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SHORT COMMUNICATION

Herpes simplex virus reactivation and dental procedures

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Abstract
Objectives Dental extraction is reported to trigger recurrent herpes labialis (RHL).
Aim This aims to prospectively study the clinical occurrence of RHL and the oral herpes simplex virus type 1 (HSV-1) viral shedding before and 3 days after different dental procedures.
Materials and methods Oral HSV-1 DNA was measured by real-time PCR before and 3 days after dental procedures of the inferior dentition in 57 immunocompetent patients (mean age 32.4 years) who were selected and divided into four distinct subgroups (dental inspection without anesthesia, $n=19$; dental filling under local anesthesia, $n=14$; molar extraction under local anesthesia, $n=15$; and molar extraction under general anesthesia, $n=9$) and compared to 32 healthy controls (mean age 33 years).
Results None of the patients suffered from RHL at day 3. Oral HSV-1 DNA was detected before and after procedure in 1.7 % (1/57) and 5.3 % (3/57), respectively [dental inspection without anesthesia, 5.3 % (1/19); molar extraction under local anesthesia, 6.7 % (1/15); and molar extraction under general anesthesia, 11 % (1/9)]. None of the controls presented RHL or detectable oral HSV-1 DNA. There was no statistically significant difference between the study groups and controls.
Conclusion Molar extraction increases the risk of oral HSV-1 shedding but not of RHL. Procedure-related nerve damage probably accounts for HSV reactivation.
Clinical relevance Antiviral prophylaxis for RHL is not routinely recommended for dental procedures, regardless of a prior history of RHL.

Keywords Herpes simplex virus · Herpes labialis · Dental extraction · Anesthesia · Triggering factors

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Introduction

Reactivation from latent herpes simplex virus type 1 (HSV-1) infection in the trigeminal nerve ganglia causes infraclinical (recurrence) or clinical (recrudescence) recurrent herpes labialis (RHL) [1, 2]. RHL occurs in 16–38 % of the population [3–5]. RHL commonly recurs at the same anatomical site, in general the vermillion border of the upper or lower lip. RHL outbreaks are typically similar in duration, pain, and lesion severity [1, 2, 6, 7].

Systemic stimuli including menses, fever, iatrogenic immunosuppression, and psychological stress may trigger RHL. Lip injury, exposure to cold or heat, UVB radiation, wind, facial laser therapy, and trauma constitute local triggers [1, 2, 6, 8].

RHL may occur after dental procedures, prosthodontic treatments, surgery of the oral cavity and orofacial fractures, and neurosurgical procedures of the trigeminal ganglia [9–21]. Sometimes, HSV-1 infections after dental extractions may be particularly severe and extend beyond the usual site of recurrence. The time interval between the dental intervention and RHL varies between 2 and 3 days [22]. Intravenous antiviral therapy is usually required for these patients [22].

Whether a specific dental and/or anesthetic procedure presents an increased risk for HSV reactivation remains

undetermined. Furthermore, there are no data on the incidence of dental procedure-related RHL (DIRR). It is not known whether prophylactic antiviral therapy should be routinely recommended or only in selected patients. It is also unclear whether a prior history of RHL is a risk factor for DIRR.

A single-center prospective pilot study evaluated the occurrence of clinical DIRR and measured by real-time PCR the HSV viral load of the oral cavity before and after a series of dental procedures.

Material and methods

The study was performed in accordance with the Helsinki Convention on Human Rights. The institutional ethic committee approved the design of the study. The patients were informed about the procedures and were invited to fill in a medical questionnaire. All the patients signed the informed consent forms.

Patients

Patients randomly attending the dentistry department for conventional dental care (dental inspection without anesthesia, dental filling with local anesthesia, molar extraction with local anesthesia, and molar extraction under general anesthesia) were asked to participate in this study. Data were gathered concerning age, sex, and a prior history of RHL and/or DIRR. Immunocompromised patients, pregnant women, and patients presenting RHL at the time of the study were excluded. Furthermore, patients having used antiviral agents during and 1 month prior to the study were also excluded.

The selected patients (n=57, m=27, f=30, mean age 32.4 years) were prospectively divided into four distinct groups (dental inspection without anesthesia, n=19, m=9, f=10, mean age 54 years; dental filling with local anesthesia, n=14, m=10, f=4, mean age 31.4 years; molar extraction with local anesthesia, n=15, m=3, f=11, mean age 28 years; and molar extraction under general anesthesia n=9, m=4, f=5, mean age 16.2 years). Only patients with procedures concerning the inferior dentition were included in order to reduce the number of variables and to limit the number of study groups.

