

# Effects Of The Drugs And Interventions, Used For The Management Of Cancer Treatment-Related Oral Mucositis, On The Induced Oral Pain.

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## Abstract

Management of mucositis-induced pain usually requires use of topical anesthetic agents, such as 2% viscous lidocaine equally mixed with diphenhydramine and a soothing covering agent. In more severe cases, systemic analgesics including opioids are necessary. Various methods have been noted so as to manage oral mucositis. Some of the most indicative ones are agents, drugs or interventions such as anti-inflammatory agents, cytokines, growth factors, aminoacids, antioxidants, cryotherapy, low energy laser, prostaglandins and corticosteroids. Although several studies evaluate their efficiency on mucositis management, only few of them actually examine the effects of these interventions on mucositis-induced pain. The aim of this review is to study the effectiveness of the interventions for the cancer-related oral mucositis on the mucositis-induced pain.

## INTRODUCTION

Radiation therapy for head and neck cancer, as well as chemotherapy agents, affect oral mucosa's epithelial cells, causing oral mucositis (OM); an erythematous, inflammatory and ulcerative response [1]. OM is very painful and leads to difficulties in swallowing, speaking and sleeping [2], [3], [4], affecting nutrition capability and patients' quality of life [5]. It can be a dose-limiting side-effect, increasing both morbidity and mortality.

As patients report, mucositis-induced oral pain is the most severe and debilitating symptom [6] met in their therapy. Not just the physical aspect of pain has to be taken under consideration, but also the psychological one, due to the cancer diagnosis and the therapy stress [7]. The impaired ability of eating, speaking and sleeping, as well as the need to follow complex mouth care processes, lead to inadequate functioning, decreased socialization, feelings of isolation and identity loss [8].

The incidence of oral pain in chemotherapy is 40-70%, almost 100% in radiotherapy and 60-85% in bone marrow transplantation [7]. Elting et al. [9] report pain in 37% of patients with chemotherapy-induced mucositis, but only in 1% of patients with no mucositis development. Pain increases in severity during cancer therapy. Some studies

[10], [11], conclude that there is no correlation between changes in pain and mucositis, while others [5], [12] suggest that pain increases according to the increase of mucositis. Lalla et al. [13] report a very strong ( $r=+0.91$ ) and statistically significant ( $p=0.01$ ) correlation in the score changing between pain and mucositis.

Sonis et al. [1] have introduced a five-phase model for the mucosal barrier injury: initiation, upregulation with generation of messengers, signaling and amplification, ulceration with inflammation and finally healing. During the upregulation phase, activation of the cyclooxygenase (COX) pathway occurs. COX pathway mediates the transformation of arachidonic acid to proinflammatory prostaglandins, like  $PGE_2$  and  $PGI_2$ . They both affect the neural noniceptors  $A\delta$  and C causing pain and hyperalgesia [13]. They also affect the  $A\delta$  fibers causing allodynia [14], [15]. Yet, inflammation and ulceration lead to edema, resulting to even more pain [16].

Management of mucositis-induced pain usually requires use of topical anesthetic agents, such as 2% viscous lidocaine equally mixed with diphenhydramine and a soothing covering agent [13], [17]. In more severe cases, systemic analgesics including opioids are necessary.

Various methods have been noted so as to manage oral mucositis. Some of the most indicative ones are agents, drugs or interventions such as anti-inflammatory agents, cytokines, growth factors, aminoacids, antioxidants, cryotherapy, low energy laser, prostaglandins and corticosteroids. Although several studies evaluate their efficiency on mucositis management, only few of them actually examine the effects of these interventions on mucositis-induced pain.

The aim of this review is to study the effectiveness of the interventions for the cancer-related oral mucositis on the mucositis-induced pain.

## METHODS

### SEARCH STRATEGY

PubMed database was searched for English medical literature published from January 2000 to December 2010. The algorithm used was (“Mucositis”[Mesh] OR “Stomatitis”[MeSH]) AND “Neoplasms”[MeSH] OR “Cancer”[MeSH] AND “Randomized Controlled Trial”[PT]. In addition, all reference lists of the included literature were also examined.

Through the search process 125 articles were found regarding randomized controlled clinical studies (RCTs). After the elimination process, 22 of them were finally included in this study.

