Scientific Research Publishing

Open Journal of Anesthesiology, 2023, 13, 108-117
https://www.scirp.org/journal/ojanes
ISSN Online: 2164-5558
ISSN Print: 2164-5531

Administration of Nebulised Ketamine for Managing Pain in the Intensive Care Unit of Obstetrics and Gynaecology

Yassine Hafiani[1], Mohammad Khalayla[1*], Mohamed Elmouhajir[2], Anas Erragh[1], Soufiane Saadaoui[1], Ibtissame Nabih[1], Ihsane Mousaid[1], Smael Elyoussoufi[1], Said Salmi[1]

[1]Anesthesiology and Critical Care, Ibn Rochd University Hospital of Casablanca, Hassan II University, Casablanca, Morocco
[2]Faculty of Medicine and Pharmacy of Rabat UM5, CEDOC, Simulation Center, Rabat, Morocco
Email: *dr.khalailah@gmail.com

How to cite this paper: Hafiani, Y., Khalayla, M., Elmouhajir, M., Erragh, A., Saadaoui, S., Nabih, I., Mousaid, I., Elyoussoufi, S. and Salmi, S. (2023) Administration of Nebulised Ketamine for Managing Pain in the Intensive Care Unit of Obstetrics and Gynaecology. *Open Journal of Anesthesiology*, **13**, 108-117.
https://doi.org/10.4236/ojanes.2023.135011

Received: July 27, 2022
Accepted: May 28, 2023
Published: May 31, 2023

Abstract

Introduction: The use of inhaled ketamine to manage a variety of painful conditions has been endorsed by the American College of Emergency Physicians and the American Academy of Emergency Medicine. Nebulized analgesia has multiple benefits, including rapid, effective and titratable analgesic delivery. The aim of our study is to assess the efficacy and safety of intranasal analgesic-dose ketamine compared to multimodal analgesia in patients presenting with acute postoperative pain or headache after a spinal anaesthetic in the intensive care unit of obstetrics and gynaecology. **Materials and Methods:** This was a prospective descriptive study, with hospital Ethics Committee approval and written informed consent from study participants. We compared the effect of nebulized ketamine and multimodal analgesia postoperatively in 120 patients belonging to the physical status I - II of the American Society of Anesthesiologists, in the intensive care unit of obstetrics and gynaecology, at the Ibn Rochd University Hospital Center in Casablanca from June 2021 to June 2022. **Results:** We included 120 patients in our study divided into two groups of 60 patients: the average age was 35 years, with extremes ranging from 18 to 45 years, All patients were hospitalized for postoperative care: all women underwent locoregional anaesthesia with a standard dose according to the service protocol (10 mg of bupivacaine, 25 γ of fentanyl, 100 γ of morphine), where pain was the common denominator. Among these patients, 59 were admitted for management of postpartum haemorrhage, 43 for postoperative monitoring, 15 for post-spinal anaesthesia headache and 3 for pelviperitonitis. The results of the pain assessment 30 minutes after the ketamine nebulization were marked by a request for analgesia in 12 patients, which is 20% of group A, including 5 patients, whose visual analogue scale (VAS) on

admission was between 5 and 7, and 7 patients whose VAS at admission was ≥8; all these patients received a second dose of ketamine by nebulization; the evaluation 30 min after the second dose was marked by a request for analgesia in 4 patients, which is 7% of Group A; in all these patients the VAS at admission was ≥8. Of the total number of patients of Group A, only 4 received morphine when they were requested for analgesia after the second dose of nebulized ketamine. **Conclusion:** The primary outcome of nebulized ketamine use is a significant reduction in VAS pain score. We believe that nebulized ketamine has a potential effect of reducing pain in the intensive care unit of obstetrics and gynaecology; this may be an additional analgesic modality for clinicians to provide rapid, effective and non-invasive pain relief.

