Effect of Implementing an Integrated Algorithm on Severity and Duration of Oropharyngeal Mucositis for Patients Receiving Allogenic Hematopoietic Stem Cell Transplantation

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Abstract

Background: *Because of the conditioning regimen's toxicity, oropharyngeal mucositis (OPM) arises in the context of allogenic hematopoietic stem cell transplantation (HSCT). It culminates in inflammation, ulceration, as well as diminished oropharyngeal epithelium renewal rate. Patients' life quality is reduced by OPM, which is joined by severe pain, infection, bleeding and undernourishment. Few therapies are accessible right now. Creating algorithms and a multiagent system is projected to be more prosperous than employing a solitary intervention.* ***Aim:*** *Evaluate the effect of implementing an integrated algorithm on severity and duration of OPM for patients receiving allogenic HSCT.* ***Settings:*** *The present study was conducted at the Bone Marrow Transplant Unit, Nasser Institute Hospital for Treatment and Research, Cairo.* ***Subjects:*** *A convenience sample of 30 adult patients who were admitted for performing allogenic HSCT, followed the inclusion criteria and were assigned randomly into two equal groups (control group and study group), 15 patients in each group.* ***Tools:*** *five tools were used. Tool one: Bio sociodemographic data structured questionnaire. Tool two: Oral health management knowledge structured interview questionnaire. Tool three: Modified oral assessment guide (MOAG). Tool four: Swallowing exercises observational rating scale. Tool five: National Cancer Institute grading for oral mucositis severity and duration.* ***Results:*** *The study illustrated that there was a significant improvement in oral health management knowledge in the study group compared with the control group patients post transplantation (^{MC}p <0.001*). Moreover, there was significant improvement in the total score of oral assessment in study group patients started from +6 day post transplantation compared with the control group (^{MC}p<0.001*). Furthermore, there was significant improvement in the practice of the swallowing exercises post transplantation for the study group compared with control group (^{MC}p<0.001*). Also, there was significant decline in severity and duration of OPM in study group compared with control group started from +6 day post transplantation (^{MC}p <0.001).* ***Conclusion:*** *The integrated algorithm for patients receiving allogenic HSCT showed a positive effect on severity and duration of OPM as evidenced by improvement in oral health management knowledge, the overall total score of MOAG and practice of swallowing exercises. As well as significant decline in grade and duration of OPM.* ***Recommendations:*** *Replication of this study using large probability sample.*

Keywords: Allogenic hematopoietic stem cell transplantation, Integrated algorithm, Oropharyngeal Mucositis
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Introduction

The process of swapping ruined or aberrant stem cells in a patient by intravenous infusion of autologous or allogeneic hematopoietic precursor cells retrieved from peripheral blood, bone marrow or umbilical cord blood is recognized as HSCT (Galgano et al, 2023). The intent of this procedure is to recuperate normal hematopoietic and immune function and to permit for hematopoietic reconstitution in cases of congenital or acquired life-threatening abnormal bone marrow or immune function (Pranay et al., 2022).

With a population of over 100 million in 2020, Egypt has a transplant rate of 8.4 per million, which are yet distant from the Western standards that reached 36 to 40 per million. (Mahmoud et al., 2020). Relying on the adult registry, the total number of transplants completed at the Nasser Institute from 2018 till 2022, was 43 (9%) autologous and 435 (91%) allogenic transplants. (Statistical records of Bone Marrow Transplant Unit, Nasser Institute Hospital, 2022).

There are two primary varieties in HSCT: autologous and allogenic, whereas bone marrow, peripheral blood, or umbilical cord blood are sources of allogenic stem cells (American Cancer Society, 2024). Myeloid cancers (58%), lymphoid cancers (28%), and non-malignant illnesses (13%) were the primary indications for allogeneic HSCT (Passweg et al., 2023).

Prior to getting an allogeneic HSCT, the patient goes through a conditioning regimen that may entail immunotherapies, chemotherapies, and targeted therapies with or without whole body radiation (Zulu & Kenyon, 2023). A conditioning regimen is applied to make space in the bone marrow for the incoming stem cells, it helps get rid of any cancer cells that may still be present in the body and prevent transplant rejection by repression the recipient's immune system (Hoeben et al., 2021).

The strength of conditioning regimens varies; nonmyeloablative (lower-dose regimens) provoke myelosuppression without damaging bone marrow, and myeloablative (high-dose regimens) that demolish the bone marrow (Gagelmann & Kröger, 2021).

Myeloablative chemotherapy is a combination of chemotherapeutic agents that, when administered, should lead to serious pancytopenia and myeloablation across 1-3 weeks of administration. Pancytopenia is a persistent condition that is typically unchangeable unless hematopoiesis is back in action through the infusion of blood-forming stem cells (Feliu et al., 2020).

The three most popular myeloablative conditioning regimens in use today are busulfan (Bu)+ cyclophosphamide (Cy), busulfan (Bu) + fludarabine (Flu) and cyclophosphamide (Cy) + whole body irradiation (Gooptu et al., 2018). High toxicities, high incidence, a long duration, and a severe grade (3- 4) of OPM are typically linked to myeloablative chemotherapy protocols. (Ali et al., 2023).

Even with HSCT's benefits, there are still several complications, such as gastro-hepatic involvement, which primarily include anorexia, nausea, vomiting, diarrhea, perianal pain, sinusoidal obstruction syndrome, acute graft versus host disease, infections and OPM (Wallhult et al., 2023). In allogenic transplantation which uses myeloablative regimens, the incidence rate of OPM ranges from 60% to 100% (Bruno et al., 2022).

Oropharyngeal mucositis (OPM) usually starts 5-7 days following the chemotherapy-based regimens, can last until the 14th day of HSCT. It manifests as erythema, swelling, or ulceration and is characterized by burning sensations to excruciating painful ulcers. In addition to pain, odynophagia, dysgeusia, xerostomia, and speech difficulties, OPM can result in malnourishment, dehydration, and potentially fatal infections, which seriously

lower the patients' quality of life (Suzuki, 2022; Ali et al., 2023).

