



# Herpes Simplex Reactivation After Surgical Treatment of Trigeminal Neuralgia: A Retrospective Cohort Study

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**BACKGROUND:** Herpes simplex virus (HSV) reactivation after surgery for trigeminal neuralgia has long been recognized. Only a few studies to date have focused on this complication, and its actual incidence remains unknown. The aim of this study was to investigate the incidence of postoperative herpes labialis (HL) in a cohort of patients treated with either percutaneous balloon compression or microvascular decompression to identify potentially significant differences between different treatments.

**METHODS:** A total of 92 patients who were operated on for TN with microvascular decompression (group A) or percutaneous balloon compression (group B) in the period 2010–2017 were retrospectively evaluated. The 2 subgroups of patients were compared according to history of previous HL and incidence of postoperative HL.

**RESULTS:** The final cohort comprised 56 male and 36 female patients. Average age was 58.50 years; 30 male patients belonged to group A and 26 male patients belonged to group B. Lifetime incidence of episodes of HL before surgery in 18/58 patients in group A (31.0%) and 12/34 patients in group B (35.3%), with no statistically significant difference among subgroups. Postoperatively, 1/56 patients in group A (1.7%) experienced HL compared 5/34 patients in group B (14.7%), with a strongly statistically significant difference between the 2 subgroups.

**CONCLUSIONS:** In our clinical experience, herpes simplex virus reactivation after surgery for trigeminal neuralgia is not so rare and is still not completely understood. Postoperative herpes simplex virus reactivation could be due to a direct

mechanical injury on gasserian ganglion neurons, which is more common after percutaneous balloon compression.

## INTRODUCTION

The reactivation of herpes simplex virus (HSV) after surgical treatment of trigeminal neuralgia (TN) was first reported in 1905 by Cushing.<sup>1</sup> However, only a few studies to date have focused on this complication, and its actual incidence remains unknown. It has been suggested that HSV could be involved in the pathogenesis of TN and/or that surgical efficacy could depend on HSV reactivation.<sup>2–5</sup> The literature reports HSV reactivation after microvascular decompression (MVD), percutaneous balloon compression (PCB), surgical and radiofrequency rhizotomy, and glycerol neurolysis, although actual recurrence after these procedures is not well defined.<sup>2</sup> It has been suggested that postsurgical HSV reactivation is a marker of the effect that the different treatments have on the trigeminal ganglion, but the actual effect along with its pathogenesis and its clinical impact has been poorly understood. The present study reports our experience with surgical management of TN concerning specifically the incidence of postoperative herpes labialis (HL) in a wide cohort of patients treated with either PCB or MVD to identify possible significant differences between the different treatments regarding postoperative reactivation of the viral cytolitic effect.

## MATERIALS AND METHODS

### Study and Setting

In this retrospective observational cohort study, a retrospective analysis was performed of the incidence of postoperative HL as a

### Key words

- Herpes labialis
- Herpes simplex
- Microvascular decompression
- Percutaneous balloon compression
- Treatment
- Trigeminal neuralgia

### Abbreviations and Acronyms

- HL:** Herpes labialis
- HSV:** Herpes simplex virus
- MVD:** Microvascular decompression
- PBC:** Percutaneous balloon compression
- TN:** Trigeminal neuralgia

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postoperative complication occurring after different surgical treatments of a cohort of patients with TN who underwent surgery between 2010 and 2017 in neurosurgical departments of the Policlinico Umberto I University Hospital of Rome and the San Carlo Borromeo Hospital of Milan. The study was approved by the institutional review board. Before the surgical procedure, all patients gave informed written consent after receiving appropriate information. Data reported in the study have been completely anonymized. The different treatments were not randomized, but rather performed according to surgical indications as detailed subsequently. Data were collected by an independent researcher, who reviewed the radiologic and clinical records. This researcher was aware of the treatment modality (MVD or PBC) but was blinded to the objective of the study.

