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Use of Esketamine in the Treatment of Migraine Resistant to Standard Therapy – A Case Report

Upotreba esketamina u zbrinjavanju migrene rezistentne na standardnu terapiju – prikaz slučaja

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Abstract. ***Aim***: This case report aims to describe the management of migraine resistant to standard therapy in the emergency department (ED) using intravenous esketamine, a novel treatment modality and a potent analgesic agent. ***Case report***: A 24-year-old female presented to the ED with a chief complaint of intense headache lasting for 3 hours. She had a history of migraine headaches that were successfully treated with non-steroidal anti-inflammatory drugs (NSAIDs). The neurologic status was without abnormalities. The patient reported a pain intensity of 9/10 on the visual analogue scale (VAS). A peripheral venous cannula was placed. She was administered 10 mg of metoclopramide over 10 minutes intravenously, without a significant improvement in the VAS. After half an hour, she was administered another 10mg of metoclopramide, followed by 100 mg of ketoprofen over 30 minutes intravenously. Her VAS remained at 9/10, therefore a computed tomography (CT) scan of the brain with intravenous contrast was ordered. The laboratory tests were all within reference intervals. The CT scan reported no intracranial pathology. Due to persistent pain with a VAS of 9/10, the patient was administered 0.05 mg/kg of esketamine as an infusion over 30 minutes, followed by an infusion of 12 mg of dexamethasone, after which she reported a decrease in VAS from 9/10 to 2/10. Following symptom resolution and observation without any adverse events noted, the patient was discharged home with detailed return precautions. ***Conclusion***: Esketamine is a potent analgesic which can be used an effective third-line therapy for migraine headache refractory to conventional treatment.

Keywords: emergency medicine; esketamine; migraine disorders; pain management

Sažetak. ***Cilj***: Ovaj prikaz slučaja ima za cilj opisati zbrinjavanje migrene rezistentne na standardnu terapiju u hitnoj medicinskoj službi (HMS) korištenjem intravenskog esketamina, novog modaliteta liječenja i snažnog analgetskog lijeka. ***Prikaz slučaja***: 24-godišnja bolesnica javila se u HMS zbog jake bilateralne glavobolje lokalizirane u sljepoočnom području, u trajanju od tri sata. Od ranije boluje od migrenoznih glavobolja koje su prethodno uspješno liječene nesteroidnim antireumaticima (NSAR). Neurološki je status bio uredan. Bolesnica je procijenila intenzitet boli na 9/10 na vizualnoj analognoj skali (VAS). Postavljena je periferna venska kanila. Primijenjeno je 10 mg metoklopramida venski tijekom 10 minuta, bez značajnijeg poboljšanja u VAS-u. Nakon pola sata primijenjeno je još 10 mg metoklopramida te 100 mg ketoprofena intravenski tijekom 30 minuta. VAS je ostao 9/10, stoga je učinjena kompjutorizirana tomografija (engl. *computed tomography;* CT) mozga s intravenskim kontrastom. Nalazi laboratorijskih pretraga bili su unutar referentnih intervala, a CT nije pokazao intrakranijsku patologiju. Zbog perzistirajuće boli s VAS-om 9/10, primijenjeno je 0,05 mg/kg esketamina u infuziji tijekom 30 minuta, nakon čega je primijenjeno 12 mg deksametazona u infuziji. Bolesnica je javila smanjenje VAS-a s 9/10 na 2/10. Nakon smanjenja tegoba te opservacije koja je protekla uredno bolesnica je otpuštena kući s detaljnim uputama za ponovno javljanje u HMS u slučaju pogoršanja. ***Zaključak***:

http://hrcak.srce.hr/medicina

Esketamin je snažan analgetik koji se može primijeniti kao učinkovita terapija treće linije za migrenoznu glavobolju refrakternu na uobičajenu terapiju.

Ključne riječi: esketamin; hitna medicina; migrenozni poremećaji; zbrinjavanje boli

INTRODUCTION

Migraine headaches are a highly prevalent neurologic condition, affecting around 12% of the general population, with 17% of women and 6% of men reporting migraines each year[1]. As a neurologic condition, migraine headache has a specific distribution based on patient age – both the prevalence and frequency of migraine headache episodes start increasing during puberty and continue to grow until they reach a peak between the ages of 35 and 39, regressing during the 40 s and hitting a trough following menopause in women[2]. On a wider population scale, migraine headache is a serious condition, being the second most significant contributor to global disability (with chronic back pain being the first), measured by years of life lived with disability (YLD)[3].