As reviewed in Society of Oral Oncology& Mucositis Study Group, prevention of OPM can be effectively achieved through applying protocols for oral care that combine multiple agents. (Judge et al., 2021& Colella et al., 2023). The process of creating a multiagent algorithm is a care pathway that consists of several decision points based on reliable evidence and others that depend on unanimity to generate proposals for management. (Eubank et al., 2024).

The present clinical approaches recommend some combinations of the following to prevent and treat OPM caused by chemotherapy, which comprise, low level laser therapy or photo biomodulation, keratinocytes growth factors, patient-controlled analgesia, fundamental practices for oropharyngeal hygiene, bland mouth washes, oral cryotherapy, anti-inflammatory, antioxidants as vitamin E, natural agents as honey, nutritional supplements, instructing patients on oropharyngeal care, therapeutic swallowing techniques and dietary strategies (Hong et al., 2019; Zadic et al., 2019).

Oncological nurses have a crucial task in the management of OPM. Using accurate and dependable tools to assess the oropharyngeal cavity, identifying OPM risk factors, teaching oropharyngeal care, creating and putting into action evidence-based procedures. The nurses ought to try their best to design individualized plans that are meant to produce the best results for each patient. OPM is regarded by oncology nurses as a very difficult problem. There aren't many therapies that can treat or lessen mucositis symptoms. Accordingly, additional research is required currently. (Gündogdu & Sayar, 2022; Ferreira et al., 2022).

Aim of the Study

This study aims to evaluate the effect of implementing an integrated algorithm on severity and duration of oropharyngeal mucositis for patients receiving allogenic hematopoietic stem cell transplantation.

Research hypotheses

- Patients with allogenic hematopoietic stem cell transplantation who received integrated algorithm exhibit less severity of oropharyngeal mucositis than those who didn't receive it.

- Patients with allogenic hematopoietic stem cell transplantation who received integrated algorithm exhibit less duration of oropharyngeal mucositis than those who didn't receive it.

Operational definition

Integrated algorithm: is comprising of a series of care steps and numerous agents, which include oropharyngeal hygiene, cryotherapy for oropharynx, isotonic saline plus sodium bicarbonate mouth wash, topical vitamin E, topical sidr honey, propolis-filled capsules, swallowing drills techniques, and patient teaching.

Materials and Method

Materials

Design: A quasi-experimental research design was utilized for this study.

Setting: The present study was conducted at the Bone Marrow Transplant Unit, Nasser Institute hospital for treatment and research, Cairo affiliated to the Ministry of Health

Subjects: A convenience sample of 30 adult patients who were admitted to the previous mentioned setting for performing allogenic hematopoietic stem cell transplantation, were included, and assigned to two equal groups (control and study), fifteen patients in each group. The study sample was

selected based on Epi info -7 program which used to estimate the sample size using the following parameters: population size = 35 over 4 months, expected frequency =50%, acceptable error =5%, confidence coefficient =95%, minimum sample size =30.

The study group was exposed to integrated algorithm and routine unit care related to basic oral antimicrobial agents. The control group was exposed to standard hospital care only that included antimicrobial mouth rinse nystatin and hexitol or betadine mouth wash, along transplantation period. Also, the control group received magic mouth wash that composed of (250 ml normal saline+ amp sodium bicarbonate +4 tablets zyloric+ mycostatin bottle+ amp lidocaine) and opioid medications as pethidine if needed. It was prescribed since the start of oral mucositis and continues for two weeks, three times daily. All studied patients were selected according to the following criteria: adult patient, (18- 60) years old, diagnosed with hematologic malignancy or non-hematologic malignancy that necessitate allogenic HSCT, conditioning regimen was myeloablative chemotherapy protocol {Busulfan (Bu)+ Fludarabine (Flu)+ post cyclophosphamide (Post Cy)} according to standard written hospital protocol. Patients who had history of asthma, diabetes, bee products allergy and patients who had any mucositis degree at admission were excluded.

Tools: To fulfill the aim of the study, five tools were used for data collection:

Tool I: Bio sociodemographic data structured questionnaire: This tool was developed by researcher after reviewing related literatures to identify patient's bio sociodemographic characteristics, it included two parts as the following: **part I:** patient's sociodemographic characteristics as gender, age, level of education, marital status, occupation, and residence area (Tay et al., 2019; Solh et al., 2020). **Part II**: Patient's clinical data: as diagnosis, source of transplant, donor type, pre transplantation conditioning period, conditioning protocol used, type of conditioning regimen, graft versus host disease prophylaxis medications, and comorbidity index score (Valeh et al., 2018; Mishkin et al., 2019; Solh et al., 2020).

Tool II: Modified oral assessment guide (MOAG): This tool was adopted from Cheng et al. (2004) to assess oral health in cancer patients. It consisted of eight assessment classes: voice, swallowing, , lips, tongue, saliva, mucous membranes (buccal mucosa, palate), mucous membranes (labial mucosa) and gingiva. Each class includes 3 different criteria as voice may be normal, deeper or raspy and difficult talking or painful speech. The scoring system was expressed from 1 to 3 for each category. The total score ranged from 8- 24. The best possible score of 8 points is indicative of good oral health; the score of (9- 16) is indicative of poor oral health and the worst possible score of (17-24) points is indicative of very poor oral health (Ribeiro et al., 2019).

Tool III: Oral health management knowledge structured interview questionnaire: This tool was developed by researcher based on a review of related literature (Schubert et al., 2016; Marx et al., 2016), to assess patient's knowledge related to oral health management along transplantation process. It included 25 closed ended questions (Q), regarding patient's information about HSCT process (2 Q), gastrointestinal side effects of preparative chemotherapy regimen (7 Q), relation between oral health and transplantation process (1Q), correct oral hygiene technique (10 Q), meal modification and behavior related dietary strategies (5 Q). The scoring system: correct and complete answer was given a score of (3), correct incomplete answer was given a score of (2) and score (1) was given for wrong or no answer. The total score ranged from 25 to 75. The total score for every patient was summed up and converted into a percentage score. The percent score was classified as

the following: a score less than 60% was considered poor level of knowledge, a score of 60% to less than 75% was considered fair level of knowledge, and a score of 75% and more was considered good level of knowledge.

