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Ketamine's second life : Treatment of acute and chronic pain

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Chapter 6

Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1

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6.1 Introduction

Complex Regional Pain Syndrome Type 1 (CRPS-1) is a chronic pain syndrome typically affecting an extremity after a local trauma or surgical intervention.[1] The initial phase of the syndrome is characterized by pain, edema, changes in skin temperature and color, and hyperhydrosis.[1] Although the recovery rate of CRPS is unknown, a substantial number of patients develop chronic disease with severe pain, disability, and loss of quality of life.[2] In the Netherlands the incidence of CRPS-1 is 26 per 100,000 person years, with predominance in women.[3] At present, the pathophysiology of CRPS-1 remains largely unknown. In contrast to neuropathic chronic pain syndromes there is no proof of a clinically evident nerve lesion as a causative factor in CRPS-1.[4] As in the treatment of most chronic pain syndromes, the common strategy in managing CRPS-1 is characterized by a trial and error approach. There is no evidence that commonly used treatments with opioids, antidepressants, antiepileptics, and sympathetic blockade are effective in CRPS.[5] Dimethylsulfoxide cream, N-acetylcysteine, and physiotherapy reduce symptoms of CRPS, but their effect is often limited.[5–7] Spinal cord stimulation is used as a last resort and is effective in the management of chronic pain in CRPS-1, although its efficacy tends to decline over the years.[8] Recent studies implicate the N-methyl-D-aspartic acid receptor (NMDAR) in the etiology and perseverance of chronic pain. In chronic pain states the NMDAR is activated and upregulated in the spinal cord (central sensitization).[9,10] This results in enhanced signal transmission in the pain circuitry from the spinal cord to the cortex leading to spontaneous pain, allodynia (pain perception from a non-noxious stimulus) and hyperalgesia (increased pain sensitivity). Considering the involvement of the NMDAR in chronic pain, antagonists of the NMDAR may play an important role in chronic pain treatment.[11] One such NMDAR antagonist is the intravenous anesthetic agent ketamine, which is currently the only potent NMDAR antagonist clinically available. A major issue with the use of ketamine is the development of psychomimetic side effects such as hallucinations and drug high.[11] This limits its use, especially when used at high dose. However, several open-label case studies in which ketamine treatment was used in CRPS-1 patients showed a benefit in pain reduction with an acceptable side effect profile.[12–16] Furthermore, few randomized clinical trials of long-term ketamine administration in cancer pain patients with and without neuropathic pain, demonstrated the efficacy and safety of ketamine infusion.[17,18] In this study we evaluate the short-term and long-term efficacy of prolonged ketamine administration on pain in patients with CRPS-1.

6.2 Methods

This study is registered in the Netherlands Trial Register (www.trialregister.nl) under № NTR507 (ISRCTN 30472359).

Patients

Patients referred to our outpatient pain clinic between January 2006 and January 2008, and who were diagnosed with CRPS-1, were eligible for inclusion in the study. The diagnosis of CRPS-1 was based on the International Association for the Study of Pain criteria:[19,20] (i) The presence of an initiating noxious event, or a cause of immobilization; (ii) Continuing pain, allodynia or hyperalgesia, with the pain being disproportionate to any inciting event; (iii) Evidence at some time of edema, changes in skin blood flow and/or abnormal sudomotor activity in the region of pain; (iv) Exclusion of other conditions that would otherwise account for the degree of pain and dysfunction. Exclusion criteria were: pain score of less than 5 of 10, age $<$ 18 years, pregnancy/lactation, increased intracranial pressure, a history of psychosis, a serious medical disease (*e.g.*, cardiovascular, renal or liver disease) and use of strong opioid medication. Patients were allowed to continue the following pain medications: paracetamol, non-steroidal anti-inflammatory drugs, tramadol, amitryptiline, selective serotonin reuptake-inhibitors, gabapentin and pregabalin. The pain medication was kept constant during the 12-week study period. Patients consent was obtained according to the Declaration of Helsinki and the study was approved by The Medical Ethics Committee of the Leiden University Medical Center.

