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Review

Prevention and Treatment of Oral Mucositis in Pediatric Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials

CHRYSI STEFANIA ANDRIAKOPOULOU[1], CHRISTOS YAPIJAKIS[1,2], IOANNIS KOUTELEKOS[3] and PANTELIS PERDIKARIS[4]

[1]*First Department of Pediatrics, School of Medicine, National and Kapodistrian University of Athens, "Agia Sophia" Children's Hospital, Athens, Greece;*
[2]*Unit of Orofacial Genetics, University Research Institute of Maternal and Child Health and Precision Medicine, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece;*
[3]*Department of Nursing, University of West Attica, School of Health and Care Sciences, Athens, Greece;*
[4]*Department of Nursing, School of Health Sciences, University of Peloponnese, Tripolis, Greece*

Abstract. *Background/Aim: Oral mucositis (OM) is a common and serious side effect of cancer treatment. The incidence of chemotherapy-induced OM in pediatric patients can reach up to 91.5% and has a major impact on patients' quality of life. The aim of the study was to assess the efficacy of current interventions and agents for the management of OM in children undergoing chemo/radiotherapy or hematopoietic stem cell transplantation (HSCT). Materials and Methods: A systematic search of randomized controlled trials (RCTs) was conducted in the MEDLINE and Scopus databases from January 2000 until March 2023. Thirty-four randomized studies meeting the inclusion criteria were identified and five RCTs investigating the efficacy of Low Level Laser Therapy (LLLT) intervention or the agent honey were included in the meta-analysis. Results: The meta-analysis of two RCTs indicated that topical application of honey on oral mucosa was effective in shortening the mean duration of hospital stay in children with severe OM (MD=–4.33, p=0.002). However, LLLT was not found to be effective for the prevention or treatment of OM grade ≥II (RR=0.99, p=0.99). Moreover, the therapeutic application of LLLT did not show significant benefit for lower risk of OM grade ≥II (RR=0.48, p=0.58). Conclusion: Various interventions and agents were examined in the present study for the management of OM. Honey could be a promising candidate for the treatment of OM in pediatric patients. Further high-quality RCTs are required to enhance our findings.*

Correspondence to: Chrysi Stefania Andriakopoulou, Fedonos 21 Str., Dafni, 172 36, Athens, Greece. E-mail: cs.andriakopoulou.md@gmail.com

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Oral mucositis (OM), also referred to as stomatitis, is a common and serious complication of chemotherapy, and/or radiotherapy in patients undergoing cancer treatment or hematopoietic cell transplant (HSCT) for malignant or non-malignant diseases (1). This condition affects approximately 40% of patients receiving conventional chemotherapy and 60%-85% patients undergoing high-dose chemotherapy for bone marrow transplantation (2, 3). Research has indicated that up to 90% of patients receiving a combination of chemo- and radiotherapy for head and neck cancer will experience OM, and 19% of them will require admission to hospital for management (3). Furthermore, the incidence of chemotherapy-induced OM in children is higher than adults and can reach up to 80%-91.5%, depending on the underlying primary disease and treatment regimen (4, 5).

The duration of chemotherapy-induced OM among children persists for around three weeks and is clinically manifested with severe pain, difficulty in swallowing (dysphagia), weight loss and a significant decline in the patients' overall quality of life. OM often leads to inability of alimenting, necessitating the administration of total parenteral nutrition or gastrostomy tube placement to achieve feeding. Consequently, the length of hospital stay is

