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IMPACTO DA EDUCAÇÃO EM SAÚDE BUCAL NA INCIDÊNCIA E GRAVIDADE DE MUCOSITE ORAL EM PACIENTES ONCOPEDIÁTRICOS

PAULA MARIA MARACAJÁ BEZERRA

2020

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IMPACTO DA EDUCAÇÃO EM SAÚDE BUCAL NA INCIDÊNCIA E GRAVIDADE DE MUCOSITE ORAL EM PACIENTES ONCOPEDIÁTRICOS

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DEDICATÓRIA

Às crianças e adolescentes em tratamento antineoplásico no Hospital Napoleão Laureano e suas famílias: este trabalho é fruto da sua confiança em nossa equipe.

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“É justo que muito custe o que muito vale.”
Santa Teresa D'Ávila

RESUMO

A educação em saúde bucal está entre as principais medidas preventivas para mucosite oral (MO), favorecendo o autocuidado dos pacientes na ausência da equipe multiprofissional. Avaliou-se o impacto de intervenções educativas em saúde bucal na incidência e gravidade de MO em pacientes oncopediátricos, por intermédio de uma revisão sistemática da literatura com metanálise (capítulo 1) e de um estudo quase-experimental (capítulo 2). A revisão sistemática objetivou sintetizar e qualificar a evidência científica sobre esta temática disponível na literatura até agosto de 2020. Foram realizadas buscas nas principais bases de dados nacionais e internacionais, por dois examinadores independentes. Buscaram-se estudos primários com amostras compostas por pacientes oncopediátricos de 0-19 anos, submetidos à educação em saúde bucal, tendo como desfecho MO. A avaliação da qualidade dos estudos foi conduzida com o instrumento ROBINS-I e realizou-se síntese qualitativa e quantitativa (metanálise, α=5%). Seis artigos foram selecionados para síntese qualitativa e três para metanálise. Apesar da heterogeneidade metodológica dos seis estudos, todos apontaram para um impacto positivo da educação em saúde bucal frente a MO. A metanálise demonstrou uma menor chance de ocorrência do desfecho após a intervenção, em comparação com grupo controle (p=0,01). O estudo quase-experimental, do tipo coorte histórica controlada, avaliou a efetividade de um Programa Educativo e Preventivo de Saúde Bucal (PEPSB) em reduzir a incidência e a gravidade de MO. Foram comparados dois grupos pareados de pacientes oncopediátricos previamente assistidos: submetidos e não submetidos ao PEPSB, cada um com 14 indivíduos. Os dois grupos foram examinados por seis semanas por meio do Guia de Avaliação Oral modificado (OAG), por examinadores calibrados (k>0,8). A incidência de MO e da sua forma grave nos grupos foi comparada por meio do teste Qui-quadrado (α=5%). O risco relativo e a efetividade do PEPSB foram calculados, com poder de 0,97. A diferença entre os OAGs totais dos grupos foi mensurada pelo teste de Mann-Whitney (α=5%).Observou-se maior incidência de MO em pacientes não submetidos à intervenção (p<0,005) e menor risco de acometimento pela MO pelos pacientes submetidos à mesma (RR 0,73; IC 0,60 – 0,92). O PEPSB reduziu o risco dos pacientes desenvolverem MO em 1,4 vezes, com efetividade de 27%. Houve diferença entre os valores de OAG total (p=0,041). Concluiu-se que o PEPSB foi efetivo em reduzir a incidência de MO. Esta dissertação permite sugerir que estratégias educativas em saúde bucal sejam implementadas nos centros de oncologia pediátrica, a fim de proporcionar a redução da incidência e gravidade da MO.

Palavras-chave: Educação em saúde bucal; Mucosite; Odontopediatria.

ABSTRACT

Oral health education is among the main preventive measures for oral mucositis (OM), which favors patients' self-care in the absence of the multi-professional team. The impact of educational interventions in oral health on the incidence and severity of OM in oncopediatric patients was evaluated, through a systematic literature review and meta-analysis (chapter 1) and a quasi-experimental study (chapter 2). The systematic review aimed to synthesize and qualify the scientific evidence on this topic available in the literature until August 2020. Searches were carried out in the main national and international databases, by two independent examiners. Primary studies were sought with samples composed of oncopediatric patients aged 0-19 years, who underwent oral health education, with the outcome MO. The evaluation of the quality of the studies was conducted with the ROBINS-I instrument and a qualitative and quantitative synthesis (meta-analysis, α=5%) was performed. Six articles were selected for qualitative synthesis and three for meta-analysis. Despite the methodological heterogeneity of the six studies, all tended to an oral health education positive impact on OM. The meta-analysis demonstrated a lower chance of the outcome occurring in a group submitted to the intervention, compared to the control group ($p=0.01$). The quasi-experimental study, of the controlled historical cohort type, evaluated the effectiveness of an Educational and Preventive Program on the Oral Health (EPPOH) in reducing the incidence and severity of OM. Two paired groups of previously assisted oncopediatric patients were compared: submitted and not submitted to EPPOH, each with 14 individuals. Both groups were examined for six weeks using the modified Oral Assessment Guide (OAG), by calibrated examiners ($k>0.8$). The incidence of OM and its severe form in the groups were compared using the Chi-square test (α=5%). The relative risk and effectiveness of the EPPOH were calculated, with a power of 0.97. The difference between the total OAGs of the groups was measured by the Mann-Whitney test (α=5%). There was a higher incidence of OM in patients not submitted to the program ($p<0.005$) and a lower risk of being affected by OM by patients undergoing the intervention (RR 0.73; CI 0.60 - 0.92). EPPOH reduced the risk of patients developing OM by 1.4 times, with an effectiveness of 27%. There was a difference between the total OAG values ($p=0.041$). It was concluded that the EPPOH was effective in reducing the incidence of OM. This dissertation allows us to suggest that educational strategies in oral health are implemented in pediatric oncology centers in order to reducing the incidence and severity of OM.

Keywords: Health education, dental; Mucositis; Pediatric dentistry.