Keywords

Ketamine, Nebulized, Pain, Postoperative

1. Introduction

Ketamine is an N-methyl-uncompetitive antagonist of the D-aspartate/glutamate receptor complex, which causes a "wind-up" phenomenon in the spinal cord (dorsal ganglion) and the central nervous system. This unique property reduces pain by reducing central sensitization and hyperalgesia [1].

The use of inhaled ketamine to manage a variety of painful conditions has been endorsed by the American College of Emergency Physicians and the American Academy of Emergency Medicine. Nebulized analgesia has multiple benefits, including rapid, effective and titratable analgesic delivery [2] [3].

Over the past 10 years, the use of ketamine has changed a lot. It has evolved from a purely sedative/anaesthetic drug to an anti-hyperalgesia drug. Laboratory and clinical investigations have reported the clinical impact of hyperalgesia. This can lead to acute and persistent pain, especially after surgery [4] [5].

Ketamine as a sub-anaesthetic dose may be an appropriate option for the management of acute pain in the surgical setting; therefore, the intranasal route may be a convenient and effective route for drug administration. In addition to being simple and non-invasive, the intranasal route is very suitable for patients suffering from nausea or vomiting [6].

The aim of our study is to assess the efficacy and safety of intranasal analgesic-dose ketamine compared to analgesia multimodal in patients presenting with acute postoperative pain or headache after a spinal anaesthetic in the intensive care unit of obstetrics and gynaecology.

2. Materials and Methods

This was a prospective descriptive study. With hospital Ethics Committee approval and written informed consent from study participants, we compared the effects of nebulized ketamine and multimodal analgesia postoperatively in 120

patients belonging to physical status I-II of the American Society of Anesthesiologists in the intensive care unit of obstetrics and gynaecology, at the Ibn Rochd University Hospital Center in Casablanca from June 2021 to June 2022.

Inclusion criteria:

- VAS ≥ 5
- Age: 18 - 45 years
- ASA I and II
- Caesarean section under spinal anaesthesia

Exclusion criteria:

- VAS < 5
- Preeclampsia/eclampsia/HELLP syndrome
- History of hypersensitivity to ketamine or NSAIDs
- Caesarean section under general anaesthesia

The patients were divided into the following two groups:

Group A patients were nebulized with 1 mg/kg of ketamine plus 3 mL normal saline. Group A was divided into two subgroups according to the visual analogue scale (VAS): Group A1 (5 < VAS < 8) and Group A2 (VAS ≥ 8).

Group B patients received multimodal analgesia consisting of paracetamol 1 g 3 times per day and nefopam 20 mg 3 times per day. Group B was divided into two subgroups according to the VAS: Group B1 (5 < VAS < 8) and Group B2 (VAS ≥ 8).

The data was collected by a resident doctor in the intensive care unit department with evaluation of the efficacy and adverse effects related to ketamine (fatigue, dizziness, headaches, nausea, feeling of unreality, changes in hearing, changes in vision, mood swings and hallucinations). The nebulizer solution was prepared by the resident doctor. Patients were nebulized using a nebulizer for 15 min. The choice of patients was randomly selected for nebulized ketamine or multimodal analgesia. Standard monitoring was applied (non-invasive blood pressure, pulse oximetry and an electrocardiogram).

3. Results

We included 120 patients in our study. They were divided into two groups of 60 patients; the average age was 35 years with extremes ranging from 18 to 45 years, All patients were hospitalized for postoperative care; all women underwent locoregional anaesthesia with a standard dose according to the service protocol (10 mg of bupivacaine, 25γ of fentanyl, 100γ of morphine), where pain was the common denominator; among these patients, 59 were admitted for management of postpartum haemorrhage, 43 for postoperative monitoring, 15 for post-spinal anaesthesia headache and 3 for pelviperitonitis.