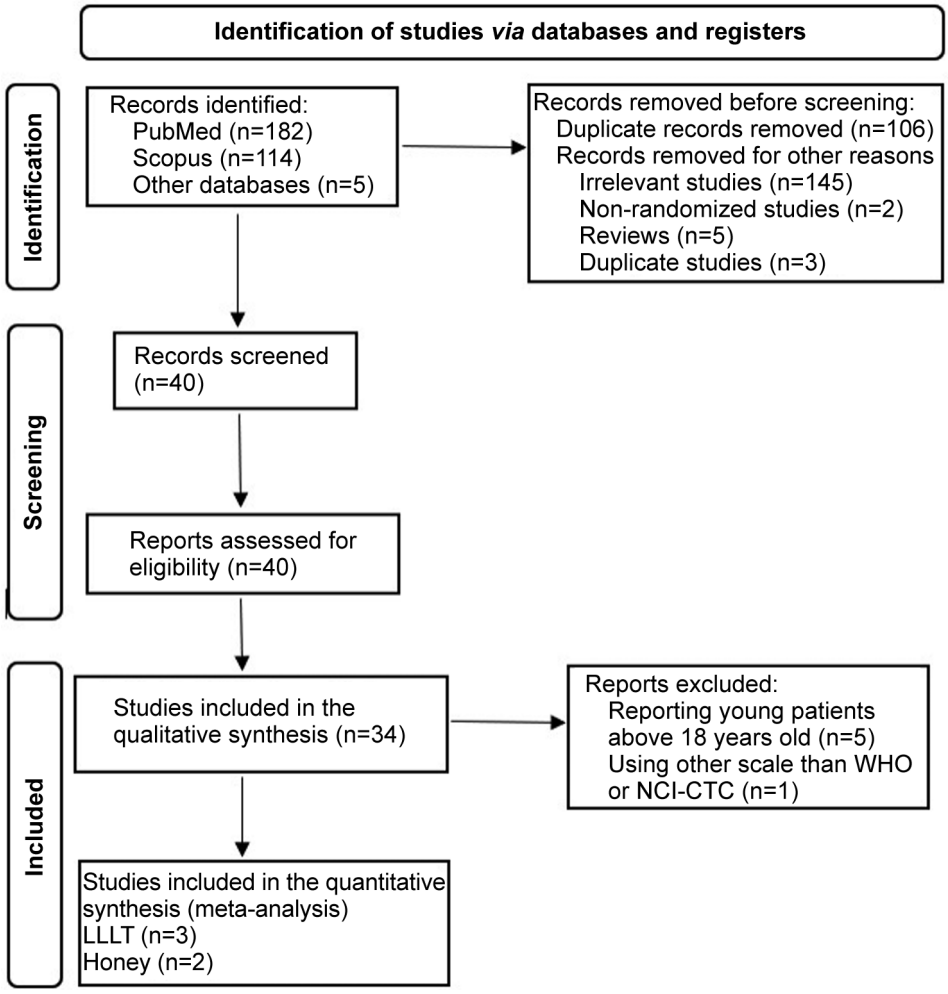

Figure 1. *PRISMA analysis of study selection process.*

prolonged, leading to increased inpatient costs (6). Moreover, the presence of ulcerative stomatitis is potentially complicated with secondary infections involving pathogens, such as Herpes simplex virus and Candida species, and in case of chemotherapy-induced neutropenia, patients face a heightened risk of life-threatening sepsis. It is estimated that severe OM (grade III-IV) can increase mortality by 40% (7).

Toxicity grading of OM is clinically assessed with various tools. Two of the commonly-used scales are the World Health Organization (WHO; Grade I: soreness±erythema, grade II: erythema, ulcers; patients' ability to swallow solid foods, grade III: ulcers with extensive erythema; patients not being able to swallow solid foods, and grade IV: mucositis to the extent that alimentation is not possible) and Common Toxicity Criteria Scale of the National Cancer Institute (NCI-CTC; 0=none; 1=painless ulcers, erythema, or mild soreness in the absence of lesions; 2=painful erythema, edema or ulcers, but able to eat; 3=painful erythema, edema or ulcers, requiring intravenous hydration; 4=requires parenteral or enteral nutrition support) (8). These two grading scales are considered similar as they identically assess the damage of oral mucosa and the patient's ability to eat.

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) published in 2014 guidelines for the treatment of OM (1). These guidelines are presented as recommendations in favor or against an intervention (evidence level I-II) and suggestions in favor or against an intervention (evidence level III-V) (1). Furthermore, MASCC/ISOO published in 2020 a review of 45 studies (including 21 randomized controlled trials) that demonstrates interventions and agents for the management of OM in pediatric and young patients. These studies have included oral hygiene protocols, cryotherapy, low level laser therapy (LLLT), honey, analgesics (*e.g.*, morphine), antiseptics (*e.g.*, chlorhexidine),

anti-inflammatory agents (*e.g.*, benzydamine), growth factors (*e.g.*, palifermin) and other treatments (9).

Many studies have been conducted in adult patients or a mixed population for the management of OM, but only a limited number of them have enrolled children and young individuals (10-16). The present study aimed to assess the efficacy of current interventions and agents for the prevention and treatment of OM specifically in pediatric patients.

Material and Methods

The protocol of the systematic review and meta-analysis was registered on PROSPERO (http://www.crd.york.ac.uk, study ID: CRD42023452934).

Search strategy. A systematic review of the literature was performed on MEDLINE *via* PubMed and Scopus databases until March 2023 using the MeSH terms: ("chemother*"[Text Word] OR "radiother*"[Text Word] OR "autolog*"[Text Word] OR "transplan*"[Text Word]) AND ("child" [MeSH Terms] OR pediatr*[Text Word] OR infant* [Text Word] OR adolescen* [Text Word]) AND ("mucositis"[MeSH Terms] OR "stomatitis/chemically induced"[MeSH Terms] OR mucositis [Text Word] OR stomatitis [Text Word]).

Study selection. Two independent reviewers (CSA, PP) carried out separately a systematic search for study selection. The PRISMA statement was used to report the study selection process as seen in Figure 1 (17).

A study was included only if 1) the full-text version of the article was available; 2) publication year was from January 2000 until March 2023; 3) it was written in English language; 4) it was a randomized controlled trial (RCT) that presented the efficacy of at least one intervention or agent for the prevention or treatment of OM compared to placebo or another intervention or agent; 5) it included only pediatric patients; 6) grading of OM was evaluated with WHO or NCI-CTC scale; 7) the number of patients with OM was reported.

A study was excluded if: 1) it presented duplicate data with another study from the same center (the RCT with the greater number of patients was included in the data analysis); 2) the number of patients with OM was zero or not reported.

Data extraction. Data extraction included the following variables for each eligible study: principal investigator, year of publication, study design, origin and period of the study, number of patients, age of patients, type of intervention or agent, type of cancer or disease, type of treatment, definition of OM, follow-up period regarding the development of OM, number of patients with OM or length of hospital stay due to OM in each group. The Jadad scale was used for the assessment of the RCTs included in the qualitative synthesis (18), while the Cochrane Risk of Bias tool (19) was used for the RCTs included to the meta-analysis.