LISTA DE ABREVIATURAS E SIGLAS

PEPSB – Programa Educativo e Preventivo de Saúde Bucal

MO – Mucosite Oral

OAG – *Oral Assessment Guide*

RR – Risco Relativo

IC – Intervalo de Confiança

EPPOH – *Educational and Prevention Program on the Oral Health*

RHC – Registros Hospitalares de Câncer

LLA – Leucemia Linfoblástica Aguda

OMS – Organização Mundial de Saúde

NF-κB – Fator nuclear kappa B

NRF2 – Fator nuclear do eritróide 2

TNF-α – Fator de Necrose Tumoral α

IL-6 – Interleucina 6

IL-1β – Interleucina 1β

TLR – Receptor celular semelhante a Toll

MOG – Mucosite Oral Grave

MASCC–*Multinational Association of Supportive Care in Cancer*

HNL – Hospital Napoleão Laureano

OM – *Oral Mucositis*

MAPK – *Mitogen-activated protein kinase*

PAMP – *Pathogen-associated molecular pattern*

PICO – *Patient, Intervention, Comparison, Outcome*

JBI – *Joana Briggs Institute*

WHO – *World Health Organization*

WCCNR – *Western Consortium for Cancer Nursing Research*

PRISMA – *Preferred Reporting Items for Systematic Reviews and Meta-Analysis*

PROSPERO – *International prospective register of systematic reviews*

SIGLE – *System for Information on Gray Literature in Europe*

LILACS – *Latin American and Caribbean Health Sciences Literature*

MeSH – *Medical Subject Headings*

PMMB – Paula Maria Maracajá Bezerra

TIV – Thiago Isidro Vieira

AMGV – Ana Maria Gondim Valença

SAS – Simone Alves de Sousa

NRS – *Non-randomised study*

ALL – A*cute Lymphoblastic Leukemia*

AAPD – *American Academy of Pediatric Dentistry*

SPSS – *Statistical Package for the Social Sciences*

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1. INTRODUÇÃO

De acordo com os Registros Hospitalares de Câncer (RHC), neoplasias em crianças e adolescentes correspondem a 2,8% de todos os tumores informados, constituindo-se em um agravo raro cujas peculiaridades devem ser consideradas (1). Dentre os tipos de tumores que mais acometem esta população estão as leucemias, os tumores do sistema nervoso central e os linfomas (2). A leucemia linfoblástica aguda (LLA) é o câncer pediátrico mais comum, cuja prevalência mundial é estimada em 25% dentre os tumores infantojuvenis (3).

No Brasil, o câncer infantojuvenil é a principal causa de morte por doença na faixa etária de 0 a 19 anos (1). O coeficiente de proliferação tumoral nesses pacientes é mais elevado que em adultos, o que implica em maior velocidade de progressão da doença e, em contrapartida, resposta mais satisfatória frente a terapias antineoplásicas. Assim, estima-se que cerca de 70% dos pacientes pediátricos diagnosticados com câncer são curados (4).

Os tratamentos antineoplásicos são responsáveis pelo desenvolvimento de comorbidades que acompanham o curso terapêutico. Estas podem ser locais ou sistêmicas, a depender do tipo de terapia instituída (5). As cirurgias desencadeiam traumas físicos e psicológicos; a quimioterapia provoca supressão imunológica e a radioterapia pode alterar o desenvolvimento ósseo, causar comprometimento intelectual e gerar patologias endócrinas (6). Não obstante, a cavidade oral tende a ser prejudicada, especialmente pelos dois últimos tratamentos (7).

As comorbidades orais comprometem a qualidade de vida dos pacientes, uma vez que causam desconforto associado a dor, prejuízo da deglutição, fonação e nutrição, culminando, em alguns casos, na interrupção do tratamento do câncer (8). A sua etiologia pode ser decorrente da imunodepressão e colonização por microrganismos oportunistas; da diminuição do fluxo salivar; ou diretamente por inflamação e dano teciduais causados pela citotoxicidade dos agentes terapêuticos, quando são denomina-se mucosite oral (MO) (9).

Esta última apresenta-se, inicialmente, como um eritema na mucosa oral, que pode evoluir para erosão e ulceração recoberta por pseudomembrana. Os sítios mais afetados são as regiões de mucosa não ceratinizada (10). Pacientes submetidos à quimioterapia tendem a desenvolver mucosite de 7 a 15 dias após a administração inicial das doses; já em pacientes irradiados, os primeiros sinais e sintomas de mucosite oral ocorrem da segunda para a terceira semana de radioterapia (11). O diagnóstico da mucosite oral é clínico, baseado no histórico terapêutico e nos sinais e sintomas autorrelatados (12).

Existem diversos instrumentos de mensuração do agravo, sendo os mais utilizados a Escala da Organização Mundial de Saúde (OMS) e o Guia de Avaliação Oral Modificado (*Oral Assessment Guide* – OAG) (13). Uma revisão sistemática da literatura acerca das escalas de mensuração da mucosite oral concluiu que é mais recomendável o uso do OAG para avaliar crianças e adultos jovens com câncer, em função da facilidade do instrumento e sua confiabilidade para esta população (14).

A patogênese da MO é complexa e envolve não apenas o epitélio oral, mas tecidos subcutâneos (15). Os danos teciduais causados pelos agentes antineoplásicos podem iniciar diretamente por quebras irreversíveis nas fitas de DNA das células basais do epitélio oral, ocasionando apoptose; ou pela produção exacerbada de espécies reativas de oxigênio que podem danificar as proteínas de junção epitelial, desencadeando aumento da permeabilidade e disfunção tecidual (16). Didaticamente, sua patogênese é dividida em cinco fases: iniciação; autorregulação e ativação; amplificação do sinal; ulceração com inflamação; e cicatrização (17).

