© Med Sci Monit, 2011; 17(10): CR572-576
PMID: 21959611

WWW.MEDSCIMONIT.COM
Clinical Research

Received: 2011.03.14
Accepted: 2011.06.17
Published: 2011.10.01

The effect of polyvinylpyrrolidone-sodium hyaluronate gel (Gelclair) on oral microbial colonization and pain control compared with other rinsing solutions in patients with oral mucositis after allogeneic stem cells transplantation

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Source of support: Departmental sources

Summary

Background: Gelclair is an oral lubricating gel used in the management of oral mucositis (OM). We evaluated its efficacy, tolerance and impact on oral cavity microbial colonization in patients with OM after allogeneic hematopoietic stem cells transplantation.

Material/Method: Gelclair was administered in a group of 22 patients with active OM. A control group of 15 patients used other rinsing solutions (chlorhexidine, benzydamine, salvia). Tests with oral cavity swabs for microbiology analysis were performed once a week.

Results: The characteristics of OM in both groups were comparable, and rinsing solutions had satisfactory tolerability. There was no difference in the median improvement of oral intake and OM-related pain relief, which was assessed mostly as "slight effect". In the Gelclair group, the effect duration was longer (median 3 [0–5] vs. 1 [0–3] hours, p=0.001). There was significant increase of *Enterococcus faecalis* and *Candida sp.* colonization of the oral cavity over the course of the hospitalization and significantly reduced incidence of such colonization in patients with OM in the Gelclair group: 1/22 (5%) *vs.* 6/15 (40%), p=0.01. *In vitro* tests showed inhibited growth of *Enterococcus faecalis* and *Candida sp.* colonies within the area of the Gelclair application.

Conclusions: Gelclair may be individually helpful in the management of OM and pain in patients after allogeneic stem cells transplantation. Its use did not lead to worsened oral bacterial and yeast colonization and probably even helped to protect mucosa from *Enterococcus* and *Candida sp.* Further studies based on larger cohorts are needed.

key words: **Gelclair • oral mucositis • pain • nursing • *Enterococcus* • *Candida* • microbiology**

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=881983
Word count: 2132
Tables: 2
Figures: 2
References: 17

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Background

Gelclair (Helsinn Healthcare SA, Switzerland) is a concentrated oral gel containing polyvinylpyrrolidone and sodium hyaluronate. It forms an adherent barrier and layer covering oral mucosa lesions, thus protecting sensitive nerve endings and lubricating the tissue. Several studies have suggested that it can help to manage pain and potentially can improve the ability to eat and drink in patients with oral mucositis (OM) after intensive chemotherapy or radiotherapy [1–5].

OM is a significant medical and nursing problem in high-dose chemotherapy and stem cells transplantation settings. This oral mucosa damage and injury is associated with pain and reduced oral intake. Since infections may also play a role in the pathophysiology of OM, antimicrobial mouthwashes such as chlorhexidine, benzydamine, povidone-iodine, and various local antibiotics/antimycotics are widely used in the nursing care and management of OM. However, there is little evidence supporting the use of these agents in the prophylaxis and treatment of this complication [6,7]. On the other hand, they are important in the treatment of oral bacterial and fungal infections [8,9]. Oral cavity cooling (cryotherapy) provided during high-dose melphalan bolus or short infusion administration contributes to local lower blood circulation and cytotoxic drug exposure and can significantly reduce OM in melphalan-containing protocols [10,11]. Effective analgesic therapy is necessary in patients suffering from this painful complication. Patient-controlled analgesia with morphine is a treatment of choice according to MASCC (Multinational Association of Supportive Care in Cancer), NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) recommendations [12–16].

Our observational study aimed to evaluate safety of Gelclair use with respect to the extent of bacterial and yeast colonization within the oral cavity, and to verify its clinical efficacy and tolerance in patients after allogeneic stem cells transplantation.

