View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Jefferson Digital Commons

Thomas Jefferson University
Jefferson Digital Commons

Department of Anesthesiology Faculty Papers

Department of Anesthesiology

11-1-2018

Ketamine for Refractory Headache: A Retrospective Analysis.

Eric S. Schwenk
Thomas Jefferson University, eric.schwenk@jefferson.edu

Amir C. Dayan
Thomas Jefferson University, amir.dayan@jefferson.edu

Ashwin Rangavajjula
Thomas Jefferson University, ashwin.Rangavajjula@jefferson.edu

Marc C. Torjman
Thomas Jefferson University, marc.torjman@jefferson.edu

Mauricio G. Hernandez
Thomas Jefferson University, mauricio.hernandez@jefferson.edu

See next page for additional authors

Let us know how access to this document benefits you

Follow this and additional works at: https://jdc.jefferson.edu/anfp

Part of the Anesthesiology Commons, and the Neurology Commons

Recommended Citation

Schwenk, Eric S.; Dayan, Amir C.; Rangavajjula, Ashwin; Torjman, Marc C.; Hernandez, Mauricio G.; Lauritsen, Clinton G.; Silberstein, Stephen D.; Young, William B.; and Viscusi, Eugene R., "Ketamine for Refractory Headache: A Retrospective Analysis." (2018). *Department of Anesthesiology Faculty Papers.* Paper 43.
https://jdc.jefferson.edu/anfp/43

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's Center for Teaching and Learning (CTL). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Department of Anesthesiology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

Authors
Eric S. Schwenk, Amir C. Dayan, Ashwin Rangavajjula, Marc C. Torjman, Mauricio G. Hernandez, Clinton G. Lauritsen, Stephen D. Silberstein, William B. Young, and Eugene R. Viscusi

This article is available at Jefferson Digital Commons: https://jdc.jefferson.edu/anfp/43

Ketamine for Refractory Headache: a Retrospective Analysis

Corresponding Author:
Eric S. Schwenk, MD
Department of Anesthesiology; Sidney Kimmel Medical College at Thomas Jefferson University
Suite 8130, Gibbon Building
111 South 11th Street
Philadelphia, PA 19107
Phone: 215-955-6161
Fax: 215-955-0677
Email: Eric.Schwenk@jefferson.edu

Co-Authors:
Amir C. Dayan, MD
Department of Anesthesiology; Sidney Kimmel Medical College at Thomas Jefferson University

Ashwin Rangavajjula, MD
Department of Anesthesiology; Thomas Jefferson University Hospital

Marc C. Torjman, PhD
Department of Anesthesiology; Sidney Kimmel Medical College at Thomas Jefferson University

Mauricio G. Hernandez, BS
Department of Anesthesiology; Sidney Kimmel Medical College at Thomas Jefferson University

Clinton G. Lauritsen, DO
Department of Neurology; Thomas Jefferson University

Stephen D Silberstein, MD
Department of Neurology; Thomas Jefferson University

William Young, MD
Department of Neurology; Thomas Jefferson University

Eugene R. Viscusi, MD
Department of Anesthesiology; Sidney Kimmel Medical College at Thomas Jefferson University

Institutional Affiliation of Manuscript:
Department of Anesthesiology; Sidney Kimmel Medical College at Thomas Jefferson University

Source of Funding:
Departmental funding

Word count: 2,416

Conflicts of Interest:
Amir Dayan, Ashwin Rangavajjula, Marc Torjman, and Mauricio Hernandez have no conflicts of interest or disclosures to declare.

Eric Schwenk has received consulting fees from Avenue Therapeutics.

Clinton Lauritsen has received honoraria from Cefaly Technology.

Stephen Silberstein receives, or has received, honoraria from Alder Biopharmaceuticals; Allergan, Inc.; Amgen; Avanir Pharmaceuticals, Inc.; Curelator, Inc.; Dr. Reddy's Laboratories; eNeura Inc.; electroCore Medical, LLC; Lilly USA, LLC; Medscape, LLC.; NINDS; Supernus Pharmaceuticals, Inc.; Teva Pharmaceuticals; Theranica; and Trigemina, Inc.

William Young has received consulting fees from Allergan; he is on the Advisory Board for Amgen, Avanir, Cipla, Alder, Eli Lilly, and Supernus. He has received research support from Allergan, Amgen, Autonomic Technologies, Colucis, Cumberland, Dr. Reddy Laboratories, Eli Lilly, Novartis, PCORI, Scion, Teva, and Zosano.