### INCLUSION AND EXCLUSION CRITERIA

The material used for this study had to meet specific criteria. Articles where one or all of the following did not apply, were excluded from the study:

Randomized controlled clinical studies.

Studies published in English.

Each study should be on adults’ population sample; with at least 10 participants (broader age frame is accepted).

Included articles should refer to interventions on cancer related mucositis.

All included articles should have mucositis-induced oral pain measurement as an endpoint.

Pain measurement results should be published.

## RESULTS

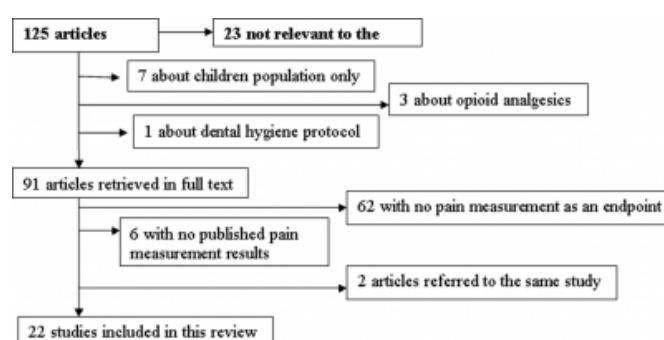
### SEARCH RESULTS

Out of the 125 articles, through the following elimination process, 103 were excluded. 23 were not relevant with this study, 7 were about children population only, 3 were about opioid analgesics and 1 was about dental hygiene protocol. 91 articles were retrieved in full text. 68 of them were excluded as 62 of them didn’t have the pain measurement as an endpoint and 6 had not published results, even though the authors mentioned that pain measurement was an endpoint. 2 of the articles referred to the same study thus they were examined as one (Cella et al. 2003[5] & Gilles et al. 2003 [18]). The results are presented in Fig. 1.

A total of 22 articles were included in this review.

**Figure 1**

Flow diagram of the study



### DATA EXTRACTION AND ASSESSMENT OF STUDIES QUALITY

Articles were reviewed by the first author (MK) who also performed data extraction. The results were checked by another author (PS). In case of disagreement the two authors reviewed the studies and reached a consensus.

Information collected from the articles, included the authors and the publication year, the study design, the type of cancer therapy, the number of the participants in total and in each group (intervention/control), the intervention characteristics and the pain measurement results.

Jadad scale was used to assess the methodological quality of all included RCTs.

### INTERVENTION STRATEGIES

Through the various interventions evaluated on mucositis management, only the ones offering mucositis-induced pain as a measured and published endpoint are presented.

## TOPICAL ANTIBIOTIC, ANTISEPTIC AND ANTI-INFLAMMATORY AGENTS

Only one study by Cheng et al. [19] was found on the use of chlorhexidine in mucositis management regarding oral pain. They conducted a double-blind RCT (Randomized Controlled Study) in 14 adult participants who went under radiotherapy, randomized to receive an oral rinse of either chlorhexidine or benzydamine, in a 1:1 ratio. A VAS (Visual Analog Scale), (0-10 scale), was used for pain measurement. There was no statistically significant difference in pain outcomes between the two groups,  $p>0.05$ . There was a statistically significant correlation though, between pain and mucositis degree,  $p<0.01$ . (Table 1).

Three studies of Isegagan noted oral pain as an endpoint conducted by Cella et al. & Giles et al., [5] & [18]; Giles et al. [20]; Trotti et al. [21]. They were double-blind RCTs, on chemotherapy related mucositis, except for Trotti et al. [21], which was on radiotherapy related mucositis. A total of 1336 participants were randomized in either an isegagan mouthwash, or a placebo one. All of these studies had a statistically significant reduce of pain;  $p=0.041$ ,  $p=0.028$  and  $p=0.036$  respectively. (Table 1).

El-Sayed et al. [22] conducted a study about BCoG (Bacitracin, Clotrimazole, Gentamicin) lozenges versus placebo and Wijers et al. [23] another one about PTA (Polymyxin E, Tobramycin, Amphotericin B) paste versus placebo. They both were double blind RCTs, on radiotherapy-induced mucositis, with 137 and 77 participants respectively. In regard to pain results, there were no statistically significant differences. (Table 1).

A double-blind RCT took place by Epstein et al. [24] on the effects of benzydamine or placebo mouthwash on radiotherapy related mucositis. 31 adults participated in this study. No difference was found in pain outcomes,  $p=0.064$ . (Table 1).