Data analysis. A meta-analysis was performed on the following outcomes: 1) efficacy of LLLT for the prevention or treatment of OM grade ≥II; 2) efficacy of LLLT for the treatment of OM grade ≥II; 3) efficacy of honey regarding the length of hospital stay due to severe OM (grade ≥III). The program Review Manager 5.4 (Cochrane Collaboration, Nordic Cochrane Centre) was used for statistical analysis. The Mantel–Haenszel method was applied for the calculation of pooled risk ratio (RR) for 1) and 2) outcomes. The pooled mean difference (MD) was calculated for (3) outcome with 95% confidence interval (CI). Statistical heterogeneity among studies in each analysis was calculated using the I^2 method ($p<0.10$, significant heterogeneity). The random effects model was applied.

Results

Thirty-four RCTs were eligible for qualitative analysis from systematic search of the literature regarding the management of OM in pediatric patients. The characteristics of the included studies are presented in Table I. Various interventions and agents were found to be examined for the prevention and treatment of OM using WHO or NCI-CTC scale. For this reason, four categories of studies were created depending on the intervention or agent that was proposed: 1) LLLT; 2) Honey; 3) Growth factors; 4) Other interventions/agents.

Low level laser therapy. LLLT intervention was investigated in eleven studies (20-30). The primary aim of seven studies was to examine the efficacy of LLLT in the prevention (21) or the treatment (20, 23-25, 27, 30) of OM compared to sham laser (placebo) or no intervention in children receiving chemotherapy for cancer or undergoing HSCT. Two RCTs focused on the efficacy of photodynamic therapy (PDT) (22) or the combination of PDT and LLLT (26) compared to LLLT in the treatment of chemotherapy-induced OM in pediatric patients with cancer. One RCT compared topical application of Andiroba oil on oral mucosa with LLLT in the treatment of OM in children with cancer and found a significant reduction in the severity of OM in andiroba oil group (28). One RCT compared three different setting of LLLT for the treatment of chemotherapy-induced OM and showed no difference between groups (29). From the above RCTs, Gobbo *et al*. (23) suggested that LLLT was effective in reducing OM severity (grade <III) on the seventh day of evaluation ($p=0.01$) and Karaman *et al*. (24) concluded that average OM grade was lower in LLLT group at the seventh day of evaluation. The percentage of events ($p=0.029$) and mean duration ($p=0.004$) of OM were lower in LLLT group according to Kuhn *et al*. (25) and a significant decline in OM with LLLT ($p=0.003$) was marked as reported by Reyad *et al*. (27). Furthermore, significant regression of OM was observed in LLLT group compared to sham laser group at the seventh day of evaluation in the study of Vitale *et al*. (30) and the combination of PDT and LLLT had a significant grater effect compared with LLLT intervention in reducing the severity of OM ($p=0.005$) in the study of Medeiros-Filho *et al*. (26). However, other pediatric studies found no significant benefit from the application of LLLT. Specifically, Amadori *et al*. (20) concluded that LLLT was

Table I. *Characteristics of the included studies in qualitative synthesis.*

First author & year of publication	Design of the study	Region & period of the study	Number of patients	Age (years)	Compared groups		Type of cancer/disease	Type of treatment	Definition of OM	Follow up	Quality score[a]
Amadori *et al.* 2016 (20)	MC DB RCT	Europe Jan 2012-Dec 2013	123	3-18	LLLT	Placebo	Leukemia, Lymphoma, Solid tumor	Chemotherapy, HSCT	WHO	7 d	4
Cruz *et al.* 2007 (21)	SC RCT	South America May 2003-Feb 2005	60	3-18	LLLT	None	Leukemia, Lymphoma, Solid tumor	Chemotherapy, HSCT	NCI-CTC	15 d	1
Gobbo *et al.* 2018 (23)	MC DB RCT	Europe Sep 2013-Oct 2015	99	3-18	LLLT	Placebo	ALL, AML, Lymphoma, Solid tumor, BMT	Chemotherapy	WHO	11 d	5
Karaman *et al.* 2022 (24)	SC RCT	Asia June 2019-Dec 2019	40	3-18	LLLT	None	ALL, AML	Chemotherapy	WHO	11 d	1
Kuhn *et al.* 2009 (25)	SC DB RCT	South America Oct 2005-May 2006	21	NR	LLLT	Placebo	Leukemia, Lymphoma, Solid tumor	Chemotherapy, HSCT	NCI-CTC	12 d	5
Medeiros-filho *et al.* 2017 (26)	SC RCT	South America Oct 2014- Jan 2015	15	3-16	PDT+LLLT	LLLT	Leukemia, Lymphoma, Sarcoma, Osteosarcoma, Medullo-blastoma	Chemotherapy, ±Radiotherapy	WHO	8 d	3
Reyad *et. al.* 2022 (27)	SC RCT	Africa Oct 2020-Nov 2021	44	2-14	LLLT	None	ALL	Chemotherapy	WHO	14 d	3
Ribeiro da Silva *et al.* 2018 (22)	MC DB RCT	South America Nov 2016-Mar 2017	29	10 months-18 years	PDT	LLLT	ALL, NHL, Osteosarcoma	Chemotherapy	WHO	7 d	4
Soares *et al.* 2021 (28)	SC DB RCT	South America Oct 2015-Mar 2016	60	4-12	LLLT	Andiroba oil	Leukemia	Chemotherapy	WHO	12 d	4
Tomaževič *et al.* 2020 (29)	SC RCT	Europe Jan 2014-April 2018	42	NR	LLLT 250 mV	LLLT 500 mV / LLLT 250 mV (half energy density)	ALL, AML, Lymphoma, Neuroblastoma, Rhabdo-myosarcoma, Bone sarcoma	Chemotherapy	WHO	NR	2
Vitale *et al.* 2017 (30)	MC RCT	Europe Sep 2013-Jul 2015	16	3-18	LLLT	Placebo	NR	Chemotherapy, HSCT	NCI-CTC	11 d	4