The pain assessment was based on the use of the VAS, which is very practical and easy to use for both patients and health professionals. Group A patients received the first dose of nebulization after their admission to intensive care. All Group B patients received multimodal analgesia at H0 postoperatively. With regard to the patients who were admitted for post-spinal anaesthesia headaches,

the indication for hospitalization in intensive care was based on the intensity of the pain; VAS greater than 7 and we divided them equally between the two groups A and B.

Protocol for Nebulized Ketamine

A single dose of ketamine (1 mg/kg) was used for all Group A patients. All the patients admitted were eligible to receive up to 2 doses of nebulized ketamine for pain control, taking into consideration that the second dose corresponds to the initial dosing regimen. The pain assessment took 30 - 60 minutes to judge the need for a second dose of ketamine.

Protocol for Multimodal Analgesia

All the Group B patients received a multimodal analgesia according to a prescription of 3 g of paracetamol divided into three doses, 20 mg of nefopam in 3 daily doses; initially, a dose of paracetamol was given, followed by a dose of nefopam. Pain assessment took 30 - 60 minutes.

The assessment of pain before the administration of ketamine or multimodal analgesia was made 10 minutes after mobilization of the lower limbs for patients under spinal anaesthesia, and immediately after admission to the intensive care unit for post-spinal anaesthesia headache.

The results of the pain assessment (Table 1) 30 minutes after the ketamine nebulization was marked by a request for analgesia in 12 patients, that's 20% of group A, including 5 patients whose VAS on admission was between 5 and 7, and 7 patients whose VAS at admission was ≥8; all these patients received a second dose of ketamine by nebulization; the evaluation 30 min after the second dose was marked by the request for analgesia in 4 patients, which is 7% of Group A, who all had a VAS ≥ 8 at the time of admission. Of the total number of patients in Group A, only 4 patients received morphine when they were requested for analgesia after the second dose of nebulized ketamine.

The pain assessment after multimodal analgesia (Table 2) was marked by a request for analgesia in 21 patients, which is 35% of group B, including 8 patients who had VAS between 5 and 7 at the time of admission, and 13 patients who had VAS ≥ 8 at the time of admission; all these patients had recourse to opioids to relieve pain.

Table 1. Results of the pain assessment for Group A.

VAS of Group A	VAS < 8	VAS ≥ 8
Request for analgesia after the first dose of ketamine	5 patients (8%)	7 patients (12%)
Request for analgesia after the second dose of ketamine	0 patients 0%	4 patients (7%)

Table 2. Results of the pain assessment for Group B.

VAS of Group B	VAS < 8	VAS ≥ 8
Request for analgesia	8 patients (13%)	13 patients (22%)

The request for analgesia was marked in patients with a VAS ≥ 5, however analgesia was considered effective after a decrease in VAS < 5.

In this study we did not find any adverse effects among the patients with multimodal analgesia. The following were the adverse effects during this study after nebulized ketamine: drowsiness was marked in 6 patients in Group A, which is 10%; dizziness, nausea and vomiting were noted in 3 patients, which is 3%; only 1 patient presented with a bad taste in the mouth.

4. Discussion

Postoperative pain is one of the most significant concerns for women after a caesarean section, and it can interfere with the mother's ability to provide desirable attention and nutritional care to the new born. The risk of thromboembolic disease, which increases during pregnancy, is likely to be further exacerbated by immobility because of pain during postpartum [7] [8].

Additionally, painful stimulation is a major cause of postpartum depression, which necessitates postoperative analgesia. Intranasal ketamine has the potential to improve depressive symptoms [9] [10].

Ketamine has been used as an anaesthetic agent for over 50 years and is widely used in emergency departments for sedation and as an induction agent [11]. Several studies have focused on the use of nebulized ketamine and have suggested that nebulized ketamine can be used alone or as an adjuvant analgesic for effective and safe pain relief [12] [13].

