Subanesthetic Ketamine Infusions for Treatment of Chronic Migraines:

A Case Report

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Introduction: Migraine is a paroxysmal disorder with a natural variance between a high and low frequency pattern in-part influenced by modifiable and non-modifiable risk factors (D’Alonzo, 2010). Increased attack frequency can lead to chronic migraines which becomes less responsive to acute and prophylactic medications. With increased interference to daily quality of life, migraines can be very disabling and challenging to treat. As-such, not many options are available for patients that have gone through various trials of different classes of medications with no relief. The participation of N-methyl-D-aspartate (NMDA) glutamate receptor has been demonstrated to be in transmission in the trigeminocervical complex which suggests a clear pre-clinical role of glutamatergic mechanisms in primary headache syndromes such as migraines (Storer, 1990). Ketamine is one of few candidates available for the treatment of refractory chronic migraines. Ketamine is a dissociative anesthetic which primarily works at the glutamate receptor NMDA as an antagonist. During placebo administration, a typical pain activation network (thalamus, insula, cingulate, and prefrontal cortex) was found, whereas decreased pain perception with ketamine was associated with a dose-dependent reduction of pain-induced cerebral activations (Sprenger, 2006). This desensitization with ketamine is responsible for the effective treatment of pain conditions and hence been tested for chronic migraines. Presented is a case of a young patient who found increasing relief of chronic symptoms with the help of subanesthetic ketamine infusions.
Case Study: 19 years old right-handed Caucasian male with onset of daily headaches approximately 8 years prior to presentation. He described them as throbbing in nature with no associated auras. Visual analogue scale (VAS) was used to score the severity of the pain. Initially, VAS score was 7 in the mornings and improved to a VAS of 2 by mid-afternoon. Within a year, severity progressed to a VAS of 9-10 in the mornings followed by longer duration and eventual improvement to a VAS of 3-4 by the evenings. The associated symptoms include light headedness, photophobia, sonophobia, nausea, weight loss, impaired appetite, trouble sleeping, impaired concentration, decreased energy levels and easy fatigability. With increasing pain severity, the symptoms would also increase leading to functional impairment. As such, the disabling nature of the headaches started to take a toll on his academia and social life. He denies deja vu, jamais vu, forced recollection, visual or auditory hallucinations, disassociation, forced thinking or distortion of time of body image, rise in epigastric sensations, autonomic manifestations. He states that the headaches always come on as if hit by a baseball bat and has lost consciousness numerous times. He has experienced more than 10 syncopal episodes in the past 2 years. He reports no improvement with a myriad of traditional prophylactic and abortive medications. He achieved minor transient relief with chiropractic therapy which helped reduce his VAS score by 1. He admits to trying botulinum toxin type A (Botox) with no change in both the severity or quantity of headaches. He has also tried acupuncture with no relief. After various failed treatments, he presented to an outpatient ketamine center. After being informed about the side effects and associated risks with the ketamine infusions, informed consent was obtained. Migraine disability assessment (MIDAS) was obtained prior to initial infusion. VAS scores were obtained prior to and after every infusion. Beck depression inventory (BDI) was
taken prior to first and last infusion in series. Protocol for this specific center included doing a 5-infusion series over a 5-day period while starting the patient at a dose of 1mg/kg and increasing the dose incrementally as tolerated until a target VAS score was achieved. He was monitored at 10-minute intervals to ensure no adverse effects or intolerance to the dissociative effects. The patient was also contacted weekly post series for VAS score follow up.


Duration of illness was 8 years at admission. The number of abortive medications tried was 5. The number of preventative medications tried was 4. He wasn’t taking any medications during admission. No previous psychiatric disorders. No concomitant chronic pain disorders. No intracranial pathology. MIDAS score prior to infusion series was 55. VAS score prior to initial infusion was 9 in the mornings and decreased to 4-5 around approximately 4pm. Beck depression inventory was 11. He was started on IV Ketamine at a dose of 1mg/kg. With increasing dose of infusions, the length was also increased from 1 hour during first infusion to approximately 3 hours for the last infusion. He experienced mild dissociative effects which were
tolerated well and no other side effects. Target VAS score of 4 was achieved with an infusion time of 14h spread over 5 days which implicated significant improvement. He reported a VAS score of 4 in the mornings which improved to 1-2 by early afternoon. He stated he could complete daily tasks without impaired function. This improvement lasted for 12 days at which point the headaches gradually started to increase in intensity and duration. He came in for a second series of 5 infusions two weeks after his initial series. His VAS score before initial infusion of the second series was 7-8 in the mornings which decreased to 3-4 by 3pm which was better than baseline but not near target range. MIDAS score was 44. He was started on IV ketamine at the last dose of the first series. Target VAS score of 4 was reached in 9h by the third infusion day and the remaining infusions were completed to try and obtain better scores with prolonged relief. After the second series of infusions, he reported a VAS score of 4 in the mornings which decreased to 1-2 by noon. This relief lasted for approximately 24 days before gradually returning to a VAS score of 6 in the mornings which decreased to 2-3 by 3pm.

**Discussion:** The patient presented in this report achieved target pain relief with a 5-infusion series. He felt mild dissociative effects and tolerated them well. Target pain relief lasted for 12 days. He underwent a second series of 5-infusions which again helped reach his target pain relief score. The second series helped maintain this relief for approximately 24 days. The pain never returned to baseline and was lower after each series. Intravenous ketamine has recently been used successfully for the treatment of refractory depression (Coyle, 2014). There is also evidence that long term treatment of chronic pain with ketamine will cause prolonged pain relief (Neisters, 2014). Ketamine produces strong analgesia in neuropathic pain states, presumably by inhibition of the NMDAR. The NMDAR is an excitatory glutamatergic receptor
present at spinal and supraspinal sites and involved in the afferent transmission of nociceptive signal (Neisters, 2014). There is now ample evidence that NMDAR antagonists that block the NMDAR, such as ketamine, can halt the excessive barrage of nociceptive input to the brain and are therefore potential alternatives to existing treatments of chronic pain syndromes (Petrenko, 2014). There is a finite amount of literature on ketamine use for chronic migraines. This case report, although defined to a single patient, brings up the question to whether multiple series of intravenous ketamine infusions can gradually decrease the severity and duration of chronic migraines for an elongated period. Prior publications have noted short term relief with a single series (Lauritsen 2016). Repeated ketamine infusions may be a viable option for sustaining relief from refractory migraines. Further research needs to be done whilst administering multiple series of infusions over an extended period of time.

References:
Lauritsen, Clinton; Mazuera, Santiago; Lipton, Richard B.; and Ashina, Sait. Intravenous ketamine for subacute treatment of refractory chronic migraine: a case series. Department of Neurology Faculty Papers, 2016. Paper 125.