Tool IV: Swallowing exercises observational rating scale: This tool was developed by researcher based on reviewing of related literature (Guillen-Sola et al., 2019) to assess and improve patient's ability to swallow effectively after chemotherapy protocol. The checklist included 30 steps related to patient preparation, jaw exercises, lip/ cheek exercises, tongue exercises, tongue base exercises, laryngeal exercises, Strap muscle exercises, duration, and time of exercises. The scoring system varied between done correctly that was given a score of (3), while done incorrectly was given a score of (2) and score (1) was given for not done. The total score ranged from 30 to 90. The total score for every patient was summed up and converted into a percentage score. The percentage score was classified as the following: a score of less than 60% was considered poor level of practice, a score of 60% to less than 75% was considered fair level of practice, and a score of 75% and more was considered good level of practice.

Tool V: National Cancer Institute Grading for oral mucositis severity and duration. This tool was adopted from United States Department of Health and Human Health et al. (2017) by the researcher to assess severity of oropharyngeal mucositis. It consisted of 6 grades from zero to five, each grade contained criteria that describe mucositis severity. Each participant took one of the following scores: **zero**: none, **one**: painless ulcers, erythema, or mild soreness, **two**: painful erythema, edema or ulcers but swallowing possible, modified diet indicated, **three**: painful erythema or ulcer interfering with oral intake, requiring IV hydration, **four**: severe ulcerations, or requires parenteral/enteral nutritional support or prophylactic intubation, and **five**: death related to toxicity.

Method

An approval from The Ethical Research Committee, Faculty of Nursing, Alexandria University was obtained. An official permission was obtained from the Faculty of Nursing, Alexandria University to responsible authorities of the selected setting to obtain their approval to collect the data after explaining the aim of the study. An official permission was obtained from the hospital director and head of the department of the selected setting after explaining the aim of the study. The study tools were tested for content validity by three experts in medical surgical nursing and two experts in hematological field and accordingly, the necessary modification was done. The reliability of tools was tested by means of Cronbach's alpha. Reliability coefficient for tool I was 0.76, tool III was 0.90, tool IV was 0.99, while tools II and V were adopted which means all tools were reliable. A pilot study was carried out on 5 patients, for testing clarity and applicability of the study tools and necessary modifications were done accordingly. Data obtained was excluded from the current study. The data collection was started and continued for a period of 10 months from November 2021 to August 2022. The data was collected by the researcher from control group first, and then the study group to prevent data contamination.

The study was carried out through four phases: Phase I: assessment phase: Initial assessment was carried out by the researcher for every patient in both study and control group at unit admission to collect baseline data regarding bio sociodemographic characteristics using tool I, assessment of oropharyngeal cavity using tool II, assessment of oral health management knowledge using tool III, and swallowing exercises observation using tool IV. Assessment was ranged of 90- 120 minutes

on individual basis, including auditing of patient's medical record.

Phase II: Planning phase: Based on data collected from the assessment phase and literature review, the integrated algorithm for OPM was developed by researcher according to the patient risk, needs and problems. Moreover, a colored booklet in Arabic language was developed by the researcher and distributed to each patient after assessment phase, it was sent to the patient's mobile inside HSCT isolation's capsule (room), in case the patient has no smart phone, the researcher explained the booklet to the patient through isolation capsule's window. The integrated algorithm for OPM is anticipated to evaluate and change patient's knowledge and practice related to oral cavity health and decrease severity of chemotherapy induced OPM.

Phase III: Implementation phase: The developed algorithm was implemented individually for each patient in the above-mentioned setting. During the interview, the purpose of the study was explained to each participant of the study group, booklet software was sent to each patient. The proposed oropharyngeal algorithm was implemented as following:

Part I: it was started since admission till the (+4) day post transplantation, it consisted of 11 days and included the following:

1- **Patient education sessions:** Four sessions of patient's education were carried out in the first 48 hours of admission at the patient's isolation capsule in which the researcher be in the pre isolation area and communicate with the patient through isolation capsule's window. The duration of each session was 60- 90 minutes depending on the patient's understanding and cooperation. **The first session** included education about stages of HSCT, gastrointestinal complications of allogenic HSCT, factors that increase occurrence of OPM, treatment of OPM, importance of maintaining oral health and how to care oropharyngeal cavity along transplantation process. **The second session included** repetition of the learned information by the patient and reexplanation by the researcher if needed.

The third session included swallowing exercises demonstration at admission by the researcher, through isolation capsules' window, they included: jaw exercises, lip/cheek exercises, tongue exercises, tongue base exercises as effortful swallow & masako swallow, laryngeal exercises, and strap muscle exercises. These exercises were repeated 3 times/ day; each exercise was carried out 5-10 times. Patient was asked to continue these exercises from admission till 3 weeks post transplantation. **The fourth session** included: return demonstration of swallowing exercises by the patient and reexplanation by the researcher if needed.

2- **Basic oral & oropharyngeal care hygiene:** Basic oral care was carried out using antimicrobial mouth rinse nystatin 100000 units/ml and hexitol 0.125 %. This step was carried out for study and control group as a part of standard hospital care. Antimicrobial agents were used three times daily from unit admission until discharge.

Duration of oral rinsing for study group was 60-120 seconds. Using ultra soft toothbrush that brought by the researcher to the patient in the conditioning period only. It was used gently at least once daily according to the patient's tolerance, through technique of modified bass sulcular brushing then the mouth was rinsed with normal saline 0.9%.

3- **Oral cryotherapy sessions:** cryotherapy was applied through small ice cubes with rounded edges to avoid irritation. Boxes of ice cubes were prepared by researcher prior to starting each chemotherapy cycle with sufficient quantity.