**Figure 2**

Table 1

Reference	Ca-Treatment	Study	Participants n Intervention/ Control	Intervention Type	Application	Results
<b>Topical antibiotics, antiseptic and anti-inflammatory agents</b>						
<b>Chlorhexidine</b>						
Cheng et al. 2006	Radio-therapy	Double-blinded	14 (7/7)	Chlorhexidine/ Benzydamine	Mouth wash	No difference $p=0.05$ pain value in a. chlorhexidine group: 0.7/10 b. benzydamine group: 0.5.3/10
<b>Isegagan</b>						
Trotti et al. 2004	Radio-therapy	Double-blinded	511 (253/171/67)	Isegagan/ Placebo/ SOC-standard of care oral hygiene	Mouth wash	<b>Pain reduction</b> in isegagan group versus SOC group $p=0.036$ values 2.8/3.2
Giles et al. 2004	Chemo-therapy	Double-blinded	302 (251/251)	Isegagan/ Placebo	Mouth wash	<b>Pain reduction</b> $p=0.028$ values 1.0±1.2/1.2±1.3
Cella et al. 2003 & Giles et al. 2003	Chemo-radio-therapy	Double-Blinded	363 (163/160)	Isegagan/ Placebo	Mouth wash	<b>Pain reduction</b> $p=0.041$ grade 0-9 6%/15%
<b>Topical antibiotics</b>						
El-Sayed et al. 2002	Radio-therapy	Double-Blinded	137 (69/68)	BCoG/ placebo	Lozenges	No difference $p=0.20$
Wijers et al. 2001	Radio-therapy	Double-blinded	77(39/38)	PTA paste/ placebo	Paste	No difference $p=0.72$ (in max. pain intensity)
<b>Anti-inflammatory agents</b>						
Epstein et al. 2001	Radio-therapy	Double-blinded	31 (16/15)	Benzydamine/ Placebo	Mouth wash	No difference $p=0.064$ 25.8% pain reduction

## CYTOCINES

Saarilahti et al. [25] conducted a double-blind RCT on radiotherapy-induced mucositis, with 40 participants. This was randomized on GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), or sucralfate mouthwashes. There was no statistically significant reduction of pain in the intervention group,  $p=0.058$ . No statistically significant reduction on oral pain ( $p=0.386$ ) was also the outcome in Sprinzl et al. [26] RCT. The latter used 35 participants, randomized on either a GM-CSF, or a hydrocortisone-pantocaine mouthwash. (Table 2).

Penpattanagul [27] reported findings from an RCT in 13 adults. The intervention group had 0.5ml/kg/day of immunokine (WF10), iv (intravenously), for the management of chemo-radio-therapy related mucositis. The control group had no intervention at all. No difference was spotted on oral pain results ( $p=0.429$ ). (Table 2).

## GROWTH FACTORS

A double-blind RCT was conducted by Vadhan-Raj et al. [28], on the prophylactic effects of a single iv dose of palifermine (180µg/kg) on chemotherapy related mucositis, versus placebo. 48 participants were randomized in a 2:1 ratio. A significant reduce of pain was reported ( $p=0.002$ ). (Table 2).

Freytes et al. [29] conducted a double-blind RCT. 42 adult patients were randomized in the repifermine group (25mg/kg or 50mg/kg, iv) or the placebo group, in a 1:1:1 ratio. The patients were treated with chemotherapy. Although there were no statistically significant differences between the three groups in regard of the peak pain measures, there was a significant difference in pain on swallowing between the placebo group and the group which had 50mg/kg repifermin iv ( $p=0.044$ ). (Table 2).