Treatment

Patients were randomly allocated to receive S(+)-ketamine (Ketanest S, Pfizer BV, Capelle aan de IJssel, The Netherlands) or placebo (normal saline). A physician otherwise not involved in the study performed randomization (using a computer-generated list) and prepared the syringes. Patients were admitted to a short stay ward for 5 days, and they received two iv lines on the morning of admission (day 1), one for drug infusion, and the other for blood sampling. The drug infusion rate started at 1.2 μg/kg^{-1}/min^{-1} (or 5 mg/h for a 70-kg patient) at 8 AM on day 1 and was titrated at regular intervals (max. thrice daily) to a maximum of 7.2 μg/kg^{-1}/min^{-1} (or 30 mg/h for a 70-kg patient). The infusion rate was increased when pain relief was insufficient (based on reported visual analogue pain scores reported at 2 h (day)8 h (night) intervals) and side effects were acceptable to the patients. If side effects were unacceptable but pain relief insufficient, the infusion rate was decreased one step for one interval and subsequently increased again. In case of full pain relief, the infusion rate was not increased further and was kept constant until the end of the treatment period. The treatment ended on day 5 around noon. Blood sampling was performed at regular intervals during drug infusion and was continued up to 10 h after the infusion had ended. After unblinding of the study, patients who had received placebo were given the opportunity to receive an additional ketamine treatment in an open fashion.

Measurements

Measurements were performed in the week prior to the treatment week (baseline), during treatment (week 1) and in the 11-week follow-up period. The primary outcome

of the study was the course of spontaneous pain reported by the patients during the 12-week study period. Pain scores were assessed by a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (unbearable pain) at baseline and weekly until week 12. Secondary outcomes were the course of parameters that were measured at baseline and weeks 1, 3, 6 and 12: (i) ability to use the affected limb in normal day-to-day activity assessed using the Radboud Skills Questionnaire (RASQ) and the Walking Ability Questionnaire (WAQ) for upper and lower limbs, respectively;[21,22] (ii) active range of motion (AROM) assessed by goniometric measurements;[23,24] (iii) threshold for touch assessed using SemmesWeinstein monofilaments on the affected and contralateral limbs;[25] (iv) skin temperature of the affected and contralateral limbs measured by infrared thermometry;[23,24] (v) volumetric measurements of the affected and contralateral limbs using the water displacement method.[23,24] During the treatment week liver functions (once daily) and blood pressure (thrice daily) were measured and the occurrence of nausea/vomiting and psychomimetic side effects (drug high and hallucinations) was continuously monitored.

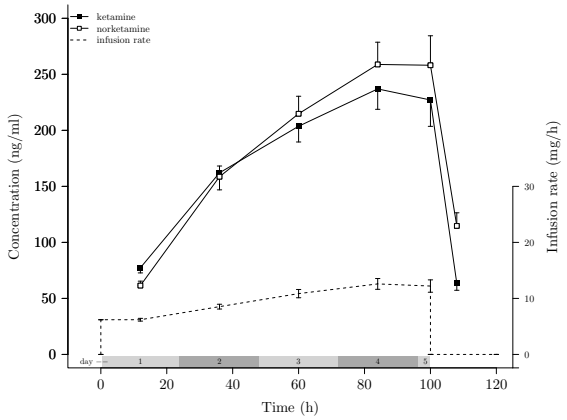
Sample size and data analysis

This study was powered to detect a two-point reduction in NRS pain for the ketamine group versus placebo group. Based on a power of 0.80, α of 0.05 (two-sided) and a standard deviation of 2.5, we calculated that 25 patients were needed per group. Assuming that some patients would be lost in follow-up, we planned to enroll 30 patients per group. Statistical analysis included all patients, according to the intention-to-treat principle. A linear mixed model with an autoregressive correlation structure was used to determine the effect of ketamine versus placebo during the 12-week study period on the course of spontaneous pain (primary end-point) and other (secondary) end-points. To determine the effect of treatment on spontaneous pain at the end of the study a univariate linear regression was used to evaluate which baseline characteristics influenced pain. Next, in a multivariable linear regression model, treatment, all variables with a P-value < 0.10 in the univariate analysis, and variables determined clinically relevant (disease duration, pain at baseline, sex and age) were included to determine the effect of treatment on pain at the end of the study period, while controlling for other factors influencing pain perception. Since it is conceivable that some covariates may modulate the effect of others, interaction terms of clinically relevant combinations were tested for significance. Statistical analyses were performed using SPSS 16.0 (Chicago, IL). P-values < 0.05 were considered significant. Data are presented as mean standard error of the mean (SEM) unless otherwise stated.