Eugene Viscusi has served as a consultant for AcelRx, Medicines Company, Mallinkrodt, Trevena, Cara Pharmaceuticals, Salix, Astra Zeneca and Merck. His institution has received research grants in the past from AcelRx, Adolor, Progenics and Pacira. He has been a paid lecturer for AcelRx, Merck, Salix, and Mallinkrodt. None of these companies were involved in any aspect of the development of this manuscript.

Running Title:
Ketamine for refractory headache

Abstract (247 words)

Introduction

The burden of chronic headache disorders in the U.S. is substantial. Some patients are treatment-refractory. Ketamine, an N-methyl-D-aspartate antagonist, provides potent analgesia in subanesthetic doses in chronic pain and limited data suggest it may alleviate headache in some patients.

Methods

We performed a retrospective study of 61 patients admitted over 3 years for 5 days of intravenous therapy that included continuous ketamine to determine responder rate and patient and ketamine infusion characteristics. Pain ratings at two follow-up visits were recorded. An immediate responder was a patient with ≥ 2-point decrease in numerical rating scale (0-10 NRS) from starting to final pain in the hospital. Sustained response at office visits 1 and 2 was determined based on maintaining the 2-point improvement at those visits. Patients were assessed daily for pain and adverse events (AEs).

Results

Forty-eight out of the 61 patients (77%) were immediate responders. There were no differences regarding demographics, opioid use, or fibromyalgia between immediate responders and non-responders. Maximum improvement occurred 4.56 days (mean) into treatment. Sustained response occurred in 40% of patients at visit 1 (mean 38.1 days) and 39% of patients at visit 2 (mean 101.3 days). The mean maximum ketamine rate was 65.2 ± 2.8 mg/h; 0.76 mg/kg/h).

Ketamine rates did not differ between groups. AEs occurred equally in responders and non-responders and were mild.

Discussion

Ketamine was associated with short-term analgesia in many refractory headache patients with tolerable AEs. A prospective study is warranted to confirm this and elucidate responder characteristics.

1 **Introduction**

2 Ketamine, a phencyclidine derivative, is a dissociative anesthetic that provides potent
3 analgesia at subanesthetic doses. It is an N-methyl-D-aspartate (NMDA)-receptor antagonist,
4 which is thought to be the primary mechanism responsible for its analgesic properties. In
5 addition, ketamine acts on opioid, non-NMDA glutamatergic, and muscarinic cholinergic
6 receptors, facilitates GABA signaling, and has local anesthetic properties.[1] Subanesthetic
7 ketamine may also be effective for short-term relief of chronic migraine and other refractory
8 headache disorders,[2; 3] which affect up to 2% of the population of the United States, inflicting a
9 major clinical and financial burden on patients and the healthcare system.[4] The mechanism by
10 which ketamine is effective in treating headache pain is not entirely clear. However,
11 memantine,[5; 6] magnesium,[7] and amantadine,[8] all NMDA-receptor antagonists, may be effective
12 for headache and migraine prophylaxis, which supports the involvement of the NMDA receptor.
13 NMDA-receptor antagonism may decrease chronic pain by inhibiting glutamate-induced
14 neurotoxicity, decreasing central sensitization and specifically in migraines by inhibiting cortical
15 spreading depression (CSD).[9] Our clinical experience suggests that there are many patients who
16 experience substantial relief and a smaller group of others who do not benefit from this therapy.
17 We therefore performed a retrospective analysis of patients admitted to our hospital for treatment
18 of refractory headaches over a 3-year period to determine responder rate and patient and
19 ketamine infusion characteristics.

