https://orcid.org/0000-0003-3238-390X

ABSTRACT

Cluster Headache is a debilitating primary disorder in the headache spectrum which is oftentimes impervious to standardized treatment modalities. New therapeutic options are urgently required. This type of headache has a low incidence of 0.1% and a male predominance. The disease has no direct impact on mortality but can lead to significant impairment of quality of life due to its clustered nature and the intensity of pain during the attacks. The pain appears in 50% of cases at night at the same time (circadian rhythm) and is described as devastating. Suicide attempts are not rare (64.2% active suicide attempts and 35.8% passive attempts/suicidal ideation in one study 1). The pain is stabbing and unilateral and in 90% of patients located in the general region of the eye, oftentimes radiating to the jaw, ear, back of the head, and neck accompanied by ipsilateral eye tearing and nasal congestion. The duration is 20 minutes to 3 hours. Triggers are various and non-specific, except for alcohol which triggers attacks in most patients. Cluster Headache belongs to the spectrum of **Trigeminal autonomic cephalalgias** (TAC) along with *Chronic paroxysmal hemicrania* (CPH), *Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing* (SUNCT) and *Short-lasting neuralgiform headache with cranial autonomic symptoms* (SUNA).

The pathophysiology is as yet unclear. The hypothalamus, brain stem and genetic factors such as G1246-polymorphism are known to play a role. Cluster headache manifests itself as Episodic Cluster (EC) and Chronic Cluster (CC).

1 Lee M J, Cho S-J, Wook Park J et al., Increased suicidality in patients with cluster headaches, Cephalalgia, April 24, 201

https://orcid.org/0000-0003-3238-390X

We have evaluated 47 patients (43 male, 13 female, aged 21 to 72 years) with a frequency of 1 to 30 daily attacks in a controlled monitored setting over a period of 3 years. The patients received intravenous ketamine, an NMDA antagonist, once daily over 40 minutes at a dosage of 0.5 to 0.75 mg/kg, administered in 3 to 11 sessions in intervals of 1 to 4 days for each infusion. All patients tolerated the infusions well.

In 37.8% of patients a complete cessation of attacks was observed, lasting 3 months to 3 years ("super-responders"). In patients with less favorable response (62.2%) oral methadone (also in part an NMDA-antagonist) was added with gradual dosage increases up to a maximum of 40mg daily and for a maximum duration of 4 weeks, with subsequent tapering to zero. Of this group, 32.0% responded favorably (no attacks for at least 3 months). Hence, the favorable response was 70.3%, either with ketamine alone or in combination with a short-duration regimen of oral methadone. 18.9% were "partial responders", i.e. the attacks were milder and less frequent but did not rise to the level of the above mentioned "favorable response". 4.3% were "non-responders" who, in most cases, did not tolerate ketamine and/or methadone and 6.4% were "drop-outs". 84% of all patients fell into the category of episodic cluster (EC).

All patients had previously received other treatments such as pericranial botox injections and occipital nerve blocks. The pre-existing baseline therapy – mostly verapamil and topiramat – was upheld during the ketamine infusions. Our

results suggest that intravenous ketamine with or without methadone plays a role in the prolonged interruption of cluster attacks, especially in patients with EC and if the above described regimen is initiated early in episodic cluster cycle.
Neuro-plastic phenomena and neuro-remodulation can be postulated as possible mechanisms of action for the efficacy of ketamine and methadone.
Since both ketamine and methadone are an “off-label” treatment for cluster headaches our results should be considered as a suggestion for further research and not as a therapy recommendation.

INTRODUCTION

Cluster headache – a clinical challenge.
This disease is often correctly diagnosed only 2-5 years after its initial manifestation 2,3,4. The pathophysiology is unknown except for a genetic component being proposed as playing a role (G1246 polymorphism). Prophylactic treatment is mostly ineffective.
In its chronic form the frequency of attacks can reach 10 times a day. The pain intensity is high. Suicidality is significant. Along with the patients their families suffer greatly as does their quality of life.