Ketamine can be used by different routes: IV, SC and IM, epidural, intrathecal, intra-articular, intranasal, oral and topical for short-term pain relief. In these situations, fast-acting routes of administration such as injection or the intranasal route can be used, and the doses should be kept as low as possible [14]. Intranasal administration has been proposed as a promising route of administration for ketamine and other agents. Administration of ketamine by inhalation has been successfully tested; it is a needle-free option and has a 45% greater bioavailability, superior to most other methods of administration. It produces a rapid induction of pain relief, whose clinical efficacy is probably explained by the absorption of the drug by the nasal mucosa, allowing it to act on the brain without undergoing hepatic first-pass metabolism [15] [16]. In addition, the nostrils and sinus cavities have a large surface area, uniform temperature, high permeability and extensive vascularization, facilitating systemic absorption. If safe and effective, intranasal ketamine could potentially offer clinicians a simple option. Ketamine might also modulate central sensitization and hyperalgesia, which could potentially help reduce the overall severity of pain [17] [18].

The optimal dosage of intranasal analgesic dose ketamine remains uncertain, with three out of four studies using the practical dosage of 1 mg/kg and one study using 1.5 mg/kg [19]. Dove *et al.* [20] performed a prospective, randomized, double-blind clinical trial to compare the analgesic efficacy of three different dosages of inhaled ketamine (0.75 mg/kg, 1 mg/kg, 1.5 mg/kg). They

found no difference between the three doses of nebulized ketamine for the treatment of severe pain.

Previous results of some studies have shown the dose-independent efficacy of intranasal ketamine. A lack of increased analgesic effect at a higher dose of ketamine was reported in a clinical study in adult patients' emergency ward [21]. Moreover, dose-independent efficacy could also be because of complete saturation of the receptors at a lower dose. The recommended intranasal drug volume for mice is only 10 μL for a total nasal volume of 0.03 mL and an average nasal epithelial area of 2.8 cm^2. Despite a smaller surface area, intranasal ketamine was very effective even at the lowest dose. The low-dose efficacy of intranasal ketamine is also attributed to a proportionally larger olfactory region in mice, which makes up to 50% of the nasal cavity versus 10% in humans [22] [23] [24]. In this study, we involved a therapeutic regimen in our patients taking into consideration the analysis of previous results, and therefore, all patients received the same dose of intranasal ketamine, which is 1 mg/kg.

This study presented a pain score after nasal administration of ketamine for patients admitted to the intensive care unit of obstetrics and gynaecology; the overall effect of nebulized ketamine on pain relief was significantly marked, with a significant reduction in the VAS pain score of group A in 80% of patients after the first dose of nebulization. Our study is consistent with other studies carried out for the management of acute pain in the emergency department. An observational study by Yeaman *et al.* [25] found that 1 mg/kg of nebulized ketamine was moderately effective as a single agent in relieving severe pain in adult patients in an emergency setting. Another observational study by Andolfatto *et al.* [26] reported that nebulization significantly reduced VAS pain scores in 88% of emergency department patients.

In our structure, morphine is commonly used to reduce postoperative pain in clinical practice. Morphine consumption reflects the extent of pain in patients. In the multimodal analgesia group, the need for morphine was more marked in patients who received nebulized ketamine. Bouida *et al.* [27] demonstrated a significantly lower need for opioids in a group receiving nebulized ketamine compared to the placebo group. Shimonovich *et al.* [28] conducted a clinical trial to study the efficacy and safety of nebulized ketamine compared to IV and IM morphine for the analgesia of acute traumatic pain in the emergency department and concluded that nebulized ketamine was as effective as IV morphine for pain control. Farnia *et al.* [29] and Pouraghaei *et al.* [30] also showed that nebulized ketamine was as effective as IV morphine for pain control. Additionally, ketamine is being studied as a first-line analgesic treatment for acute pain to minimize opioid consumption [31]. In this study, we also assessed the impact of nebulized ketamine on morphine consumption after caesarean section. Overall, opioid consumption was significantly reduced in the nebulized ketamine group compared to the group receiving multimodal analgesia. Altogether, we reported that morphine consumption had significantly decreased.