Age-matched healthy individuals were included as controls (m=6, f=26, mean age 33 years).

Both patient groups were subdivided in those with and without a previous history of RHL (less or more than four outbreaks per year).

Clinical examination for RHL was performed before and 3 days after the dental intervention by a dermatologist. One month after the study, the patients were interviewed by phone to inquire whether RHL had occurred since the last visit.

DNA sampling

In order to study the relation between the dental procedure and eventual local procedure-related HSV shedding, HSV DNA was sampled by local swabbing with a cervibroom (ThinPrep®, Hologic, Inc., Bedford, MA, USA) the internal and external mucosal aspects of the inferior jaw at the immediate vicinity of the dental procedure under standardized conditions. The cervibroom was subsequently immerged in the transport medium vial.

Real time PCR

The DNA extraction was performed on 250 μl of ThinPrep solution by using NucleoSpin Tissue (Machery-Nagel, Düren, Germany) according the manufacturer's instructions. All extracted samples were run by the Argene HSV1 HSV2 R-gene™ assay (Celtic Molecular Diagnostics, Mowbray, South Africa) based on the detection of the amplified product with a TaqMan probe. PCR amplification was performed with a LightCycler® 480 instrument (Roche Diagnostics SA, Vilvoorde, Belgium). Ten microliters of DNA sample was subjected to PCR. Quantification of samples was performed using a standard curve of known HSV-1 and HSV-2 DNA concentrations. The results were reported in copies/milliliter of sample and validated by the sensitivity control, negative control provided with the kit, and a universal inhibition control (Diagenode, Liege, Belgium). Three replicate samples were analyzed from each patient. The analytical sensitivity is two copies/PCR for the two viruses, which is similar to other available kits for the detection of HSV but also other DNA viruses, such as CMV, HPV, etc.

Statistics were performed using the chi-square test for comparison of proportions, using the study groups and control group irrespective of the prior history of RHL in order to have the highest possible number of patients in every group.

Results

None of the patients and controls presented a prior history of DIRR. At days 0 and 3 and after 1 month, no case of DIRR was clinically evidenced among the four groups and the controls.

Oral HSV-1 DNA was detected before and after procedure in 1.7 % (1/57, 1 f) of the patients and in 5.3 % (3/57, 2 f/1 m), respectively [dental inspection without anesthesia, 5.3 % (1/19); molar extraction under local anesthesia, 6.7 % (1/15); and molar extraction under general anesthesia, 11 % (1/9)]. All the positive real-time PCR results revealed HSV-1, and no cases of HSV-2 were identified.

There was no clear correlation between the positive real-time PCR results and a prior history of RHL or the anesthetic procedure.

None of the controls presented RHL or detectable oral HSV-1 DNA at inclusion or at day 3. The test results of the individual groups are summarized in Table 1.

There was no statistical difference between the total study group and the controls (difference, 5.26 %, 95 % CI −6.397 to 14.62 %, chi-square 0.501, *df* 1, significance level $p=0.479$).

Discussion

Orolabial HSV-1 infections have been reported following dental procedures [9, 13–15, 17]. Sometimes, they may be particularly severe, requiring hospitalization and intravenous antiviral therapy [22].

Data concerning the incidence of clinical DIRR is scarce. In a group of 20 patients with a history of RHL, 4 patients (20 %) presented DIRR after dental extractions, whereas no DIRR occurred in 19 patients without a prior history of RHL [17]. Another study evaluated the value of antiviral prophylaxis with valaciclovir for dental interventions, including periodontal, restorative, endodontic, orthodontic, and oral surgical procedures, in patients with a prior history of RHL (at least once per year and at least one recrudescence within the previous year). This study showed that after dental treatment, 7/62 (11.3 %) of the patients receiving valaciclovir presented a clinical HSV outbreak versus 13/63 (20.6 %) of the patients receiving placebo. These results are, however, in contrast with our study where none of the patients presented clinical DIRR 3 days after dental procedure. A large clinical study evaluating the complications of 3,818 dental extractions showed no single case of HSV recrudescence [23], which is more consistent with our results. These differences are probably not age related as the mean ages were similar in Miller's study and in our study. A further explanation may reside in the criteria used for clinical diagnosis of RHL. It is indeed curious to notice that 16 % of the patients presented DIRR, although only 4.8 % of them presented a positive HSV viral culture [14].