5 Voticovschi_Iosob C, Allena M, De Cillis I, Nappi G, Sjaastad O, Antonaci F, Diagnostic and Therapeutic Errors in Cluster Headache: a Hospital-based Study. J Headache and Pain 2014; 15(1): 56
6 Bahra A, Goadsby PJ, Headache Group, Institute of Neurology, Queen’s Square, London, UK. Diagnostic Delays and Mismanagement in Cluster Headache.
7 May Kung Y, Cluster Headache: Hastening Diagnosis and Treatment

Consumption of triptans can be exorbitant. Work and productivity are compromised, and many times patients are not taken seriously or unfairly treated in the workplace, in part because they are “normal” between attacks. Our goal was to stop attacks of either form of cluster headache (EC or CC) for as long as possible. Based on clinical observation and experience we proposed that a complete cessation of symptoms for a period of 3 months should be considered as successful outcome. We chose ketamine with or without methadone for treatment. Ketamine, first synthesized in 1964, is a derivative of phencyclidine. It is an anesthetic and an analgesic but has recently also gained attention in the treatment of depression resistant to conventional treatment. Furthermore, it has shown good results in the treatment of neuropathic pain. Ketamine causes a synaptic down-regulation in the prefrontal cortex and in the hippocampus. Its efficacy is thought to be due to an NMDA (N-Methyl-D-Aspartate)-antagonism followed by a release of glutamate.
We decided to divide our patients into four groups: “super-responders”, “full responders”, “partial responders”, and “non-responders”. In “non-responders” and “partial responders” we added a short-duration regimen of oral methadone, which itself - apart from being an opioid analgesic - also has an effect on NMDA-receptors.

https://orcid.org/0000-0003-3238-390X

METHODOLOGY

We examined 47 patients in our pain center, from 2016 to 2019. 34 were male, 13 female which corresponds to the statistical gender distribution of 2.5:1, with an age range of 21 to 72 (average age 43) and an attack range of 1-30 per diem. 66% were smokers (12.8% of which also consumed cannabis). 72.4% were gainfully employed. EC to CC ratio was 3:1 and 10.7% had additional trigemino-autonomic symptoms. One patient (2.1%) had hypnic headaches (nocturnal headaches responsive to caffeine). Patients maintained their baseline therapy, usually consisting of verapamil and topiramate which, however, did not prevent the cluster attacks. All patients had been treated with pericranial botox injections, occipital nerve blocks and a 15-day (including tapering off) regimen of high-dose oral steroids (including tapering off) with unsatisfactory results within the preceding 30 days. Exclusion criteria were seizure disorder, pregnancy, cardiac disease, uncontrolled hypertension, cognitive impairment, psychosis and other mental conditions with a dissociative component, drug abuse except cannabis (patients were encouraged to stop cannabis consumption during ketamine treatment). NPO status for 4 hours prior to ketamine was stipulated as well as refraining from driving after the procedure and availability of an accompanying person.
The patients received racemic ketamine 0.5mg/kg, plus magnesium sulfate 1g, propofol 50mg, dexamethasone 5mg, ondansetron 4mg, the latter two as antiemetic prophylaxis

and all medications by intravenous route over 40-60 minutes via an infusion pump in short intervals (usually every 2-3 days) for a total of 3-11 sessions.

RESULTS

All patients tolerated the infusions well, except for one case of nausea, treated by additional ondansetron and three episodes of hypertension, treated with i.v. Urapidil. Mild symptoms of mental dissociation where treated with verbal reassurance. In a typical pattern, patients would experience insomnia after the first infusion but subsequently have improved sleep over their baselines. There were no cases of cystitis or hepatotoxicity as have occasionally been described in ultra-high dosing of ketamine (usually related to illicit use).
In “super-responders” (38.3%) cluster attacks stopped within 2 weeks and did not return for a duration of 3 months to to 3 years. In the super-responder group 93.6% were EC-patients and 6.4% CC-patients. Age did not influence the outcome. 16 EC-patients had 1-3 and one had 12 attacks daily prior to ketamine. In 61.7% the response was less satisfactory than in the super-responder group whereupon oral methadone was added as a short-duration regimen of maximally 4 weeks with appropriate tapering off (maximum daily dose 40mg). 32% of patients taking methadone were labeled as “full responders”. These patients had approximately the same outcome as the super responders but needed the additional short methadone regimen. The remainder of all patients

(29.7%) were partial responders (19.2% or 9 of 47 patients; various degrees of allevation of intensity but no cessation of attacks) or non-responders and “drop-outs” (in total 5 of 47 patients). Methadone is used in pain management as an analgesic and should only be administered by experienced practitioners. Intolerance to methadone was an important factor in “partial” and “non-responders”. Main complaints were sexual dysfunction and fatigue combined with the patients’ unwillingness to wait for the onset of tolerance to the opioid after which these untoward side effects tend to wane. In these patients it was not possible to “titrate up” the methadone to the level required for cluster symptom relief. No patient developed QT-interval prolongation. All in all, 85% of full responders (ketamine plus methadone) belonged to the EC category. The EC-patients were all within the first week of their cluster cycle (a cluster cycle has a typical duration of 2 to 4 months). Treating the patients in the early phase of the cluster cycle tended to lead to better results.