The safety of analgesic drugs is as crucial as their effectiveness. Therefore, analgesics with fewer adverse effects for pain control are desired. Oliveira *et al.* [32] found no serious adverse events associated with intranasal ketamine. This is consistent with our study, in which no serious adverse effects were reported with nebulized ketamine. In this study, common non-serious and transient side effects associated with ketamine IN were dizziness, nausea, vomiting, drowsiness and dry mouth. Dizziness and nausea caused by nebulized ketamine are most likely because of the blockade of NMDA receptors in the vestibular system [33]. Cognitive disorders such as difficulty concentrating or confusion are because of the blocking effect of NMDA receptors and the reduction of presynaptic release of glutamate in the central nervous system. In addition, the anti-muscarinic effect of ketamine is a possible cause of dry mouth [34] [35].

This study had certain limitations. Firstly, the time and dose of ketamine administration differ according to the studies included. None of the studies reported the optimal clinical dose and timing of ketamine administration. Secondly, the population studied in the included studies and the baseline characteristics of the patients were different, which could increase the heterogeneity of the included studies. Most of the studies of nebulized ketamine were carried out in children and in the emergency department, therefore the outcome measures were not identical. Thirdly, the sample size was too small to obtain satisfactory results. However, this study provides reliable evidence supporting the use of ketamine in the intensive care unit of obstetrics and gynaecology.

The final results of our study suggest that the use of nebulized ketamine could decrease the pain score and reduce the consumption of postoperative intravenous analgesic drugs.

5. Conclusions

The primary outcome of nebulized ketamine use includes a significant reduction in VAS pain score. We believe that nebulized ketamine has a potential effect of reducing pain in the intensive care unit of obstetrics and gynaecology. This may be an additional analgesic modality for clinicians to provide rapid, effective and non-invasive pain relief.

The benefit of nebulized ketamine on postoperative hyperalgesia remains to be demonstrated, probably by studies on larger populations with objective methods of pain and hyperalgesia assessment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Zanos, P., *et al.* (2018) Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacological Reviews*, **70**, 621-660.

https://doi.org/10.1124/pr.117.015198

[2] ACEP Policy Statement (2021) Sub-Dissociative Dose Ketamine for Analgesia. American College of Emergency Physicians, 1-3.

[3] Motov, S., *et al.* (2018) The Treatment of Acute Pain in the Emergency Department: A White Paper Position Statement Prepared for the American Academy of Emergency Medicine. *The Journal of Emergency Medicine*, **54**, 731-736. https://doi.org/10.1016/j.jemermed.2018.01.020

[4] Rivat, C., Laulin, J.-P., Corcuff, J.-B., Célèrier, E., Pain, L. and Simonnet, G. (2002) Fentanyl Enhancement of Carrageenan-Induced Long-Lasting Hyperalgesia in Rats: Prevention by the N-Methyl-Daspartate Receptor Antagonist Ketamine. *Anesthesiology*, **96**, 381-391. https://doi.org/10.1097/00000542-200202000-00025

[5] Lavand'homme, P., De Kock, M. and Waterloos, H. (2005) Intraoperative Epidural Analgesia Combined with Ketamine Provides Effective Preventive Analgesia in Patients Undergoing Major Digestive Surgery. *Anesthesiology*, **103**, 813-820. https://doi.org/10.1097/00000542-200510000-00020

[6] Goswami, N., Aleem, M. and Manda, K. (2021) Intranasal Ketamine for Acute Pain: Behavioral and Neurophysiological Safety Analysis in Mice. *Current Therapeutic Research*, **94**, Article ID: 100627. https://doi.org/10.1016/j.curtheres.2021.100627

[7] Gadsden, J., Hart, S. and Santos, A.C. (2005) Post-Cesarean Delivery Analgesia. *Anesthesia & Analgesia*, **101**, S62-S69. https://doi.org/10.1213/01.ANE.0000177100.08599.C8

[8] Kodali, B.S. and Oberoi, J.S. (2010) Management of Postoperative Pain. UpToDate, Waltham.