O processo inflamatório é dependente da produção do fator nuclear kappa B (NF-κB) e do fator nuclear do eritroide 2 (NRF2), o qual estimulará a liberação de citocinas inflamatórias e sinalização através de metaloproteinases de matriz extracelular; a injúria tecidual é sustentada pela produção da ciclo-oxigenase 2 (COX2) e da proteína quinase ativada por mitógeno (MAPK) (16). Os mediadores inflamatórios essenciais a este processo são o fator de necrose tumoral-α (TNF-α) e as interleucinas 6 e 1β (IL-6 e IL-1β) (18). O papel desempenhado pela imunidade inata do hospedeiro está em elucidação e aponta-se que os receptores celulares de reconhecimento de padrão semelhantes a Toll (TLR) podem mediar a lesão em mucosa, sendo sua função na patogênese da MO dependente da classe de quimioterápicos (15).

Os TLRs reconhecem sinais liberados por células mortas ou danificadas e induzem a ativação da resposta inata adaptativa antígeno específica e não específica (19). Estes receptores também podem ser induzidos por padrões moleculares associados a patógenos expressados por bactérias a sinalizar a produção de IL-1β, IL-6 e TNF, amplificando a resposta pró-inflamatória (20). As células epiteliais gengivais expressam diversos TLRs e, uma vez que a expressão destes receptores é aumentada mediante exposição contínua a ligantes, tecidos gengivais inflamados tendem a aumentar a expressão de TLRs (21).

Outra via de sinalização da MO que pode ser exacerbada por influência da microbiota oral é a da MAPK (20). Microrganismos presentes no biofilme dental como *Porphyromonas gingivalis*, *Fusobacterium nucleatum* e *Streptococcus gordonii* podem modular esta via, induzindo resposta pró-inflamatória (22,23), impactando na incidência ou gravidade da MO (20). Dessa

forma, compreende-se que a microbiota oral pode influenciar em todas as fases patogênese da MO, não sendo apenas um fator contribuinte à fase ulcerativa (15).

A higiene oral deficiente e as infecções odontológicas, portanto, desencadeiam níveis aumentados de citocinas inflamatórias, as quais estão associadas à ocorrência de lesões ulceradas de MO, isto é, mucosite oral grave (MOG) (24), as quais são dolorosas e prejudicam a qualidade de vida dos pacientes (11). Apesar de ser uma condição multifatorial, boas condições de higiene oral podem contribuir para a redução da incidência ou gravidade da MO (24). Dessa forma, é fundamental que os pacientes que irão se submeter a terapias antineoplásicas sejam encaminhados para um condicionamento prévio da cavidade oral com um cirurgião-dentista e sejam motivados a manter bons níveis de higienização oral durante todo o curso do tratamento (25).

A Associação Multinacional de Cuidados de Suporte em Câncer (*Multinational Association of Supportive Care in Cancer* - MASCC) orienta que as boas práticas de higiene oral são medidas relevantes para o manejo da mucosite oral (25, 26). Em 2019, a partir de uma revisão sistemática da literatura que identificou estudos nos quais a educação em saúde bucal impactou positivamente na qualidade de vida de pacientes oncológicos adultos, esta intervenção passou a ser recomendada pela MASCC como uma das medidas importantes para a prevenção da mucosite oral (27).

Pacientes instruídos sobre a MO e esclarecidos acerca dos seus principais sinais e sintomas podem contribuir no processo diagnóstico desta comorbidade (28). Especialmente no contexto da oncopediatria, a sensibilização das crianças e de seus cuidadores favorece maiores cuidados com sua alimentação e higienização, mesmo quando não estiverem sob os cuidados da equipe multiprofissional (29, 30).

Neste sentido, foi desenvolvido na Turquia um programa educativo em saúde bucal que assistiu 16 pacientes oncopediátricos um dia antes e 21 dias após o início da terapia antineoplásica, mediante a orientação de boas práticas de higienização, distribuição de kits e acompanhamento da condição de saúde bucal por meio de índices. Foi verificada redução na incidência e gravidade de mucosite oral, mensurada pela escala OMS, nos pacientes submetidos ao programa, bem como redução dos níveis de dor associada à comorbidade (31).

Dois estudos controlados realizados em Hong Kong avaliaram o impacto de estratégias educativas sobre a incidência e gravidade de MO em pacientes oncopediátricos, utilizando recursos pedagógicos como vídeo sobre saúde bucal, folheto informativo e diário de práticas de higiene. Foi demonstrada redução nos índices de mucosite oral, mensurados pela escala do OAG modificado nos pacientes que receberam a intervenção educativa. Estes

pacientes também apresentaram menores níveis de dor autorrelatada e, portanto, menor prejuízo da qualidade de vida (32, 33).

Estratégias de educação em saúde bucal constituem-se como intervenções de baixo custo, que contribuem para o desenvolvimento da autonomia do cuidado de pacientes e cuidadores, a fim de que exerçam seu protagonismo na higienização bucal ainda que na ausência da equipe multiprofissional (28). Além disso, programas desta natureza endossam a importância da vigilância em saúde bucal e da implementação de boas práticas de higiene oral como protocolo em hospitais oncológicos pediátricos, bem como reforçam a necessidade da presença do cirurgião-dentista no contexto hospitalar (31).

Reiterando tais resultados, no ano de 2018, foi realizado no setor de Oncologia Pediátrica do Hospital Napoleão Laureano (HNL), um Programa Educativo e Preventivo de Saúde Bucal (PEPSB), cujo objetivo foi favorecer o autocuidado e autonomia dos pacientes pediátricos e seus responsáveis no que tange aos cuidados odontológicos. Esse programa consistiu em um acompanhamento sistemático dos pacientes por 10 semanas, iniciando anteriormente à instituição da terapêutica antineoplásica, por meio de orientações lúdicas por vídeos e encartes, entrega de kits de higiene, cartões para os pacientes relatarem como foram seus hábitos diariamente, mediante reforço positivo quando obtivessem resultados satisfatórios. Observou-se progressiva melhora nos hábitos de higiene dos pacientes, por incorporação das orientações repassadas, o que impactou na diminuição da incidência e gravidade de mucosite oral, ao longo das semanas (34).

O referido estudo conduziu o PEPSB por um maior tempo de acompanhamento que os estudos disponíveis na literatura (31, 32, 33), utilizando como instrumento de mensuração o OAG modificado, o qual é apropriado para a faixa etária selecionada e ampliando a ludicidade das estratégias de educação em saúde empregadas. Contudo, não foi realizada uma comparação da incidência de MO e MOG com pacientes não submetidos à intervenção.