**Figure 4**

Table 2

Reference	Ca-Treatment	Study	Participants n Intervention/ Control	Intervention Type	Application	Results
<b>Cytocines</b>						
<b>GM-CSF</b>						
Saarihtti et al. 2002	Radio-therapy	Double-blinded	40 (21/19)	GM-CSF/ Sucralfate	Mouth wash	No difference $p=0.038$
Spirnal et al. 2001	Chemo-therapy	Controlled	35 (17/18)	GM-CSF/ Hydrocortisone-Pantocaine	Mouth wash	No difference $p=0.386$
<b>Immunokine (WFI0)</b>						
Perpottuagui 2007	Chemo-radio-therapy	Controlled Open label	13 (6/7)	Immunokine/ No intervention	Iv	No difference $p=0.429$
<b>Growth Factors</b>						
<b>Palifermine</b>						
Varian-Raj et al. 2010	Chemo-therapy	Double-blinded	48 (32/16)	Palifermine/ Placebo	Iv	<b>Pain reduction</b> $p=0.002$ median values 1/5
<b>Repifermine</b>						
Freytes et al. 2004	Chemo-therapy	Double-blinded	42 (14/14/14)	Repifermine/ Placebo	Iv	<b>Pain reduction (swallowing)</b> $p=0.044$ values 2.143 2/4.643 2

## AMINOACIDS

Cerciotti et al. [30] pooled data from 29 adults in a double-blind RCT, about how L-alanyl-L-glutamine affects the chemo-radio-therapy-induced mucositis. The dose was 0.4g/kg, iv. The control group had placebo. The results in pain reduction were statistically significant,  $p=0.008$ . (Table 3).

## ACTOVEGIN

Wu et al. [12] conducted a randomized controlled study on the results of Actovegin in chemo-radiotherapy-induced mucositis. 156 adults participated in the study randomized in three groups. 53 had actovegin, as a prophylactic agent, 51 had actovegin as a therapy agent, and 52 were in the control group having placebo. Actovegin was administered iv, 1200mg actovegin in 250 glucose solution 5%. A statistically significant pain reduction was found between the prolepsis and the control group,  $p=0.011$ . (Table 3).

## ANTIACIDS

A statistically significant pain reduction ( $p=0.003$ ) was reported in the double-blind RCT conducted by Watanabe et al. [31], about the use of polaprezinc mouthwash versus azulene mouthwash. There were 31 participants treated with

chemo-radio-therapy, (16 had polaprezinc and 15 had azulene). (Table 3).

**Figure 5**

Table 4

Reference	Ca-Treatment	Study	Participants n Intervention/ Control	Intervention Type	Application	Results
<b>Mouth Coating Factors</b>						
<b>Sucralfate</b>						
Dodd et al. 2003	Radio-therapy	Randomized	30	Sucralfate/ Salt & Soda	Mouth wash	No difference $p=0.54$ values 2.141.1/ 2.440.9
Etiz et al. 2000	Radio-therapy	Double-blinded	44 (23/21)	Sucralfate/ Placebo	Oral sup	No difference $p=0.09$ values 30423/ 50424
<b>Gelclair</b>						
Barber et al. 2007	Radio-therapy	Single-blinded	20 (10/10)	Gelclair/ Sucralfate	Oral gel	No difference $p=0.236$
<b>Plant Extracts</b>						
Maddokcks-Jennings et al. 2009	Radio-therapy	Controlled Single-blinded	19 (6/6/7)	Manuka & Kanuka/ Placebo/ Control	Mouth wash	<b>Pain reduction</b> Grade $\geq 3$ 2 out of 6/ 5 out of 7/ 4 out of 6 patients
Puvvurana et al. 2009	Radio-therapy	Single-blinded	60 (30/30)	Payeyor/ Benzylamine	Mouth wash	<b>Pain reduction</b> $p=0.001$ values 0.12-0.66/ 0.50-0.88
<b>Locally Applied Non Pharmaceutical Methods</b>						
<b>Cryotherapy</b>						
Lilleby et al. 2006	Chemo-therapy	Controlled	40 (21/19)	Ice chips/ Normal Saline	Local application	<b>Pain reduction</b> $p=0.003$ Median values 0.6/2.7
<b>Laser</b>						
Arun Maya et al. 2006	Radio-therapy	Single-blinded	50 (25/25)	He-Ne Laser/ Analgesics, Local Anesthetics	Local application	<b>Pain reduction</b> $p=0.001$ values 2.64/0.64/ 6.63/1.44

## MOUTH-COATING AGENTS

Two studies involved sucralfate as an oral suspension ([32], [33]) in radiotherapy treatment. There was no pain reduction in neither of the studies, ( $p=0.54$ ,  $p=0.09$  respectively). Dodd et al [32], in their RTC had 30 participants, 14 for sucralfate and 16 for salt and soda mouthwash. Etiz et al. [33] in their double-blind RCT had 44 participants, 23 for sucralfate and 21 for placebo. Eventhought there was no pain reduction, there was a significant reduction in topical anesthetic use ( $p=0.0001$ ), as well as in systemic analgesic use ( $p=0.04$ ). (Table 4).