Material and Methods

We conducted a single-centre prospective and observational study in adult patients with oral mucositis developed after allogeneic hematopoietic stem cells transplantation (HSCT) in 2008–2009. The HSCT conditioning regimens were BuCY2 (busulphan total dose 16 mg/kg, cyclophosphamide total dose 120 mg/kg) or FLU/MEL (fludarabine total dose 120 mg/m^2, melphalan 140 mg/m^2). Patients were given the standard systemic antimycotic, antibacterial and antiviral prophylaxis (fluconazole, chinolons, acyclovir).

The patients signed informed consent. As Gelclair had already been implemented in the standard nursing care for several months at our institution, no Ethics Committee approval was necessary for this study. The study was non-sponsored.

The oral cavity nursing started on the first day of the conditioning chemotherapy administration and covered the whole inpatient stay. Prior to OM development, the patients were allowed to use chlorhexidine, benzydamine or salvia solutions for regular oral rinses. On the day of first signs of OM development (WHO criteria), the first 22 patients were consecutively assigned to the Gelclair treatment (Gelclair group) and afterwards the other 15 consecutive patients were assigned to carry on using the original oral rinses (Control group). After the patients recovered from OM (post-OM phase), all enrolled patients either carried on (Control group) or returned back (Gelclair group) to the standard oral care with benzydamine, chlorhexidine or salvia solutions. The oral rinses were recommended to be used at least 3 times a day and the Gelclair was used in concordance with the product brochure (Gelclair package insert, Helsinn Healthcare SA, Switzerland, 2006) and specific web pages instructions at www.gelclair.com.

The monitoring, assessment and definitions

OM was assessed daily using the WHO grading 0–4 (0 = absent; 1 = pain and erythema; 2 = ulcers, patient can swallow solid food; 3 = ulcers, patient cannot swallow solid food; 4 = mucositis to the extent that alimentation is not possible). The tolerability of oral rinses was evaluated daily by the patients, using the Visual Analog Scale (VAS) scoring: 1–5 (1 = tolerable without any problems, 2 = satisfactory, 3 = indifferent, 4 = unsatisfactory, 5 = intolerable). The OM pain reduction and food intake improvement were assessed daily by the patients using the VAS scoring: 1–5 (1 = excellent, 2 = good, 3 = slight effect, 4 = almost no effect, 5 = no effect at all).

Tests with oral cavity swabs for microbiology analysis were performed once a week in the morning — on the admission to the transplantation unit (pre-OM phase), during active OM (OM-phase) and after the OM resolution (post-OM phase). The smears comprised buccal, palatal and sublingual mucosa.

In vitro Gelclair inhibition test was performed using the *Enterococcus faecalis, Candida albicans, Candida parapsilosis* and *Candida krusei* strains suspensions inoculated separately onto Müller-Hinton agar and 3 drops of Gelclair were added on the inoculated area. The plate samples were incubated in stable temperature 37°C for 24 hour (48 hours in *Candida krusei* sample). All the microbiology samples were processed and cultivated under controlled laboratory conditions in the institutional Department of Microbiology.

Colonies of generally physiological oral bacteria (*Streptococcus viridans* or *Neisseria spec.* or *Staphylococcus* coagulase-negative) were considered potentially pathogenic because of the significant immunodeficiency of transplanted patients.

Statistics

Basic statistical univariate analyses were performed using statistical software (GraphPad InStat, GraphPad Software) with the Fisher's exact test and Unpaired T test. The "p" values <0.05 were considered as statistically significant differences.

Results

A total of 22 patients were enrolled into OM treatment with Gelclair and 15 patients into the Control group using standard oral solutions with chlorhexidine (8/15, 53%), benzydamine (6/15, 40%) or salvia (1/15, 7%). Characteristics of the groups are shown in Table 1.

There was no difference in the median value of tolerability of the rinses in the Gelclair *vs.* Control group: 2 (1–5) *vs.*

Table 1. Characteristics of patients with oral mucositis (OM) after allogeneic stem cells transplantation.