Esta dissertação se propôs, portanto, por meio de uma abordagem retrospectiva, a mensurar a efetividade do PEPSB, pela comparação dos pacientes submetidos ao programa com pacientes do mesmo centro de oncologia pediátrica, assistidos em períodos anteriores, quando o programa ainda não havia sido implementado. Justifica-se a realização desta pesquisa pela necessidade de construção de evidência científica confiável acerca desta temática, apoiada em parâmetros metodológicos rígidos, como o pareamento dos grupos, para limitar o efeito de variáveis confundidoras na explicação do desfecho de interesse (36).

Adicionalmente, objetivou-se compilar a evidência encontrada em estudos disponíveis nas principais bases de dados sobre o impacto que a educação em saúde bucal pode exercer na incidência e gravidade de MO, por meio de uma revisão sistemática da literatura. Justifica-se a realização da mesma para suportar a recomendação da MASCC de que a educação em saúde bucal contribui para a prevenção da MO em crianças e adolescentes, tendo em vista que a mesma foi suportada por estudos de qualidade de vida em adultos (27).

Assim, a principal hipótese desta pesquisa foi que estratégias de educação em saúde bucal para crianças e adolescentes em tratamento antineoplásico, bem como para seus pais e cuidadores, impactam na incidência e gravidade da mucosite oral.

2. CAPÍTULO 1

O manuscrito a seguir será submetido para publicação no periódico *Supportive Care in Cancer*.

The impact of oral health education on the incidence and severity of oral mucositis in pediatric cancer patients: a systematic review and meta-analysis

Abstract

Oral health education is an effective measure to prevent oral mucositis (OM) by improving self-management and effectively engaging patients in their health care. This systematic review aimed to determine the impact of oral health education interventions on the incidence and severity of OM. Bibliographical searches were carried out by two independent examiners in Medline, Scopus, Web of Science, LILACS, Cochrane Library and SIGLE, until August 2020. The eligibility criteria were based on the PICO strategy, considering studies with pediatric oncology patients, aged 0 to 19 years, who had attended oral health education activities and had been examined for the incidence and/or severity of OM. Data were extracted for qualitative synthesis and organized in spreadsheets. The quality assessment of the selected studies was performed using the ROBINS-I tool. Meta-analysis was based on the group frequencies of OM ulcerative lesions ($P \leq 0.05$). The primary search retrieved 444 articles. After removing duplicate records and screening titles and abstracts for eligibility, a total of 12 articles were selected for full-text analysis. Of these, six eligible studies were included for data extraction and qualitative synthesis, while three studies were selected for quantitative synthesis. All studies had a longitudinal design; three performed a before-after comparison and three were controlled studies. OM was assessed by the OAG scale in four studies, by the WHO scale in one study, and by the WCCNR scale in one study. While data analysis of the selected studies was heterogeneous, the implementation of oral health education strategies was found to reduce the incidence and severity of OM during the follow-up period. The meta-analysis showed a favorable outcome for the educational intervention. The likelihood of patients attending oral health education activities to manifest OM ulcerative lesions was significantly lower ($P = 0.01$) than that of the control. To conclude, oral health education interventions ameliorate OM outcomes in pediatric oncology patients with a moderate overall risk of bias.

Keywords: Mucositis; Health education, dental; Patient education as topic; Pediatric dentistry.

Introduction

Most pediatric patients undergoing antineoplastic treatment may experience dental conditions that are usually underestimated and not regarded as healthcare priorities [1, 2]. Some dental issues, such as untreated cavitated caries, can trigger an inflammatory response in the host. For instance, *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Streptococcus gordonii*, which are microorganisms commonly present in oral biofilms, may exacerbate the inflammatory response via the MAPK (mitogen-activated protein kinase) signaling pathway [3]. Oral microbiome dysbiosis is considered a risk factor for the onset and progression of oral mucositis (OM) [4]. The pathogen-associated molecular pattern (PAMP) expressed by bacteria may induce toll-like receptors (TLRs) in oral tissues to produce interleukins and tumor necrosis factor (IL-1β, IL-6 and TNF), which amplify the inflammatory cascade associated with the pathogenesis of OM [5, 6]. Thus, interventions aimed at re-establishing a symbiotic state in the oral microbiome are highly desirable [7, 8].

The implementation of oral health education programs is an important measure to prevent the development of OM. The clinical practice guidelines for the management of cancer treatment-induced OM of the Multinational Association of Supportive Care in Cancer (MASCC), updated in 2019, listed patient education for adults as a new intervention category which may contribute to prevent OM lesions. Patient education improves self-management and effectively engages patients in their oral health care [8].

Pediatric patients are more susceptible to develop OM due to their intense cell turnover [7]. Health education is especially relevant in this population group and should be converted into ludic strategies to instruct children and adolescents as well as their caregivers for better compliance , once verbal education has been proven to be inefficient [9, 10]. Educational activities are variable and may include video presentations, recreational activities, positive reinforcement rewards, impress guidance, and the use of dental toys. However, the impact of these strategies on the incidence of OM in pediatric cancer patients is largely underexplored given that reliable evidence about this topic is complex to obtain [7, 11–17].

Compiling oral health education strategies for children may be a helpful approach to develop a standardized protocol applicable to oncology facilities worldwide. Thus, this systematic review aimed to synthesize the existing evidence concerning this topic to answer the following question: Do oral health education interventions influence the incidence and/or severity of OM in pediatric cancer patients?

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [18] and was registered in the PROSPERO database under registration number CRD42020154152. Bibliographical searches were carried out between October 2019 and August 2020 in PubMed (MEDLINE), Scopus, Web of Science, LILACS (Latin American and Caribbean Health Sciences Literature), Cochrane Library, and System for Information on Gray Literature in Europe (SIGLE).

Additional publications were retrieved from the reference lists of included studies, and unpublished studies were retrieved from relevant meeting abstracts. If further information was needed, the authors were contacted directly by our research team.

