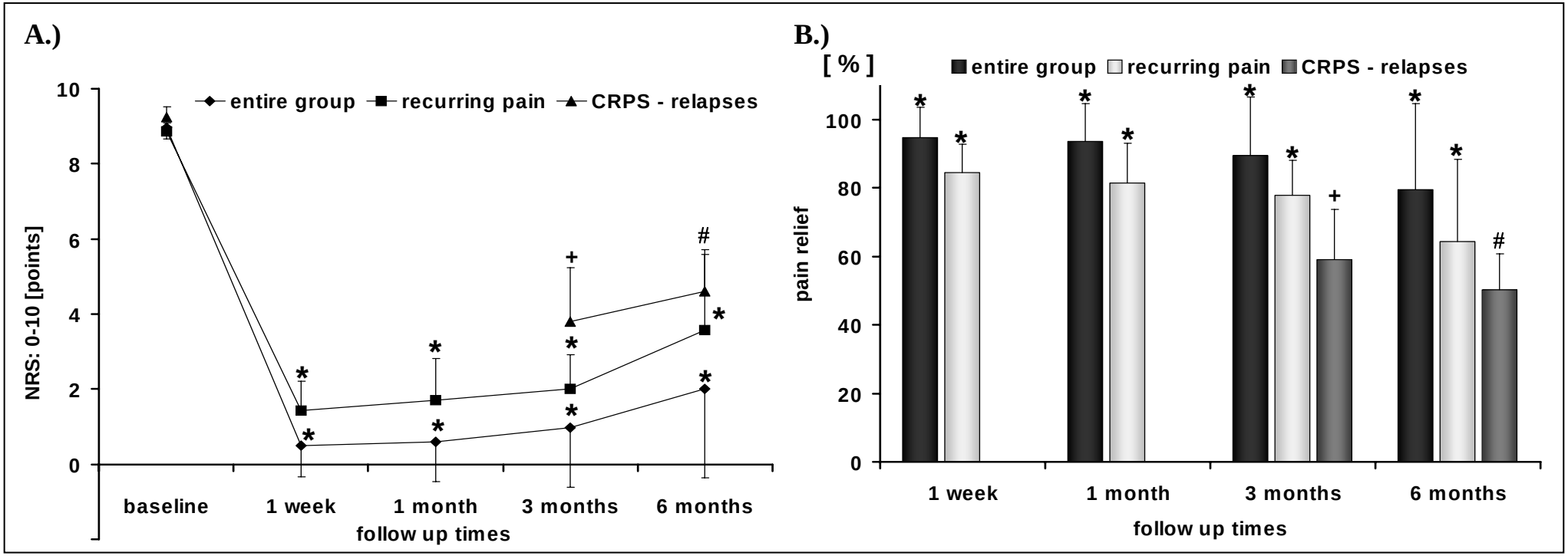
Table 4

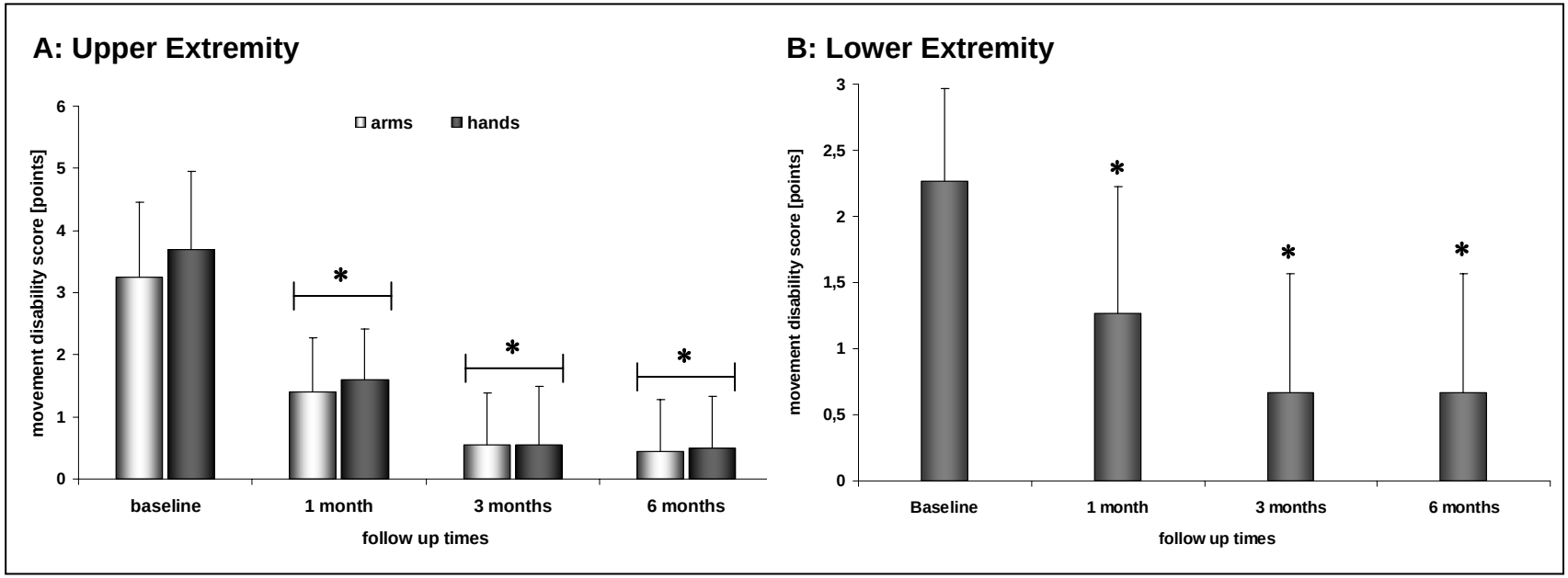
Patient #	Trigger-Point-Infiltrations	Nerve-blocks		Sympathetic Blocks							i.v. Lidocaine	Spinal Cord Stimulation	Intrathecal Sytems
		Selective Nerve Blocks	Brachial Plexus Block	IVRSB	Intrapleural Block	Stellate Ganglion blocks	Cervical Epidural	Thoracic Epidural	Lumbar Epidural	Lumbar Sympathetic Chain Block			
1		2	2	1		3							
2					2						3		
3					3						2		
4	>8	>4		2	2	>4			>3		3		
5	>10	>2			>3						3		
6	>4	>4		2					4	2	4		+
7		>6							>4	2	2	+	+
8		>8							2	1	1		
9	>4	>5	2	2	2	>6					2		
10	5	>6			2				>3	1	2	+	
11	> 4	>5		2	2	> 6			2		1		
12	>6	>6			2	>4			>4	1	2	+	
13	>8	>8	3	>5	1			1	1		1		
14	>8	>8		2	1	>6	2	1			1		
15	>6	>8			2	>6	1		3		2	+	
16	.>4	>6	2			>4					1		
17	>10	>8	2			>8			>3		2		
18	>6	>4		2		2					1		
19		3		1					1		1		
20	>8	>11		2					3	2	2	+	+

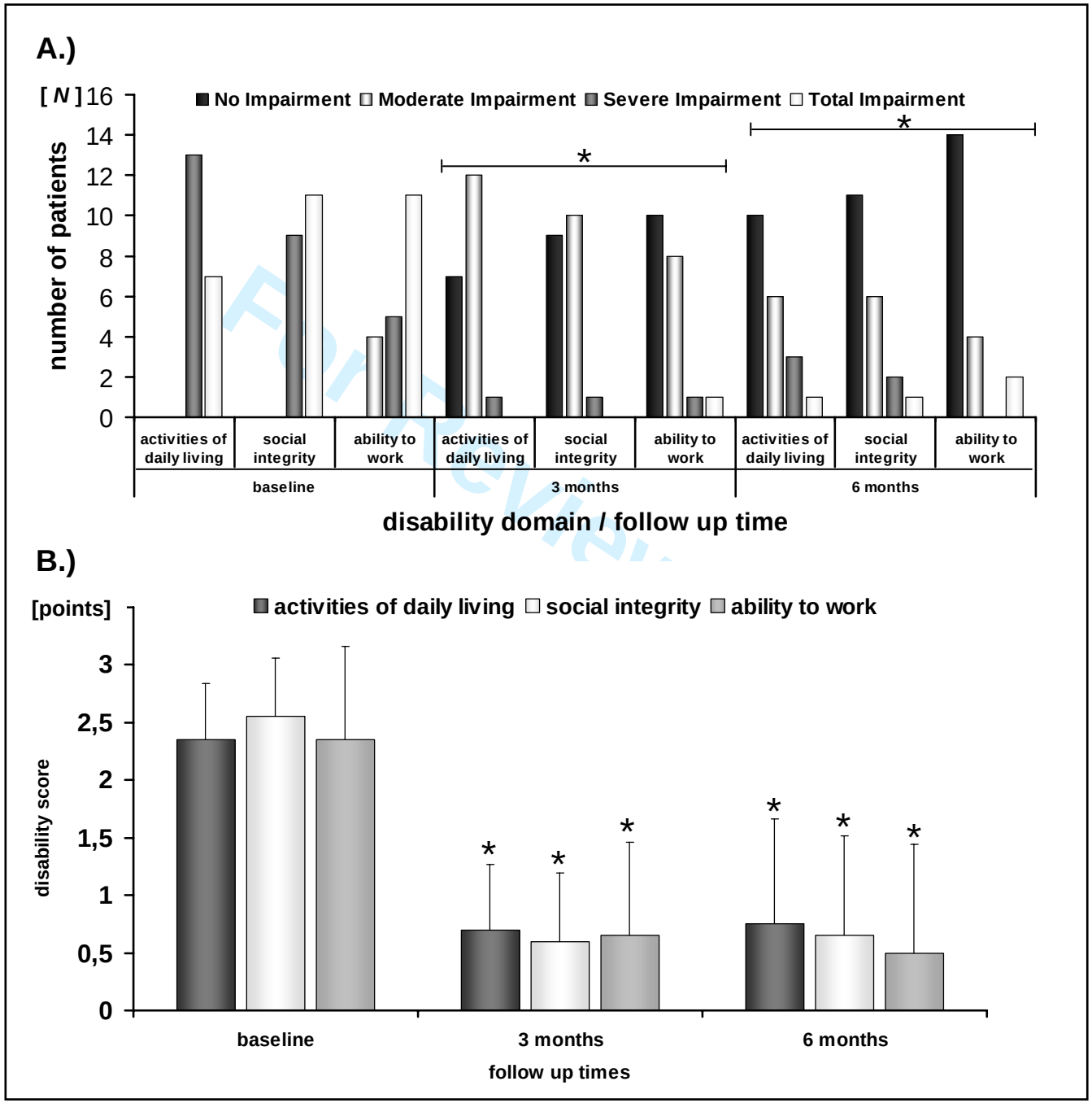
Table 5

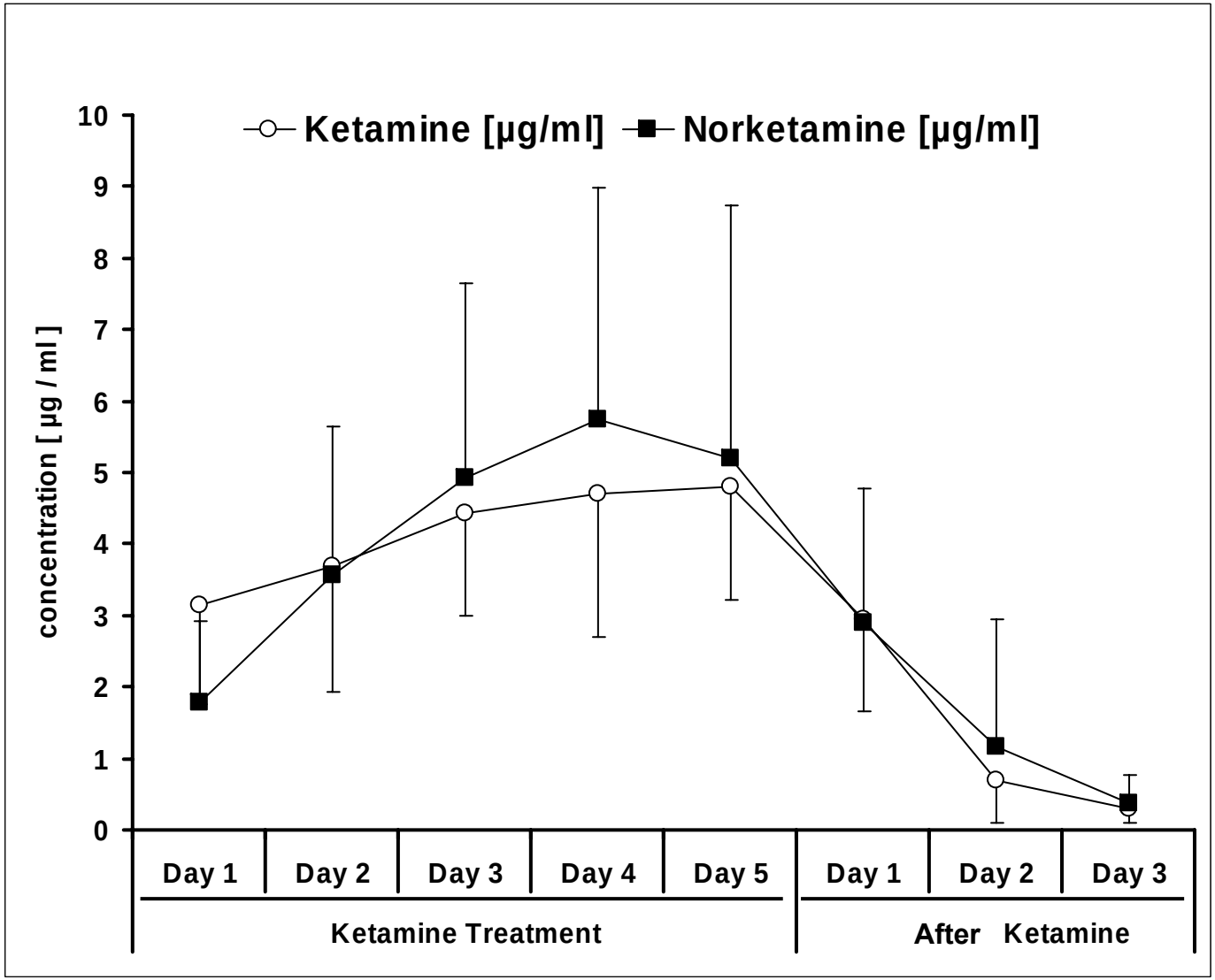
	Pain			Movement Disorders			Activities of Daily Living			Social Integration			Ability to work		
Patient #	**1 month**	**3 months**	**6 months**	**baseline**	**3 months**	**6 months**	**baseline**	**3 months**	**6 months**	**baseline**	**3 months**	**6 months**	**baseline**	**3 months**	**6 months**
