

Topical (S)-ketamine for pain management of postherpetic neuralgia *

(S)-cetamina tópica no tratamento da dor da neuralgia pós-herpética

Guilherme Antonio Moreira de Barros¹

Ademir Massarico Braz³

Marcos Aristoteles Borges⁵

Hélio Amante Miot²

Flávia Ramos⁴

Abstract: Herpes zoster infection may cause postherpetic neuralgia, which is defined by prolonged pain predominantly mediated by central nervous system hypersensitivity. This phenomenon may be reversed by (S)-ketamine (SKET), but its use results in intolerable side effects, while its topical administration seems to be safe. It is a cross-over design study with 12 patients randomly divided into two groups. There was a significant effect of time on pain intensity, but no statistical difference in pain scores for SKET or placebo use in this sample in this treatment regimen. Only few mild cutaneous reactions were observed with topical SKET use.

Keywords: Administration, topical; Ketamine; Neuralgia, postherpetic

Resumo: O herpes zoster pode resultar em neuralgia pós-herpética, que é definida como dor prolongada predominantemente mediada por hiperatividade do sistema nervoso central. Esse fenômeno pode ser revertido pelo uso da (S)-cetamina, mas seu uso pode resultar em efeitos adversos intoleráveis, enquanto seu uso tópico parece ser seguro. Este é um estudo "cross-over" com 12 pacientes distribuídos aleatoriamente em dois grupos. Observou-se efeito importante do tempo sobre a intensidade da dor, mas não houve diferenças estatísticas do uso da SKET, ou do placebo, no escore da dor, neste esquema de tratamento. Discretas reações cutâneas foram observadas com o uso de SKET tópico.

Palavras-chave: Administração tópica; Ketamina; Neuralgia pós-herpética

Herpes zoster (HZ) follows a decrease in cellular immunity caused by aging or immunosuppression. It is usually more severe in older adults and among immunocompromised patients. It is estimated that approximately 1 in 3 individuals will develop herpes zoster in their lifetime.¹ Postherpetic neuralgia (PHN), a debilitating condition, is the most common chronic complication of HZ. It is defined by prolonged pain in the same dermatome where the HZ eruption occurred. Its incidence increases with age, and it is estimated to affect 10 to 15 percent of all patients with HZ, most commonly people over 60 years old.^{2,3}

PHN results from damaged sensory nerves, causing neuropathic pain (NP). Effective therapy often requires use of multiple drugs, which impacts the quality of life of the elderly, who are usually taking a lot of medicine. Unfortunately, there is no intervention that promptly relieves PHN.³

PHN, as many other types of NP, is characterized by central nervous system hypersensitivity, which is predomi-

nantly mediated by N-methyl-D-aspartate receptors (NMDA). (S)-ketamine (SKET) is a NMDA antagonist that has been used for the management of some NP, although its use is currently classified as a third-line medication in the management of these conditions. Additionally, SKET has been proved to reverse hyperalgesia and the wind-up phenomenon observed in PHN.³

When SKET is systemically administered (e.g. for general anesthesia), some side effects may occur, including somnolence, hallucination, nystagmus, among others.³ Alternative administration routes have been studied, and the topical one has been proved to be the safest regarding occurrence of side effects.⁴ Some patients with NP showed high levels of satisfaction when a topical ketamine cream associated with topical amitriptyline was used. However, these results have not yet been confirmed by randomized controlled trials.³ This study aims to evaluate the effectiveness and

Received on 22.12.2011.

Approved by the Advisory Board and accepted for publication on 23.01.2012.

* Work conducted at the Service of Pain Management and Palliative Care, Clinics Hospital, School of Medicine of Botucatu – Universidade Estadual Paulista “Julio de Mesquita Filho” (FMB-UNESP) and at the Department of Anesthesiology, School of Medicine of Botucatu – Universidade Estadual Paulista “Julio de Mesquita Filho” (FMB-UNESP) – Botucatu (SP), Brazil.

Conflict of interest: Professor AM de Barros gives lectures and has already participated in multicenter studies funded by Laboratórios Cristália - Produtos Químicos e Farmacêuticos Ltda

Financial funding: This study was financially supported by scholarships granted to Ademir M. Braz and Flávia Ramos through the Institutional Program of Scholarships for Scientific Initiation – PIBIC. Topical ketamine was kindly provided by Laboratórios Cristália – Produtos Químicos e Farmacêuticos Ltda

¹ PhD – Assistant Professor, Department of Anesthesiology, School of Medicine of Botucatu (Faculdade de Medicina de Botucatu) – Universidade Estadual Paulista “Julio de Mesquita Filho” (FMB-UNESP) – Botucatu (SP), Brazil.

² PhD – Assistant Professor, Department of Dermatology and Radiotherapy, School of Medicine of Botucatu - Universidade Estadual Paulista “Julio de Mesquita Filho” (FMB-UNESP) – Botucatu (SP), Brazil.

³ Degree in Medicine – Resident physician, Department of Surgery and Orthopedics, School of Medicine of Botucatu - Universidade Estadual Paulista “Julio de Mesquita Filho” (FMB-UNESP) – Botucatu (SP), Brazil.

⁴ Degree in Medicine – Resident Physician, Department of Internal Medicine, School of Medicine of Botucatu - Universidade Estadual Paulista “Julio de Mesquita Filho” (FMB-UNESP) – Botucatu (SP), Brazil.