DISCUSSION

Ketamine, which is a derivative of phenylpiperidine is known to have a specific neurobiological effect: it changes the neuronal structure via a phenomenon called neuroplasticity due to its NMDA-receptor antagonism: neuro-regeneration, re-modulation and interactions with biogenic amines can be subsumed under this concept. As a consequence,

an uncoupling of the thalamo-cortical system from the limbic system has been observed. In addition, ketamine blocks the re-uptake of catecholamines and serotonin.
Methadone is a fully synthetic opioid with profound analgesic effect via mu- and delta-receptor agonism. In addition, methadone has been shown to demonstrate a significant NMDA-receptor antagonism. NMDA-receptors are ionotropic
glutamate-receptors located on the cell membrane that change the membrane potential.
Methadone functions as a channel blocker, as does ketamine and other similar substances such as phencyclidine and MK-801 (dizocilpine). Methadone has a half-life of 90 hours and may lead to QT-interval prolongation. Therefore, it is imperative that only experienced pain management practitioners administer this drug.
An additive effect of ketamine and methadone in the treatment of cluster attacks but also a certain prophylactic effect may be postulated. However, our results should merely point toward the necessity for further research and should not serve as an ipso facto therapy recommendation.

https://orcid.org/0000-0003-3238-390X

CONCLUSIONS

The results of this study show the positive impact on patients' quality of life, especially when the attacks are completely stopped. A placebo-controlled study, as hard as it
seems to achieve, would be very desirable, as ketamine is still "off-label" for cluster headache treatment. We observed that a series of ketamine administrations in close intervals led to improved outcomes.The development of an oral NMDA-receptor antagonist with properties similar to ketamine, phencyclidine and dizocilpine that might treat and prevent cluster headaches would be highly desirable. Another field of interest is ketamine treatment for obsessive compulsive disorder (OCD) with or without deep transcranial magnetic stimulation (deep TMS) in severe cases or such cases that are resistant to other therapies.
By now, the efficacy of ketamine in the treatment of depression and many other chronic pain conditions is well known. [8,9]
In summary, NMDA-receptor antagonists such as ketamine and methadone may play an important role in the treatment of cluster headache. Further studies and research will hopefully remove the "off-label" label from this very useful medication named ketamine.

8. Maurizio Fava, Marlene P. Freeman, Martina Flynn, Heidi Judge, Bettina B. Hoeppner, Cristina Cusin, Dawn F. Ionescu, Sanjay J. Mathew, Lee C. Chang, Dan V. Iosifescu, James Murrough, Charles Debattista, Alan F. Schatzberg, Madhukar H. Trivedi, Manish K Jha, Gerard Sanacora, Samuel T. Wilkinson, George I. Papakostas. **Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD)**. *Molecular Psychiatry*, 2018; DOI:
9. Cohen S, Bhatia A, Hooten W, Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiology.

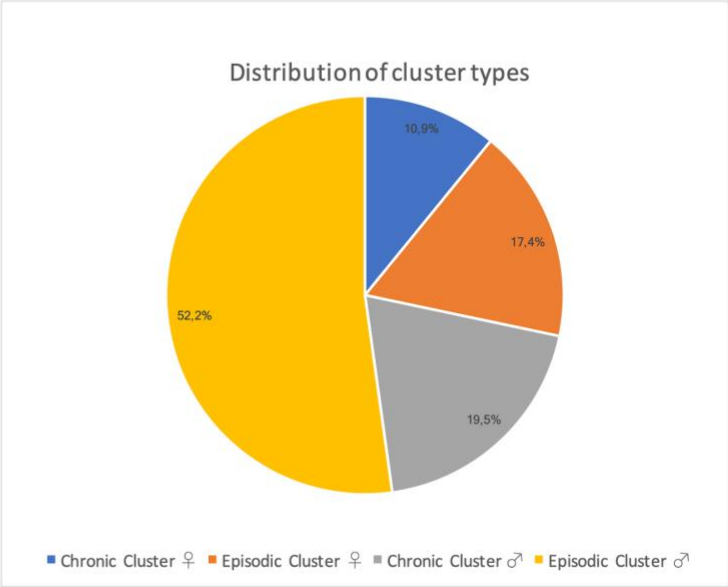
https://orcid.org/0000-0003-3238-390X

TOTALS

Schmerzzentrum
Dr. med. Granata

- 47 patients
  - ♀: 13 ➔ 27,7%
  - ♂: 34 ➔ 72,3% (!)