1	**FR**	**FR**	**FR**	**3/3/0**	**0/0/0**	**0/0/0**	**TI**	**NI**	**NI**	**TI**	**NI**	**NI**	**TI**	**NI**	**NI**
2	**FR**	**FR**	**FR**	**4/5/0**	**0/0/0**	**0/0/0**	**SI**	**NI**	**NI**	**SI**	**NI**	**NI**	**SI**	**NI**	**NI**
3	**RP**	**FR**	**FR**	**4/4/0**	**0/0/0**	**0/0/0**	**SI**	**MI**	**NI**	**SI**	**MI**	**NI**	**SI**	**NI**	**NI**
4	**RP**	**CRPS**	**CRPS**	**4/5/2**	**2/2/1**	**2/2/1**	**SI**	**MI**	**SI**	**TI**	**MI**	**SI**	**TI**	**MI**	**TI**
5	**FR**	**FR**	**RP**	**2/3/0**	**1/0/0**	**1/1/0**	**SI**	**MI**	**SI**	**SI**	**NI**	**SI**	**TI**	**MI**	**NI**
6	**FR**	**FR**	**FR**	**5/5/3**	**0/0/0**	**0/0/0**	**TI**	**MI**	**MI**	**TI**	**MI**	**NI**	**TI**	**MI**	**NI**
7	**RP**	**CRPS**	**CRPS**	**4/5/3**	**2/3/3**	**2/3/3**	**TI**	**SI**	**TI**	**TI**	**SI**	**TI**	**TI**	**TI**	**TI**
8	**FR**	**FR**	**RP**	**2/4/2**	**0/0/1**	**0/0/1**	**SI**	**MI**	**MI**	**SI**	**MI**	**MI**	**MI**	**NI**	**NI**
9	**FR**	**FR**	**FR**	**2/3/1**	**0/0/0**	**0/0/0**	**SI**	**NI**	**NI**	**SI**	**NI**	**NI**	**SI**	**NI**	**NI**