The Population, Intervention, Comparison, and Outcome (PICO) strategy guided the search strategy. As shown in Table 1, MeSH terms and entry terms associated with oral health education for children and adolescents undergoing cancer treatment were applied, combined with Boolean operators [19].

The eligibility criteria were as follows: pediatric patients, aged 0 to 19 years, attending oral health education activities - which could comprise verbal instructions, training on toothbrushing techniques, video presentations, formal education diagrams, and any other didactic strategies addressing the importance of oral health care; the outcome should be the incidence and/or severity of OM based on a valid assessment tool, such as the World Health Organization (WHO) Oral Mucositis Grading Scale, the Oral Assessment Guide (OAG) or the Western Consortium for Cancer Nursing Research (WCCNR) scale. Studies with patients undergoing bone marrow transplant, in which antimicrobial substances were administered in the control group, or whose sample had received another intervention, were excluded from the analysis.

Table 1. PICO-based search strategy and Boolean operators.

	Mesh term	OR	**Entry terms**
P	Child; Child, preschool; Infant, Newborn; Adolescent;Pediatrics	OR	Children; Preschool Children; Newborn Infants; Newborns; Newborn; Neonate; Neonates; Adolescents; Adolescence; Teens; Teen; Teenagers; Teenager; Youth; Youths; Female Adolescent; Female Adolescents; Male Adolescent; Male Adolescents; Childhood; Oncopediatric; paediatrics
		AND	
	Neoplasms; Induction Chemotherapy; Antineoplastic Agents	OR	Neoplasia; Neoplasias; Neoplasm; Tumors; Tumor; Cancer; Cancers; Malignancy; Malignancies; Malignant Neoplasms; Malignant Neoplasm; Induction; Chemotherapies; Chemotherapy; Antineoplastic agents; Antineoplastic Drugs; Antineoplastics;

			Chemotherapeutic Anticancer Drug; Antitumor Drugs; Cancer Chemotherapy Agents; Drugs, Cancer; Chemotherapy; Chemotherapeutic Anticancer Agents; Anticancer Agents; Antitumor Agents; radiotherapy; radiotherapies
			AND
I	Health Education, Dental; Comprehensive Dental Care; Patient Education as Topic; Oral Hygiene; Oral Health	OR	Dental Health Education; Oral health education; Oral health education program; mouth care; oral care protocol; Dental Care Comprehensive; Oral care; Patient Education; Education of Patients; Dental Hygiene; Hygiene, Dental
			AND
C	-	OR	-
			AND
O	Stomatitis	OR	Stomatitides; Oral Mucositis; Oral Mucositides; Oromucositis; Oromucositides; Mucositis

Prospective and retrospective interventional studies were retrieved using a reference manager software (Mendeley Desktop, version 1.16.1, ©2008–2016 Mendeley Ltd., Elsevier Inc., NY, USA). Duplicate records were removed and the titles and abstracts were screened for eligibility. Two independent examiners (PMMB and TIV) carried out a full-text analysis to select eligible studies for the final review and meta-analysis. Any disagreement during the selection process was discussed with a third and fourth examiner (AMGV and SAS).

Two examiners (PMMB and TIV) independently collected the data from the included studies into a spreadsheet, as follows: year of publication; sample size; number of participants in each group; patients' age; method of application of the oral health education intervention and the strategies used to do so; OM assessment tool; statistical analysis; main results (including the incidence and/or severity of OM) and conclusions. When necessary, the third and fourth examiners (AMGV and SAS) reviewed the data.

The risk of bias assessment of the included studies was performed by two examiners (PMMB and TIV) using the Risk of Bias in Non-randomized Studies of Interventions tool (ROBINS-I) [20]. The studies were examined as for seven domains: confounding, selection of participants into the study, classification of intervention, deviations from intended interventions, missing data, measurements of outcomes, and selection of the reported result. Each domain was assigned a low, moderate, serious, critical, or "no information" risk of bias. Based on these seven domains, an overall risk of bias was determined for each study [20].

The qualitative synthesis was conducted by summarizing information from the data extraction table, whereas the quantitative synthesis (meta-

analysis) was performed in the RevMan software (Review Manager v. 5.3, The Cochrane Collaboration; Copenhagen, Denmark) to assess the impact of patient education on the incidence and/or severity of OM in pediatric cancer patients. The meta-analysis included studies with low and moderate risk of bias [21], considering a 95% confidence interval (CI). The random effect model was applied because the studies were not functionally equivalent [22]. Heterogeneity was tested using the I^2 index, and the main findings of included studies were described in a narrative synthesis.