6.3 Results

Patients

Sixty patients underwent randomization (see figure 6.1 for patients flowchart and table 6.1 for patients characteristics). The eleven patients who refused to participate did not



(a)

Figure 6.1: Mean infusion rate and plasma concentrations of ketamine

Mean infusion rate and plasma concentrations of ketamine and its active metabolite norketamine during and 10 h after the ketamine infusion. Ketamine and norketamine concentrations rapidly declined upon the termination of ketamine infusion. Values are means ± SEM.

differ in characteristics from the patients who underwent randomization. The majority of patients were female (80%) and the median (range) disease duration was 7.4 (0.1 – 31.9) years. Treatment groups differed in depression and anxiety scores, and in health status measurements (HADS and SF-36, table 6.1). However, these differences were either well below the cut-off point for psychopathology (HADS; cut-off = 8) or small (SF-36). Furthermore, no effect of the difference in these baseline parameters was observed on the outcome in the univariate regression analysis. The medical history did not reveal a significant difference in prevalence of psychiatric diseases (CIRS, table 6.1) A few patients were lost for determination of secondary end-points but not for primary end-points (figure 6.1).

Table 6.1: patients characteristics

	all patients	**ketamine**	**placebo**	**p-value**
Number (n)	60	30	30	
Sex				.33*
Male	12	8	4	
Female	48	22	26	
Age (yr)	45.6 ± 12.4	43.7 ± 11.5	47.5 ± 13.1	.23
Weight (kg)	79.1 ± 18.8	78.9 ± 17.8	79.3 ± 20.1	.94
Height (cm)	171.9 ± 9.9	173.6 ± 9.9	170.1 ± 9.7	.17
BMI (kg m-2)	26.7 ± 5.8	26.1 ± 5.4	27.3 ± 6.3	.43
Disease duration (yr)	7.78 ± 6.8	9.43 ± 8.0	6.12 ± 5.1	.06
Number of extremities affected				.29
One	36	15	21	
Two	16	11	5	
Three	3	1	2	
Four	5	3	2	
First affected				.61
Lower extremity	22	11	11	
Upper extremity	23	10	13	
Both extremities	15	9	6	
Pain at baseline McGill [26]	7.0 ± 1.3	7.2 ± 1.2	6.9 ± 1.4	.32
PRI	27.0 ± 11.7	28.6 ± 10.4	25.1 ± 12.9	.30
NWC	13.1 ± 4.5	13.1 ± 4.0	13.0 ± 5.1	.93
RASQ (upper extremity) [21,22]	3.3 ± 0.9	3.4 ± 0.7	3.3 ± 1.2	.95