10	**RP**	**FR**	**FR**	**2/3/2**	**0/0/0**	**0/0/0**	**TI**	**NI**	**NI**	**TI**	**NI**	**NI**	**MI**	**NI**	**NI**
11	**RP**	**CRPS**	**CRPS**	**2/3/3**	**2/2/1**	**2/2/1**	**SI**	**MI**	**SI**	**SI**	**MI**	**MI**	**MI**	**MI**	**MI**
12	**RP**	**RP**	**RP**	**5/5/3**	**2/2/2**	**2/2/2**	**TI**	**MI**	**MI**	**TI**	**MI**	**MI**	**TI**	**MI**	**MI**
13	**RP**	**FR**	**FR**	**5/6/3**	**1/0/0**	**0/0/0**	**TI**	**MI**	**NI**	**TI**	**MI**	**NI**	**TI**	**MI**	**NI**
14	**FR**	**FR**	**RP**	**4/2/2**	**1/1/0**	**0/1/0**	**SI**	**MI**	**NI**	**TI**	**NI**	**NI**	**MI**	**NI**	**NI**
15	**FR**	**RP**	**RP**	**2/2/1**	**0/0/0**	**0/0/0**	**SI**	**MI**	**MI**	**TI**	**MI**	**MI**	**SI**	**MI**	**NI**
16	**FR**	**FR**	**FR**	**3/3/2**	**0/0/0**	**0/0/0**	**SI**	**NI**	**NI**	**SI**	**NI**	**NI**	**SI**	**NI**	**NI**
17	**FR**	**FR**	**FR**	**1/1/0**	**0/0/0**	**0/0/0**	**SI**	**MI**	**NI**	**SI**	**NI**	**NI**	**TI**	**NI**	**NI**
18	**RP**	**RP**	**CRPS**	**4/4/2**	**0/1/1**	**0/0/1**	**SI**	**MI**	**MI**	**TI**	**MI**	**MI**	**TI**	**MI**	**MI**
19	**FR**	**FR**	**FR**	**4/4/3**	**0/0/0**	**0/0/0**	**TI**	**NI**	**NI**	**TI**	**NI**	**NI**	**TI**	**NI**	**NI**