The chemotherapy protocol that was selected in this study included two main chemotherapeutic agents: oral busulfan (Bu) and intravenous fludarabine (Flu). Busulfan (Myleran) was taken orally/ 6 hours for 4 days, so cryotherapy was started one hour

after Bu administration and lasting for 2 hours, 3 sessions/ day and skipping the night session. Moreover, Flu was given through intravenous infusion half hour/ day for four days, so cryotherapy session for this medication beginning 10 minutes pre infusion, continuing through the infusion and for 10 minutes post infusion, one session/ day.

4-Topical vitamin E application: Topical application of vitamin E 400 IU capsule in the oral cavity, two capsules/ once daily. Vitamin E was kept in the mouth for (5-10) minutes, swished then spit out, as agreed and prescribed by the treating physician.

Part II: it was started fifth day post transplantation till +21day post transplantation and included the following:

1-Bland mouth rinsing using cold normal saline and sodium bicarbonate solution. Bland mouth rinse was conducted using 250 ml normal saline 0.9% plus one vial 50 ml sodium bicarbonate, mixed and preserved in the refrigerator. The oropharyngeal cavity was rinsed every 4 hours or as required. Duration of oral rinsing was 60 seconds then spit out. As prescribed and agreed by the treating physician.

2-Topical oral& oropharyngeal sidr honey: Topical application of concentrated Egyptian sidr honey three times daily in oral cavity by the researcher. Honey samples were retrieved from the outlets of the faculty of agriculture, Cairo, extra filtered and placed in sterile boxes. Sidr honey was applied using tipped cotton swab applicator to the complete oral mucosa. The patient was asked to keep the honey in the mouth for (5-10) minutes, then the patient was asked to rinse mouth with half cup of warm water, gargled and swallowed. As agreed by the treating physician.

3- Propolis capsules

One capsule of propolis 1000 mg administered orally every morning, started (+10) day till (+21) day post transplantation, as agreed and prescribed by the treating physician. It is considered a dietary supplement that contains fats, carbohydrates, and proteins.

Phase IV: Evaluation phase: The oral cavity was reassessed at -1day pre transplant and every 2 days post transplantation, till +21day post transplantation using tool II. Patient's knowledge regarding oral health management and swallowing exercises practice was reassessed at +4day post transplantation using tool III and tool IV. Severity and duration of oral mucositis were assessed every 2 days from -3day pre transplantation till +21day post transplantation using tool V.

Ethical considerations:

Written informed patients' consent was achieved before data collection and after explanation of the aim of the study. The patient was informed that his or her engagement in the study is voluntary and he/she can withdraw at any time and his or her withdrawal will not impact the care he/she receives at the hospital. The privacy of the study participants was declared. Confidentiality of the collected data was affirmed (Faculty Ethical Research Committee Approval 14/3/2021).

Statistical Analysis

Data was fed to the computer and analyzed utilizing IBM SPSS software package version 20.0. (George & Mallery, 2019). Qualitative data were described using numbers and percentages. The Shapiro-Wilk test was used to confirm the normality of distribution. Quantitative data were described using range (minimum and maximum), arithmetic mean, standard deviation and median. Significance of the obtained results was judged at the 5% level (Cooksey, 2020).

Results

Table 1 shows percentage distribution of patients with allogenic HSCT of both studied groups according to patient's socio demographic characteristics. It was observed

that more than half (60%, 53.3%) of both studied groups were in age group (20-> 40) years and were females. Two thirds (66.7%) of both studied groups were married, around half (46.7%) of the control group patients were university educated, while around half (53.3%) of the study group patients were diplom educated. There were no statistically significant differences between patients of both studied groups in all above-mentioned items

Table 2 illustrates percentage distribution of patients with allogenic HSCT of both studied groups according to patient's clinical data. Concerning patient's diagnosis, it was observed that the majority (53.3%, 73.3%) of patients of both studied groups were diagnosed with acute myeloid leukemia, without statistically significant difference (χ^2=3.913, ^{MC}p=0.265). Moreover, regarding source of hematopoietic stem cell, type of donor and pre transplantation conditioning period**,** all patients (100%) of both studied groups received hematopoietic stem cells from peripheral blood hematopoietic stem cell of sibling donor and they had a period of 6 days pre transplantation.

In relation to conditioning protocol, type of conditioning regimen and graft versus host disease prophylaxis medications, the table showed that all patients (100%) of both studied groups submitted to (busulfan+ fludarabine+ post cyclophosphamide) myeloablative conditioning regimen and received cyclosporine A plus post cyclophosphamide graft versus host disease prophylaxis medications. There were no statistically significant differences between patients of both studied groups in all above-mentioned items.

Table 3 presents comparison between the two studied groups according to total score of modified oral assessment guide (MOAG) since admission till +21 days post transplantation**.** It was noted that the majority (93.3%, 100%, 100%, 100%, 100%, 66.7%) of the control group had worst oral health since +6 till +16 days post transplantation, while the majority (80%,100%, 66.7%, 66.7%, 60%, 100%) of the study group had improved oral health either poor or good oral health at the same mentioned periods, with statistically significant differences (^{MC}p<0.001*, p <0.001, p <0.001, p <0.001, ^{MC}p<0.001*, ^{MC}p<0.001*) respectively.

Table 4 reveals comparison between the two studied groups according to the overall of oral health management knowledge at admission and at +4day post transplantation**.** It was observed that the study group patients expressed improved knowledge regarding oral health management compared with control group at +4day post transplantation with statistically significant difference between control and study group patients at +4day post transplantation (χ^2=26.313*, ^{MC}p <0.001*).

Table 5 presents comparison between the two studied groups according to overall swallowing exercises observational rating scale. Concerning swallowing exercises compliance, the table illustrated that the study group had good and improved practice regarding swallowing exercises compared with control group at +4day post transplantation with statistically significant difference between both studied groups (χ^2=24.468, ^{MC}p<0.001).