Results

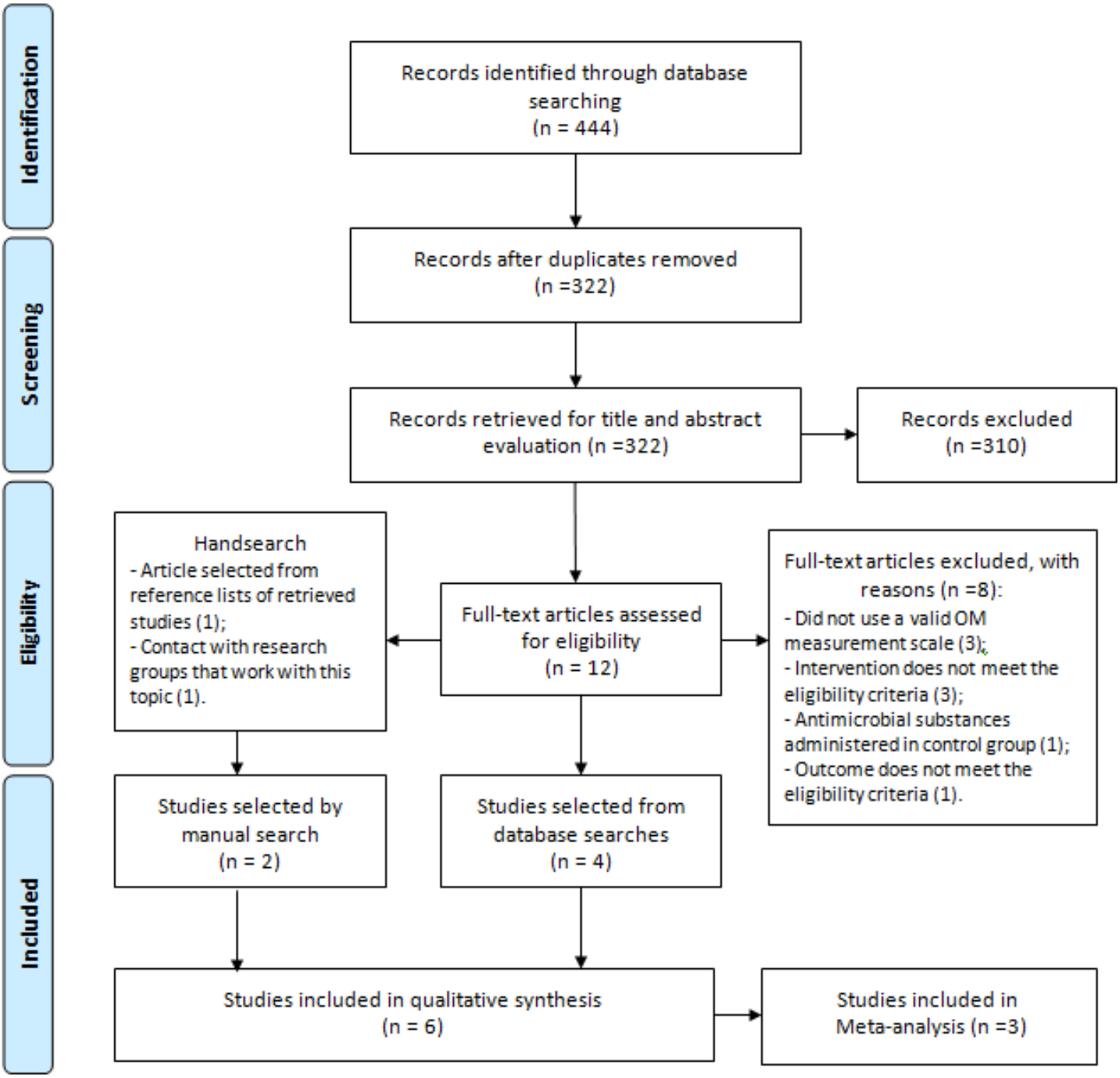
Study selection

Database searches retrieved a total of 444 records, as follows: 139 in PubMed, 176 in Scopus, 72 in the Web of Science, 38 in Cochrane Library, 17 in LILACS, and 2 in Open Grey. After duplicate records were removed, 322 articles were screened for eligibility based on their titles and abstracts. Of these, 310 articles were excluded because they did not meet the eligibility criteria. Twelve articles were selected for full-text analysis, of which 8 were excluded due to the following reasons: three did not use a valid OM assessment scale [13, 17, 23]; three did not address an oral health education intervention [24–26]; one reported the use of antimicrobial substances in the control group [27]; one did not assess OM as the study outcome [10]. Therefore, four studies were selected based on database searches, and two additional studies were included by manual search – one was retrieved from the reference lists of the selected studies [15] and one was obtained by direct contact with oncology pediatric research groups [28]. In total, six articles were included for data extraction and qualitative synthesis [7, 11, 12, 14–16], as shown in the PRISMA flow diagram (Fig 1).

Characteristics of included studies

The included studies were published between 2001 and 2020 and were carried out in five different countries, namely: Hong Kong [7, 12], Turkey [16], Taiwan [11], Brazil [28], and Egypt [15]. They presented a longitudinal design, with a non-randomized group of intervention. The sample sizes ranged from 14 to 42 participants. Three studies conducted a before-after comparison with the same group of patients [11, 15, 16], whereas three studies compared against a control group, which was assessed before the intervention group in the same oncology facility [7, 12, 28]. Two studies were conducted by the same research group in the same oncology service [7, 12]. To ensure that there was no sample overlapping, we contacted the authors, who declared that those were two different samples. The main characteristics of the selected studies are detailed in Table 2.

Figure 1. PRISMA Flow Diagram of literature searches.



Overall, the follow up period of the selected studies ranged from 2 weeks (one study) [11] to approximately three weeks (four studies) [7, 12, 15, 16] to 6 weeks (one study) [28]. The incidence and/or severity of OM was assessed in one study with the WHO scale [16], in four studies with the OAG – original (one study) [11] and modified versions (three studies) [7, 12, 28] – and was assessed in another study with the WCCNR scale [15].

The six selected studies reported the same outcome, albeit in a very heterogeneous way. Some authors reported the incidence rates of OM in the groups before and after the educational intervention. The findings revealed that the incidence of OM significantly decreased in the experimental groups, according to Chi-square test (two studies) [7, 12]. This statistical test also indicated a significant difference regarding the severity of OM between the groups (two studies) [15, 16]. One article described that the OAG mean score significantly decreased over time after the implementation of the oral health education activity [11]. One study showed a statistical difference between the occurrence of OM episodes in experimental and control groups after 6 weeks [28].

Oral health education strategies

All studies focused their oral health plan on patients and caregivers by providing instructions on toothbrushing and recommending oral hygiene at least twice a day. Mouth rinsing was prescribed in five studies, and different rinse solutions were recommended, namely: sodium chloride and chlorhexidine [7, 12], salty water [11, 15, 16], glutamine [16], and baking soda [15]. All studies delivered verbal and written instructions, and patients were given handouts containing detailed protocols. Some studies used audiovisual recourses to reinforce the educational intervention, such as computer and video presentations [7, 12, 16, 28].

One of the studies also examined the impact of games and positive reinforcement rewards on OM outcomes [28]. Two studies gave new soft-bristle toothbrushes to participants [16,28]. A detailed description of the oral health education strategies applied in all studies can be found in Table 3.

Table 2. Characteristics of the studies selected in this systematic review.