20

21

Methods

After approval by the institutional review board (Thomas Jefferson University, January 16, 2014, Control #14D.552), we conducted a retrospective chart review of 61 consecutive patients from January 2014 through December 2016 admitted to Thomas Jefferson University Hospital for intravenous treatment of refractory headache with ketamine infusion. All patients with data available were included. Patients who had previously received ketamine for refractory headache were excluded. Patients were admitted to the neurology service in conjunction with the Jefferson Headache Center for aggressive intravenous (IV) therapy and the acute pain management service (APMS) was consulted for management of intravenous ketamine for each patient. The APMS consists of a physician-led, nurse-driven team that provides coverage 24 hours per day, 7 days per week with weekend time being covered by residents. APMS nurses are permitted to adjust ketamine infusion rates within the context of a protocol but they do not give bolus doses (Appendix A). Admission and scheduling was based on bed availability and patients were not necessarily experiencing migraine exacerbations on admission. The electronic medical records, daily APMS notes, and the pre- and post-admission clinic notes from the Jefferson Headache Center were retrieved and the following data were recorded: name; medical record number; demographics; home medications; diagnosis, based on International Classification of Headache Disorders (ICHD-3) criteria;[10] pain level on admission, daily pain level during and at the end of hospitalization; ketamine infusion rates and changes during admission; the presence of adverse events (AEs); and medications given to manage AEs. Pain levels from the first two office visits after discharge were recorded.

Ketamine infusions were typically started at 10 mg/h for most patients with a few exceptions and titrated up in increments of 5 mg/h every 3-4 h to a soft upper limit of 1 mg/kg/h

of body weight. AEs, including hallucinations, delirium, blurry vision, nightmares, nausea, and hypertension, were routinely assessed. These AEs were the primary limiting factor in the rate and degree of titration. Admissions were planned to be 5 days unless a patient could not tolerate the full course of treatment or other factors dictated a longer admission. A clonidine patch was used for management of psychomimetic and sympathomimetic adverse effects. A benzodiazepine was also available as needed for treatment of AEs. Other medications routinely ordered by the headache service included, but were not limited to, prochlorperazine, metoclopramide, methylprednisolone, and ketorolac. In general, home analgesics were continued. Daily opioids were being used for management of other comorbid refractory chronic pain conditions, not for the management of refractory headache. In general, patients are routinely counseled by the outpatient headache providers on the risk of opioid use, including MOH. Opioids were being prescribed by non-headache providers. Patients are encouraged to minimize the daily dose of opioids and attempts are made to coordinate alternative management of chronic non-headache pain disorders with other providers.

We pre-defined an "immediate responder" as a patient who experienced a decrease in pain rating of 2 points on a 0 to 10 numerical rating scale (NRS) from beginning pain to end pain, consistent with previous investigations.[2; 11] A "sustained responder" was defined as an immediate responder who maintained at least a 2-point decrease at the first two post-discharge office visits in the Jefferson Headache Center, each of which was analyzed independently. These two visits are intended to occur at 30 and 90 days after discharge but due to scheduling reasons can vary by several weeks.

Continuous parametric data were analyzed using the Student's t-test for independent groups and the Chi Square test or Fisher's exact test, as appropriate, for categorical data. All

statistical analyses were performed using Systat, v.13 (Systat Software Inc., San Jose, CA) with $p < 0.05$ set for statistical significance. Data are reported as mean ± standard error of the mean (SEM) unless otherwise stated. For office visits 1 and 2, percentages of patients with sustained response were based on patients with available data. Missing patients were not included in those analyses.

Results

Headache Pain Outcomes

A total of 61 unique patients were identified and included in the study. Demographics are shown in Table 1. It is notable that 13 patients (27%) of the immediate responders and 5 patients (39%) of the non-responders used daily opioids and met the criteria for medication overuse headache (MOH).[12] There was no difference between groups regarding MOH ($p = 0.499$). Additional medications administered during admission included dihydroergotamine, non-steroidal anti-inflammatory drugs, neuroleptics, and anti-convulsants (Table 4). Fifty-nine out of the 61 patients had a diagnosis of refractory migraine on admission and 2 patients had cluster headache. The mean length of infusion was 5.1 ± 0.1 days. The mean pain rating on admission was 7.5 ± 0.2 out of 10 (NRS); this decreased to 3.4 ± 0.3 at the end of ketamine therapy ($p < 0.001$).

Using the pre-determined definition of immediate responder as a patient with a decrease in pain rating of 2 out of 10 or greater, 48 of 61 patients (77%) were classified as immediate responders. There were no differences between immediate responders and non-responders with regard to age, sex, history of opioid use, history of fibromyalgia, and presence of AEs (Tables 1 and 3). The mean NRS initial pain rating for immediate responders was 7.8 ± 0.23 and 6.8 ± 0.64 for non-responders. At the end of treatment, the mean pain rating for immediate responders was 2.63 ± 0.28 compared to 6.62 ± 0.68 for non-responders ($p < 0.01$; Figure 1). The mean time to lowest pain rating was 4.56 days into the admission for immediate responders.