20	**FR**	**RP**	**RP**	**3/4/2**	**0/0/1**	**0/0/1**	**SI**	**NI**	**MI**	**SI**	**MI**	**MI**	**TI**	**MI**	**MI**


Patient Screening
Neuropsychological Screening
Recruitment / Inclusion (N=20)
Baseline (N=20)
• Patient Characteristics / Medical history
• CRPS specific medical history
medication
therapeutic interventions
• Pain Intensities
• CRPS related disabilities:
Motor Dysfunction
Activities of daily living
Social integrity
Ability to work
Ketamine Treatment (Day 1)
End of Ketamine Treatment (Day 5)
Discharge ICU (Days 8 - 10)
• Continuous ICU-monitoring
• Screening for infectious complications
• Ketamine plasma levels
• Ketamine side effects
• Documention of complications
Peripheral Ward (Days 8 - 14)
Follow up : 1 week (Day 12) (N=20)
Hospital Discharge (Days 10 - 16)
• Pain Intensities
• Degree of Pain Relief
• Ketamine side effects
• Documentation of complications
Follow up : 1 month (N=20)
• Pain Intensities
• Degree of Pain Relief
Follow up : 3 months (N=20)
Follow up : 6 months (N=20)
• Pain Intensities
• Degree of Pain Relief
• CRPS related disabilities:
Motor Dysfunction
Activities of daily living
Social integrity
Ability to work


A.)
entire group
recurring pain
CRPS - relapses
NRS: 0-10 [points]
10