Author/year (Country)	Study design	Follow-up	Comparative	Sample size	Matching	OM Assessment	Outcome
Cheng *et al.*, 2001 (Hong Kong)	Longitudinal Prospective	Baseline and twice per week for 3 weeks (day 1 to 21)	Control group	Convenience sampling Control group (n=21) Experimental group (n=21)	No	Modified OAG	Incidence of ulcerative lesions: Control group: 71%; Experimental group: 33% (X^2= 6.1, *P*=0.01); Mean OM score over time (F=30.79, *P*<.01).
Cheng; Molassiotis; Chang, 2002 (Hong Kong)	Longitudinal Prospective	Baseline and twice per week for 3 weeks (day 1 to 21)	Control group	Convenience sampling Control group (n=7) Experimental group (n=7)	No	Modified OAG	Incidence of ulcerative lesions: Control group: 85.7%; Experimental group: 42.8% (X^2= 2.8, *P*=0.09); Mean OM score over time (F=19.3, *P*<.01).
Chen *et al.*, 2004 (Taiwan)	Quasi-experimental	Pretest, posttest 1, posttest 2 (2 weeks)	Before-after	Random sampling (n=30)	NA	OAG	Mean OAG score: pretest: 10.83; posttest 1: 9.77; posttest 2: 9.43 (*t* test, *P*<.01).
Yavuz; Yilmaz, 2015 (Turkey)	Longitudinal Prospective	Baseline + 21 days	Before-after	Convenience sampling (n=16)	NA	WHO	Severity of OM before and after intervention (x^2 = 154.79; *P*<.05).
Okby; El-abbassy, 2017 (Egypt)	Quasi-experimental	Baseline, 1st intervention, 2nd intervention (17 days)	Before-after	Convenience sampling (n=30)	NA	WCCNR scale	Difference in oral health status before and after the 1st intervention for all WCCNR items(*P*<.05) Difference in oral health status between the 1st and 2ndinterventions for all WCCNR items(*P*<.05)
Bezerra *et al.*, 2020 (Brazil)	Quasi-experimental	6 weeks	Control group	Convenience sampling (n=28)	Yes	Modified OAG	Incidence of ulcerative lesions: Intervention group: 64.2%; Comparative: 71.4% Difference in OM episodes: Intervention group: 58.3%; Comparative: 78.6% (*P*<.01)

NA – Not applicable

Table 3. Oral health education strategies used in the selected studies.

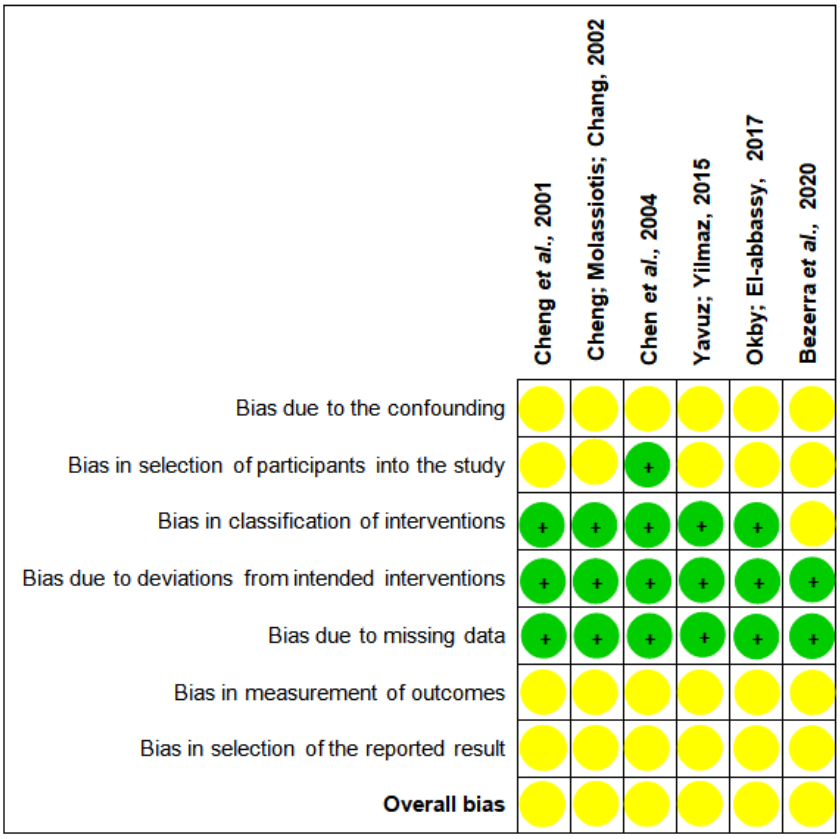
Study	Oral health education strategies
Cheng *et al.*, 2001	Oral care intervention: patients and their parents attended a 10-min videotaped oral care program and were given a brochure outlining the oral care protocol. Moreover, an oral care practice diary was given to patients to record their oral care daily routine. Patients were instructed to toothbrush at least twice daily and to rinse the mouth with sodium chloride and chlorhexidine.
Cheng; Molassiotis; Chang, 2002	Oral care intervention: patients and caregivers attended a 10-min videotaped oral care program and were given a handout describing the protocol. Each patient received an oral care practice diary to record their daily oral care routine. The main instructions were: toothbrush twice a day, and rinse the mouth with 0.9% sodium chloride solution and 0.2% chlorhexidine.
Chen *et al*., 2004	Oral hygiene regimen: a nurse instructed caregivers and patients on how to use the OAG and how to perform the oral hygiene regimen. Patients and caregivers were provided flashlights, assessment tools, and oral hygiene sheets. The following instructions were given: toothbrush after each meal and at bedtime, rinse the mouth with saline solution, apply petroleum jelly lip balm when lips are dry, use chewing gum when salivary flow is reduced, and perform an oral assessment every morning using a flashlight.
Yavuz; Yilmaz, 2015	Planned Mouth Care Education to Prevent Oral Mucositis in Pediatric Oncology Patients: 2 separate sessions, with a total duration of 60 min. Patients were given a handout with instructions. In the first session, participants attended a computer presentation entitled “Guidelines for Planned Mouth Care in Children Receiving Chemotherapy”. In the second session, children first showed how they brushed their teeth; then, the examiners explained to them the most effective toothbrushing technique. Each patient received 3 soft-bristle toothbrushes and was advised to brush twice a day; 600 mL of salty water (0.9% NaCl) and glutamine were provided to participants to be used as a mouthwash. The participants’ mothers were given a “Daily Mouth Care Follow-Up Chart” to monitor their children’s toothbrushing habits.
OKby; El-abbassy, 2017	Implementation of oral hygiene instructions: each patient received verbal and written guidance about daily oral care according to the American Academy of Pediatric Dentistry. A booklet with guidelines, descriptions, and pictures of lesions was provided to all children. Individual instructions were also provided; participants were first asked to show how they normally brushed their teeth; then, the examiners explained to them individually the most effective toothbrushing technique using a tooth model. Next, participating children were asked to practice the technique on the model, and then they were observed while brushing their teeth. The frequency of oral hygiene should be at least twice a day. Participants were recommended to rinse the mouth after meals and before bedtime with either a saline solution, a baking soda solution or a combination of both.
Bezerra *et al*., 2020	Education and Prevention Program on Oral Health: Participants attended a 7-min educational video presentation, were given handouts with oral hygiene instructions, and engaged in entertaining guidance through games and storytelling. Direct and individual oral hygiene guidance was provided using the modified Bass technique. Soft-bristle toothbrushes and fluoride toothpaste were provided. Positive reinforcement was performed every 2 weeks. The program had a total duration of 10 weeks; every week a “healthy smile card” and a diary were given to patients, and every 15 days, oral hygiene guidance was reinforced.