Table I. *Continued*

Table I. *Continued*

First author & year of publication	Design of the study	Region & period of the study	Number of patients	Age (years)	Compared groups		Type of cancer/disease	Type of treatment	Definition of OM	Follow up	Quality score[a]
					Honey						
Abdulrhman *et al*. 2012 (31)	SC RCT	Africa Jun 2010-Jun 2011	90	2-18	Honey	Honey, Beeswax, Olive oil-propolis extract None	ALL	Chemotherapy	NCI-CTC	10 d	2
Al Jaouni *et al*. 2017 (32)	SC RCT	Asia NR	40	>1	Honey	None	ALL, AML, Burkitt's lymphoma, Langerhans cell histiocytosis, Wilms tumor, Neuroblastoma, Medulloblastoma	Chemotherapy, Radiotherapy	WHO	1 yr	1
					Growth factors						
Cesaro *et al*. 2013 (33)	MC RCT	Europe May 2007-Jun 2011	61	0-17	Pegfilgrastim	Filgrastim	ALL, NHL, Hodgkin Lymphoma, Neuroblastoma, Ewing sarcoma/PNET, Medulloblastoma, Wilms tumor, CNS tumor	PBSCT	WHO	23 d	2
de Koning *et al*. 2007 (34)	SC DB RCT	Europe Oct 2001- Jun 2004	25	0-18	TGF-β2	Placebo	ALL, AML, NHL, Bone tumor	Chemotherapy	WHO	NR	5
Lucchese *et al*. 2016 (35)	SC DB RCT	Europe Apr 2010-Jan 2014	46	9-15	Palifermin	Placebo	ALL	HSCT	WHO	60 d	3
Tsurusawa *et al*. 2015 (36)	MC RCT	Asia Nov 2004-Jan 2011	58	NR	Lenograstim	None	NHL	Chemotherapy	NCI-CTC	NR	1
					Other						
Alkhouli *et. al*. 2020 (37)	SC DB RCT	Asia Jun 2018-May 2019	22	3-6	Aloe Vera	Bicarbonate	ALL	Chemotherapy	WHO	8 wks	3
Bardellini *et. al*. 2016 (38)	MC BD RCT	Europe NR	56	5-18	Verbascoside, PVP, sodium Hyaluronate	Placebo	ALL	Chemotherapy	WHO	8 d	4

Table I. *Continued*

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First author & year of publication	Design of the study	Region & period of the study	Number of patients	Age (years)	Compared groups		Type of cancer/disease	Type of treatment	Definition of OM	Follow up	Quality score[a]
Cheng *et al.* 2003 (39)	SC RCT	Asia April 2000-April 2001	34	6-17	Chlorhexidine	Benzydamine	Leukemia, Lymphoma, Liver cancer, Bone cancer, Soft tissue sarcoma	Chemotherapy	WHO	21 d	2
Cubukçu *et al.* 2007 (40)	SC RCT	Asia Feb 2002-Sep 2005	40	1-14	Debridement	None	Medulloblastoma, Osteosarcoma, Lymphoma	Chemotherapy	WHO	21 d	1
Eghbali *et al.* 2016 (41)	SC RCT	Asia Apr 2014-Jun 2015	130	5-15	Sugar-free gum	None	ALL, AML, T- lymphoblastic Leukemia, Osteosarcoma, Rhabdomyosarcoma, Ewing's sarcoma	Chemotherapy	WHO	15 d	1
Gandemer *et al.* 2007 (42)	MC RCT	Europe Mar 1999-Dec 2002	140	5-18	Fluoride-containing sugar-free gum	None	ALL, AML, Solid tumor	Chemotherapy	WHO	32 d	2
Hamidieh *et al.* 2015 (43)	SC DB RCT	Asia Jun 2012-Jan 2014	28	1-15	Calcitriol	Placebo	Fanconi anemia	HSCT	WHO	NR	4
Immonen *et al.* 2020 (44)	MC DB RCT	Europe Aug 2016-Dec 2019	32	2-18	Supersaturated calcium phosphate rinse	Saline	Hematological, Solid tumor, CNS tumor	Chemotherapy	WHO	14 d	5
Kamsvåg *et al.* 2020 (53)	MC RCT	Europe Sep 2012-Jun 2016	49	4-17	Cryotherapy	None	ALL, AML, CML, Lymphoma, Neuroblastoma, Ewing's sarcoma, MDS, Non-malignant disease	HSCT	WHO	20 d	3
Khurana *et al.* 2013 (45)	MC RCT	Asia NR	72	6-15	Glycerin Vitamin E	Pycnogenol	ALL, AML, NHL	Chemotherapy	WHO	7 d	2
Pattanakitsakul *et al.* 2020 (46)	SC quasi-RCT	Asia May 2017- Aug 2018	30	1- 18	Vitamin A	None	ALL, ANLL, CML, NHL, T-cell lymphoma, MDS, Neuroblastoma, Medulloblastoma, Non-malignant disease	HSCT	WHO	7 d	2