8
6
4
2
0
baseline
1 week
1 month
3 months
6 months
follow up times
B.)
[%]
entire group
recurring pain
CRPS - relapses
pain relief
100
80
60
40
20
0
1 week
1 month
3 months
6 months
follow up times


A: Upper Extremity
arms
hands
movement disability score [points]
0
1
2
3
4
5
6
*
*
*
baseline
1 month
3 months
6 months
follow up times
B: Lower Extremity
movement disability score [points]
0
0,5
1
1,5
2
2,5
3
*
*
*
Baseline
1 month
3 months
6 months
follow up times


A.)
[N]
No Impairment
Moderate Impairment
Severe Impairment
Total Impairment
number of patients
0
2
4
6
8
10
12
14
16
*
*
activities of daily living
social integrity
ability to work
activities of daily living
social integrity
ability to work
activities of daily living
social integrity
ability to work
baseline
3 months
6 months
disability domain / follow up time
B.)
[points]
activities of daily living
social integrity
ability to work
disability score
0
0,5
1
1,5
2
2,5
3
*
*
*
*
*
*
baseline
3 months
6 months
follow up times


Ketamine [µg/ml]
Norketamine [µg/ml]
concentration [µg / ml]
10
9
8
7
6
5
4
3
2
1
0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 1
Day 2
Day 3
Ketamine Treatment
After Ketamine