Platelet-rich fibrin has a healing effect on chemotherapy-induced mucositis in hamsters

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Objective. The aim of this study was to evaluate the healing effect of topically applied platelet-rich fibrin (PRF) on experimental oral mucositis induced by chemotherapy in hamsters.
Study Design. Oral mucositis was induced in 93 Syrian golden hamsters by an intraperitoneal injection of 5-fluorouracil, which was followed by light scratching of the cheek pouch. The hamsters were randomly divided into a PRF group, a fibrin group, and an untreated control group. The recovery stage of oral mucositis was evaluated through daily weighing, measurements of the ulcer area, histopathologic analysis, and a myeloperoxidase activity assay.
Results. The PRF group exhibited significant improvements in the size and histologic features of the ulcer and in the myeloperoxidase activity compared with the control group ($P < .05$).
Conclusions. The current findings suggest the consideration for future clinical trials in humans. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:445-453)

Oral mucositis is a painful and often debilitating side effect of chemotherapy and can substantially affect nutritional intake, daily functioning, and the quality of life. Approximately 20% to 40% of patients given cytotoxic agents for malignancies develop oral complications.[1-4] These oral complications can result in increased infections, delays or interruptions in treatment, and dose reductions, and they can decrease disease remission and survival.[1,2,5] The treatment costs can increase the economic burden on the patient, with costs increasing in proportion to the severity of the mucositis.[1]

The clinical interventions for oral mucositis are divided into 2 approaches: the prevention[6-11] of oral mucositis or the treatment of established oral mucositis.[12-16] According to the guidelines of the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO), several recommendations are provided for the management of established chemotherapy-related mucositis. The panel suggests that transdermal fentanyl may be effective in treating pain caused by oral mucositis in patients receiving conventional and high-dose chemotherapy with or without total body irradiation.[12] Also, 0.5% doxepin mouthwash is suggested to be effective in treating pain from oral mucositis.[13] Although not included in the guidelines, there are additional interventions for the management of established chemotherapy-related oral mucositis, such as polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair),[14] a supersaturated calcium phosphate mouthrinse,[15] and antiseptic and antimicrobial mouthrinses.[16] Many of these treatments are interventions to control pain, but there are few interventions to promote the healing of established oral mucositis directly.

Inflammation is the first phase of wound healing and is marked by the formation of a blood clot containing red blood cells, macrophages, and a platelet plug.[17] This blood clot provides a provisional extracellular matrix for cell migration. Fibrin glue has been developed to function as a provisional artificial extracellular matrix to stimulate healing, and it has been used to seal various types of wounds.[18-20] In the oral cavity, fibrin sealant is applied to flap and graft procedures and promotes cellular migration and fibroblastic growth into the area of the fibrin seal application.[20-23] The use of fibrin sealant remains controversial because of the complexity of the production protocols, the manufacturing

Statement of Clinical Relevance

Oral mucositis is the most common adverse effect of chemotherapy and can hinder cancer care. Our studies suggest the healing effects of platelet-rich fibrin on oral mucositis in hamsters and support future clinical trials in patients.

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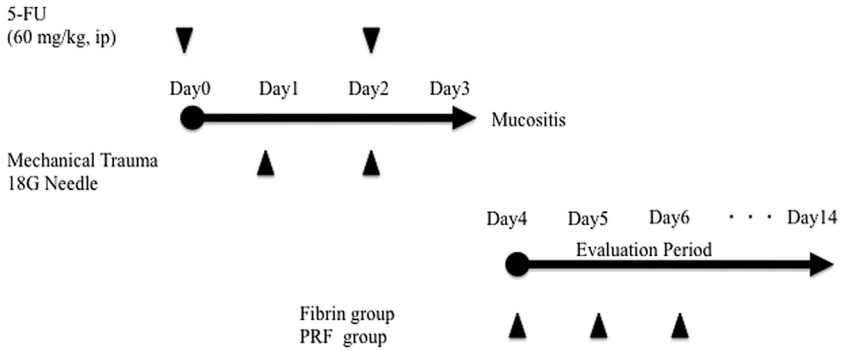