Table 6 presents comparison between the two studied groups according to National Cancer Institute grading scale for mucositis severity and duration. As regards mucositis severity, the table illustrated that more than half (60%) of the control group developed grade 3 mucositis since + 8 day till + 16day post transplantation, while one third (33.3%) of the study group patients developed grade 1 mucositis since +10 till +12day post transplantation with statistically significant difference at +10 and +12 day between both studied groups (^{MC}p <0.001, ^{MC}p <0.001) respectively. Also, it was concluded that duration of oropharyngeal mucositis in the most of control group lasting for 13 days since +8 till +18day post transplantation,

while the duration of oropharyngeal mucositis lasts around 3-4 days only since + 10 till +12day post transplantation for study group patients who developed mucositis.

Discussion

Oropharyngeal mucositis (OPM) is one of the most crippling consequences of toxicity due to HSCT conditioning regimens. It results from the inflammation of the oral mucosal barrier and is paired with erythema, ulcers, difficulty eating or drinking and pain (Guberti et al., 2022). Myeloablative conditioning protocols are often distinguished by a higher toxicity, which may suggest an increased occurrence and severity of OPM in patients receiving treatment with these regimens (Wysocka-Słowik et al., 2021). Severe cases of OPM are linked to intense discomfort, affecting patients' life quality and transplantation results (Guberti et al., 2022).

According to recent research, carrying out a multi-agent combination oral care protocol is advantageous for the prevention OPM during HSCT. (Hong, et al, 2019). Also, they recommend regarding the topical use of natural remedies, including honey, vitamin E, propolis and others. These composite agents comprise a diverse range of compounds that are biologically active, which may disrupt the pathogenic mechanism underlying OPM. (Guberti et al., 2022).

Regarding clinical data, as for diagnosis, the current study reflected that more than half of the control group and around three quarters of the study group patients were diagnosed with acute myeloid leukemia. This finding is consistent with American Cancer Society [ACS] (2023) that stated that acute myeloid leukemia is one of the most prevalent kinds of leukemia in adults. Moreover, Gooptu et al. (2018) mentioned that myeloid malignancies was dominant in myeloablative conditioning cohorts, and lately, Bu/ Flu is often the most popular chemotherapy myeloablative regimen in the present day, rather than myeloablative Bu/ Cy.

Additionally, Patel et al. (2020) concluded that patients with myelodysplastic syndrome and acute myeloid leukemia who might not be candidates for the conventional myeloablative chemotherapy protocol may be capable of reaping advantages from alternative myeloablative Bu/ Flu regimen in HSCT. This result could be interpreted as, this study was focused on Bu/ Flu post Cy chemotherapy protocol, it was one of the prevalent myeloablative protocols for adults in the hospital of data collection. Also, Myeloid malignancies were frequently treated with myeloablative protocols. So, this may interpret why more than half of the studied patients had acute myeloid leukemia.

In relation to the source of hematopoietic stem cell, the results illustrated that all control and study groups received peripheral blood stem cells from related donors. This finding is consistent with Bazinet and Popradi (2019) who stated that the most utilized source of stem cells for allogeneic grafts at the moment is the peripheral blood. When utilizing peripheral blood stem cells for a stem-cell graft instead of bone marrow, there are several pros to consider, these include easier access to larger doses of stem cells, quicker immune system recovery and engraftment, and reduced rates of graft failure. However, these advantages are outweighed by a higher risk of graft-versus-host disease when compared to bone marrow stem cells.

Morevor, Nagler et al. (2022) stated that accessibility and advancement of suitable graft versus host disease prophylaxis medications, allowing greater controlling on graft versus host disease and using of peripheral blood as an excellent source of stem cell in an allogenic transplant.

As regards type of conditioning regimen, the results showed that all control and study group patients received Bu+ Flu+ post Cy myeloablative conditioning

regimen. Selection of myeloablative chemotherapy protocol was agreed with Gooptu et al. (2018) who mentioned that Myeloablative regimens are typically linked to increased toxicity, a higher frequency, and a higher degree of OPM.

They mentioned that, nowadays, one of the three most utilized myeloablative chemotherapy regimens is Bu/Flu. This new chemotherapy regimen showed similar rates of relapse with reduced toxicity. In this study, it was found that Bu/Flu chemotherapy protocol was one of regular myeloablative regimens for adult patients in the hospital of data collection.

As for graft versus host disease prophylactic medications, the results illustrated that, in the chosen chemotherapy protocol (Bu/Flu+ post Cy), all control and study groups received cyclosporine A and post Cy as immunosuppressant and graft versus host disease prophylactic drugs. This finding is consistent with Sharaf El-Deen et al. (2023) who concluded that the adding of high-dose cyclophosphamide then cyclosporine A, together can decrease the possibility of graft versus host disease between these patients without raising the chance of relapse, engraftment delay nor complications related to transplantation.

Furthermore, Kwon et al. (2019) found that no statistically significant differences were found regarding the occurrence of grade II to IV oral mucositis between the group who received methotrexate and cyclosporine A and the groups who received post cyclophosphamide prophylaxis. This finding appeared in this study as, there are a few numbers of patients don't exceed ten percent in control and study groups who developed acute graft versus host disease grade I. All patients in the control group developed grade III oropharyngeal mucositis, despite two thirds of the study group didn't develop.

This means that the transplant related complications were managed and diminished with this graft versus host disease medications, but OPM still present with grade III. So, these medications did not be considered generally as a risk factor that increasing OPM rather than controlling or mitigating it.

Regarding oral health management knowledge, the current results illustrated that the most of control group had poor knowledge regarding oral health management pre and post transplantation, while all the study group patients had poor knowledge at admission and expressed improved and good knowledge post transplantation. This came in line with Mohamed et al. (2018) who concluded that patient education had a favorable outcome on enhancing self-efficacy and awareness between studied patients with chemotherapy induced OPM.

Furthermore, Yüce and Yurtsever (2019) concluded that the incidence of OPM can be declined, if nurses inform patients and their families about oral health care fundamentals, provide consultation and education for them during chemotherapy. In this study, this finding could be attributed to the patients` adherence to educational knowledge regarding oral health management, detailed and repeated explanation to those patients, using different teaching methods to deliver the information as demonstration, interactive discussion, and using teaching media as a colored booklet.

