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Sucralfate oral suspension for management of mucositis-induced odynophagia in allogeneic hematopoietic cell transplant recipients: a case-control study

Abstract

Background: Allogeneic hematopoietic cell transplantation (HCT) often leads to oral mucositis (OM) and odynophagia, which increase morbidity and treatment costs. Sucralfate has been proposed for mucosal protection, but its role in managing mucositis-induced odynophagia remains unclear.

Methods: We conducted a case-control study comparing allogeneic HCT recipients treated with sucralfate oral suspension for odynophagia (study group) to a matched control group without sucralfate. Outcomes assessed included incidence and severity of OM, duration of parenteral nutrition, analgesic use, hospital length of stay, and treatment costs.

Results: The incidence and severity of OM were similar between groups. However, sucralfate use was associated with a significant reduction in parenteral nutrition duration (2.62 vs. 6.64 days, p=0.001) and lower consumption of morphine, fentanyl patches, and hexomedine ($p < 0.05$). No differences were observed in tramadol or pethidine use. Overall treatment costs were reduced by 51% in the sucralfate group despite the additional cost of the drug. Adherence to sucralfate therapy was high (>80%), with few adverse effects.

Conclusion: Sucralfate effectively reduces odynophagia-related parenteral nutrition and opioid use in allogeneic HCT recipients with mucositis, representing a potential cost-effective supportive care strategy. Randomized controlled trials are needed to confirm these findings.

Keywords: allogeneic hematopoietic cell transplantation, mucositis, odynophagia, sucralfate

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Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a curative therapy for various oncological and hematological diseases.[1-3] Early complications include transient aplasia, nausea, vomiting, diarrhea, mucositis, and acute graft-versus-host disease (GVHD).[4-6] Mucositis is an inflammatory reaction of the oral, oropharyngeal, and gastrointestinal mucosa following chemotherapy, with or without radiotherapy, used in transplant conditioning. When severe, mucositis significantly contributes to increased treatment-related mortality.[5-11] Several interventions have been proposed for the prevention and management of oral and oropharyngeal mucositis (OM). These include the use of keratinocyte growth factor, low-level laser therapy, local control measures, and reduced-intensity conditioning regimens, all of which have helped reduce OM severity in HCT patients.[10-19] However, significant odynophagia due to oropharyngeal and esophageal mucositis remains common. Some studies have reported positive correlations between OM severity and prolonged parenteral nutrition, analgesic use, duration of fever, and length of hospital stay.[7,20]

Sucralfate, an aluminum hydroxide and sucrose sulfate compound, is widely used to manage gastric and duodenal ulcers because of its cytoprotective effect, attributed to its polyanionic properties. Its primary mechanism involves forming a protective barrier over injured tissue.[21,22] Although several studies have assessed sucralfate's efficacy in reducing OM incidence with largely disappointing results,[10,11,23] to our knowledge, no studies have specifically evaluated its use for managing odynophagia related to OM. Therefore, this study aims to evaluate the impact of sucralfate oral suspension on odynophagia management, focusing on parenteral nutrition and analgesic use, in patients undergoing allogeneic HCT for various diagnoses, compared with a case-control population that did not receive sucralfate for odynophagia

Materials and methods

This case-control study was approved by the Research Ethics Committee of the proponent institution (protocol number 27534819.4.0000.5440) and included consecutive adult and pediatric patients undergoing their first allogeneic HCT for any diagnosis and conditioning regimen intensity at our institution. Patients who received sucralfate for odynophagia management formed the study group, and a matched case-control group who did not receive the medication was assembled for comparison. Categorical variables were analyzed using the chi-square (χ^2) test, while numerical variables were compared using the Mann–Whitney test. Statistical significance was set at $p \leq 0.05$.

All patients received daily low-level laser therapy to prevent and treat OM, using a low-power diode laser applied over the entire oral mucosa. Areas without injury were treated with a red laser (660 nm wavelength), while injured areas received an infrared laser (808 nm wavelength). Both treatments were applied for 10 seconds per point, with a power of 100 mW, delivering 1 J of energy and an energy density of 33 J/cm².

Exclusion criteria included prior allogeneic HCT, presence of oral mucosal lesions, dysphagia or odynophagia at conditioning onset, cognitive impairment, pre-transplant swallowing disorders, psychiatric illness, history of opioid dependence, failure to achieve neutrophil engraftment within 30 days post-transplant, death prior to neutrophil recovery, and absence of oral/oropharyngeal mucositis development. The study group was prospectively identified between June 2022 and November 2024, while the case-control group was retrospectively assembled from patients treated between February 2020 and May 2022, following completion of study group accrual. Both cohorts were evaluated and followed according to our institution's Oral Medicine standard practice.