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Table 6.1 – Continued

	all patients	ketamine	placebo	P-value
Walking Ability Questionnaire[21,22]				
Walking inside the house	5.9 ± 2.7	6.1 ± 2.5	5.6 ± 3.0	.57
Walking outside	6.8 ± 2.6	7.1 ± 2.6	6.5 ± 2.7	.58
Standing up	7.7 ± 3.0	7.1 ± 3.3	7.2 ± 2.7	.91
TSK[27]	38.8 ± 10.9	38.0 ± 6.8	39.6 ± 14.2	.63
Euroqol Health Valuation (VAS)[28]	54.1 ± 19.9	55.0 ± 18.8	53.1 ± 21.4	.78
HADS[29]				
Depression	3.8 ± 2.7	4.7 ± 3.1	2.8 ± 1.8	.02
Anxiety	5.3 ± 2.9	6.1 ± 3.1	4.4 ± 2.4	.04
PCI[30]	73.0 ±11.7	74.1 ± 9.8	71.7 ± 13.5	.50
Short Form-36[31]				
SF-36 PH	31.4 ± 19.2	30.0 ± 19.2	33.0 ± 19.6	.60
SF-36 MHS	58.6 ± 19.0	51.8 ± 20.8	65.9 ± 13.7	.009
CIRS co-morbidity[32]				
Number affected organ systems	3.8 ± 3.0	4.1 ± 3.6	3.5 ± 2.3	.47
Severity Index	1.2 ± 0.5	1.2 ± 0.5	1.21 ± 0.5	.90
Pain co medication				
paracetamol	15	6	9	.37
NSAIDs	14	9	5	.23
Benzodiazepines	19	10	9	.78
Tramadol hydrochloride	15	6	9	.37
TCA	10	5	5	1.00
SSRI's	6	3	3	1.00
Gabapentin/pregabalin	9	7	2	.15

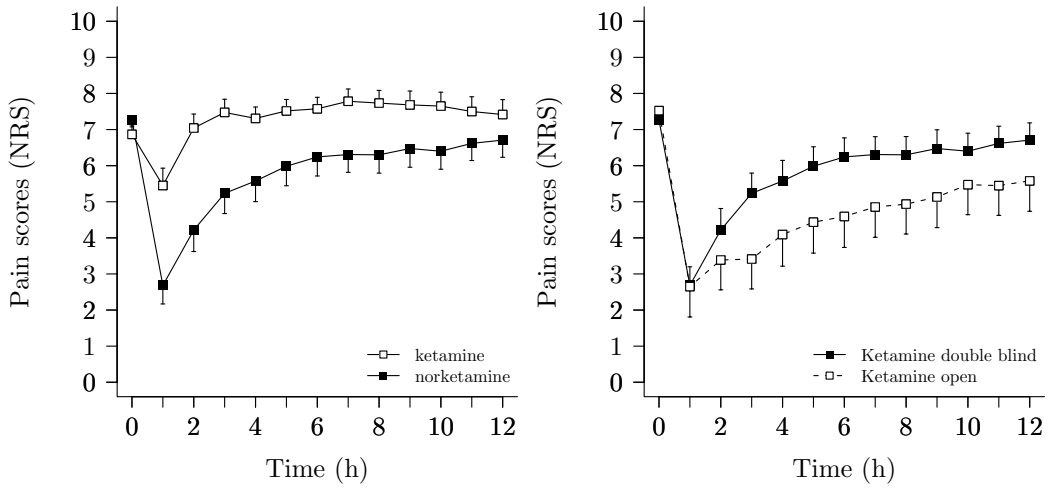
BSL, baseline; BMI, body mass index; PRI, McGill pain rating index; NWC, McGill total number of words chosen; RASQ, Radboud Skills Questionnaire; TSK, Tampa Scale of Kinesiophobia; HADS, Hospital Anxiety and Depression Scale; PCI, Pain Coping Inventory; SF-36 PH, short-form 36 physical health sumscore; SF-36 MHS, short-form 36 mental health status sumscore; CIRS, Cumulative Illness Rating Scale (co-morbidity evaluation); NSAIDs, non-steroidal anti-inflammatory drugs; TCAs, tricyclic antidepressants; SSRI, selective serotonin reuptake-inhibitor. * Group differences are tested with a Students t-test or χ^2-test; values are mean ± SD. Significant differences are printed in bold.

Treatment procedure

Drug infusion was carried out as planned in 58/60 patients. Due to a severe feeling of high, drug infusion was terminated in two patients on day 3 and day 4, respectively. These patients were monitored throughout the complete follow-up period and were included in the data analysis. The mean ketamine infusion rate was 22.2 ± 2.0 mg/h (normalized to a 70-kg patient) at the end of the treatment phase (figure 6.2). A steady state in the plasma concentration for ketamine and its metabolite norketamine was reached at the end of the treatment period after which the concentrations showed a brisk decline.