While there are several different established definitions of migraine headache disorder, the one that is most used is the definition established by the International Classification of Headache Disorders 3 (ICHD-3)[4]. According to that definition, migraine headache disorder can be divided into migraine with aura, migraine without aura, chronic migraine, complications of migraine, probable migraine and episodic syndromes that may be associated with migraine. Each subgroup mentioned above has further specific criteria that must be met to establish a definitive diagnosis. For example, in order to establish a diagnosis of migraine without aura, the patients' needs to have had at least five episodic headache attacks fulfilling the following criteria: an attack lasting 4-72 hours, having at least two prespecified distinct features (unilateral location, pulsating quality, moderate/severe pain intensity, aggravation by or causing avoidance of routine physical activity), accompanied by nausea/vomiting or photophobia/phonophobia and not being better accounted for by another ICHD-3 diagnosis.

Migraine headache is also a common presentation in the emergency department (ED) according to data from the United States, it is the fourth to fifth most common chief complaint/reason of ED visit (depending on the registry perused), accounting for around 3% of ED visits annually[5]. Besides establishing adequate pain control and attempting to achieve definitive termination of the migraine episode affecting the patient, ED visits due to (presumed) migraine headache also involve excluding potentially life-threatening causes of headache, such as subarachnoid haemorrhage (SAH), intracerebral haemorrhage (ICH), ischemic cerebrovascular incident (iCVI) and meningitis.

In patients with a chief complaint of headache, a comprehensive approach is required to establish a diagnosis of migraine headache disorder. A thorough medical history and a detailed neurologic examination are essential in establishing a differential diagnosis list and navigating the diagnostic process successfully without overlooking any possible life-threatening diagnoses.

This case report describes a 24-year-old female patient who presented to the ED with a chief complaint of a severe episode of migraine headache.

CASE REPORT

A 24-year-old female presented to the ED with a chief complaint of intense headache localized bilateral parietal lasting for about 3 hours. She had a history of migraine headaches that were successfully treated with non-steroidal anti-inflammatory drugs (NSAIDs) like naproxen 550 mg tablet 1 x orally or ketoprofen 100 mg tablet 1 x orally. However, she had described the headache she presented with as the most intense she had ever felt. The patient's vital signs were within reference intervals: a respiratory rate of 14 breaths per minute, blood pressure of 125/90 mmHg, pulse rate of 85/min, body temperature (measured tympanically) of 36.8°C and a peripheral oxygen saturation of 98% on room air. The neurologic status was without abnormalities, with preserved visual and bulbomotoric function,

absence of nystagmus, normal and symmetrical vestibular function, lack of lateralization signs and symmetrical deep tendon reflexes. There was also no reported nuchal rigidity. The patient reported a pain intensity of 9/10 on the visual analogue scale (VAS), without improvement after taking naproxen 550 mg tablet 1 x orally. Regarding relevant medical history, she reported having no medication allergies. Her family history was positive for arterial hypertension, structural heart disease and hereditary angioedema. She did have a personal medical history of arterial hypertension; however, she was not currently undergoing active antihypertensive treatment as her blood pressure values were normal at the time of the visit. At the time of the examination, she had been taking oral hormonal contraceptives for 2 months. A peripheral venous cannula was placed in a superficial antebrachial vein of the right arm and blood samples were taken for laboratory testing. Metoclopramide 10 mg in 100 mL of 0.9% sodium chloride over 10 minutes was administered venously without a significant improvement in the VAS. After half an hour, the patient's pain and neurologic status were re-evaluated and another 10 mg of metoclopramide in 100 mL of 0.9% sodium chloride over 10 minutes was administered, followed by 100 mg of ketoprofen in 500 mL of 0.9% sodium chloride over 30 minutes, due to lack of improvement in the pain score. Following the administration of the therapy, her VAS remained at 9/10, therefore a computed tomography (CT) scan of the brain with intravenous contrast was ordered. The laboratory tests, which included a complete blood count, C-reactive protein, beta human chorion gonadotropin (beta-HCG), creatinine and an electrolyte panel were all within reference intervals. The CT scan reported no intracranial pathology. Due to persistent pain with a VAS of 9/10 and a stable neurologic status without any detected abnormalities in the observation period, the patient was administered 0.05mg/kg of esketamine in 100 mL of 0.9% sodium chloride over 30 minutes, followed by 12 mg of dexamethasone in 500 mL of 0.9% sodium chloride over 30 minutes. The patient's pain was once again re-evaluated, along with the neurologic exam at 30 minutes following the administration of dexamethasone. She reported a decrease in the VAS from 9/10 to 2/10. Since there were no concerning findings on repeat neurologic examinations or CT scan, the patient was discharged home following a 6-hour observation period (counted from the index time of ED visit). For future episodes of migraine, abortive oral therapy has been recommended. This includes taking one tablet of metoclopramide 10 mg orally and one tablet of Dexketoprofen 25 mg orally as needed. Detailed return precautions were provided to the patient. She was instructed to contact the nearest emergency neurological clinic if her headache recurs and is accompanied by vomiting, nausea, imbalance, dizziness, or any other concerning neurological symptoms.