Patient data (age, sex, presence or absence of an obvious neurovascular conflict, neurologic status before and after surgery, preoperative and postoperative incidence of HL) were recorded. TN diagnosis was verified according to the usual clinical criteria (presence of trigger points, plain neurologic examination of cranial nerve V function, paroxysmal pain). Drug resistance, defined as a failure in pain control with carbamazepine at a maximum dosage of 1200 mg per day for 6 months, was also verified.

### Participants and Eligibility

From the initial cohort of surgically treated patients with TN, we excluded patients whose preoperative and postoperative radiologic investigations and surgical and clinical records were incomplete from the final cohort. We also excluded patients whose length of follow-up was shorter than 1 year or whose clinical records after 1 year were incomplete.

All patients included in the present cohort underwent a similar dedicated follow-up protocol that consisted of postoperative examinations at 1 month, 6 months, and 12 months. Thereafter, in the absence of further problems, the patients were re-evaluated once per year. The clinical events collected for the present study encompass the first 12 months of follow-up.

A total of 92 patients met the aforementioned inclusion and exclusion criteria, and their clinical records were retrospectively re-evaluated for this study. Of 92 patients, 58 received MVD and were assigned to group A, and 34 received PBC and were assigned to group B.

All included patients underwent preoperative brain magnetic resonance imaging including a high field 1.5T or 3.0T volumetric study with the following sequences before and after intravenous administration of paramagnetic contrast agent: T2-weighted, isotropic volumetric T1-weighted magnetization-prepared rapid acquisition gradient echo, and fluid attenuated inversion recovery. Angiographic contrast-enhanced magnetic resonance imaging and constructive interference in steady state completed the protocol for TN investigations.

All MVD procedures (group A) were performed according to the technique reported by McLaughlin and Jannetta<sup>6</sup> using polytetrafluoroethylene (Teflon) balls. The patients who underwent this technique had a primary form of TN, and magnetic resonance imaging showed a neurovascular conflict. All procedures were performed with a Leica M500N OHS-1 Operative Microscope (Leica Microsystems GmbH, Wetzlar, Germany). All PBC procedures (group B) were performed according to the technique reported by Mullan and Lichtor.<sup>7</sup> The patients who underwent this technique had secondary

TN or pain recurrence after a first MVD procedure. For both subgroups, a standard total intravenous anesthesia protocol with propofol (1 mg/kg) and remifentanyl (0.5 µg/kg/minute) was used. Muscle relaxants were routinely administered.

The clinical history of previous HL was recorded for every patient included in the final cohort in dichotomous fashion (0/1—no/yes). The incidence of postoperative HL was considered in the time span of the clinical follow-up and recorded in a similar dichotomous fashion (0/1—no/yes). The treatment performed was also considered as a dichotomous variable. HL was diagnosed clinically.

### Statistical Analysis and Potential Source of Bias

The sample was analyzed with SPSS Version 18 software (SPSS Inc., Chicago, Illinois, USA). Comparisons between nominal variables were made with  $\chi^2$  test odds ratio with respective confidence interval completing the first level examination. Wilcoxon signed rank and McNemar tests were performed to identify treatment-related significant differences in the postoperative incidence of HL. Threshold of statistical significance was considered  $P < 0.05$ . A potential source of bias is expected from narrowness of the sample, which nevertheless, concerning the endpoints selected, presents an excellent post hoc statistical estimated power ( $1 - \beta = 0.902$  for  $\alpha = 0.05$  and effect size = 0.643).

