Complementary Therapies in Medicine 29 (2016) 29–34

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevierhealth.com/journals/ctim

Evaluating the effect of *Matricaria recutita* and *Mentha piperita* herbal mouthwash on management of oral mucositis in patients undergoing hematopoietic stem cell transplantation: A randomized, double blind, placebo controlled clinical trial

Maria Tavakoli Ardakani (PhD PharmD)[a,f], Sara Ghassemi (PharmD)[c], Mahshid Mehdizadeh (MD)[b,d,*], Faraz Mojab (PhD PharmD)[e,f], Jamshid Salamzadeh (PhD PharmD)[a], Samaneh Ghassemi (PharmD)[c], Abbas Hajifathali (MD)[b]

[a] *Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[b] *Taleghani Bone Marrow Transplantation Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[c] *Student Research Committee, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[d] *Pediatric Congenital Hematologic Disorders Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[e] *Department of Pharmacognosy, School of Pharmacy and, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[f] *Pharmaceutical sciences research center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Article history:
Received 5 October 2015
Received in revised form 14 July 2016
Accepted 1 August 2016
Available online 30 August 2016

Keywords:
Hematopoietic stem cell transplantation
Oral mucositis
Matricaria recutita
Mentha piperita
Mouthwash
Herbal preparation

ABSTRACT

Objectives: To investigate the effects of *Matricaria recutita* and *Mentha piperita* on oral mucositis (OM) in patients undergoing hematopoietic stem cell transplantation (HSCT).
Design: Randomized double blind placebo controlled clinical trial.
Setting: Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, and Bone Marrow Transplantation Center at Taleghani Teaching Hospital, Tehran, Iran.
Participants: Sixty patients undergoing HSCT were randomly assigned to two groups: placebo (n = 33), and herbal mouthwash group (n = 27).
Interventions: All patients received the mouthwash one week before HSCT and were instructed to use it three times daily for at least 30 s.
Main outcome measures: OM was graded using National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale (grade 0–5). The Numerical Rating Scale (NRS: 0–10 scale) measured the severity of OM symptoms.
Results: The duration, maximum and average daily grade of OM were significantly reduced in the treatment group ($P < 0.05$). The use of herbal mouthwash led to significant improvements in pain intensity ($P = 0.009$), dryness ($P = 0.04$) and dysphagia ($P = 0.009$). Other significant results included: reduced need for complementary medications ($P = 0.03$), narcotic analgesics ($P = 0.047$), total parenteral nutrition (TPN) ($P = 0.02$) and the duration of TPN ($P = 0.03$).
Conclusion: This study shows that patients receiving the herbal mouthwash experienced less complications and symptoms associated with OM. In summary, it seems that the use of our prepared herbal mouthwash is beneficial for patients undergoing HSCT.

1. Introduction

Oral mucositis (OM) is considered one of the most common and disturbing side effects of high dose chemotherapy in patients undergoing stem cell transplantation and can affect up to 76% of this group of patients. The symptoms associated with OM include erythema, pain and edema which can lead to ulcers. Severe OM

* Corresponding author at: Taleghani Bone Marrow Transplantation Center, Taleghani Hospital, Velenjak, Tehran, Iran.
E-mail address: mehdizadeh@sbmu.ac.ir (M. Mehdizadeh).

http://dx.doi.org/10.1016/j.ctim.2016.08.001
0965-2299/

can cause serious complications such as systemic infection, fever, painful ulceration and inflammation resulting in malnutrition. In these situations patients may need parenteral nutrition, high-dose narcotic analgesics and anti-microbial treatments which increase the total cost of care.[1–4] Pathogenesis OM has been investigated for a long time and a five stage model was proposed by Sonis[5]:

1. Initiation of tissue injury
2. Message generation
3. Signaling and amplification
4. Ulceration and inflammation
5. Healing

In order to decrease the symptoms associated with OM, different agents have been used by physicians.[6–8] Researchers have always had an interest in herbal medicine and some of them have evaluated the efficacy of herbal compounds in OM; however the results were controversial.[9–12] *Matricaria recutita* is one of the most recognized medicinal plants in the world. The main active constituents of chamomile include chamazulene, (-)-alpha-bisabolol, bisabolol oxides A and B, flavonoids and spiroethers. These compounds have different pharmacological activities such as antibacterial, antifungal, anti-viral, anti-inflammatory, anti-ulcer and wound healing effects.[13–20] *Mentha piperita* is another plant that has a widespread medicinal use. This plant mainly contains menthol, menthone, methyl acetate and menthofuran. Different studies have demonstrated that peppermint oil has anti-inflammatory, anti-microbial and cooling effects.[21–31] Based on pharmacological activities of *Matricaria recutita* and *Mentha piperita*, an herbal mouthwash was produced using these two medicinal plants and its efficacy was evaluated during a randomized placebo controlled clinical trial in patients hospitalized in the Bone Marrow Transplantation (BMT) Ward of Taleghani Teaching Hospital.