	Gelclair treatment group	Control group	p=
No. of patients	22	15	–
Age (years), median	49.5 (22–68)	39 (19–53)	*0.003*
Sex: males (%)	11 (50%)	8 (53%)	*1.0*
Diagnosis:			–
AML	10	8	
ALL	3	5	
CLL	2	0	
CML	1	1	
HL	0	1	
NHL	1	0	
MDS	3	0	
MM	2	0	
Chemotherapy conditioning:			
BuCY2	15	13	*0.261*
FLU/MEL	7	2	
OM duration (days), median	10 (5–16)	8 (2–19)	*0.489*
OM maximum grade WHO, median	2 (2–4)	2 (1–4)	*0.187*
No. of oral rinses per day	3 (2–3)	3 (2–6)	*0.062*
Systemic analgesic treatment with opioids	15/22 (68%)	7/15 (46%)	*0.030*

AML – acute myeloid leukaemia; ALL – acute lymphoblastic leukaemia; CLL – chronic lymphocytic leukaemia; CML – chronic myeloid leukaemia; HL – Hodgkin lymphoma; NHL – non-hodgkin lymphoma; MDS – myelodysplasia; MM – multiple myeloma.

2 (1–3), p=0.304. The individual tolerance in the Gelclair group in details was: 1 – tolerable without any problems in 9%, 2 – satisfactory in 73%, 3 – indifferent in 9%, 4 – unsatisfactory in 4.5% and 5 – intolerable in 4.5% patients. The individual tolerance in the Control group was: 1 – tolerable without any problems in 33%, 2 – satisfactory in 40% and 3 – indifferent in 27% patients.

Regarding the improvement of oral intake and OM pain relief after oral rinsing, there was no difference in the median value of improvement intensity observed between the Gelclair and the Control groups: 3 (2–4) *vs.* 3 (2–4) and 3 (2–5) *vs.* 3 (1–4) VAS score, p=0.381 and 0.190 (3 = slight effect). The median value of duration of pain relief was significantly longer in the Gelclair group: 3 (0–5) *vs.* 1 (0–3) hours, p=0.001. Significantly more patients on systemic analgesic opioid treatment were in the Gelclair group: 15/22 (68%) *vs.* 7/15 (46%), p=0.03. The analgesic medication administered in the Gelclair group was: buprenorphine 35 ug/hour transdermal patch in 13/22 (59%), buprenorphine 52.5 ug/hour transdermal patch in 1/22 (4.5%) and tramadol 4.1 mg/hour I.V. in 1/22 (4.5%) patients. The analgesic treatment administered in the Control group was: buprenorphine 35 ug/hour transdermal patch in 5/15 (33%), buprenorphine 52.5 ug/hour transdermal patch in 2/15 (13%) patients.

Oral microbiology swabs

In the whole group of 37 patients, bacterial or yeast pathogens were detected in 6 (16%) patients in oral cavity swabs during the pre-OM phase, and in 18 (49%) in the post-OM phase (p=0.0024). During the OM phase, significantly fewer pathogens were found in the Gelclair compared to the Control group: 1/22 (5%) *vs.* 6/15 (40%), p=0.01. After the OM resolution and Gelclair use termination (the post-OM phase), there was a significant increase of pathogen colonization observed in the Gelclair group in comparison with the previous condition in this group: 12/22 (55%) *vs.* 1/22 (5%), p=0.0006. Negative microbial swab results were obtained in the Gelclair group only during the OM phase and in 2 patients later on. No difference was observed in patients using either chlorhexidine or benzydamine solutions. For more details see Table 2.

***In vitro* Gelclair inhibition test**

There was evident growth inhibition of the *Enterococcus faecalis* and *Candida* colonies within the area of Gelclair application (Figures 1 and 2).

Discussion

Gelclair oral gel containing polyvinylpyrrolidone and sodium hyaluronate has been used in the management of oral mucositis, stomatitis and various ulcerative oral conditions with some positive results, suggesting that it can help to reduce pain and improve the ability to eat and drink [2–4]. In a small group of patients with radiotherapy-induced OM, there was also short-term pain relief observed initially after the use of Gelclair; however, there was no improvement in capacity of oral intake [1]. To date there has been limited experience with the use of Gelclair in allogeneic stem cells transplantation patients

Table 2. Oral cavity microbiology swab results in patients within pre-, post-, and during oral mucositis (OM) phase.

