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Preclinical Studies for Cryoprevention of Oral Mucositis

Akademisk avhandling

som för avläggande av odontologie doktorsexamen vid Sahlgrenska Akademin, Göteborgs Universitet, kommer att offentligen försvaras i Hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, onsdagen den 12 juni 2019, kl. 13.00

av

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Avhandlingen baseras på följande delarbeten:

I. **Walladbegi J**., Smith S. A., Grayson A. K., Murdoch C., Jontell M., Colley, H. E. Cooling of the oral mucosa to prevent adverse effects of chemotherapeutic agents: An in vitro study. *J Oral Pathol Med*. 2018 May;47(5):477–483.

II. **Walladbegi J**., Johnsson M., Aydogdu Ö., Jontell M., Winder M. Early events in the oral mucosa affected by chemotherapeutic agents: An in vivo study. *In manuscript*.

III. **Walladbegi J**., Gellerstedt M., Svanberg A., Jontell M. Innovative intraoral cooling device better tolerated and equally effective as ice cooling. *Cancer Chemother Pharmacol*. 2017 Nov;80(5):965-972.

IV. **Walladbegi J**., Raber-Durlacher J.E., George R., Jontell M., Milstein D.M.J. Hemodynamics of the oral mucosa during cooling. *In manuscript*.

V. **Walladbegi J**., Svanberg A., Gellerstedt M. Protocol for a randomised controlled trial to study cryoprevention of chemotherapy-induced oral mucositis after autologous stem cell transplantation. *BMJ Open*. 2018 Oct 24;8(10):e021993.

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ABSTRACT

Oral mucositis (OM) is a common debilitating adverse effect in patients with cancer who are conditioned with high-dose chemotherapy prior to hematopoietic stem cell transplantation. In its mildest form, OM is characterized by erythema. However, as it worsens, it can give rise to painful ulcerations in the oral mucosa. Overall, OM-related complications entail increased health care costs. In fact, despite its frequency, impact on patients, and healthcare and economic burdens, current literature indicates few evidence-based interventions with confirmed efficacy for the prevention of OM. In response to this gap in the knowledge, a novel intraoral cooling device has been developed.

The long-term goal of the research described in this thesis is to establish an effective and well-tolerated method for cryoprevention of OM. The specific aims of this thesis were to: (*i*) investigate whether cooling, using a constant low temperature, is effective for oral tissue preservation; (*ii*) develop an animal model to study the early events which precede OM; (*iii*) assess the effectiveness of a novel intraoral cooling device as a cryopreventive method; (*iv*) evaluate whether local cooling affects the oral hemodynamics; and (*v*) establish how a research protocol should be designed for a randomized controlled trial to evaluate cryoprevention of OM.

Oral tissue preservation was better at lower temperatures (*Study I*). Proinflammatory cytokines were significantly upregulated (*Study II*). Several promising results were obtained with the intraoral cooling device (*Study III*). Local cooling may elicit other mechanisms in the oral mucosa than previously suggested that may be of importance for the prevention of OM (*Study IV*). A research protocol, to assess cryoprevention of OM, should be established through multidisciplinary collaborations and should include both objective- and subjective assessments (*Study V*).

In conclusion, this thesis is the first to focus on the prevention of OM using an alternative cryotherapeutic technique. The work is mainly concerned with preclinical studies to identify the ideal temperature for the prevention of OM. Furthermore, this thesis demonstrates the tolerability and cooling efficacy of the intraoral cooling device and shows that cooling may elicit other mechanisms in the oral mucosa than previously suggested. However, despite its promising capacity, the randomized controlled trial will elucidate the definite role of the intraoral cooling device in cryoprevention.

Keywords: Animal model, chemotherapy, cryotherapy, hematopoietic stem cell transplantation, ice chips, intraoral cooling device, microcirculation, randomized controlled trial, tissue-engineered oral mucosa, tissue oxygen saturation, tolerability

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