## RESULTS

### Descriptive Data

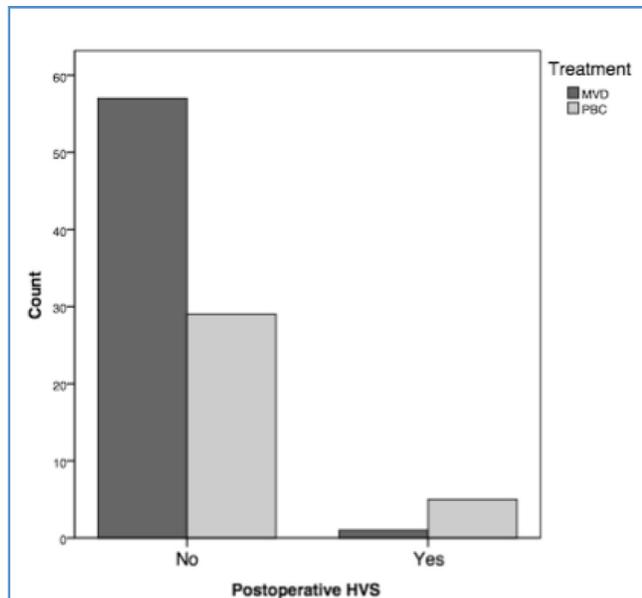
Between 2010 and 2017, 92 patients with TN underwent surgery and were retrospectively evaluated for this study. The final cohort consisted of 56 men and 36 women with average age 58.50 years; 30 male patients belonged to group A, and 26 male patients belonged to group B. The lifetime incidence of episodes of HL before surgery was 18 of 58 patients in group A (31.0%) and 12 of 34 patients in group B (35.3%). Postoperative incidence of HL was 1 of 56 (1.7%) patients in group A and 5 of 34 patients (14.7%) in group B.

### Outcome Data and Main Results

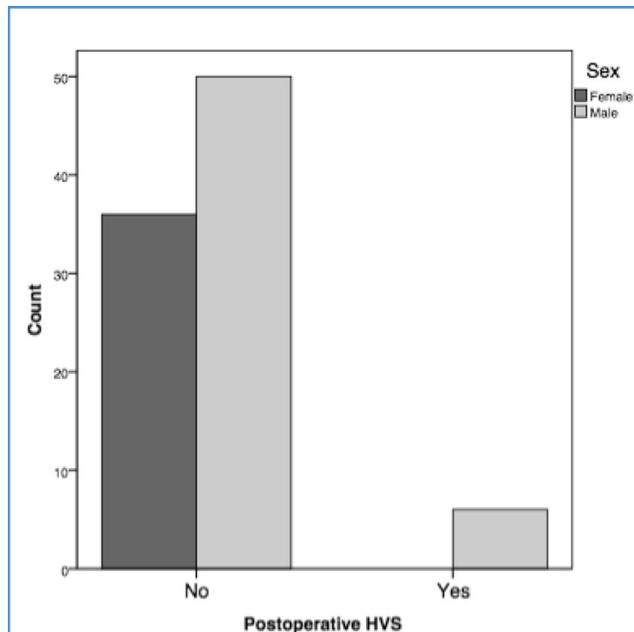
A statistically significant association between PBC treatment and the incidence of postoperative HL was found ( $P = 0.025$ ) (Figure 1). In our cohort, PBC treatment was more likely to be associated with postoperative HL. Conversely, there was no statistically significant association between preoperative history of HL and the different treatments ( $P = 0.422$ ) (Figure 2). There was also no statistically significant difference between the age of patients who had preoperative HL and the patients who did not. Moreover, there was no statistically significant difference concerning age of patients between the 2 subgroups A and B. Sex showed no statistically significant association with preoperative incidence of herpetic symptoms, whereas there was a statistically significant association between male sex and a higher postoperative incidence of HL ( $P = 0.046$ ) (Figure 3). As expected, preoperative and postoperative incidence of HL were strongly associated ( $P = 0.001$ ) (Figure 4).

### Complications

In 2 cases, a transitory diplopia was noted after PBC procedures, which spontaneously regressed after 2 weeks. No further complications were recorded.



**Figure 1.** Percutaneous balloon compression treatment and the incidence of postoperative herpes labialis. HSV, herpes simplex virus; MVD, microvascular depression; PBC, percutaneous balloon compression.