Regarding swallowing exercises, the results revealed that, around three quarters of the study group had good practice of swallowing exercises post transplantation after implementation of integrated algorithm compared with control group with high statistical difference between the control and study groups post transplantation. This finding came in line with Mohammed et al. (2022) who found that the patients who had trouble swallowing pre swallowing exercises program, had a quality improvement in swallowing post program application.

Furthermore, Guillen-Sola et al. (2019) mentioned that chemo radio therapy impacts target regions and may result in absence of synchronization of swallowing phases, inflammation, and edema in the oropharyngeal mucosa, extended oropharyngeal time in swallowing, and resulting in malnutrition and weight loss. This finding could be attributed to patients` compliance with swallowing exercises application that strengthen swallowing muscles, even when combined with topical application of agents that contain bioactive substances as vitamin E and sidr honey.

As for mucositis severity and duration in this study, the current results illustrated that the median duration of OPM was fifteen days in the control group, and they reached to grade 3 mucositis while one third of the study group developed grade 1 mucositis for around 3- 4 days only with median duration of mucositis zero after application of oropharyngeal integrated algorithm. There were statistical differences between both studied groups regarding OPM severity and duration during transplantation weeks.

These findings were congruent with Ben-Barouch et al. (2016) who found that the risk of grade 3–4 mucositis was similar in Bu/ Flu protocol compared with conventional myeloablative protocols. Moreover, Wysocka-Słowik et al. (2021) found that the duration and intensity of oral lesions differed based on period of neutropenia, and level of myelosuppression. They mentioned that in some studies the average duration is 8 days while it was 11 days in others. And the highest degree of mucositis occurred 3–4 days before neutropenia peaks, which is on the 14th day following the initiation of chemotherapy. In this study, the peak mucositis severity occurred at +8 to +10days post transplantation, which is in 14- 16 days after the initiation of chemotherapy.

Furthermore, the mitigation of OPM duration and severity in the study group returned to the combined effect of part I and part II integrated algorithm. It was observed that part I affected more on the incidence and late emergence of OPM, and part II affected more on the maintenance of less severity of OPM and lessen its duration in the study group.

This could be brought back to the impact of part I of integrated algorithm. First, the patients were fed at admission with knowledge regarding phases of HSCT, adverse effects of preparative regimen on the gastrointestinal system, relation between oral health and transplantation process, proper method for maintaining oral hygiene pre and post transplantation, meal modification and dietary tactics related to behavior. Also, teaching various swallowing exercises to enhance the swallowing muscles' functional ability.

Second, the utilize of topical mouth wash as chlorhexidine in both studied groups aid in governing oropharyngeal plaque and infection. Cardona et al. (2017) mentioned that mouth wash comprising chlorhexidine has fungicidal, bactericidal, and virucidal properties. Chlorhexidine kills enormous number of Grams bacteria in just 30 seconds, breakdown membranes of microbial cell, causing intracellular material to leak out. Additionally, nystatin mouth wash is applied topically, it acts as a wide range oral antifungal agent. It works by attaching itself to sterols in the fungal cells' plasma membranes, which causes the fungal cells to burst and ultimately kill the fungal cells (Rai et al., 2022).

Moreover, in this study, the patient received around sixteen sessions of oral cryotherapy along 4 days of conditioning chemotherapy. Oku et al. (2023) supported this finding that they found oral cryotherapy worked well in preventing occurrence of OPM in allogenic recipients, through initiation of cooling, vasoconstriction and declined the allocation of chemotherapy in the oropharyngeal cavity epithelium.

Furthermore, topical application of vitamin E 400 IU/ two capsules in the oral

cavity, once daily in the first part of this study, it appeared to be successful in decreasing incidence and severity of OPM. Donnelly et al. (2022) stated that as an antioxidant, vitamin E may lessen the amount of free oxygen radicals that harm tissues, which could lessen the severity of mucositis during cancer treatments. Also, they found that studies in local administration of vitamin E could work better than systematic delivery of vitamin E in treatment of cancer in humans.

Additionally, the effect of part II integrated algorithm returned to the use of normal saline plus sodium bicarbonate as a mouth hydrating agent. In this study, frequent mouth rinsing every 4 hours with this mixture was supported by Naibaho et al. (2020) who mentioned that mouth wash made of sodium bicarbonate and normal saline can moisturize the mouth, stop crusting, soothe mucosa, effectively lessen the pain associated with mucositis.

Moreover, Egyptian monofloral sidr honey was used in part II, this was supported by Hegazi et al. (2022) who studied sidr honey characteristics from various geographic sources, and they found that the biological activity disclosed that the Egyptian and Saudi sidr honeys have the highest levels of flavonoids and total phenolics along with the strongest antibacterial activity.

Also, Ismail et al. (2019) concluded in their study that sidr honey might work in minimizing the pain & severity of oral mucositis. They mentioned that the identified potential function for sidr honey in the management of OPM may be due to the acidic ph that is minimal enough to stop many microorganisms from growing, the amount of sugar in sidr honey, which is sufficiently high to prevent microbial growth, anti-inflammatory impact, and its stimulatory effects on, epithelization, granulation and angiogenesis.

Additionally, in part II, propolis capsule 1000 mg was administered as a dietary supplement for 12 days. This was supported by Salehi et al. (2018) who concluded that propolis tablets may be helpful in both preventing and treating chemotherapy-induced oral mucositis. They mentioned that more than 300 natural compounds, such as phenolic aldehyde, polyphenol, steroids, amino acids, terpenes, and quinones, have been reported to be present in propolis. Moreover, it has antimicrobial, anti-inflammatory, antioxidant, and anti-ulcer properties.

Finally, OPM provokes considerable discomfort and impedes the patient's life quality. The present study translated the prior research and trials findings and puts them into practice through applying of an integrated algorithm that comprised mainly of natural agents, rich combinations of multiagent in this protocol oppose the toxic impact of cytotoxic chemotherapy on the oropharyngeal cells. Also, this algorithm allows the nurse to be on the path of updated and advanced management for chemotherapy induced OPM.