DISCUSSION

Having a standardized approach to the diagnostic and treatment processes of migraine headache is crucial due to its common presentation in the emergency department. Establishing an accurate timeline of events and obtaining a thorough characterization of the pain is essential for evaluating if the patient's history aligns with the criteria for migraine or other headache disorders.

In the case of our patient, her description of "the worst headache of my life" was a significant trigger that raised suspicion for possible subarachnoid hemorrhage (SAH). This is because most cases of SAH present with patients experiencing severe, sudden-onset headaches often described as "thunderclap" headaches[6]. Therefore, despite no concerning findings on the neurologic examination, a CT scan of the head was planned early in the case of persisting pain. Besides the native scan of the head, a CT angiography of the head with the venous phase included was also planned since the patient was taking oral hormonal contraceptives and had a family history of hereditary angioedema, both of which are significant risk factors for cerebral venous thrombosis, which also might present as a severe headache[7].

A detailed laboratory workup was also conducted parallel to the neurologic examination and history taking to exclude possible pregnancy and biochemical causes of headache, such as severe dehydration and electrolyte abnormalities.

Regarding the therapeutic approach to pain control in migraine headaches, there are several different guidelines and recommendations. The American Headache Society (AHS) released a guideline for the management of acute migraine headache in adult patients in the emergency department in 2016, evaluating the different available therapies and the evidence for their effectiveness and safety[8]. In the conclusion of their guideline, titled "Putting the Evidence into a Clinical Context", the authors sorted the available treatment options into five distinct categories: "must offer", "should offer", "may offer", "may avoid" and "no recommendation". For acute pain management, no medications were placed into the "must offer" category. In the "should offer" category, intravenous metoclopramide, intravenous prochlorperazine and subcutaneous sumatriptan were recommended. In their evidence analysis, the authors concluded that, in randomized control trials, metoclopramide was equivalent or superior (effectiveness-wise) to NSAIDs and other antiemetics (haloperidol, prochlorperazine), while having less adverse events. Acetaminophen and NSAIDs were placed in the "may offer" category, while opioids and lidocaine were placed in the "may avoid" category. For prevention of migraine recurrence, no medications were listed in the "must offer" category, while parenteral Dexamethasone was listed in the "should offer" category.

Guidelines for the management of migraine attacks and prevention of migraine headache from the German Migraine and Headache Society and the German Society of Neurology recommend intravenous metoclopramide, lysine acetylsalicylate or subcutaneous sumatriptan for pain control in the ED[9]. The authors also mention metamizole in a 1000 mg intravenous dose as a possible effective treatment option, however they warn that a drop in blood pressure and allergic reactions are possible and expected side-effects. The use of opioids is not recommended.

Our treatment of the patient's pain closely followed the AHS guidelines, starting with an intravenous dose of metoclopramide 10 mg, administered as a slow infusion following evidence that such a manner of administration significantly reduces the incidence of akathisia in patients receiving antiemetics[10]. Following the lack of a satisfactory clinical response to therapy, metoclopramide was redosed and an NSAID was administered following the second dose of metoclopramide. Triptans or lysine acetylsalicylate are not available in our ED, therefore they were not used during the treatment process. Following the administration of an NSAID and 30 mg of metoclopramide over three doses, the need for an adjunctive third-line therapy became evident.