Fig. 1. The chemotherapy consisted of 2 intraperitoneal injections of 5-FU administered at 60 mg/kg on experimental days 0 and 2. The left cheek pouches were everted and irritated by superficial scratching on days 1 and 2. This light scratching was performed with 18-gauge needles within a 100-mm^2 area. Treatment was performed from day 4 to the day when the samples were processed for hematoxylin-eosin staining or myeloperoxidase activity. (*5-FU*, 5-fluorouracil; *ip*, intraperitoneal; *PRF*, platelet-rich fibrin.)

costs, and the risks of cross-infections from the use of commercial products.[18,24]

As a natural fibrin, platelet-rich fibrin (PRF) is produced from biomaterials and contains several growth factors (GFs) and cytokines derived from autochthonous platelets and leukocytes. The natural concentrate is produced without anticoagulants or bovine thrombin.[18,24-26] The PRF protocol, which was developed in France by Choukroun et al.,[27] is simple and inexpensive. Recently, several reports have described applications of the PRF membrane for the improvement of soft tissue healing. In plastic surgery, PRF membranes applied to fresh postoperative hand wounds promote favorable tissue healing compared with the standard treatment in a randomized controlled clinical trial.[25] The use of PRF membranes is highly efficient for root coverage[28] and prevents peri-implant gingival recession.[29] These reports were based on small samples and focused on normal gingival healing. To the best of our knowledge, there have not been any in vivo animal experiments evaluating the efficacy of PRF application in healing oral mucositis induced by a chemotherapy agent.

This study aimed to evaluate whether PRF therapy can be extended as a curative approach in the treatment of oral chemotherapy-induced mucositis. To address this issue, the effect of locally applied PRF on chemotherapy-induced oral mucositis in a hamster model was studied by determining the body weight, ulcer area, histopathologic features, and myeloperoxidase (MPO) activity of the animals, which allowed for an assessment of their overall condition, healing, and inflammation.

MATERIALS AND METHODS

Animals

Male Syrian golden hamsters (Japan SLC, Nagoya, Japan), 7 weeks old and weighing 90 to 120 g, were used in the experiments. All the animals were housed in a room maintained at 22°C ± 2°C under a 12-hour/12-hour light-dark cycle with the lights turned on at 8 AM. The hamsters were fed a standard rodent diet and given water ad libitum. This study was approved by the Institutional Animal Care and Use Committee of the Nagoya City University Graduate School of Medical Sciences, and the study was carried out in accordance with the guidelines for the center of experimental animal science.

Oral mucositis model

Hamsters were used in the present study based on the experimental mucositis model of Sonis et al.[30] The chemotherapy involved 2 intraperitoneal injections of 5-fluorouracil (5-FU) (5-FU Injection 250 Kyowa; Kyowa Hakko Kirin Co Ltd, Tokyo, Japan) administered at 60 mg/kg on days 0 and 2 of the experiments (Figure 1). The 5-FU sterile solution was freshly prepared before each experiment. In combination with 5-FU to induce mucosal ulceration, the hamsters were anesthetized with pentobarbital sodium (Somnopentyl; Kyoritsu Seiyaku Co Ltd, Tokyo, Japan), and the left cheek pouches were everted and irritated by superficial scratching on days 1 and 2. This light scratching was performed with 18-gauge needles within a 100-mm^2 area.

Treatment groups

Beginning on day 4 of the experiment, the hamsters with ulcerations induced by chemotherapy were randomly divided into 3 different treatment groups: the PRF, fibrin, and control groups. The hamsters were anesthetized with pentobarbital sodium before the treatments were applied.

PRF group. PRF was prepared according to a previous protocol developed by Dohan et al.[24] Blood collections were performed on 8 healthy volunteer men who were nonsmokers between the ages of 25 and 40.