[9] Lapidus, K.A., *et al.* (2014) A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder. *Biological Psychiatry*, **76**, 970-976. https://doi.org/10.1016/j.biopsych.2014.03.026

[10] Wang, J., Xu, M.S.Z., Feng, Z., Ma, R. and Zhang, X. (2020) Impact of Ketamine on Pain Management in Cesarean Section: A Systematic Review and Meta-Analysis. *Pain Physician*, **23**, 135-148. https://doi.org/10.36076/ppj.2020/23/135

[11] Pourmand, A., *et al.* (2017) Low Dose Ketamine Use in the Emergency Department, a New Direction in Pain Management. *American Journal of Emergency Medicine*, **35**, 918-921. https://doi.org/10.1016/j.ajem.2017.03.005

[12] Karlow, N., Mazer-Amirshahi, M., Royall, C., Alhawas, R. and Shesser, R. (2018) A Systematic Review and Meta-Analysis of Ketamine as an Alternative to Opioids for Acute Pain in the Emergency Department. *Academic Emergency Medicine*, **25**, 1086-1097. https://doi.org/10.1111/acem.13502

[13] Yousefifard, M., *et al.* (2019) The Efficacy of Ketamine Administration in Prehospital Pain Management of Trauma Patients: A Systematic Review and Meta-Analysis. *Archives of Academic Emergency Medicine*, **8**, 1-11.

[14] Bell, R.F. (2009) Ketamine for Chronic Non-Cancer Pain. *Pain*, **141**, 210-214. https://doi.org/10.1016/j.pain.2008.12.003

[15] Yanagihara, Y., *et al.* (2003) Plasma Concentration Profiles of Ketamine and Norketamine after Administration of Various Ketamine Preparations to Healthy Japanese Volunteers. *Biopharmaceutics and Drug Disposition*, **24**, 37-43. https://doi.org/10.1002/bdd.336

[16] Carr, D.B., *et al.* (2004) Safety and Efficacy of Intranasal Ketamine for the Treatment of Breakthrough Pain in Patients with Chronic Pain: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study. *Pain*, **108**, 17-27. https://doi.org/10.1016/j.pain.2003.07.001

[17] Dale, O., Hjortkjaer, R. and Kharasch, E.D. (2002) Nasal Administration of Opioids for Pain Management in Adults. *Acta Anaesthesiologica Scandinavica*, **46**, 759-770. https://doi.org/10.1034/j.1399-6576.2002.460702.x

[18] Jonkman, K., Duma, A., Velzen, M. and Dahan, A. (2017) Ketamine Inhalation. *British Journal of Anaesthesia*, **118**, 268-269. https://doi.org/10.1093/bja/aew457

[19] Frey, T.M., *et al.* (2019) Effect of Intranasal Ketamine vs Fentanyl on Pain Reduction for Extremity Injuries in Children: The PRIME Randomized Clinical Trial. *JAMA Pediatrics*, **173**, 140-146. https://doi.org/10.1001/jamapediatrics.2018.4582

[20] Dove, D., *et al.* (2021) Comparison of Nebulized Ketamine at Three Different Dosing Regimens for Treating Acute and Chronic Painful Conditions in the Emergency Department: A Prospective, Randomized, Double-Blind Clinical Trial. *Annals of Emergency Medicine*, **78**, 779-787. https://doi.org/10.1016/j.annemergmed.2021.04.031

[21] Yeaman F, *et al.* (2014) Sub-Dissociative-Dose Intranasal Ketamine for Moderate to Severe Pain in Adult Emergency Department Patients. *Emergency Medicine Australasia*, **26**, 237-242. https://doi.org/10.1111/1742-6723.12173

[22] Gross, E.A., *et al.* (1982) Comparative Morphometry of the Nasal Cavity in Rats and Mice. *Journal of Anatomy*, **135**, 83-88.