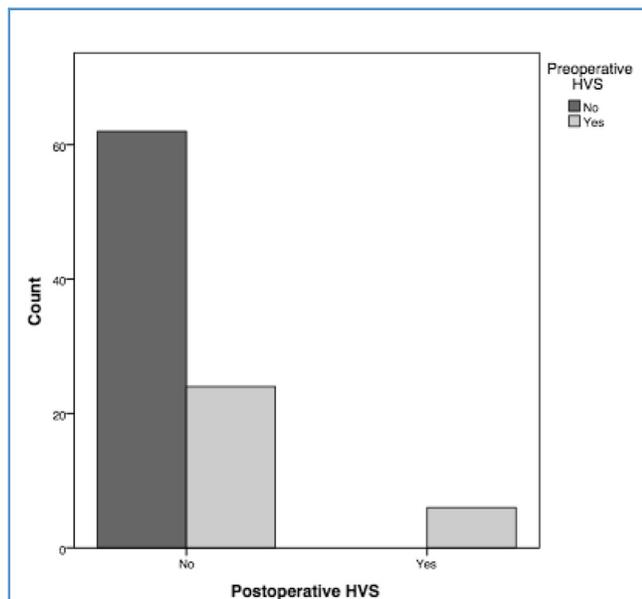


**Figure 3.** Association between male sex and higher postoperative incidence of herpes labialis. HSV, herpes simplex virus.

**DISCUSSION**

Several authors have argued that surgical TN treatments totally or partially alter the function of the ganglion neurons resulting in the alleviation of pain. Moreover, several authors have suggested that

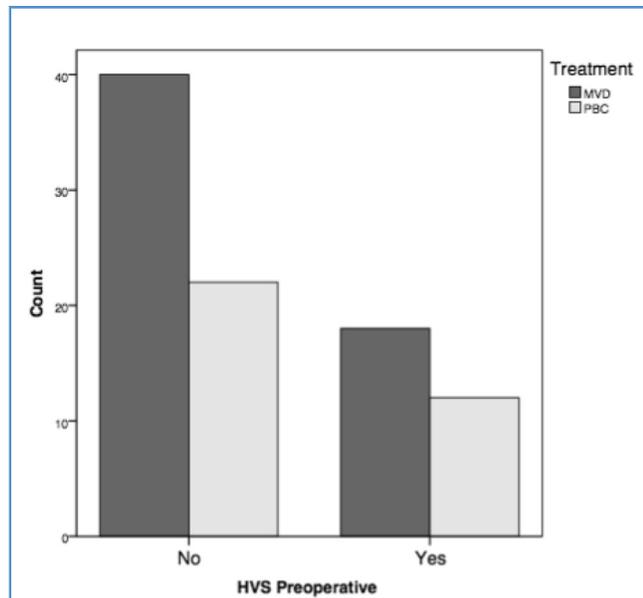
mechanical injury could play a role in the effectiveness of the surgical treatment.<sup>3,4,8-12</sup> In the present study, we analyzed a series of patients with TN who were operated on with MVD and PBC. In MVD, a suboccipital craniotomy is performed to expose the borders of the transverse and sigmoid sinuses. The dura mater is incised, and cerebrospinal fluid is carefully drained to expose the cerebellopontine angle. The trigeminal nerve is seen draped over a compressive artery. It is dissected away from the nerve, and Teflon pledgets are placed between the nerve and compressive artery to maintain their separation.