Conclusion

Oropharyngeal integrated algorithm protocol application for study group patients verified to have a positive outcome on OPM duration, and severity. As displayed in significant differences between control and study group patients related to their oral health management knowledge, practice of swallowing exercises and oral assessment findings.

Recommendations:

In line with the findings of the study, it is recommended to replicate this study using large probability sample size.

Table (1): Percentage distribution of patients with allogenic hematopoietic stem cell transplantation of both studied groups according to patient's socio demographic characteristics (N= 30)

Socio demographic characteristics	Control (N =15)		Study (N =15)		Significance test
	No.	%	No.	%	
Age					
20 - <30	5	33.3	5	33.3	χ^2=1.159 ^{MC}p=1.000
30- <40	4	26.7	4	26.7	
40- < 50	5	33.3	6	40.0	
50- ≤_ 65	1	6.7	0	0.0	
Mean ± SD.	34.40 ± 10.27		35.13 ± 10.04		t=0.198 p=0.845
Gender					
Male	7	46.7	7	46.7	χ^2=0.000 p=1.000
Female	8	53.3	8	53.3	
Marital status					
Single	5	33.3	3	20.0	χ^2=2.386 ^{MC}p=0.681
Married	10	66.7	10	66.7	
Widow	0	0.0	1	6.7	
Divorced	0	0.0	1	6.7	
Level of education					
Illiterate	0	0.0	2	13.3	χ^2=3.572 ^{MC}p=0.279
Secondary	2	13.3	2	13.3	
Diplom	6	40.0	8	53.3	
University education	7	46.7	3	20.0	
Occupation					
Clerk work	5	33.3	4	26.7	χ^2=2.287 ^{MC}p=0.873
Technical work	3	20.0	1	6.7	
Manual work	2	13.3	2	13.3	
No work	5	33.3	8	53.3	
Residence					
Urban	8	53.3	7	46.7	χ^2=0.133 p=0.715
Rural	7	46.7	8	53.3	

χ^2: **Chi square test** MC: **Monte Carlo**
p: p value for comparing between the two studied groups
*: Statistically significant at p ≤ 0.05

Table (2): Percentage distribution of patients with allogenic hematopoietic stem cell transplantation of both studied groups according to patient's clinical data (N= 30)

Patient's Clinical data	Control (N =15)		Study (N =15)		Significance test
	No.	%	No.	%	
1. Medical diagnosis					χ^2=3.913 ^{MC}p=0.265
Acute myeloid leukemia	8	53.3	11	73.3	
Chronic myeloid leukemia	2	13.3	0	0.0	
Severe aplastic anemia	2	13.3	0	0.0	
Myelodysplastic syndrome	3	20.0	4	26.7	
2. Source of stem cells					–
Peripheral blood	15	100.0	15	100.0	
3. Donor type					–
Sibling	15	100.0	15	100.0	
4. Pre transplantation conditioning period (6 days)	15	100.0	15	100.0	–
5. Conditioning protocol					–
Busulfan/ Fludarabine/ post cyclophosphamide	15	100.0	15	100.0	
6. Type of conditioning regimen					–
Myeloablative conditioning	15	100.0	15	100.0	
7. Graft versus host disease prophylaxis medication:					–
Cyclosporine A	15	100.0	15	100.0	–
Post cyclophosphamide	15	100.0	15	100.0	–
Others (corticosteroids)	1	6.7	1	6.7	χ^2=0.000 p=1.000
8. Comorbidity index score (HCT-CI)					χ^2=0.600 p=0.439
Zero (low comorbidity score)	9	60.0	11	73.3	
1-2 (intermediate comorbidity score)	6	40.0	4	26.7	

χ^2: **Chi square test** MC: **Monte Carlo**
p: p value for comparing between the two studied groups
*: Statistically significant at $p \leq 0.05$
#: Some patients had more than one graft versus host disease prophylaxis medication

Table (3): Comparison between the two studied groups according to the total score of modified oral assessment guide (MOAG) since admission till +21 day post transplantation (N=30)

Modified oral assessment guide (MOAG)	Control (N = 15)		Study (N = 15)		Significance test
	No.	%	No.	%	
At admission					
Good oral health (8)	15	100.0	15	100.0	–
Poor oral health (9 – <16)	0	0.0	0	0.0	
Worst possible (16 – 24)	0	0.0	0	0.0	
(-1) day					
Good oral health (8)	9	60.0	15	100.0	χ^2=7.500*
Poor oral health (9 – <16)	6	40.0	0	0.0	^{FE}p=0.017*
Worst possible (16 – 24)	0	0.0	0	0.0	
(+1) day					
Good oral health (8)	4	26.7	15	100.0	χ^2=17.368*
Poor oral health (9 – <16)	11	73.3	0	0.0	(p<0.001*)
Worst possible (16 – 24)	0	0.0	0	0.0	
(+4) day					
Good oral health (8)	0	0.0	13	86.7	χ^2=25.448*
Poor oral health (9 – <16)	9	60.0	2	13.3	^{MC}p(<0.001*)
Worst possible (16 – 24)	6	40.0	0	0.0	
(+6) day					
Good oral health (8)	0	0.0	3	20.0	χ^2=28.785*
Poor oral health (9 – <16)	1	6.7	12	80.0	^{MC}p(<0.001*)
Worst possible (16 – 24)	14	93.3	0	0.0	
(+8) day					
Good oral health (8)	0	0.0	0	0.0	χ^2=30.000*
Poor oral health (9 – <16)	0	0.0	15	100.0	(p <0.001*)
Worst possible (16 – 24)	15	100.0	0	0.0	
(+10) day					
Good oral health (8)	0	0.0	0	0.0	χ^2=15.000*
Poor oral health (9 – <16)	0	0.0	10	66.7	(p <0.001*)
Worst possible (16 – 24)	15	100.0	5	33.3	
(+12) day					
Good oral health (8)	0	0.0	0	0.0	χ^2=15.000*
Poor oral health (9 – <16)	0	0.0	10	66.7	(p <0.001*)
Worst possible (16 – 24)	15	100.0	5	33.3	
(+14) day					
Good oral health (8)	0	0.0	9	60.0	χ^2=33.520*
Poor oral health (9 – <16)	0	0.0	6	40.0	(^{MC}p<0.001*)
Worst possible (16 – 24)	15	100.0	0	0.0	
(+16) day					
Good oral health (8)	0	0.0	15	100.0	χ^2=33.597*
Poor oral health (9 – <16)	5	33.3	0	0.0	(^{MC}p<0.001*)
Worst possible (16 – 24)	10	66.7	0	0.0	
(+21) day					
Good oral health (8)	2	13.3	15	100.0	χ^2=24.158*
Poor oral health (9 – <16)	10	66.7	0	0.0	(^{MC}p<0.001*)
Worst possible (16 – 24)	3	20.0	0	0.0	