Primary and secondary outcomes

Mean (SD) baseline pain scores were 7.20 (1.16) for ketamine and 6.87 (1.43) for placebo (P = 0.32). The lowest NRS scores were observed at the end of week 1 (ketamine 2.68 ± 0.51 and placebo 5.45 ± 0.48). Ketamine modulated the course of pain during the 12-week study period more favorably than placebo (P < 0.001, figure 6.3a). Significant differences in pain reduction between ketamine and placebo were maintained till week 11; at week 12, ketamines treatment effect lost significance (P = 0.07). Compared to placebo treatment, none of the secondary outcome measures improved significantly on ketamine treatment (table 6.2). Univariate analysis showed that baseline pain (P = 0.004) and McGill pain rating index (P = 0.042) predicted pain at week 12. Multivariate analysis revealed that the McGill pain rating index was the only significant determinant (B = 0.07, 95% CI: 0.01 –: 0.13, P = 0.027) of NRS pain at week 12. Particularly, the ketamine effect was independent of disease duration, which ranged from 0.1 to 31.9 years.



(a) (n = 30 in each group)

(b) Twenty patients initially treated with placebo took the opportunity to receive ketamine in an open fashion after unblinding of the data.

Figure 6.2: Pain scores (NRS)

(a)S(+)-ketamine treatment had a significantly more favorable effect on pain scores than placebo treatment with a main effect of $P < 0.001$. (b) These patients had a similar reduction in NRS pain in week 1 as observed after blinded ketamine treatment. However, the subsequent course of NRS pain towards baseline was slower compared to the blinded study with a 12 NRS difference. For comparative reasons the blinded ketamine data are included (n = 30). Values are means ± SEM.

Side effects

During drug infusion most patients experienced side effects, and, with the exception of headache, the incidence was greater in subjects receiving ketamine: nausea 63% versus 17% in placebo group ($P < 0.001$, χ^2-test), vomiting 47% versus 10% in placebo group ($P = 0.004$), psychomimetic effects 93% versus 17% in placebo group ($P < 0.001$) and headache 37% versus 33% in placebo group ($P = 0.78$). Liver functions and blood pressure remained unaffected by ketamine administration.

Blinding

At the end of infusion, 28 patients receiving ketamine correctly indicated treatment assignment against 18 patients receiving placebo ($\kappa = 0.53$, 95% CI: 0.33 – 0.74, $P < 0.001$). The investigators assumptions were correct in 26 patients receiving ketamine and 27 patients receiving placebo ($\kappa = 0.77$, 95% CI: 0.60 – 0.93, $P < 0.001$).

Open treatment

Despite an increased analgesic effect during the 12-week treatment course (Fig. 3b), open ketamine treatment was not associated with an increased incidence of side effects compared to blinded treatment: nausea 71%, vomiting 48%, psychomimetic effects 76% and headache 43%.

6.4 Discussion

Ketamine has multiple sites of action but its effect on the NMDAR is generally considered to be the basis for its modulatory effect on pain responses.[9,10] The current observation of a beneficiary effect of ketamine on pain suggests an important role for the sensitized NMDAR in the maintenance of pain in CRPS-1. Our findings show that 4 days of ketamine infusion may result in a clinically significant pain reduction over a prolonged period of 10 weeks. Interestingly, the effect of ketamine on acute experimental pain and EEG slowing is directly linked to its plasma concentration and disappears rapidly upon termination of infusion.[33,34] The differential findings of ketamine on spontaneous pain in CRPS-1 may suggest that these effects are obtained by long-term desensitization of the NMDAR in the central nervous system (for example at the spinal cord level). Further proof for this could be found in a reduction of hyperalgesia and allodynia. The current study, however, provided insufficient information on these measures of NMDAR sensitization. Brain imaging studies indicate various abnormalities encompassing regions involved in emotional, autonomic, sensoromotor and pain processing.[35–40] Reorganization of the somatosensory cortex contralateral to the CRPS affected side appeared to be linked to the severity of pain.[37,39] Additionally, neurophysiological studies revealed motor cortex disinhibition.[36] In patients who recovered from CRPS the reduction of pain was associated with regaining of the cortical map size and restoration of impaired tactile discrimination.[38,40] Together these findings suggest that the development and resolution of CRPS are associated with cortical changes, but