**Figure 2.** Preoperative history of herpes labialis and the different treatments performed. HSV, herpes simplex virus.

Percutaneous treatments, such as radiofrequency rhizotomy, glycerol rhizotomy, and PBC, involve entry of a needle through the foramen ovale to introduce injury to the trigeminal nerve. A needle is introduced 2.5 cm lateral to the labial fissure. The needle is advanced medial to the ramus of the jaw into the foramen ovale using oblique view fluoroscopic imaging. A lateral radiograph is used to confirm the location of the needle. Once positioned, trigeminal nerve injury is performed.<sup>13</sup>

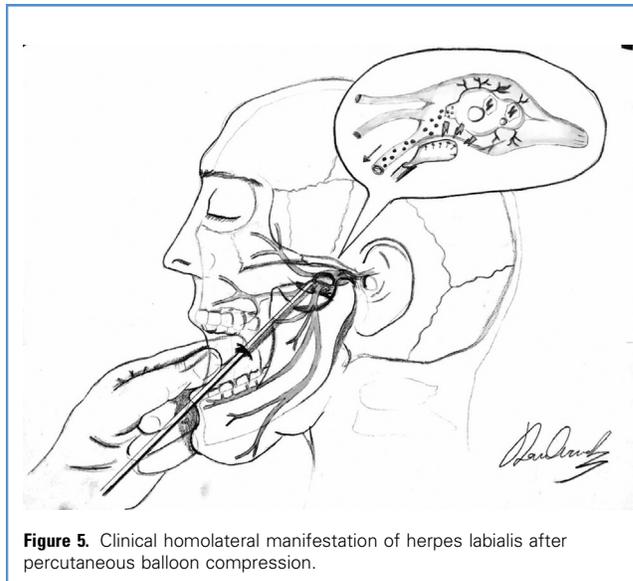
HSV reactivation, which can occur after MVD or other types of TN surgery, highlights an altered trigeminal ganglion neuron function. A previous historical study suggested that minimal stimulation or unapparent trauma to the trigeminal rootlets is sufficient to activate latent HSV in humans.<sup>14</sup> With contemporary microsurgical techniques and equipment, the stimulation on the sensory root is remarkably reduced, although in the setting of PBC, direct mechanical injury to a trigeminal ganglion could per se explain the clinical efficacy of the procedure. The concept of mechanical injury as a causative agent of pain relief in TN surgery has been discussed by many authors in the literature.<sup>1,4,5,15,16</sup> This hypothesis would be congruent with a trigeminal ganglion basis of TN as reported by Devor et al.<sup>4</sup>



**Figure 4.** Association between preoperative and postoperative incidence of herpes labialis. HSV, herpes simplex virus; MVD, microvascular depression; PBC, percutaneous balloon compression.

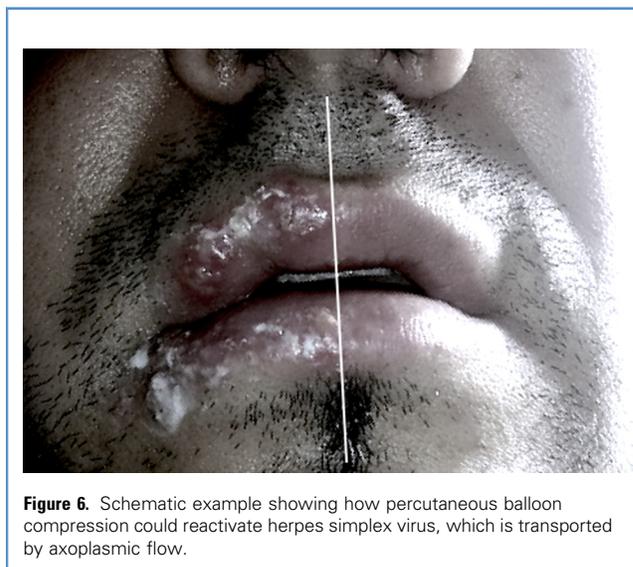
Recurrent HL is a common, widespread infectious disease primarily caused by HSV. Classic labial lesions involve the sequential development of erythema, papules, vesicles, pustules, and ultimately scabs. Viral titers peak in the first 24 hours after lesion formation, at which time most lesions are in the vesicle stage. Following primary infection, HSV establishes a latent infection in neuronal cells in human peripheral ganglia. However, the detailed mechanisms of viral latency and reactivation have yet to be unraveled. Latent viral DNA exists in an “end-less” state, where the ends of the virus genome are joined to form structures consistent with unit length episomes.<sup>17</sup> When HSV reactivation occurs in latently infected neurons, HSV is transported by axoplasmic flow to mucosal surfaces, resulting in an asymptomatic colonization of the virus or a clinically relevant infection.<sup>5</sup> During HSV latency, viral DNA is present in ganglion neuronal nuclei in episomal form.<sup>18</sup>