At the first office visit, which occurred 38.1 ± 4.7 days after hospital discharge, 52 of the original 61 patients had follow-up data available for analysis. Of the 52 patients, 21 (40%) had a sustained decrease in pain of 2 points and were classified as sustained responders. Thirty patients

(58%) no longer had sustained response and 1 patient was not an immediate responder but did improve at 1 month compared to the end of hospitalization. Sustained responders did not differ significantly from non-responders with regards to age ($p = 0.437$) or gender ($p = 0.150$). At the second office visit, which occurred 101.3 ± 8.8 days after hospital discharge, 49 of the original 61 patients had follow-up data available for analysis. Of these, 19 (39%) were classified as sustained responders (Figure 2), while 30 (61%) were not sustained responders at the second office visit. There were no differences between sustained responders and non-responders at this second office visit according to age ($p = 0.188$) or gender ($p = 0.979$).

Ketamine Infusion Characteristics

The mean starting ketamine infusion rate for all patients was 11.0 ± 0.6 mg/h (Table 2; Figure 3). The mean weight was 85.4 ± 2.7 kg. The mean maximum ketamine infusion rate was 65.2 ± 2.8 mg/h, which is 0.76 mg/kg/h. At the time of the lowest pain rating, the mean ketamine infusion rate was 54.5 ± 3.5 mg/h. There was no difference in mean ketamine infusion rate in immediate responders compared to non-responders over the entire course of treatment (43.7 ± 4.2 vs. 44.1 ± 1.9 mg/h; $p = 0.933$). There was also no difference in the mean maximum ketamine infusion rate between immediate responders and non-responders (64.8 ± 3.0 vs. 66.8 ± 7.2 mg/h; $p = 0.794$).

Adverse Events

Patients were asked daily about the presence of AEs, including central nervous system events (hallucinations, vivid dreams, blurry vision) and nausea and/or vomiting. Sedation was recorded based on nursing or physician observations. Results were recorded as “present” or “absent” and no severity was recorded. Results are shown in Table 3 in decreasing order of

1 frequency. All AEs were considered mild and improved following a decrease in ketamine
2 infusion rate, with the exception of one patient, a 52-year-old female who experienced nausea,
3 blurry vision, and sedation on day 2 of treatment and elected to stop ketamine.

Discussion

Our retrospective study of inpatient ketamine infusion shows that over three quarters of patients with refractory headache were immediate responders and about half maintained the improvement up to 3 months after the infusion. Although it cannot be proven that ketamine was solely responsible for the pain relief due to the retrospective nature of the study, it is encouraging and suggests the need for larger, prospective studies in this challenging patient population. The U.S. burden of chronic migraine, which comprised 97% of the diagnoses in our cohort, is substantial, with a prevalence of about 1% of the population.[13] The subset of this group carrying a refractory migraine diagnosis is about 5%[13] and these patients have substantial disability and poor overall quality of life.

Our results mirror and expand upon other retrospective studies with positive results using ketamine for immediate relief of refractory headache.[2; 3] One prospective, randomized, double-blinded study reported that subcutaneous ketamine improved acute and subacute pain associated with migraine headaches in 17 patients, although the dosing strategy was unusual.[14]

Our patients achieved maximum pain relief after more than 4 days into their admission. This suggests that satisfactory pain relief may not be achieved after 1 day of treatment and, importantly, not achieving the desired effect during the first few days does not mean further improvement will not occur. Although the mean ketamine infusion rate increased from day 1 to day 4, by day 3 the mean ketamine rate was over 80% of the eventual maximum rate, yet patients continued to experience additional improvement in headache pain. Non-responders experienced mild improvement by day 2 but no further reduction in headache intensity beyond that. Taken together, this suggests clinicians should be patient and wait at least 4 or 5 days before

determining that someone did not respond to ketamine. For most patients, this requires a full 5-day treatment course.