Sucralfate was administered as a 200 mg/mL oral suspension available in 5 mL and 10 mL bottles. Prescription began at the onset of odynophagia following conditioning. Patients were instructed to rinse the suspension in the mouth for 1 to 2 minutes before swallowing. Dosage was every 8 hours, preferably 30 minutes before meals, as follows: (1) adults and children over 20 kg: 10 mL; (2) children 10–20 kg: 5 mL; (3) children under 10 kg: 2.5 mL. Oral medications were delayed for 1 to 2 hours after sucralfate administration.[21,22]

To assemble the case-control group, the hospital database was searched for patients meeting the same inclusion and exclusion criteria as the study group. Four risk factors for OM and odynophagia conditioning type, age, gender, and underlying disease were used to pair control patients to the study group, ensuring comparable cohorts.

After assembling the matched cohorts, similarities between groups were tested by comparing gender, age, underlying disease, conditioning regimen, and weight. The primary outcomes compared were: (1) incidence, severity, and duration of OM (severe OM defined as grade III or IV per the World Health Organization scale);[24] (2) days of parenteral nutrition use; (3) specific analgesic use, including tramadol (ampoules), morphine (ampoules), pethidine (ampoules), fentanyl (patches), and hexomedine (topical bottles); and (4) length of hospital stay. For patients transplanted for sickle cell anemia, painkiller prescriptions related to sickle cell crises were excluded.

Cost data were obtained from the institution's purchasing and quotation control system and are presented in Brazilian Reais (BRL). A cost-minimization analysis was performed from the hospital's perspective. Direct medical costs, including analgesic use, parenteral nutrition, and sucralfate expenditure, were calculated based on actual institutional prices during the study period. Standard cost-comparison methods were applied to evaluate differences in resource consumption between groups. All costs are reported in local currency and reflect real-world expenditure. Additionally, direct costs of analgesic use and parenteral nutrition were analyzed for both groups. Analgesic cost calculations included the volume of physiological solution used for dilution. Indirect costs were not evaluated.

Treatment adherence to sucralfate suspension was assessed using the validated Portuguese version of the Medication Adherence Rating Scale (MARS).[25]

Results

The characteristics of the study population (Table 1) were similar between the study and control groups. Most patients were male, with a median age of 31 years (range 7–60). Both groups were comparable in conditioning intensity (control: 26 myeloablative and 13 non-myeloablative; study: 28 myeloablative and 11 non-myeloablative) and transplant type (control: 36 matched related, 6 unrelated, 1 haploidentical, and 3 mismatched [3 haploidentical]; study: 33 matched related, 7 unrelated, 1 haploidentical, and 6 mismatched [5 haploidentical, 1 unrelated]).

Table 1 Characteristics of study and control population

Characteristics	Groups		Statistical analysis
	Control (N=39)	Study (N=39)	
Gender (Male/female), n	19/20	15/24	p=0.36*
Age (mean/SD), years	31 (±16)	30(±16)	p=0.65***
Weight (Kg)	68 (±17)	66 (±19)	p=0.35***
Underline disease, n (%)			
Acute myeloid leukemia	14 (36)	11 (28)	p=0.94**
Sickle cell anemia	8 (20)	9 (23)	
Acute lymphoid leukemia	8 (20)	10 (25)	
Severe aplastic anemia	4 (10)	4 (10)	
Lymphoma	2 (5)	2 (5)	
Chronic myeloid leukemia	1 (3)	1 (3)	
Myelodysplastic syndrome	1 (3)	0 (0)	
Fanconi anemia	1 (3)	1 (3)	
Myelofibrosis	0 (0)	1 (3)	
Conditioning, n (%)			
FluBu	19 (48)	19 (48)	p=1.00**
Cy	4 (10)	4 (10)	
BuCy	4 (10)	4 (10)	
FluCy + TBI	3 (8)	4 (10)	
Cy + TBI	2 (5)	2 (5)	
FluCy	2 (5)	1 (3)	
TANDEM	2 (5)	2 (5)	
FluCy + Mel	1 (3)	1 (3)	
FluMel	1 (3)	1 (3)	
Flu + TBI	1 (3)	1 (3)	

*X^2 test; **X^2 exact test; ***Mann-Whitney test

Abbreviations: Flu, Fludarabine; Bu, Busulfan; Cy, Cyclophosphamide; TBI, total body irradiation; Mel=Melfalan

As shown in Table 2, the incidence of severe OM (grade III and IV) was 28.2% (11/39) in the study group and 25.6% (10/39) in the control group. The duration of OM longer than seven days occurred in 23.1% (9/39) of study patients and 25.6% (10/39) of controls. Compared to controls, the study group showed a significant reduction in days of parenteral nutrition use (2.62 vs. 6.64 days; p = 0.001).