the question remains whether these changes are the primary or secondary phenomena and if they are related to functional improvement. In our study, the functional status of patients did not improve despite significant pain relief, even in the initial weeks following treatment. Although relief of pain with an NMDAR antagonist is likely to be associated with changes in inhibitory/excitatory state of the nervous system, this may have been insufficient in duration and intensity in our study to allow for amelioration of the patients physical status. More prolonged treatment possibly in combination with physical therapy or rehabilitation strategies may be required to obtain functional benefit. Zarate *et al.*[41] described a long-lasting antidepressant effect from ketamine. It may therefore be argued that, at least part, of the pain relief observed in our patients was due to an improvement of depression- and/or anxiety-related symptoms. However, depression and anxiety scores in the majority of patients indicated the absence of clinically relevant symptoms of depression and/or anxiety (HADS, table 6.1). And although the statistical analysis did not show an effect of initial depression and anxiety scores or mental health status (SF-36 MHS) on pain relief, we cannot exclude some effect of ketamine on pain perception occurring via an improvement of the patients mental health. The observation that pain relief dissipated slowly (figure 6.3) may be related to the relatively short ketamine infusion. Some case studies allowing a longer duration of infusion show a more prolonged effect of ketamine.[12] We restricted the duration of the ketamine infusion to 4 days (100 h) in light of the concern from animal data that high-dose and long-term ketamine infusion may be associated with neurotoxicity.[12,42] Further follow-up studies are needed to explore this important issue. The available data in humans suggest that high infusion rates (50 mg/h) for durations of up to 7 days are without long-term neurotoxic effects.[43,44] We used the S(+) enantiomer of ketamine in our study, which has the advantage of a better cardiovascular profile along with a possible neuroprotective potential over racemic ketamine.[45] The use of ketamine is often avoided by pain physicians due to the fear of occurrence of psychomimetic side effects. We observed drug high in about 90% of patients receiving ketamine; hallucinations did occur in a minority of patients. Patients and investigators guesses of the administered treatment were correct in 74% and 88%, respectively. This is most likely explained by ketamines psychomimetic side effects and suggests that in future trials an active placebo and/or the addition of an active placebo or addition of a benzodiazepine to the ketamine treatment group is warranted to preclude deblinding of treatment allocation. However, our experience is such that complete blinding of ketamine treatment is difficult due to the specific nature and coloring of the psychomimetic effects. Except for two patients in whom treatment was terminated prematurely due to psychomimetic side effects, most patients considered the intensity of the side effects to be mild to moderate and acceptable. The individualized stepwise titration of ketamine according to the pain status and side effects allowed for optimizing the level of pain reduction while the occurrence of side effects was kept at an acceptable level. Of interest is the observation that in the open treatment paradigm the incidence of side effects did not increase despite a better analgesic course of the treatment. In spite of significant pain relief, ketamine did not improve the functional status of our patients. More prolonged or repetitive ketamine treatment may be required to induce longer periods of pain relief that allows patients to increase their activity level, thus enhancing opportunities for