What patient characteristics might help predict response? None of the demographic factors or the presence of fibromyalgia or current opioid use was significantly associated with response to ketamine. Fibromyalgia and opioid use are potential confounders given the evidence supporting ketamine for short-term relief in fibromyalgia[15] as well as studies showing opioid-tolerant patients especially benefit from ketamine.[16; 17] Well-designed prospective studies are needed to better elucidate these characteristics as retrospective data have limitations. Other factors might help predict response to ketamine, such as individual metabolism of the drug.[18] Metabolites of ketamine, including hydroxyketamine, dehydronorketamine, and other hydroxynorketamine molecules, may play a role in the treatment of depression[19] and they could also be important in chronic pain conditions such as complex regional pain syndrome (CRPS).[18] There is a subset of migraine and CRPS patients who have favorable response to ketamine while others have minimal relief. Tailoring treatment based on likelihood of response would be useful to patients and clinicians. This is an area worthy of future study.

The widespread use of ketamine for refractory headache disorders remains challenging. The psychomimetic AEs, including hallucinations, vivid dreams, and other central nervous system excitation, associated with ketamine deter many from using it. In addition, since it is approved as an anesthetic, it requires monitoring that varies by the state and hospital. The incidence of such undesirable AEs in one review of postoperative patients was about 7%.[20] In a mixed medical/surgical population receiving subanesthetic ketamine infusions an incidence of 16% was reported, while in a refractory headache population this was as high as 20% of patients with a mean ketamine rate of 0.53 mg/kg/h.[2] Our incidence of hallucinations (28%) was higher

1 than these reported results and this may have been a result of our fairly aggressive titration of
2 ketamine with a mean maximum rate of 65 mg/h (0.76 mg/kg/h). Despite our higher rates, only
3 one patient discontinued infusion due to intolerance of AEs. This is encouraging as higher doses
4 appear to be well tolerated by most patients.

5 In addition to the inherent limitations of any retrospective study, this study has several
6 additional limitations. First, patients were not necessarily admitted for treatment during an acute
7 exacerbation of migraine, thus initial pain ratings may not have reflected the overall state of the
8 headache disorder. Second, our ketamine protocol does not mandate a specific starting dose and
9 allows for some clinical judgment in rate increases and decreases. There is variation in the
10 titration strategy among our individual APMS physicians. Third, because 97% of patients in the
11 study had a migraine diagnosis it is not clear how generalizable these results would be to patients
12 with other headache diagnoses. Last, we were unable to retrospectively determine with certainty
13 if patients had any changes in treatment or other interventions after hospital discharge that could
14 have affected level of pain at subsequent office visits. This limitation likely did not play a major
15 role in the results as all patients in the study had refractory headaches and were unlikely to have
16 responded to other minor interventions during that time.

17 In conclusion, subanesthetic ketamine infusion was associated with improved acute pain
18 in a group of patients with refractory headaches, many of whom continued to experience
19 decreased pain 3 months after treatment. Ketamine is a promising potential therapy for thousands
20 of refractory patients who have not found relief elsewhere. Ketamine infusion is well tolerated
21 within the context of our protocol. Prospective studies should focus on responder characteristics
22 and optimal dosing strategies that minimize AEs while providing optimal headache relief.

Table 1. Demographic data

Variable	All Patients N=61		
Male/Female (N)	44/17		
Age (years), mean (range)	42.4 (20 – 65)		
Weight (kg), mean (SEM)	85.4 (2.7)		
Migraine, N (%)	59 (97)		
Cluster Headache, N (%)	2 (3)		
Variable	**Immediate Responders N=48**	**Non-Responders N=13**	**P value**
Male Patients, N (%)	13 (27)	6 (46)	0.191
Age (years), mean (SEM)	43.2 (1.7)	39.2 (3.4)	0.355
Daily Opioid Use, N (%)	32 (67)	6 (46)	0.570
Fibromyalgia, N (%)	9 (19)	2 (15)	0.781

Table 2. Ketamine infusion data

	Immediate Responders N=48	Non-Responders N=13	P value
Mean Starting Rate (mg/h)	11.0 (0.7)	10.8 (0.8)	0.853
Mean Infusion Rate (mg/h)	43.7 (4.2)	44.1 (1.9)	0.933
Maximum Infusion Rate (mg/h)	64.8 (3.0)	66.8 (7.2)	0.794

Data are presented as mean (SEM)

Table 3. Adverse events from ketamine infusions

Adverse Events	Immediate Responders N=48	Non-Responders N=13	P value
Nystagmus	36 (75)	7 (54)	0.141
Sedation	23 (48)	8 (62)	0.319
Nausea/Vomiting	19 (40)	4 (31)	0.564
Blurry Vision	17 (35)	6 (46)	0.482
Hallucinations	13 (27)	4 (31)	0.794
Vivid Dreams	5 (10)	3 (23)	0.234