Table I. *Continued*

Table I. *Continued*

First author & year of publication	Design of the study	Region & period of the study	Number of patients	Age (years)	Compared groups		Type of cancer/disease	Type of treatment	Definition of OM	Follow up	Quality score[a]
Raphael *et al*. 2014 (47)	MC DB RCT	Europe Jan 2011-Mar 2012	29	4-18	Supersaturated calcium phosphate rinse	Placebo	NR	Chemotherapy HSCT	NCI-CTC	NR	5
Rathe *et al*. 2019 (48)	MC DB RCT	Europe Mar 2013-Nov 2016	60	1- 18	Bovine Colostrum	Placebo	ALL	Chemotherapy	NCI-CTC	29 d	5
Schmid *et al*. 2006 (49)	RCT	Europe NR	30	1-18	Parental Nutrition	IV Fluid	ALL, MDS, NHL, Hodgkin's lymphoma, Hepatocellular carcinoma, Osteosarcoma/ undifferentiated sarcoma, PNET, Nasopharyngeal carcinoma	Chemotherapy	WHO	10 d	1
Sener *et al*. 2019 (50)	SC RCT	Asia Sep 2016-Nov 2017	150	≥2	Chlorhe- xidine Vita- min E	Honey	NR	NR	WHO	21 d	1
Sung *et al*. 2007 (51)	SC DB RCT	North America Jun 2001- Aug 2004	16	6-18	Vitamin E	Placebo	Ewing's sarcoma/ pPNET, Large cell lymphoma, Rhabdomyosarcoma	Doxorubicin-containing chemotherapy	WHO	17 d	5
Widjaja *et al*. 2020 (52)	SC DB RCT	Asia NR	48	1-18	Glutamine	Placebo	ALL	High-dose Methotrexate	WHO	14 d	2

ALL: Acute lymphoblastic leukemia; ANLL: acute nonlymphocytic anemia; AML: acute myeloid leukemia; BMT: bone marrow transplantation; CML: chronic myeloid leukemia; CNS: central nervous system; d: days; DB: double-blind; HSCT: hematopoietic stem cell transplantation; IV: intravenous; MC: multicenter; MDS: myelodysplastic syndrome; mos: months; NCI-CTC: National Cancer Institute Common Toxicity Criteria; NHL: non-Hodgkin lymphoma NR: not reported; PDT: photodynamic therapy; PBSC: peripheral blood stem cell transplant; PNET: peripheral neuroectodermal tumor; pPNET: peripheral neuroectodermal tumor, PVP: polyvinylpyrrolide; RCT: randomized controlled trial; SC: single center; WHO: World Health Organization; wks: weeks; yr: year; d: days; athe Jadad scale was used to evaluate the methodological quality of randomized controlled trials.

not associated with a lower percentage of events of chemotherapy-induced OM (p=0.07) while Cruz *et al*. (21) found no significant benefit of LLLT in the prevention of OM in children receiving chemotherapy or HSCT (p=0.208). Moreover, Ribeiro da Silva *et al*. (22) reported no significant difference between PDT and LLLT for the treatment of chemotherapy-induced OM in pediatric patients.

Honey. Topical application of honey on oral mucosa was examined in two studies (31, 32). These studies evaluated the efficacy of honey for the management of OM in pediatric patients with cancer receiving chemotherapy (31) or chemotherapy/radiotherapy (32). The first RCT concluded that there was a statistically significant shorter recovery time in children with OM grade II-III that were admitted to hospital for evaluation and follow-up (31). It is noted that according to OM grading, patients with severe OM (grade ≥III) have difficulty in alimenting and, therefore, hospitalization is required. The second RCT found a significant shorter length of hospital stay due to severe OM (32). A mixture of honey, beeswax, and olive oil-propolis extract (HOPE) was effective for reducing recovery time due to OM grade III (p=0.0012) but no difference was found between HOPE and honey group (p=0.6108) as reported by Abdulrhman *et al*. (31). Furthermore, there was a significant absolute risk reduction of severe OM in honey group (p=0.02) according to Al Jaouni *et al*. (32).

Growth factors. *Growth factors* were investigated in four studies (33-36). Cesaro *et al*. (33) compared pegfilgrastim and filgrastim for the treatment of OM in pediatric patients with cancer undergoing autologous peripheral blood stem cell transplant (PBSCT) and found no significant difference in the percentage of events of OM grade (p=0.2) and OM duration (p=0.7). Additionally, TGF-β2 enriched feeding and oral rinse did not reduce the duration of chemotherapy-induced OM grade III-IV compared to placebo group in children with cancer according to de Koning *et al*. (34). Lucchese *et al*. (35) succeeded to show the efficacy of palifermin in the prevention of OM grade IV (p=0.005) and reduction of the duration of severe OM (p=0.04) in pediatric patients with acute lymphoblastic leukemia (ALL) receiving HSCT. Finally, Tsurusawa *et al*. (36) found no significant benefit of lenograstim prophylaxis for the prevention of chemotherapy-induced OM in pediatric patients with B-cell non-Hodgkin lymphoma.