	Gelclair treatment group (n=22)	Control group (n=15)	p=
Pre-OM phase with standard oral solutions used in both groups	Negative: 0 Potentially pathogenic: 18/22 (82%) Pathogenic: 4/22 (18%) *E. faecalis 4/4* *C. glabrata 1/4*	Negative: 0 Potentially pathogenic: 13/15 (87%) Pathogenic: 2/15 (13%) *E. faecalis 2/2*	1.00
OM-phase with Gelclair (Gelclair group) or standard oral solution (Control group)	Negative: 13/22 (59%) Potentially pathogenic: 8/22 (36%) Pathogenic: 1/22 (5%) *E. faecalis 1/1*	Negative: 0 Potentially pathogenic: 9/15 (60%) Pathogenic: 6/15 (40%) *E. faecalis 5/6* *E. faecium 1/6*	0.011
Post-OM phase with standard oral solutions used in both groups	Negative: 2/22 (9%) Potentially pathogenic: 8/22 (36%) Pathogenic: 12/22 (55%) *E. faecalis 8/12* *E. faecium 1/12* *VRE 1/12* *C. glabrata 2/12* *C.inconspicua 1/12*	Negative: 0 Potentially pathogenic: 9/15 (60%) Pathogenic: 6/15 (40%) *E. faecalis 4/6* *E. faecium 1/6* *K. pneumoniae 1/6* *C. krusei 1/6*	0.50

Negative – no microbial species detected ever; potentially pathogenic – colonies of *Streptococcus viridans* or *Neisseria* spec. or *Staphylococcus coagulase*-negativ; pathogenic – any other microbial colonies. C. – *Candida*; E. – *Enterococcus*; OM – oral mucositis; VRE – *vancocin resistant enterococcus*.

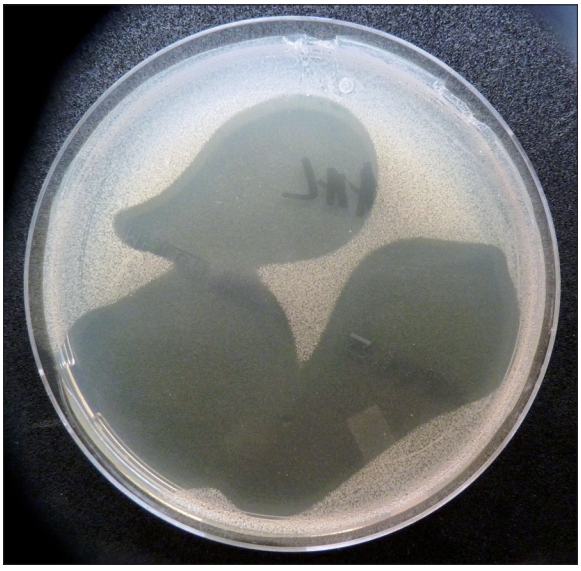

Figure 1. The inhibition of growth of *Candida albicans* colonies on the Müller-Hinton agar in the area of Gelclair application (the clear zone).

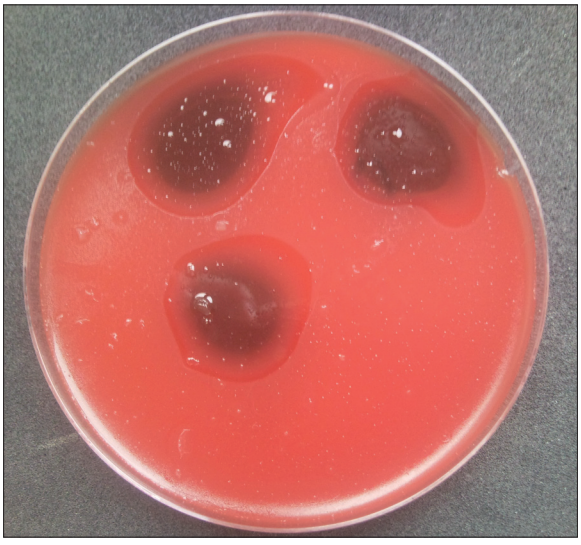

Figure 2. The inhibition of growth of *Enterococcus faecalis* colonies on the Müller-Hinton agar in the area of Gelclair application (the clear zone).

and there is no available information about Gelclair's impact on oral cavity microbial colonization. Based on the fact mentioned above, we decided to conduct this study.