Data are presented as N (%)

Table 4. Additional medications used for patients with refractory headache

	Immediate Responders N=48	**Non-Responders N=13**
IV/Nasal DHE	14 (29.1%)	1 (7.7%)
IV NSAIDs	22 (45.8%)	6 (4.6%)
PO NSAIDs	8 (16.6%)	1 (7.7%)
IV Neuroleptics	10 (20.8%)	1 (7.7%)
PO Neuroleptics	24 (50%)	8 (61.5%)
IV Anticonvulsants	2 (4.2%)	0
PO Anticonvulsants	21 (43.8%)	5 (38.4%)

DHE = dihydroergotamine; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug; PO = by mouth

Figure Legends

Figure 1. Pain experienced during admission by patients with refractory headaches being treated with continuous 5-day ketamine infusions (SEM = standard error of the mean)

Figure 2. Percentage of patients characterized as responders acutely and at office visits 1 and 2

Figure 3. Ketamine infusion rates at various points of treatment (SEM = standard error of the mean)

References

1. Bell RF. Ketamine for chronic non-cancer pain. *Pain* 2009;141:210-214.
2. Pomeroy JL, Marmura MJ, Nahas SJ, Viscusi ER. Ketamine infusions for treatment refractory headache. *Headache* 2017;57:276-282.
3. Lauritsen C, Mazuera S, Lipton RB, Ashina S. Intravenous ketamine for subacute treatment of refractory chronic migraine: A case series. *J Headache Pain* 2016;17.
4. Buse DC, Manack AN, Fanning KM et al. Chronic migraine prevalence, disability, and sociodemographic factors: Results from the american migraine prevalence and prevention study. *Headache* 2012;52:1456-1470.
5. Huang L, Bocek M, Jordan JK, Sheehan AH. Memantine for the prevention of primary headache disorders. *Ann Pharmacother* 2014;48:1507-1511.
6. Bigal M, Rapoport A, Sheftell F, Tepper D, Tepper S. Memantine in the preventive treatment of refractory migraine. *Headache* 2008;48:1337-1342.
7. von Luckner A, Riederer F. Magnesium in migraine prophylaxis - is there an evidence-based rationale? A systematic review. *Headache* 2017.
8. Kawase Y, Ikeda K, Iwasaki Y. Amantadine for migraine. *Headache* 2008;48:1380.
9. Sarchielli P, Filippo MD, Nardi K, Calabresi P. Sensitization, glutamate, and the link between migraine and fibromyalgia. *Curr Pain Headache Rep* 2007;11:343-351.
10. (IHS) HCCotIHS. The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia* 2013;33:629-808.
11. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149-158.
12. IHS classification ICHD-3. Available at: https://www.ichd-3.org/8-headache-attributed-to-a-substance-or-its-withdrawal/8-2-medication-overuse-headache-moh/8-2-4-opioid-overuse-headache/. Accessed February 16, 2018.
13. Schulman E. Refractory migraine - a review. *Headache* 2013;53:599-613.
14. Nicolodi M, Sicuteri F. Exploration of nmda reeptors in migraine: Therapeutic and theoretic implications. *Int J Clin Pharmacol Res* 1995;15:181-189.
15. Noppers IM, Niesters M, Swartjes M et al. Absence of long-term analgesic effect from a short-term s-ketamine infusion on fibromyalgia pain: A randomized, prospective, double blind, active placebo-controlled trial. *Eur J Pain* 2011;15:942-949.
16. Loftus RW, Yeager MP, Clark JA et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology* 2010;113:639-646.
17. Barreveld AM, Correll DJ, Liu X et al. Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: Results of a prospective, randomized, double-blind study. *Pain Med* 2013;14:925-934.
18. Sabia M, Hirsh RA, Torjman MC et al. Advances in translational neuropathic research: Example of enantioselective pharmacokinetic–pharmacodynamic modeling of ketamine-induced pain relief in complex regional pain syndrome. *Curr Pain Headache Rep* 2011;15:207-214.
19. Zarate CA, Brutsche N, Laje G et al. Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. *Biol Psychiatry* 2012;72:331-338.
20. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth* 2011;58:911-923.