Other interventions and agents. Other heterogenous interventions and agents were explored in seventeen studies (37-53). Alkhouli *et al*. (37) indicated that the prophylactic application of aloe vera on oral mucosa was associated with less severe chemotherapy-induced OM during the second week of treatment (p=0.001) and occurred later (p=0.001)

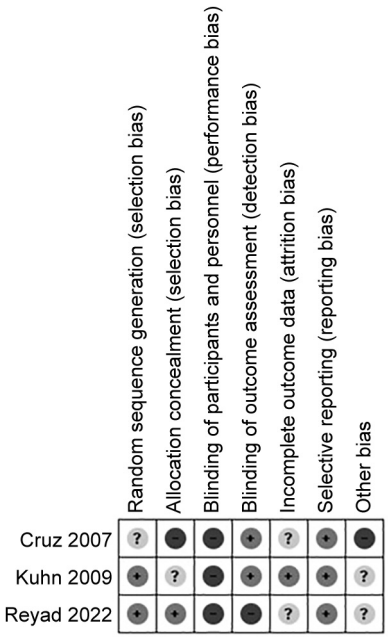

Figure 2. *Risk of bias summary for LLLT intervention showing the assessment of each risk of bias item for each included study. (+)=Low risk of bias; (?)=Unclear risk of bias; (−)=High risk of bias. LLLT: Low level laser therapy.*

compared to the sodium bicarbonate group in children with ALL. Additionally, the application of oral solution Verbascoside/PVP/sodium hyaluronate reduced the median of OM grading on eighth day in pediatric patients with ALL (p=0.038), as reported by Bardellini *et al*. (38). Cheng *et al*. (39) demonstrated the superiority of chlorhexidine over benzydamine for treating chemotherapy-induced OM grade II (4) while Cubukçu *et al*. (40) suggested that debridement effectively reduced severe OM on the sixth day of evaluation in children with cancer receiving chemotherapy. Eghbali *et al*. (41) reported that sugar-free gum was associated with a significant lower percentage of events of chemotherapy-induced OM grade I-II, but no difference was found on severe OM in the same study. Similarly, Gandemer *et al*. (42) noted that prophylactic use of fluoride-containing sugar-free gum did not decrease the percentage of events (p=0.67) or the median duration (p=0.54) of severe OM in children receiving chemotherapy. However, this agent was effective in reducing OM grade I-IV (p=0.03) when less toxic chemotherapy regiments were administrated (42). Prophylactic calcitriol supplementation did not reduce the percentage of events (p=1) and the severity of OM (p=0.54) and did not shorten the median length of hospital stay (p=0.8) in children with Fanconi anaemia undergoing HSCT, according to Hamidieh *et al*. (43). Although, baseline Vitamin D level was significantly associated with complete resolution of OM (p=0.03) and recovery from severe OM (p=0.04) in the same study. Oral

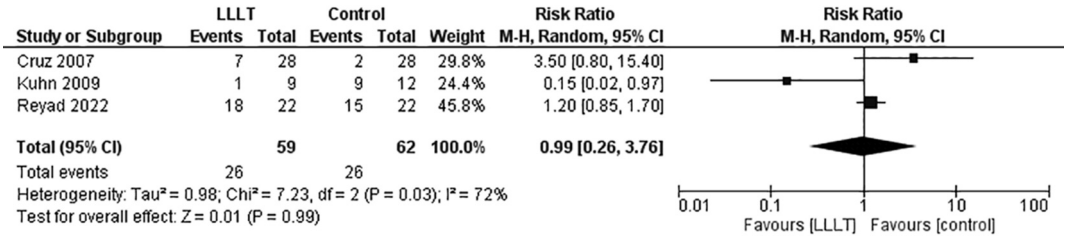

Figure 3. *Forest plot showing the efficacy of LLLT for the prevention or treatment of OM grade ≥II. OM: Oral mucositis.*

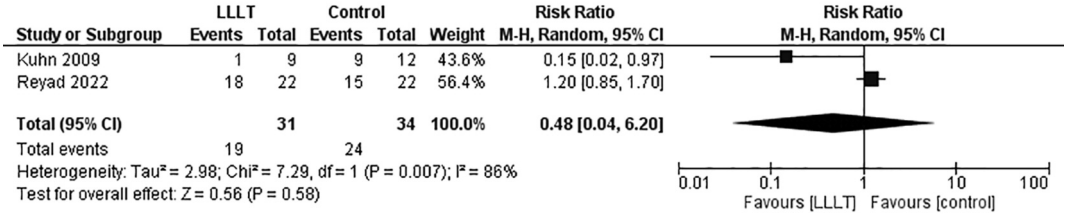

Figure 4. *Forest plot showing the efficacy of LLLT for the treatment of OM grade ≥II. OM: Oral mucositis.*