Barber et al. [10] found no difference in pain measurements ( $p=0.236$ ) using either gelclair or sucralfate oral gel, in their single-blind RCT. There were 20 participants, having radiotherapy, randomized in a 1:1 ratio. (Table 4).

## PLANT EXTRACTS

Maddokcks-Jennings et al. [34] conducted a single-blind RCT, in 19 adult participants randomized to have Manuka & Kanuka mouthwash (6 participants), placebo mouthwash (6 participants) or no intervention at all for control group (7 participants). All participants followed the radiotherapy protocol. The results showed a reduction in grade  $\geq 3$  pain in

the intervention group. Only 2 out of 6 participants felt pain graded  $\geq 3$  in the intervention group, compared to 4 out of 6 in placebo group and 5 out of 7 in control group. (Table 4).

Putwatana et al. [35], conducted a single-blind RCT, with 60 participants, randomized in a 1:1 ratio. The use of payayor mouthwash in comparison to benzydamine mouthwash resulted in a significant pain reduction,  $p=0.001$ . Participants had radiotherapy for head and neck cancer. (Table 4).

## **CRYOTHERAPY**

Lilleby et al. [36] in their RCT used ice chips for chemotherapy related mucositis management. 40 participants had either ice chips (21) or normal saline (19) during their chemotherapy. This resulted in a significant pain reduction ( $p=0.01$ ) on the intervention group. (Table 4).

## **LOW ENERGY HELIUM-NEON LASER**

A single-blind RCT was conducted by Arun Maiya et al. [37] in 50 patients having radiotherapy. They were randomized in a 1:1 ratio to either locally application of low energy laser intraoral or a normal saline/povidine 0.9% mouthwash. There was a statistically significant reduction of pain in the intervention group,  $p<0.001$ . (Table 4).

{image:5}

## **DISCUSSION**

It is rather clear that no intervention is capable of managing oral mucositis or oral mucositis-induced pain completely. In this review only some of the literature that revealed interventions was examined, due to the lack of published data on mucositis-induced pain.

There is a trend between studies regarding the same intervention (or intervention group) towards similar results. Additionally, whenever pain reduction was reported, there was also a reduction of systemic analgesic use. On the contrary interventions managing mucositis are not necessary managing mucositis induced pain.

Statistically significant reduction of pain was reported in all three studies regarding Isegran, as well as in the study regarding Glutamine, the one regarding Actovegin and the one in regard to Polaprezinc.

Growth factors, Palifermin and Repifermin have been proved to be effective in reducing the severity of oral pain. Palifermin was used in a single iv dose before the initiation of chemotherapy. Repifermin was effective in reducing the

pain experienced during swallowing.

The use of non pharmaceutical interventions such as Cryotherapy, Low Energy Laser and Plant Extracts resulted in significant pain reduction. It is very important that there were no side-effects; all of these interventions were very well tolerated from the patients. The use of these interventions is rather more preferable considering they are very easy in application and of low cost comparing to the agents used.

No pain reduction was reported in regard to the other interventions included in this review. The use of Antibiotics lozenges or paste, Chlorhexidine mouthwashes, or Benzydamine mouthwashes had no effect on pain perception. Also, the use of Cytocines (GM-CSF and Immunokine-WF10) showed no significant difference in pain measurement, while neither did the use of Mouth-Coating agents (Sucralfate and Gelclair).

A great number of studies were excluded because they didn't have pain measurements. The fact that pain measurement was not the primary end point in any of the included studies is the strongest limitation in this study, even though most of the studies had a Jadad score  $\geq 3$ . Another limitation was the lack of objectivity in pain assessment, since it is based in patients self reporting measuring scales. A well established pain assessment tool should be developed, that should include patients self reports and more objective criteria such as heart beat rate or even measurement of the prostaglandins levels in saliva and blood.

Furthermore, it is essential that studies focusing on the evaluation of the effects of the interventions on mucositis-induced pain should be designed.

In addition, interventions such as acupuncture or homeopathy medication, cheap and very well tolerated, should be under great consideration apart from using analgesics and anesthetics.

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