Although the mechanisms underlying HSV reactivation are incompletely understood, experimentally infected animal ganglia manipulation may result in reactivation of virus.<sup>19</sup> Several authors have reported that viral reactivation is likely triggered by stressors, such as pregnancy, diabetes, immunodeficiency, fatigue, infection, and dental procedures.<sup>19-22</sup> Reactivation of HSV as a possible result of TN surgery may be a reaction to the stress of surgery; although this seems an unlikely explanation, it needs to be considered. After TN surgery, both clinical HSV reactivation and subclinical reactivation have been well described.<sup>23,24</sup> In contrast, HSV reactivation after other neurosurgical procedures is uncommon. Reported cases of HSV infection and reactivation after different neurosurgical procedures mainly consist of HSV encephalitis after skull base procedures<sup>25</sup> and after cerebral surgery.<sup>26</sup>



**Figure 5.** Clinical homolateral manifestation of herpes labialis after percutaneous balloon compression.

It is suggested that altered ganglion neuron function resulting from TN surgery alters central nervous system pain transmission as a result of an altered ganglion neuropeptide transport through the central nervous system. It has been argued that a rapid hyperalgesic stimulation, such as activation of stress receptors in a paraganglionic tissue, can regulate epinephrine signaling via adrenoceptors by G protein-coupled receptor kinase 2. It is transduced in an augmented production of epinephrine.<sup>27</sup> However, epinephrine is regulated by the sympathetic nervous system. Iontophoresis of epinephrine has been used to induce HSV-I reactivation in the rabbit ocular model of infection as well as in mice and nonhuman primates, demonstrating the ability of epinephrine to impact HSV-I. The mechanism through which



**Figure 6.** Schematic example showing how percutaneous balloon compression could reactivate herpes simplex virus, which is transported by axoplasmic flow.

these stress factors impact HSV disease severity and recurrences is thought to be suppression of the immune system, permitting the viruses to escape immune surveillance.<sup>28</sup> According to several reports, surgically induced alterations in trigeminal ganglion neuron function resulted in HSV reactivation.<sup>29,30</sup> The relationship between effective TN surgery and HSV reactivation highlighting a gasserian ganglion neuronal injury may explain the effectiveness of the neurosurgical treatment itself.

In our experience, HL had a propensity to be exacerbated more often after PBC compared with MVD (Figures 5 and 6). As for other TN surgery-related complications, HL is usually a transient problem. The exact incidence of such a complication could be underestimated because of its often mild and brief appearance and because the herpetic eruptions usually appear a few days after the surgery, when the patients have already been discharged. Acyclovir was found to control HSV reactivation in a high-impact randomized trial,<sup>31</sup> but nucleoside antiviral drugs are now widely used to relieve the symptoms of HSV and hasten the

disappearance of lesions. Nucleoside antiviral drugs approved for treatment of HSV in the United Kingdom and United States include acyclovir, penciclovir, famciclovir, and valaciclovir.<sup>32,33</sup> In cases with recurrent HL, prophylactic antiviral therapy may be considered, although strong evidence is lacking.<sup>5,21</sup>

## CONCLUSIONS

In our clinical experience, HSV reactivation after TN surgery can be a common postsurgical symptom, despite the few cases previously reported, and it still is a not completely understood event. The present study emphasizes HSV reactivation as a marker of mechanical injury of ganglion neurons, occurring more commonly after PBC than after MVD. The observed relationship between clinically effective PBC procedures and a high incidence of HSV reactivation suggests that surgery does alter ganglion neuron function, in turn stimulating HSV reactivation.

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