supersaturated calcium phosphate rinse was not superior over oral saline rinse for the prevention of chemotherapy-induced OM (p=0.12) in pediatric patients as stated to the study of Immonen *et al*. (44). Moreover, Kamsvåg *et al*. (53) found no significant effect of oral cryotherapy in reducing the incidence of severe OM in children undergoing HSCT. Oral application of vitamin E and pycnogenol were effective in the treatment of OM compared to oral application of glycerin (p<0.001), but there was not significant improvement of OM between vitamin E group and pycnogenol group (p=0.0988), according to Khurana *et al*. (45). The administration of vitamin A supplementation had no benefit for the prevention of overall OM (p=1) and severe OM (p=0.27) in children receiving HSCT in the study of Pattanakitsakul *et al*. (46). Raphael *et al*. (47) found no significant difference between supersaturated calcium phosphate oral rinse and placebo for shorter duration of OM (p=0.069) in children undergoing chemotherapy or HSCT. Furthermore, prophylaxis with bovine colostrum supplementation significantly reduced the peak severity of OM in children receiving chemotherapy for ALL (p=0.02) as reported by Rathe *et al*. (48). Schmid *et al*. (49) concluded that parental nutrition did not shorten mean length of hospital stay compared to intravenous fluids in pediatric patients with chemotherapy-induced OM grade IV (p=0.817). Sener *et al*. (50) reported significant lower OM index value with Vitamin E oral care solution compared to chlorhexidine or honey oral care solution in children treated in an intensive care unit. Honey was superior to chlorhexidine in reducing the OM index value in the same study. Oral application of vitamin E did not result in a lower mean score

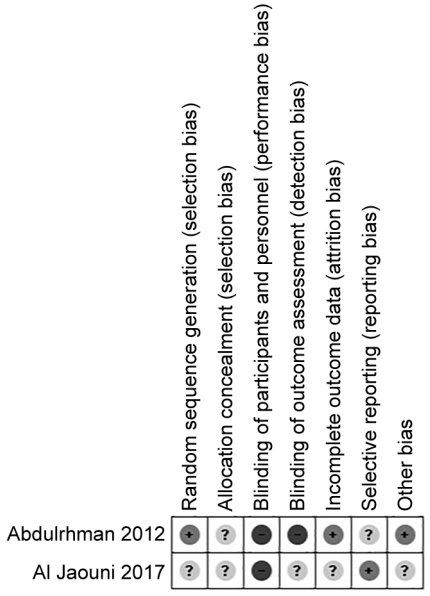

Figure 5. *Risk of bias summary for agent honey showing the assessment of each risk of bias item for each included study. (+)=Low risk of bias; (?)=Unclear risk of bias; (−)=High risk of bias.*

of doxorubicin-induced OM in pediatric patients with cancer, according to Sung *et al*. (51). Finally, prophylactic administration of oral glutamine reduced the duration of hospital stay (p=0.005) and the percentage of events of OM (p=0.001) in children with ALL receiving high-dose methotrexate in the study of Widjaja *et al*. (52).

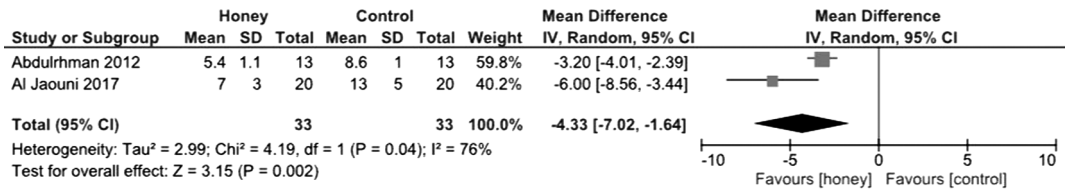

Figure 6. *Forest plot showing the efficacy of honey regarding the mean duration of hospital stay due to severe OM (grade ≥III). OM: Oral mucositis.*

Outcomes. This systematic review identified a total of thirty-four studies, but only LLLT and honey categories provided enough studies for data analysis and meta-analysis synthesis (54). The results of the analysis regarding the management of OM in pediatric patients are the following:

Among the eleven studies accessing the efficacy of LLLT, only three of them (21, 25, 27) provided data regarding the number of patients with OM grade ≥II. Consequently, quantitative analysis was feasible only for these studies. It is important to note that OM grade II is more symptomatic compared to OM grade I, as the ulcers on oral mucosa cause pain and discomfort to the patient. The data analysis included 121 pediatric patients, 28 patients in each arm (LLLT *vs*. control group) of Cruz *et al*. study (21), 22 patients in each arm (LLLT *vs*. control group) of Reyad *et al*. study (27) and a total of 21 patients (9 patients in LLLT group *vs* 12 patients in control group) in Kuhn *et al*. study (25). The risk of bias summary of the RCTs included to the meta-analysis is presented in Figure 2. The meta-analysis of three studies (21, 25, 27) involving a total of 121 children demonstrated that LLLT did not significantly reduce the risk of OM grade ≥II compared to no intervention (RR=0.99, 95%CI=0.26-3.76, p=0.99; I^2=72%, Figure 3). By excluding one of the above studies (21) which focused on the prevention of OM involving patients without OM at the beginning of the trial, no significant difference between the two groups (LLLT and no intervention) was observed regarding the risk of OM grade ≥II (RR=0.48, 95%CI=0.04-6.20, p=0.58; I^2=86%, Figure 4).

