

Department of Dentistry

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General Summary

1. Role of dentistry in sleep apnea
2. The role of nerve growth factor and its precursor forms in oral wound healing
3. Clinical investigation of patients with medication-related osteonecrosis of the jaw in our department

Research Activities

Role of dentistry in sleep apnea

1. Oral appliance

Oral appliance (OA) which was one of the conservative treatment of OSA became the insurance adaptation from 2004. In a Japanese insurance adaptation standard, as for OA production, AHI < 20 is recommended now. It is a premise that there are being diagnosed as being adaptation of OA in a medical department, the introduction from a doctor. However, OA serves as the supporting role of CPAP when the patient whom CPAP cannot use it. OSA is the breathing disorder that subsidence of the base of the tongue and stenosis of the cavity of pharynx caused by the soft palate produces during face up position sleep. OA plans an open size of the cavity of pharynx by raising a tongue forward and improves breathing disorder. In addition, it is confirmed that the daytime sleepiness lightens by OA treatment.

2. Sleep surgery

CPAP and OA are symptomatic treatments together, and an effect is maintained by using it continuously. In late years the sleep surgery attracts attention as basic treatment of OSA. Stanford University proposes Two Phase Surgery Protocol in 2007.

At first, in this protocol, the operation for soft tissues such as a nasal cavity, soft palate, the base of tongue is carried out as (phase1) for the first stage. When an effect of phase1 is insufficient, the operation for hard tissue particularly the jawbone is carried out as (Phase2) for the second stage. Dentist deals with Phase2. A method of surgery includes Genioglossal Advancement (GA) and Maxillo-Mandibular Advancement (MMA).

3. Infant pediatric orthodontic

The cause of infant OSA is adenoids, enlargement of a lymphoid organization peculiar to an infant represented by hyperplasia of palatine tonsil and nose disease, hypogrowth of upper and lower jaws. In late years the effectiveness of the maxillary rapid expansion (RMA) for the infant OSA patient that the cause does not have adenoids increase and swollen tonsils reported in the United States. RMA magnifies upper jaw in a correction device rapidly and is an antidote to fix until an extended part ossifies.

Mechanism to give to the improvement of the upper respiratory tract ventilation disorder

of RMA in a recent study becomes clear. At present, RMA is a cure indicated for the infant whom a diagnosis of OSA established. However, when it is very likely to be the future OSA onset, in acknowledgment of a clear maxilla, I perform intervention of the teeth-straightening and acquire an appropriate chin face form for the infant period, and the way of thinking to prevent the OSA onset in the adulthood is suggested.

The Role of Nerve Growth Factor (NGF) and Its Precursor Forms in Oral Wound Healing

Nerve growth factor (NGF) and its different precursor forms are secreted into human saliva by salivary glands and are also produced by an array of cells in the tissues of the oral cavity. The major forms of NGF in human saliva are forms of pro-nerve growth factor (pro-NGF) and not mature NGF. The NGF receptors tropomyosin-related kinase A (TrkA) and p75 neurotrophin receptor (p75^{NTR}) are widely expressed on cells in the soft tissues of the human oral cavity, including keratinocytes, endothelial cells, fibroblasts and leukocytes, and in ductal and acinar cells of all types of salivary glands. In vitro models show that NGF can contribute at most stages in the oral wound healing process: restitution, cell survival, apoptosis, cellular proliferation, inflammation, angiogenesis and tissue remodeling. NGF may therefore take part in the effective wound healing in the oral cavity that occurs with little scarring. As pro-NGF forms appear to be the major form of NGF in human saliva, efforts should be made to study its function, specifically in the process of wound healing. In addition, animal and clinical studies should be initiated to examine if topical application of pro-NGF or NGF can be a therapy for chronic oral ulcerations and wounds.

Clinical investigation of patients with medication-related osteonecrosis of the jaw in our department

Bisphosphonate preparations are used for the prevention and treatment of bone related events such as bone metastasis of solid cancer, paraneoplastic hypercalcemia, multiple myeloma, and bone metabolism diseases such as osteoporosis. However, the bisphosphonate-related osteonecrosis of the jaw (BRONJ), which is an adverse event, is refractory to treatment for scratching of necrotic tissue and antibiotics therapy etc. Recently, osteonecrosis of jaw associated with novel therapeutic agents such as anti-RANKL antibody preparation (denosumab) and angiogenesis inhibitor (bevacizumab, sunitinib), which have different mechanisms of action from BP preparations, have also been reported, that is commonly referred to as Medication-Related osteonecrosis of the jaw (MRONJ).

The subjects were 24 patients diagnosed as MRONJ after seeing Department of Dentistry, Jikei University School of Medicine from January 2014 to January 2016. Among the 24 cases, the primary disease was breast cancer and prostate cancer with each 14 patients. In the administration route, 18 with injections and 6 with oral drugs were administered, among them 7 cases of new therapeutic agent only administration. By site, there were 20 cases of mandible and 4 cases of maxilla, almost all cases of chemotherapy, steroid therapy, or diabetes among risk factors were recognized. In stage classification, 4 cases of I, 14 cases of II, 6 cases of III. There were 14 cases of spontaneous onset and 10 cases after surgical treatment as a trigger for onset. It was suggested that with patients receiving bone

resorption suppressive drugs or angiogenesis inhibitors, surgical invasion to the jawbone or bacterial infection may deeply involve in the onset of MRONJ.

Publications

Schenck K¹, Schreurs O¹, Hayashi K, Helge-land K¹ (Univ of Oslo). The Role of Nerve Growth Factor (NGF) and Its Precursor Forms in

Oral Wound Healing. *Int J Mol Sci.* 2017; **18**: 1-12.