Table 1 Presence and viral load (copy numbers) of HSV-1 DNA in oral saliva following different dental procedures

Patient categories	Number of patients	Day 0 Number, viral genome copies/ 100 µl	Day 3 Number, viral genome copies/ 100 µl
Controls			
Total number	32	0/32	0/32
RHL, <4/year	31	–	–
RHL, >4/year	1	–	–
Study groups			
Total number	57		
Dental inspection			
RHL, <4/year	14	1/14, 37.95	1/14, 39.47
RHL, >4/year	5	–	–
Total number	19	1/19	1/19
Dental filling under local anesthesia			
RHL, <4/year	11	–	–
RHL, >4/year	3	–	–
Total number	14	0/14	0/14
Molar extraction under local anesthesia		–	
RHL, <4/year	14	–	1/14, 31.78
RHL, >4/year	1	–	–
Total number	15	0/15	1/15
Molar extraction under general anesthesia			
RHL, <4/year	7	–	–
RHL, >4/year	2	–	1/2, 39.17
Total number	9	0/9	1/9

En dash (−) indicates negative results

RHL recurrent herpes labialis

The higher invasiveness of the procedure, such as dental extractions, may be responsible for higher incidences of DIRR, as suggested by previous studies [14, 17]. However, in our study, no cases of clinical DIRR were observed, independently from the procedure.

Our results suggest that a prior history of RHL does not represent a significant risk factor for clinical DIRR, confirming earlier data [14]. However, another study revealed that DIRR was present in 20 % of the patients with a history of RHL, but none of the patients without prior RHL [17].

PCR is the preferential method to measure HSV oral load, as it is far more sensitive compared to viral culture [18, 24, 25]. Positive HSV-1 real-time PCR results were found in 8 % [14] and 8.9 % [15] of patients before dental intervention, but on follow-up visits, the positive HSV-1 results were only detected in 1.6 % of the same patient cohort [14], similar to the 1.7 % positive HSV-1 PCR results in our study.

Three days after procedure, 5.3 % of our patients became HSV-1 positive or increased the HSV-1 real-time PCR levels, compared to 1.7 % before procedure. There was an increased viral load in one patient undergoing dental inspection and two reactivations and positive viral loads for patients undergoing molar extraction under local anesthesia and molar extraction under general anesthesia. In another study, HSV shedding increased from 7.9 to 27 % after dental procedure [14]. This contrasts with another study where the pattern of viral HSV shedding did not change substantially following dental procedures (9.8 % at day 1, 10.3 % at day 2, and 8.3 % at day 3) [15]. Another study including 48 subjects did not show statistical differences in HSV-1 shedding after conventional dental procedures [13]. Other

authors showed that only 4.5 % of healthy individuals shed HSV-1, whereas shedding increased to 20 % of patients who underwent oral surgery [10]. These differences may be attributed to sampling methods (direct fixation versus whole saliva) and/or PCR method (real-time versus conventional).

Our study suggests that the more aggressive is the procedure, the higher is the risk for reactivation or increased shedding, whereas the anesthetic procedure seems not to present a risk factor. These observations favor that nerve damage and irritation during extraction are a possible trigger for HSV reactivation, as previously suggested [10]. Others state that there was no correlation between the invasiveness of the dental procedure and the subsequent development of recurrent lesions [14].

Previous studies revealed that oral valaciclovir (2 gr twice on the day of treatment and 1 gr twice the following day) decreased both clinical DIRR and HSV-1 shedding [14]. Hence, oral valaciclovir was proposed as prophylactic therapy before dental interventions. However, our data do not support to recommend antiviral prophylaxis before dental procedures. A prior history of RHL seems not to be a risk factor, but previous DIRR certainly is [22]. Hence, antiviral prophylaxis is only recommended in selected patients.

In conclusion, our results showed no clinical episode of RHL after any kind of dental procedure. HSV-1 local oral shedding was rare after dental interventions. HSV-1 shedding seems independent from a prior history of RHL and from the type of anesthesia. HSV-1 shedding seems related to the invasiveness of the dental procedure. Although not statistically significant, these data do not favor antiviral prophylaxis before any kind of dental procedure, except for patients with previous DIRR.

Conflict of interest The authors declare that they have no conflicts of interest

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