Two studies investigated the efficacy of topical application of honey on oral mucosa compared to no intervention (control group) regarding the mean duration of hospital stay in children with OM grade ≥III (31, 32). The data analysis included 66 pediatric patients, 13 patients in each arm (honey *vs*. control group) of Abdulrhman *et al*. study (31) and 20 patients in each arm (honey *vs*. control group) of Al Jaouni *et al*. study (32). The risk of bias summary of the RCTs included to the meta-analysis is presented on Figure 5. The meta-analysis of the above studies showed a statistically significant reduction in the mean duration of hospital stay for the honey group [MD=–4.33, 95%CI=–7.02-–1.64, p=0.002; I^2=76%, Figure 6]. This conclusion is further supported by the findings of Abdulrhman *et al*. (31) for OM grade II which recorded faster recovery time for honey group (p=0.0017).

Discussion

This systematic review and meta-analysis of RCTs with pediatric patients investigated current interventions/agents for the management of OM and supports the role of topical application of honey for the management of severe OM. One previous meta-analysis of RCTs and non-RCTs involving pediatric and young adult patients with cancer supported the role of LLLT in the prevention and treatment of OM (55). One meta-analysis of RCTs including pediatric and young adult patients with cancer found only a trend for a lower incidence of OM in LLLT group compared to no intervention on 7^{th}-10^{th} day of evaluation (16). Another meta-analysis of RCTs and non-RCTs with children undergoing cancer treatment showed no significant difference in decreasing the percentage of events of OM when LLLT was applied (56). The same meta-analysis showed a significant benefit of palifermin in reducing the percentage of events severity, and duration of severe OM in children with cancer (56). Topical application of honey on oral mucosa was also found to be effective in shortening the recovery time due to OM in one meta-analysis involving children receiving radio/chemotherapy (15).

The present meta-analysis of two RCTs that included 66 pediatric patients undergoing radio/chemotherapy demonstrated a significant benefit of honey on shorter hospital stay in children with severe OM (p=0.002). Honey has a significant role in medicine, and it is popular for its anti-inflammatory, antioxidant, and antimicrobial activity. The anti-inflammatory effect is due to the reduction of plasma prostaglandin E2 concentration through inhibition of cyclooxygenase 1 or/and 2 and the antibacterial effect is due to its high viscosity since it contains high concentration of sugars and low water content, creating a protective barrier to prevent infection. In addition, the presence of organic acids (mainly gluconic acid) creates an acidic environment (pH=3.2-4.5) which is hostile for bacteria that grow mostly at pH 6.5-7.5 (57, 58). The antioxidant activity is attributed to its content of polyphenols and ascorbic acid and the activity of glucose oxidase. Hydrogen peroxide (H_2O_2) is also an important *in vivo* antioxidant agent which is produced when the enzyme glucose oxidase that is activated

during the dilution of honey acts on endogenous glucose (57, 59). All these properties of honey promote wound healing by enhancing epithelialization and minimizing scar tissue (60).

The present study also found no significant benefit when LLLT was applied for the management (prevention or treatment) (p=0.99) and the treatment (p=0.58) of OM grade ≥II in children. These meta-analyses of RCTs included 121 and 65 pediatric patients, respectively. However, further larger RCTs in children are needed to verify these findings. LLLT has been found to be effective for the prevention and management of OM in adult patients and a mixed population according to recent meta-analyses (10, 61, 62). Mechanics of LLLT's effectiveness on OM are not fully understood, but researchers found that it has significant anti-inflammatory and analgetic effects. LLLT triggers the production of growth factors, fibroblast proliferation and angiogenesis, and induces the release of endorphins (63). The commonly used parameters of LLLT are wavelength 632.8-685 nm, power 10-60 mW, fluence 1.8-3.0 J/cm^2, and total energy 0.8-3.0 J (64). Although, LLLT is well studied for its role to the management of OM in adults, it is an expensive intervention and requires special training.

Study limitations. We presented the findings of RCTs concerning two different interventions, LLLT and honey compared to a control group, and even though it seems that honey provides significantly better results than LLLT, the results of the two meta-analyses are not comparable. The comparison for LLLT concerns the differentiation in the outcome between LLLT and no intervention group with a cut off value II toxicity grade of OM, while the comparison between honey and no intervention group, is conducted with a cut off value of III. This restriction is related to the way the patients in the included studies are grouped and therefore, any alteration is not feasible. Another limitation observed in the analysis regarding honey is that the actual number of episodes of severe OM is not stated by the study of Al Jaouni *et al*. (32), only the number of patients with a reported episode of severe OM that equals 4 in honey group and 11 in control group. Still, considering a minimum of 1 episode per patient, the inference does not change, and the benefit of the honey-based intervention remains statistically significant with an expected mean difference equal or greater than 3.5 units.

Conclusion

The results of the meta-analysis demonstrate that LLLT had no significant benefit for lower risk of OM grade ≥II in pediatric patients. Topical application of honey on oral mucosa was effective in shortening the mean duration of hospital stay in children with severe OM. We conclude that honey is a potent agent for the treatment of severe OM in children. However, further RCTs are needed to investigate the role of honey in less severe OM and explore more interventions and agents for the management of OM in pediatric patients with cancer.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

CSA, CY, IK, PP contributed to study conception and design; CSA, PP performed the literature search, data extraction, risk-of-bias, and data analysis; CSA drafted the manuscript. All Authors reviewed and approved the final version of the manuscript.

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