χ^2: **Chi square test** FE**: Fisher Exact** MC: **Monte Carlo**
p: p value for comparing between the two studied groups *: Statistically significant at $p \leq 0.05$

Table (4): Comparison between the two studied groups according to the overall of oral health management knowledge at admission and at +4 post transplantation (N=30)

	Control (N = 15)				Study (N = 15)				Test of Sig.(p_1)	Test of Sig.(p_2)
	At admission		+4 day		At admission		+4 day			
	No.	%	No.	%	No.	%	No.	%		
Poor knowledge (<60%)	14	93.3	14	93.3	15	100.0	1	6.7	χ^2= 1.034 (^{FE}p= 1.000)	χ^2= 26.313* (^{MC}p <0.001*)
Fair knowledge (60-<75%)	1	6.7	1	6.7	0	0.0	2	13.3		
Good knowledge (≥75%)	0	0.0	0	0.0	0	0.0	12	80.0		

χ^2: **Chi square test** FE**: Fisher Exact** MC: **Monte Carlo**
p_1: p value for comparing between the two studied groups in **at admission**
p_2: p value for comparing between the two studied groups in **positive 4 post**
*: Statistically significant at $p \leq 0.05$

Table (5): Comparison between the two studied groups according to total score of swallowing exercises observation at admission and at +4 day post transplantation (N=30)

	Control (N = 15)				Study (N = 15)				Test of Sig.(p_1)	Test of Sig.(p_2)
	At admission		Positive (4) day		At admission		Positive (4) day			
	No.	%	No.	%	No.	%	No.	%		
Poor practice (<60%)	15	100.0	15	100.0	15	100.0	2	13.3	–	χ^2= 24.468* ^{MC}p <0.001*
Fair practice (60-<75%)	0	0.0	0	0.0	0	0.0	2	13.3		
Good practice (≥75%)	0	0.0	0	0.0	0	0.0	11	73.3		

χ^2: **Chi square test** MC: **Monte Carlo**
p_1: p value for comparing between the two studied groups in **at admission**
p_2: p value for comparing between the two studied groups in **Positive (4) day**
*: Statistically significant at $p \leq 0.05$

Table (6): Comparison between the two studied groups according to National Cancer Institute grading for mucositis severity and duration since admission till +21day post transplantation (N=30)

National Cancer Institute Grading Scale for mucositis severity& duration	Duration of follow up of oropharyngeal mucositis																							
	(-3) day		(-1) day		(+1) day		(+2) day		(+4) day		(+6) day		(+8) day		(+10) day		(+12) day		(+14) day		(+16) day		(+18) day		(+21) day	
Control (N = 15)	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
• **No findings (G0)**	15	100.0	15	100.0	11	73.3	11	73.3	11	73.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	20.0	12	80.0
• **Asymptomatic or mild symptoms painless ulcer, erythema, or mild soreness in absence of lesions (G1)**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0	0	0.0	2	13.3	9	60.0	0	0.0
• **Moderate painful erythema, edema or ulcers but patient can swallow modified diet indicated (G2)**	0	0.0	0	0.0	4	26.7	4	26.7	4	26.7	13	86.7	6	40.0	0	0.0	0	0.0	0	0.0	4	26.7	1	6.7	1	6.7
• **Severe painful erythema, edema or ulcers, interfering with oral intake requiring g IV hydration (G3)**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	6.7	9	60.0	15	100.0	15	100.0	15	100.0	9	60.0	2	13.3	2	13.3
• **Life-threatening consequences or requires parenteral/enteral nutritional support or prophylactic intubation (G4)**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• **Death due to toxicity (G5)**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Study (N = 15)																										
• **No findings (G0)**	15	100.0	15	100.0	15	100.0	15	100.0	15	100.0	15	100.0	15	100.0	10	66.7	10	66.7	13	86.7	15	100.0	15	100.0	15	100.0
• **Asymptomatic or mild symptoms (painless ulcer, erythema, or mild soreness in absence of lesions) (G1)**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	5	33.3	5	33.3	2	13.3	0	0.0	0	0.0	0	0.0
• **Moderate painful erythema, edema, or ulcers but patient can swallow, modified diet indicated (G2)**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• **Severe painful erythema, edema or ulcers, interfering with oral intake, requiring g IV hydration (G3)**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• **Life-threatening consequences or requires parenteral/enteral nutritional support or prophylactic intubation (G4)**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• **Death due to toxicity (G5)**	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
χ^2	–		–		4.615		4.615		4.615		34.493*		33.520*		33.597*		33.597*		34.251*		32.781*		20.576*		2.886	
p	–		–		FEp= 0.100		FEp= 0.100		FEp= 0.100		MCp <0.001*		MCp <0.001*		MCp <0.001*		MCp <0.001*		MCp <0.001*		MCp <0.001*		MCp <0.001*		MCp= 0.221	

χ^2: **Chi square test** FE: **Fisher Exact** MC: **Monte Carlo** G: **grade**

p: p value for comparing between the two studied groups. *: Statistically significant at $p \leq 0.05$

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