Gelclair was administered in the group of 22 patients in order to treat an active oral mucositis since the first symptoms appeared until OM was resolved. Fifteen other patients were in the control group and carried on with the standard oral care with solutions containing chlorhexidine, benzydamine or salvia. As our patients were allowed to freely select one of the 3 solutions (according to their individual preference and taste), there was in general a good tolerability of these solutions and none of control group patients considered them as "unsatisfactory" or "intolerable", which happened in the Gelclair group, where one of the patients even refused to carry on using the gel due to individual intolerance. The tolerability of Gelclair, however, was in general rather good

in the majority of cases. Thus, the results of oral rinse tolerability must be considered in a larger context.

As for the OM pain relief and oral intake improvement, those issues were assessed as "light" in both study groups, with somewhat longer duration in the Gelclair group (median duration of 3 (0–5) *vs.* 1 (0–3) hours, p=0.001). It is necessary to mention the possible impact of systemic analgesic medication administered in order to reduce the intensity OM pain in the majority of patients. However, to get the most reliable data possible, the patients were individually and specifically asked to focus only on actual local analgesic effect of the rinses applied.

The characteristics of OM in both study groups were comparable. The median value for duration of the complication in both study groups was statistically comparable, as well as the median of OM maximal intensity. It is impossible to objectively compare differences of OM in patients after the FLU/MEL or BuCY2 conditioning regimens because of the small numbers of patients and selection bias – patients without OM were not enrolled into the study.

Although there were differences in age and diagnoses variety between the study groups, in our opinion this had no significant impact on the study results.

Very interesting and somewhat surprising were the results of microbial tests with oral cavity swabs, as there has not been any information yet on antimicrobial effect of Gelclair available, and Gelclair, in fact, does not contain any specific antimicrobial agent. Firstly, we observed a significant increase of pathogens colonization (predominantly *Enterococcus faecalis* and *Candida sp.*) of the oral cavity over the course of the hospitalization. Secondly, there was a significantly reduced incidence of such pathogen colonization, and even microbial negativity, in patients with active OM (OM-phase) in the Gelclair group. The difference observed was remarkable and significant compared to the Control group colonization, and compared to the post-OM phase within the group of patients with original Gelclair treatment (that means significant increase of pathogens in the post-OM phase when Gelclair use was discontinued). Based on these clinically positive results, we decided to test the possible inhibitory effect of Gelclair *in vitro*. The tests performed on Müller-Hinton agar showed inhibited growth of *Enterococcus faecalis* and *Candida sp.* colonies within the area of Gelclair application. These results, however, should be considered only as informative, because the methodology used for the testing was not based on a standardized protocol and had no specific certification or validation. We did not use latex agglutination assay for detection of circulating *Candida* antigen [17].

Conclusions

The results of this observation suggest that Gelclair may be individually helpful in the management of OM and pains in some patients after allogeneic stem cells transplantation. The use of Gelclair did not lead to worsened local bacterial and yeast colonization in the oral cavity and probably even helped to protect mucosa from *Enterococcus* and *Candida* colonization. Gelclair use appears to be safe in patients after allogeneic stem cells transplantation. Further observations and analysis based on larger cohorts of patients are needed.

Acknowledgements

Cervena Jarmila, Dolejsova Lucie, Karasova Lenka, Kibitzova Petra, Krivankova Irena, Lastovkova Alena, Novotna Romana, Rerichova Michaela, Ruttnerova Marta, Schröderova Ruzena, Vohrnova Dana, Zikova Jindra (nurses, University Hospital Plzen, Haemato-Oncological Dept., Transplant unit) – the nursing and care for the patients.

Prim. MU Dr. Tamara Bergerova, MU Dr. Jitka Audesova and MU Dr. Helena Janouskovcova (University Hospital Plzen, Microbiology Dept.) – microbiological analysis of the samples.

Conflict of interest

The authors declare no conflict of interest.

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