Similarly, analgesic use was significantly lower in the study group for morphine (7.74 vs. 12.56 ampoules; p = 0.002), fentanyl (0.36 vs. 0.72 adhesive patches; p = 0.02), and hexomedine topical application (0.64 vs. 0.92 bottles; p = 0.003). No significant differences were observed for tramadol or pethidine use between groups. Length of

hospital stay was comparable (43 vs. 42 days for study and control groups, respectively; p = 0.36).

Table 2 Outcomes of interest according to study groups

Characteristics	Groups		Statistical analysis
	Control (n=39)	Study (n=39)	
Patients with grades III or IV mucositis, n (%)	10 (26)	11(28)	p=0.38*
Patients with OM persistent greaten than 7 days, n (%)	10 (26)	9 (23)	p=0.66*
Patients who received parenteral nutrition, n (%)	29 (74)	16 (41)	p=0.02*
Days of parenteral nutrition, mean (Sd)	6.64 (±5.69)	2.62 (±4.11)	p=0.001***
Patients required analgesics, n (%)	38(97)	37(95)	p=0.94*
Analgesics used, mean (SD)			
- Tramadol (ampoules)	9.03 (±7.94)	6.74 (±8.42)	p=0.11***
- Morphine (ampoules)	12.56 (±15.18)	7.74 (±15.79)	p=0.002***
- Pethidine (ampoules)	0.59 (±0.94)	0.33 (±0,84)	p=0.11***
- Fentanyl (patch)	0.72 (±1.15)	0.36 (±1.08)	p=0.02***
- Hexamedine + Tetracaine (bottle)	0.92 (±0.28)	0.64 (±0.48)	p = 0.003***
Duration of hospitalization, median days	41.77 (±14.82)	43.46 (±12.013)	p = 0.36***

*X^2 test; ***Mann-Whitney test

Abbreviations: OM, oral mucositis; Sd, standard deviation.

The average duration of sucralfate use in the study group was 14.13 ± 8.91 days. Since medication remnants were discarded, the number of bottles used corresponded to treatment duration. A total of 1,653 bottles of 10 mL sucralfate suspension were used throughout the study, averaging 42.38 ± 26.75 bottles per patient.

Cost analysis (Table 3) showed that, except for sucralfate (administered only to the study group), expenditures on all treatments were higher in the control group. Overall, total costs for the study group were 51% lower than for controls (R$42,374.64 vs. R$86,115.19). Parenteral nutrition was the largest cost contributor—92.38% in controls and 77% in the study group—while sucralfate was the second highest cost item in the study group (13.81%). The proportional distribution of other costs was similar between groups.

Table 3 Cost analysis of therapies received for mucositis-induce odynophagia according study and control groups

Therapies	Cost per unit*	Groups	
		Control (Disbursement in R$*)	Study (Disbursement in R$)
Sucralfate	3.54 = Flacon of 10ml	0	5 851.62
Parenteral nutritional	0.25 = 1mL of amount	79 561.45	32 640.00
Tramadol	0.90: 1 ampoule +10ml of saline	312.3	236.7
Morphine	3.78: 1 ampoule +10ml of saline	1 844.64	1 141.56
Pethidine	3.18: 1 ampoule +10ml of saline	69.96	45.34
Patch Fentanyl	104.53: 1 adhesive	2 926.84	1 463.42
Hexamedine	40.00: 1 bottle	1 400.00	1 000.00
Total		86 115.19	42 374.64

Source: Integrated material management system HCFMRP-USP

*R$ = Real Brazilian currency

Adherence to sucralfate therapy was high, exceeding 80% (Table 4). The main cause of non-adherence was nausea attributed to the medication's unpleasant taste.

Table 4 Sucralfate adherence and tolerance using MARS[24] instrument

Question	Yes	No
1. Do you ever forget to take your medicine?	20%	80%
2. Are you careless at times about taking your medicine?	0%	100%
3. When you feel better do you sometimes stop taking your medicine?	0%	100%
4. When you feel worse when you take the medicine, do you stop taking it?	20%	80%

Abbreviation: MARS, medication adherence rating scale.