- Chronic cluster: 30,4% (♂ 3 : ♀ 2)
- Episodic cluster: 69,6% (♂ 3 : ♀ 1)
- CC ♀: 10,9%
- CC ♂: 19,5%
- EC ♀: 17,4%
- EC ♂: 52,2%



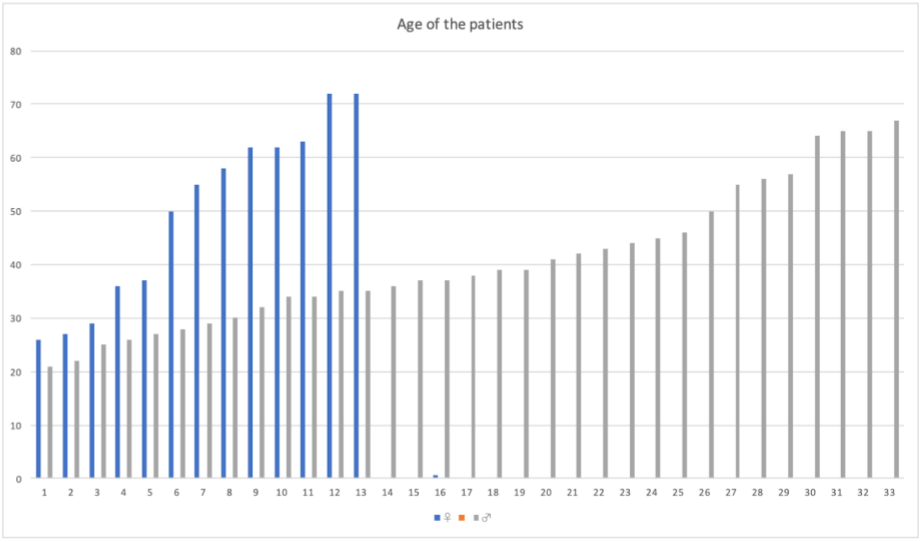
TOTALS

Schmerzzentrum
Dr. med. Granata

- Ø age: 43,3 years
  - ♀: 49,9 years
  - ♂: 40,7 years

- Min/max age
  - ♀: 26 – 72 years
  - ♂: 21 – 67 years

- Spread
  - ♀: 61%: 50+ years
  - ♂: 58%: 30-50 years



https://orcid.org/0000-0003-3238-390X

WORKING STATUS

Schmerzzentrum
Dr. med. Granata

- At work: 72,4% (♂ 4,5 : ♀ 1)
  - thereof EC 3 : CC 1
- Others: retired or not working

ATTACK FREQUENCY

Schmerzzentrum
Dr. med. Granata

- Episodic: ø 2-3 attacks/day
- Chronic: ø ±6 attacks / day

https://orcid.org/0000-0003-3238-390X

SMOKERS

Schmerzzentrum
Dr. med. Granata

- Nicotine
  - 65,9% are smoking nicotine (♂ 3,5 : ♀ 1)
- Cannabis
  - 13,0% are consuming Cannabis (♂ 5 : ♀ 1)

FURTHER FINDINGS

Schmerzzentrum
Dr. med. Granata

- trigeminoautonomic disorders: 10.7% (♂ 2 : ♀ 3)
- hypnic headaches: 2.1%

- Ketamine not tolerated: 2.1%
- Methadone not tolerated: 8.5%
- noncompliant patients (with ketamin infusions close to each other): 6.4%

- also treated with Botox: 36.2%
- also treated with ONI: 38.3%
- also treated with ONI & Botox: 19.2%

https://orcid.org/0000-0003-3238-390X

SUCCESSFUL RESULTS

Schmerzzentrum
Dr. med. Granata

patients who responded in the **first 2 weeks** of infusion with a **stop of all attacks** and kept the result for **at least 3 months**

- Super responders (Ketamine only): **38.3%** (18/47)
- Full responders (Ketamine + Methadone): **32.0%** (15/47)

70.3% (33/47)

  - → thereof EC 17/20 = 85.0% (!)
  - → thereof CC 3/20 = 15.0%
  - → thereof ♀ 3/13 = 23.1%
  - → thereof ♂ 17/33 = 51.5%

- Partial responders: 19.2% (9/47)
- Non responders (Ketamine + Methadone): 4.3% (2/47)
- Patients stopped treatment: 6.4% (3/47)