Intravenous low-dose ketamine (defined as a dose between 0.1 and 0.3 mg/kg) has been successfully used and studied for the management of severe acute pain in the ED since the early 2010s[11]. A study by Ahern et al, analysing data on 530 patients who received intravenous low-dose ketamine over a period of two years, demonstrated a favourable safety profile of ketamine analgesia, with no serious adverse events reported over a 2-year period and a total of 3.5% patients experiencing psychomimetic or dysphoric effects[12].

The use of ketamine for headaches is a relatively novel concept, with limited data available. A study by Sarvari et al. found similar effectiveness of intravenous ketorolac and intranasal ketamine for pain control in acute non-traumatic headaches, with ketamine having an earlier onset of action and greater effectiveness at 30 minutes[13]. The THINK (Treatment of Headache with Intranasal Ketamine) trial compared the effectiveness of intranasal ketamine and intravenous metoclopramide plus diphenhydramine for pain control in ED patients presenting with primary headache. The results demonstrated that ketamine therapy was equivalent to metoclopramide plus diphenhydramine effectiveness-wise, with less patients returning to the ED within 48-72 hours in the ketamine arm compared to the metoclopramide arm of the trial[14]. A study by Zitek et al. compared prochlorperazine plus diphenhydramine versus ketamine plus ondansetron for headache treatment in the ED, with the findings showing significantly better pain control in the prochlorperazine arm[15]. Etchinson et al. compared the effectiveness of 0.2 mg/kg intravenous ketamine to normal saline and found no significant difference in pain scores between the groups[16].

From the discussion above, it can be inferred that there is currently conflicting evidence regarding the effectiveness of ketamine for pain control in primary headaches, particularly in the emergency department (ED) setting. While some studies suggest potential benefits of ketamine in managing acute headache episodes, particularly in refractory cases, other research findings may not consistently support its widespread use for this indication. However, one must take into consideration the fact that alternative, third-line treatment options for severe primary headache are few and far between, with the alternative backed by evidence being intravenous propofol[17], which is administered in doses used for procedural sedation and requires extensive monitoring (SpO_2, capnography, non-invasive blood pressure monitoring).

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In this case, esketamine is used instead of racemic ketamine. Esketamine is an S-enantiomer of ketamine, which has more potent analgesic effects and binds to receptors with 2-4 times greater affinity than racemic ketamine[18]. It has also been demonstrated to have less psychomimetic side-effects than racemic ketamine in healthy volunteers, due to the majority of the psychomimetic effects being caused by R-ketamine[19]. Due to the increased receptor affinity and potency of esketamine, it is used in 2-4 times reduced doses compared to racemic ketamine to achieve the same analgesic effect.

Therefore, 0.05 mg/kg of esketamine was administered to our patient, which roughly corresponds to 0.1-0.2 mg/kg of racemic ketamine, the established dose range for analgesic effects of ketamine. It was administered as a slow infusion over 30 minutes due to evidence that points to lower incidence of psychomimetic side-effects compared to bolus administration of ketamine[20].

Following an observation period, the patient was discharged home, with both SAH and CVT being excluded by the CT scan. Since the CT scan was performed inside the 6-hour timeframe from the onset of headache, the 6-hour SAH rule was implemented, which shows satisfactory sensitivity for SAH when combined with the Ottawa SAH rule[21]. The use of a third-generation multislice CT (MSCT) scanner also bolstered the sensitivity of the test – there is evidence that CT scans performed on third-generation MSCT scanners confer a 100% sensitivity (95% confidence interval 98.3-100%) for the exclusion of SAH if the scan is performed early (24 hours within symptom onset)[22]. The patient was provided with detailed return precautions, and guideline-directed oral headache termination therapy was prescribed[9].

CONCLUSION

This case report demonstrates that intravenous low-dose esketamine can be safely used as a third-line analgesic therapy for the treatment of migraine refractory to conventional therapy. Further case series and prospective studies are necessary to establish the optimal dose and administration route of esketamine for this clinical indication.

Conflicts of Interest: Authors declare no conflicts of interest.

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