⁵ MSc – Assistant Physician, Oncology Service, Clinics Hospital (Hospital das Clínicas), School of Medicine of Botucatu - Universidade Estadual Paulista “Julio de Mesquita Filho” (FMB-UNESP) – Botucatu (SP), Brazil.

©2012 by Anais Brasileiros de Dermatologia

TABLE 1: Pain (median NVS) at three different moments of the study

	M1		M2		M4	
	Higher NVS	Current NVS	Higher NVS	Current NVS	Higher NVS	Current NVS
SKET	9	5	5	0	4.5	3
Placebo	10	4.5	4	0.5	4.5	2

safety profile of topical SKET 1% ointment in the management of PHN-related pain.

The project was approved by the Ethics Committee Clinical Research of the institution as a double-blind, randomized, placebo-controlled, cross-over study. PHN patients seen at the Pain Management Clinic (HC-FMB-Unesp, Botucatu-SP), older than 18 years old and able to understand the Numerical Verbal Scale (NVS: 0 to 10) were invited to take part in the study.⁵ They were instructed to inform the higher NVS in the period between medical appointments, as well as the current NVS score at each medical visit.⁶

PHN was defined as persistent pain in the site of HZ lesions, for at least 30 days after skin healing. Those presenting abnormal biochemical blood tests and skin lesions in the area of pain were not included in the study. All of the patients were regularly using stable doses of drugs recommended to manage PHN (amitriptyline and gabapentine) for at least one month prior to their enrollment in the study.

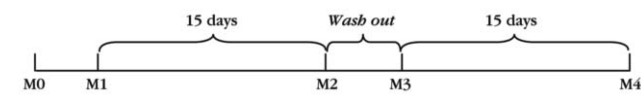
As a cross-over design, both SKET and placebo ointment were used by the same patient in different periods of time. The 12 patients included in the study were randomly divided into two groups and instructed to apply the ointment on the site of pain four times a day.

After 15 days of treatment, there was a washout period of seven days. After the washout period, treatments were inverted and carried out for the same time period, and the patients were instructed to act as described above. The patients had five medical appointments (Figure 1). All of them underwent blood cell count, as biochemical tests, prior and after the conclusion of the study period.

NVS scores were analyzed by a linear mixed model, and their correlation was assessed by Spearman's Rho (r_s). Statistical significance was set at $p < 0.05$. Data were analyzed by SPSS 20.0.

REFERENCES

1. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. *Mayo Clin Proc.* 2009;84:274-80.
2. Sabatowski R, Gálvez R, Cherry DA, Jacquot F, Vincent E, Maisonnobe P, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain.* 2004;109:26-35.
3. Collins S, Sigtermans MJ, Dahan A, Zuurmond WWA, Perez RSGM. NMDA receptor antagonists for the treatment of neuropathic Pain. *Pain Med.* 2010;11:1726-42.
4. Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. *Pain.* 2009;146:18-25.
5. Holdgate A, Asha S, Craig J, Thompson J. Comparison of a verbal numeric rating scale with the visual analogue scale for the measurement of acute pain. *Emerg Med (Fremantle).* 2003;15:441-6.
6. Poziomczyk CS, Köchell B, Dornelles MA, Dornelles SIT. Avaliação da dor em cirurgia de ceratose actínicas. *An Bras Dermatol.* 2011;86:645-50.

**FIGURE 1:** Study schema

The average age of the individuals in the study was 71.7 years, and 66.7% were female. Two patients reported mild allergic skin reaction (local pruritic erythematous plaques) associated with the use of the ointment, but it did not prevent them from continuing in the study. After the end of the research, both groups of patients decided to keep using the topical SKET formulated in a gel compound, without any side effects.

The medians of higher (between medical appointments) and current (at the moment of medical appointment) NVS before and after use of SKET are displayed in Table 1. There was a significant effect of time on NVS improvement for both groups in M1 x M2 comparison ($p < 0.05$). The use of SKET showed no statistical improvement in NVS scores at any time ($p > 0.1$).

The female gender was associated with higher NVS scores ($p = 0.01$) in M1xM2 comparison, but not with current NVS assessments. As age was not associated with NVS, it was not included in any of the analyses.

There was a significant correlation between current NVS scores in M1 and M4 ($r_s > 0.7$; $p < 0.01$) and no statistical difference in NVS scores for SKET or placebo for this sample in this treatment regimen. Despite the occurrence of a few mild cutaneous reactions, topical SKET may be considered safety.

The NVS improvement of both treatment groups evidenced by M2, but not by M4 can be related to the Hawthorne effect (of being cared for or observed) rather than to time or oral treatment. Further research should be conducted with a larger sample in order to investigate patients' subgroups, drug association (e.g. topical amitriptyline) and percutaneous delivery techniques to better understand the role of topical SKET in the management of PHN. □

MAILING ADDRESS:

Guilherme Antonio Moreira de Barros
Departamento de Anestesiologia da Faculdade de
Medicina de Botucatu - Universidade Estadual
Paulista "Julio de Mesquita Filho"
Campus de Rubião Jr
18618-970 Botucatu, SP
E-mail address: barros@fmb.unesp.br

How to cite this article: Barros GAM, Miot HA, Massarico AM, Ramos F, Borges MA. Topical (S)-ketamine for pain management of postherpetic neuralgia. *An Bras Dermatol.* 2012;87(3):00-0.