2. Patients and methods

2.1. Study design and participants

We conducted a double-blind, randomized, placebo-controlled clinical trial at the BMT Center of Taleghani Teaching Hospital, between April 21, 2011, and August 22, 2012. Our aim was to compare the efficacy of *Matricaria recutita* plus *Mentha piperita* mouthwash with placebo. The study was registered with IRCT201105183210N3 code in Iranian Registry of Clinical Trials (IRCT) and approved by the ethical committee of Shahid Beheshti University of Medical Sciences.

The inclusion criteria were defined as follows: being a non-smoker, aged 15 years or older, being able to gargle the mouthwash solution and capability of reading and communicating with staff. Exclusion criteria included: no cooperation during the study, allergic reactions to herbal mouthwash, and failure to follow the oral health protocol due to any variation of patient's health condition.

A consecutive non-probability sampling method was applied, in which all patients undergoing hematopoietic stem cell transplantation in the TaleghaniBone Marrow Transplantation Center, and those that were eligible to be included in the study (based on the inclusion and exclusion criteria), were randomly allocated in the study groups. A simple randomization method using the "RAND" command in the "Excel" software, was used for this purpose.

2.2. Mouthwash preparation

Flowers and aerial parts *of Matricaria recutita* and Peppermint oil were obtained from the Zardband Company. The herbal mouthwash was prepared under sterile conditions based on a formulation of 1% v/v Peppermint oil, 1% w/v dried extract *of Matricaria recutita* and 99% v/v ethanol 96°. Compared to herbal mouthwash, the placebo was similar in taste, smell and colour; and contained 0.02% w/v edible red colour, 0.5% v/v chlorophyllin colour, 13% v/v ethanol 96° and 71.5% v/v distilled sterile water. *Mentha pulegium* aroma water (15% v/v) was also added to replicate the flavour and odour of herbal mouthwash. No references were found to demonstrate the effectiveness of *Mentha pulegium* aroma water on OM., *Mentha pulegium* doesn't have any effect on mucositis, because it doesn't have any menthol (active component of *Mentha piperita*).

Finally, the microbial limit test was performed on random samples to ensure sterility of the final product. No microbial contamination was observed in the samples.

2.3. Intervention

In order to prevent and treat possible sources of infection, all patients underwent a complete dental examination prior to admission to the BMT center.

At the first day of hospitalization patients were provided with instructions to maintain a good oral hygiene. Based on our BMT ward protocol, during the hospitalization time, patients in both groups had to use sodium chloride and chlorhexidine mouthwash three times daily to reduce the risk of oral infections. One week before the transplantation, patients received placebo or herbal mouthwash. They were requested to dilute 1 mL of mouthwash in 50 mL of pre-boiled water and gargle the solution for at least 30 s and spit it out. The mouthwash was used three times daily, after each meal and patients had to avoid eating, drinking and rinsing their mouths for 30 min afterwards.

Oral examinations were performed from the first day of chemotherapy. If patients had symptoms of OM, alongside the routine therapy, other remedies such as morphine, nystatin oral suspension, or a cocktail of diphenhydramine, lidocaine and aluminium-magnesium hydroxide were prescribed depending on the severity of OM. In severe mucositis, Granulocyte-Colony Stimulating Factor (GCSF) was also recommended by physicians as a mouthwash.

The treatment was continued until the complete healing of OM or hospital discharge.

2.4. Assessment and outcome measures

For each patient, basic information including age, gender, type of malignancy, type of transplantation and any allergy history (especially to herbal ingredients) were initially recorded. Other data such as daily body temperature, White blood cell (WBC) count, Platelet count, blood cultures, initiation of total parenteral nutrition (TPN) and its duration (if any), different treatments received for oral mucositis and length of hospital stay were recorded until the last day of residency in the BMT center.

The main outcomes measured in both groups were: development of OM, initiation time of OM expression, duration of OM, maximum grade of OM, average daily grade of OM, necessity of other OM remedies, necessity of narcotic analgesics, necessity of TPN, duration of TPN (if any), duration of hospitalization, days with fever, infection and engraftment time. Pain, dryness of oral cavity, dysphagia and alteration in taste perception were also assessed and recorded for each patient.

WBC engraftment time was represented as the day on which the absolute neutrophil count (ANC) was greater than 500 per μL for three days in a row and Platelet count of 20,000 per μL for three consecutive days was defined as platelet engraftment time. Infection was considered as a positive blood culture and fever was defined as a single oral temperature equal or more than 38.3 °C or two oral temperatures of 38 °C with one hour interval.