[23] Salameh, T.S., Bullock, K.M. and Hujoel, I.A. (2015) Central Nervous System Delivery of Intranasal Insulin: Mechanisms of Uptake and Effects on Cognition. *Journal of Alzheimer's Disease*, **47**, 715-728. https://doi.org/10.3233/JAD-150307

[24] Erdő, F., Bors, L.A., Farkas, D., Bajza, Á. and Gizurarson, S. (2018) Evaluation of Intranasal Delivery Route of Drug Administration for Brain Targeting. *Brain Research Bulletin*, **143**, 155-170. https://doi.org/10.1016/j.brainresbull.2018.10.009

[25] Li, X., Hua, G. and Peng, F. (2021) Efficacy of Intranasal Ketamine for Acute Pain Management in Adults: A Systematic Review and Meta-Analysis. *European Review for Medical and Pharmacological Sciences*, **25**, 3286-3295.

[26] Andolfatto, G., *et al.* (2013) Intranasal Ketamine for Analgesia in the Emergency Department: A Prospective Observational Series. *Academic Emergency Medicine*, **20**, 1050-1054. https://doi.org/10.1111/acem.12229

[27] Bouida, W., *et al.* (2020) Effect on Opioids Requirement of Early Administration of Intranasal Ketamine for Acute Traumatic Pain. *The Clinical Journal of Pain*, **36**, 458-462. https://doi.org/10.1097/AJP.0000000000000821

[28] Shimonovich, S., *et al.* (2016) Intranasal Ketamine for Acute Traumatic Pain in the Emergency Department: A Prospective, Randomized Clinical Trial of Efficacy and Safety. *BMC Emergency Medicine*, **16**, Article No. 43. https://doi.org/10.1186/s12873-016-0107-0

[29] Farnia, M.R., *et al.* (2017) Comparison of Intranasal Ketamine versus IV Morphine in Reducing Pain in Patients with Renal Colic. *American Journal of Emergency Medicine*, **35**, 434-437. https://doi.org/10.1016/j.ajem.2016.11.043

[30] Pouraghaei, M., Moharamzadeh, P., Paknezhad, S.P., Rajabpour, Z.V. and Soleimanpour, H. (2021) Intranasal Ketamine versus Intravenous Morphine for Pain Management in Patients with Renal Colic: A Double Blind, Randomized, Controlled Trial. *World Journal of Urology*, **39**, 1263-1267. https://doi.org/10.1007/s00345-020-03319-4

[31] Balzer, N., *et al.* (2021) Low-Dose Ketamine for Acute Pain Control in the Emergency Department: A Systematic Review and Meta-Analysis. *Academic Emergency Medicine*, **28**, 444-454. https://doi.org/10.1111/acem.14159

[32] Oliveira, J.E.S.L., Lee, J.Y., Bellolio, F., Homme, J.L. and Anderson, J.L. (2020)

Intranasal Ketamine for Acute Pain Management in Children: A Systematic Review and Meta-Analysis. *American Journal of Emergency Medicine*, **38**, 1860-1866. https://doi.org/10.1016/j.ajem.2020.05.094

[33] Soto, E. and Vega, R. (2010) Neuropharmacology of Vestibular System Disorders. *Current Neuropharmacology*, **8**, 26-40. https://doi.org/10.2174/157015910790909511

[34] Newcomer, J.W., Farber, N.B. and Olney, J.W. (2000) NMDA Receptor Function, Memory and Brain Aging. *Dialogues in Clinical Neuroscience*, **2**, 219-232. https://doi.org/10.31887/DCNS.2000.2.3/jnewcomer

[35] Durieux, M.E. (1995) Inhibition by Ketamine of Muscarinic Acetylcholine Receptor Function. *Anesthesia & Analgesia*, **81**, 57-62. https://doi.org/10.1213/00000539-199507000-00012