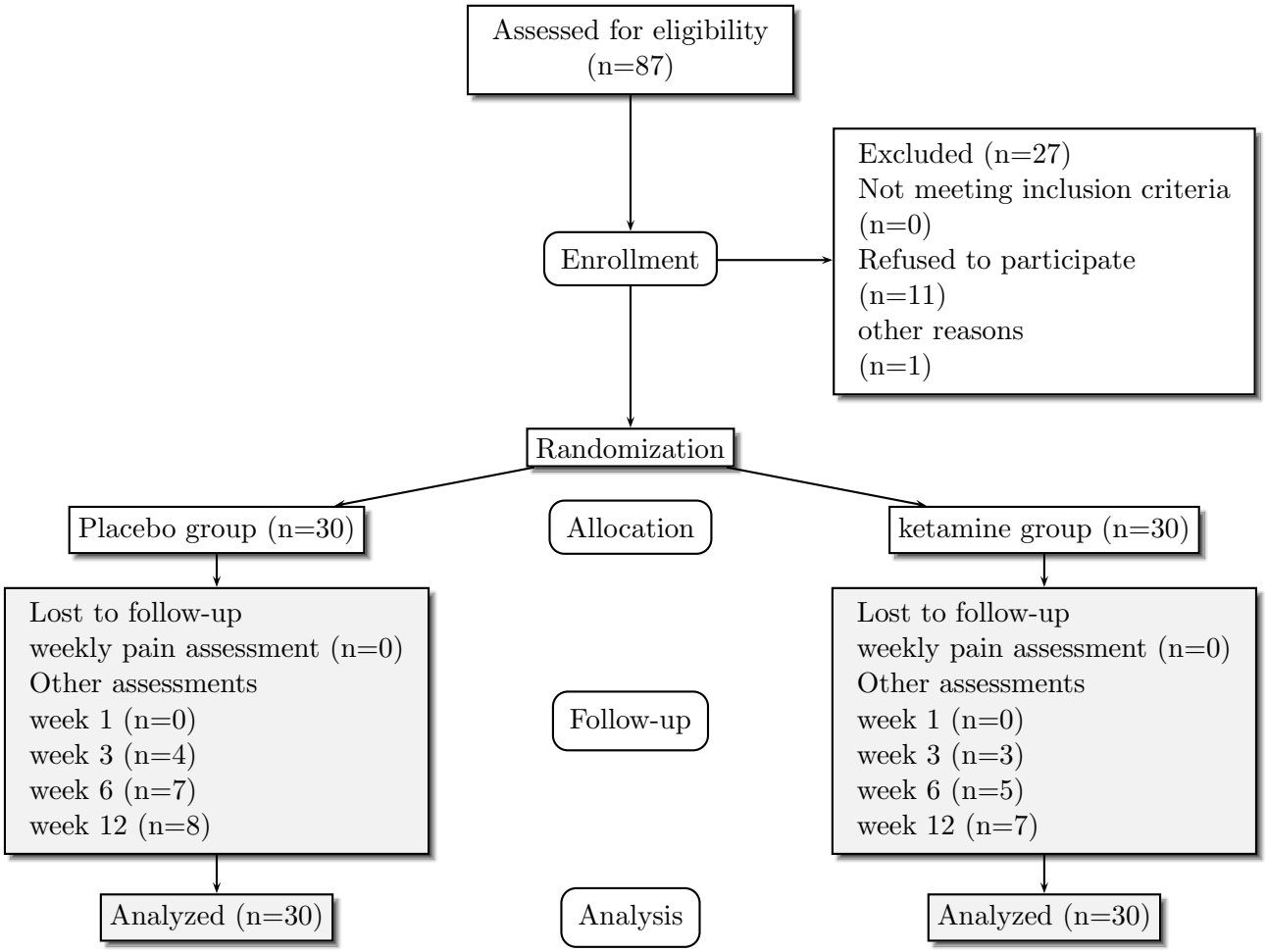


Figure 6.3: Flow chart

improvement in functional status. It is of interest to remark that the observed pain relief from ketamine was not dependent on the dose given. Since most patients were almost pain free during ketamine infusion, it can be suggested that the cessation of nociceptive input (irrespective of mechanisms) could account for the long-term pain relief. Fifty-four of our 60 patients had chronic CRPS-1 (disease duration longer than 6 months) and disease duration did not predict pain reduction by ketamine. This indicated that the duration of NMDAR sensitization apparently plays no major role in ketamines efficacy in reducing spontaneous pain in CRPS-1. This is encouraging for patients with refractory chronic CRPS-1. We conclude that CRPS-1 patients with severe pain treated with 4 days of continuous infusion of low-dose ketamine using an individualized stepwise tailoring of dosage have a clinically relevant reduction in pain lasting for 11 weeks. Although the incidence of side effects in the treatment week was high, they were relatively mild and well accepted by the patients and disappeared upon the termination of infusion. In contrast to pain, there was no improvement in functional status.

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