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Comparison of auto-fluorescence and tetracycline fluorescence for guided bone surgery of medication-related osteonecrosis of the jaw: a randomized controlled feasibility study

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Abstract. Recent studies have indicated that bone shows auto-fluorescence under an appropriate fluorescence lamp. The aim of this preliminary study was to compare the success rates of the established tetracycline fluorescence-guided bone surgery with auto-fluorescence-guided bone surgery in the treatment of medication-related osteonecrosis of the jaw (MRONJ). Forty patients suffering from MRONJ were referred for surgical treatment and were divided randomly into two groups: auto-fluorescence ($n = 20$) or tetracycline fluorescence ($n = 20$) guided bone surgery. The primary endpoint was treatment success, defined as the absence of exposed bone at 8 weeks after surgery. Secondary outcomes assessed were mucosal integrity, signs of infection, pain, and loss of sensitivity; these were evaluated descriptively at 10 days, 8 weeks, 6 months, and 1 year after surgery. At 8 weeks postoperative, 18/20 patients (90%) in the auto-fluorescence group and 17/20 patients (85%) in the tetracycline fluorescence group showed mucosal integrity ($P > 0.05$). At the last follow-up, 94% in the auto-fluorescence group and 89% in the tetracycline fluorescence group presented complete mucosal coverage with no exposed bone, infection, or pain ($P > 0.05$). There was no significant difference between the two techniques for any of the secondary outcomes ($P > 0.05$). The results of this preliminary study show that

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auto-fluorescence-guided bone surgery has comparable success rates to the established tetracycline fluorescence-guided bone surgery.

Key words: necrosis of the jaw; BRONJ; DRONJ; MRONJ; ONJ; bisphosphonate; osteonecrosis; bone fluorescence; tetracycline; auto-fluorescence; therapy; bone; VELscope.

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The primary goal of surgical therapy for medication-related osteonecrosis of the jaw (MRONJ) should always be the removal of as much bone as necessary and as little as possible.[1] Irrespective of the approach selected (minimally invasive or resective), the delineation between necrotic and viable bone is the crucial step and is a major challenge in this procedure. Indeed, the complete removal of necrotic bone is essential, as otherwise the risk of disease recurrence or progression remains.[2–4]

Prior to the introduction of tetracycline fluorescence-guided bone removal,[5] surgical experience and the surgeon's subjective impression, supported by various imprecise imaging modalities, were the only parameters available for distinguishing between healthy and diseased bone tissue.[6,7] In this respect, tetracycline fluorescence-guided bone surgery has had an important impact on the surgical management of MRONJ, as it successfully addresses this shortcoming.[8–10] Providing an objective and reproducible therapeutic approach, this technique enables the transitions between necrotic and non-necrotic bone to be defined during the surgical procedure.

Recent studies have indicated that the VELscope system (VELscope fluorescence lamp; LED Dental, White Rock, British Columbia, Canada) induces an auto-fluorescence from vital bone (but not from necrotic bone) leading to similar bone fluorescence findings without the preceding tetracycline labelling.[11,12] In a preliminary investigation, promising results were found for this technique with regard to success rates and verification of the complete removal of the necrotic bone by histological work-up. Because this surgical approach is easy to apply, is reproducible, and does not rely on the subjective impression of the surgeon, it might be used to standardize surgical MRONJ therapy and lead to an improvement in treatment.

Therefore, the purpose of this study was to examine the success rate of auto-fluorescence-guided bone surgery and to compare this technique with the valuable method of tetracycline fluorescence-guided bone surgery in MRONJ patients. Given that tetracycline-induced bone fluorescence is beneficial for the surgical treatment of MRONJ,[8,9] the investigators hypothesized that the auto-fluorescence of bone would be similarly useful. The specific aims of this preliminary study were to compare the two intervention groups in terms of (1) postoperative mucosal integrity and absence of bone exposure, (2) signs of infection, (3) pain scores, and (4) loss of sensitivity (numbness) after the fluorescence-guided bone surgery.

Materials and methods

Study sample

This study followed the Declaration of Helsinki concerning medical protocol and ethics and the CONSORT guidelines for reporting clinical trials.[13] After the approval of the institutional ethics committee had been obtained, informed consent was acquired from all patients. To address the research purpose, the investigators designed and implemented an open-label, parallel-group, randomized, feasibility clinical trial. Over a period of 12 months, the study population was prospectively referred for the treatment of MRONJ and divided randomly into two study groups: treatment with either (1) auto-fluorescence-guided bone surgery (AF group; intervention group) or (2) tetracycline fluorescence-guided bone surgery (TF group; control group).

The following inclusion criteria were applied: (1) exposed osteonecrosis of the jaw, defined as the long-standing (more than 8 weeks) transmucosal exposure of necrotic bone in the jaw with a drug history positive for anti-resorptive treatment (in accordance with the American Association of Oral and Maxillofacial Surgeons (AAOMS)[14,15]); (2) a history of anti-resorptive drug treatment (bisphosphonates and/or denosumab) in the absence of radiotherapy to the head and neck region (in accordance with the AAOMS[14,15]). Exclusion criteria were a history of head and neck irradiation, metastatic bone disease of the maxillofacial region, and contradictions to surgery under general anaesthesia.

Study variables

The primary endpoint of this feasibility study was to determine any superiority or consistency of the auto-fluorescence-guided bone surgery group over the tetracycline fluorescence-guided bone surgery group in terms of the success rate. Success was defined as the absence of a MRONJ site after surgery, specified as the maintenance of full mucosal coverage (mucosal integrity) at 8 weeks after surgery. Secondary endpoints were to identify between-study group differences in (1) mucosal integrity at the remaining measurement time points, (2) loss of sensitivity (numbness) of the alveolar nerve (Vincent sign), (3) subjective pain, and (4) signs of infection at 10 days (T1), 8 weeks (T2), 6 months (T3), and 1 year (T4) after surgery. Patient demographics and baseline characteristics were also recorded for confirmation of group comparability.

Fluorescence-guided bone surgery

All surgical procedures were performed by one of two board-certified and specialized oral and maxillofacial surgeons (C.P., B.H.M.) under general anaesthesia using nasal intubation. Surgery was performed under sterile conditions following a standardized operation protocol.[9] All patients in the TF group received 100 mg doxycycline twice a day for at least 7 days preoperatively. Patients in the AF group received ampicillin/sulbactam 2000 mg/1000 mg before the operation; however, no preoperative tetracycline labelling was performed. Patients who reported a history of hypersensitivity to penicillin or a penicillin allergy received clindamycin 600 mg three times a day instead. All patients included in this study were then treated surgically by means of the fluorescence-guided bone surgery technique, as described previously by this study group, using the VELscope Vx system (LED Dental) (Fig. 1) to induce and visualize fluorescence of the jawbone.[5,9,16]

Briefly, after surgical bone exposure, bone fluorescence showed viable bone with a bright greenish fluorescence, whereas necrotic bone areas showed no

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