Discussion

In this study, we assembled a pair-matched control group of allogeneic HCT recipients with characteristics comparable to the study group, enabling a comparative analysis of OM incidence (Table 1) and key outcomes (Tables 2 and 3) between patients treated for mucositis-induced odynophagia with sucralfate (study group) and those who did not receive this treatment (control group). Previous studies have analyzed sucralfate's impact on OM but not specifically as a strategy to relieve odynophagia as in our work.[10,11,19] Importantly, age and conditioning regimen type two of the most consistently reported risk factors for OM development and severity[26,27] were similarly represented in both groups. Patient weights were also comparable, minimizing confounding in the analysis of cost differences related to parenteral nutrition and analgesic use. The incidence of severe OM (grades III and IV) was similar between groups and consistent with previously reported rates ranging from 19% to 83%, depending on conditioning intensity.[28]

Parenteral nutrition is frequently used after allogeneic HCT, mainly due to OM and graft-versus-host disease (GVHD).[29] However, data on its incidence, duration, and cost in the early post-transplant period are scarce. Our study demonstrated that parenteral nutrition use was significantly higher in the control group (74%) compared to the study group (41%), with a corresponding reduction in duration for those treated with sucralfate.

Discomfort and pain are common in patients with OM, often requiring opioid analgesics. Pethidine is typically reserved for acute pain episodes in patients on chronic morphine therapy. Fentanyl patches reduce reliance on morphine infusions when pain control is inadequate, while topical agents such as hexomedine provide localized pain relief.[30-35] In our cohort, analgesic use followed a similar pattern across groups: tramadol, morphine, hexomedine, pethidine, and fentanyl patches in descending order.

Significant reductions in morphine, fentanyl patch, and hexomedine use were observed in the sucralfate-treated group. No significant differences in tramadol or pethidine use were found, potentially reflecting better chronic pain control with tramadol in the study group and low overall pethidine use related mainly to acute gastrointestinal mucositis pain, which was not assessed here.

The relationship between OM severity and increased HCT-related costs is well recognized, given the need for pain management and alternative nutrition. Sonis (2001) reported an average $25,000 increase in costs associated with severe OM.[7]

As anticipated, drug-related expenditures were lower in the study group. Due to its high cost at least 30 times greater than other analgesics the reduced use of fentanyl patches accounted for the largest absolute and relative cost savings (Table 3). Similar to parenteral nutrition findings, fewer patients in the study group required analgesics, particularly morphine. Although not specifically evaluated, this likely reduced opioid-associated adverse effects such as nausea, vomiting, constipation, and dizziness.[34]

Adherence to sucralfate therapy was high, and symptom improvement was notable. Despite additional costs for sucralfate, the study group's overall expenses were reduced by approximately 50%.

The decrease in parenteral nutrition and analgesic use occurred without differences in OM incidence, severity, or duration, supporting our hypothesis that sucralfate acts by forming a protective barrier to reduce mucositis-related discomfort rather than directly treating mucosal injury. Several studies have investigated strategies to manage odynophagia secondary to oral mucositis, highlighting the clinical relevance of this symptom in patients undergoing oncologic treatments. Ibáñez et al.,[36] demonstrated that oral glutamine supplementation significantly reduced both the incidence of mucositis and odynophagia in head and neck cancer patients receiving radiotherapy, also decreasing treatment interruptions and the need for analgesia and enteral support. Similarly, Naidu et al. reported that a polyherbal gel wafer (Mucotrol) was effective in reducing mucositis severity and associated pain, including odynophagia, in patients undergoing chemoradiation.[37] In contrast, Foster et al. illustrated that conservative topical treatments often fail in immunotherapy-induced mucositis, where systemic glucocorticoids become necessary to control severe pain and enable continuation of cancer treatment.[38] Tong et al.,[39] in their meta-analysis, reported a reduction in odynophagia and oral pain in patients undergoing low-level laser therapy. All patients in this study received standardized topical low-level laser therapy from the beginning of the conditioning regimen until neutrophil engraftment. These findings reinforce the multifactorial nature of odynophagia management in mucositis and the importance of tailoring interventions according to the etiology and severity of lesions. Our results align with this evidence by emphasizing the need for effective therapeutic options that not only target mucosal healing but also provide symptomatic relief of odynophagia, contributing to better adherence to oncologic protocols and improved patient quality of life.

Limitations of this study include the retrospective design of the control group, the absence of validated measures for pain and quality of life, the lack of indirect cost analysis, and variability in patient numbers, conditioning regimens, pain tolerance, and compliance between pediatric and adult populations. Nevertheless, the use of strict matching criteria and a uniform pain management protocol strengthened the comparative analysis and support the conclusion that sucralfate may represent a cost-effective strategy for managing odynophagia in allogeneic HCT patients with oral mucositis.

In conclusion, sucralfate treatment for mucositis-induced odynophagia significantly reduced parenteral nutrition use and duration, as well as morphine, fentanyl patch, and hexomedine consumption in allogeneic HCT recipients. Future randomized studies are warranted to confirm these findings.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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