The risk of bias of selected studies (qualitative synthesis)

The risk of bias assessment of selected studies is presented in Figure 2. All included studies were classified as having a moderate overall risk of bias. While confounding bias might have been expected in all studies, the authors presented measures to control it. Selection bias during participant recruitment was classified as moderate in five studies [7, 12, 15, 16, 28] and low in one study, which had a random sampling design [29]. As for the bias in classification of interventions, one study reported that the intervention status was determined retrospectively and, therefore, it was assigned a moderate risk of bias [28], whereas the other studies presented a low risk of bias in this domain [7, 8, 12, 15, 16].

The risk of bias due to deviations from intended interventions was low for all included studies. Moreover, the risk of bias about missing data was low in all selected studies, because the data reported by the authors were reasonably complete. The bias in the measurement of outcomes was moderate in all studies, because the examiners were aware of the intervention. All studies had a moderate risk of bias regarding the selection of the reported results, once they provided outcome measurements and analyses consistent with an *a priori* plan – the analyses were internally and externally consistent.

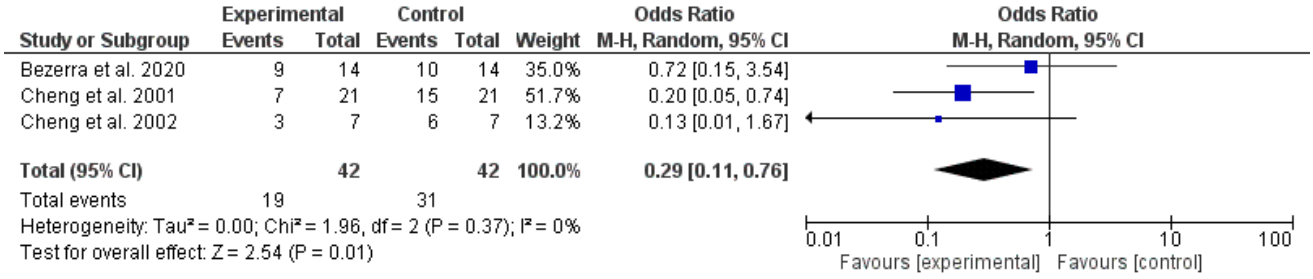
Figure 2. ROBINS-I tool assessment: yellow and green ball indicate studies with a moderate and low risk of bias, respectively.



Meta-analysis (quantitative synthesis)

The studies that measured the incidence of OM by the modified OAG tool, presented homogenous results and had a moderate overall risk of bias [7, 12, 28] were included for quantitative synthetis (*n* = 3). The meta-analysis was performed to determine the impact of patient education on the incidence of OM ulcerative lesions (score 3). As demonstrated in Figure 3, the meta-analysis showed a favorable outcome for the educational intervention. The likelihood of patients attending oral health education activities to manifest OM ulcerative lesions was significantly lower (95% CI: 0.11, -0.76; I^2= 0%; *P*=0.01) than that of the control.

Figure 3. Forest plot of the effects of oral health education interventions on the incidence of OM ulcerative lesions.



Discussion

This is the first study that summarizes published evidence – available in literature until August 2020 – about the impact of oral health education on the incidence of OM in pediatric cancer patients. This was a recent topic of discussion in the MASCC, which have added oral health education to their guidelines as an essential part of OM management. Their decision was based on a systematic review demonstrating that patient education increased the quality of life in adult patients submitted to cancer therapy [8, 30, 31]. In the present systematic review, we demonstrated that the MASCC's recommendation also applies to pediatric patients undergoing antineoplastic treatment.

Obtaining reliable scientific evidence in pediatric oncology research is a complex task. Besides the fact that cancer in children and adolescents is a rare condition, there might be other limitations to consider relative to patient follow-up, which include aggravation of the clinical condition, transfer to other hospital units, or death. Studies carried out in these settings usually consider a convenience sampling method and comprise only a restricted number of participants. Five studies included in this review had a convenience sampling design, whereas only one considered a random sampling method to select participants, although it was not possible to randomize patients into control and

experimental groups for ethical reasons [11]. The sample size of the selected studies ranged from 14 to 42 patients.

When randomization is not possible, rigorous methodological procedures are needed to strengthen the level of evidence required to infer any causality [20, 32]. The studies included herein had a non-randomized controlled design (NRS). This method has been commonly used to appraise intervention outcomes in health research. To overcome the limitations, some strategies have to be considered depending on the study design. While a before after comparison analysis favors the comparability of groups, it significantly impacts the outcome assessment in different moments of the antineoplastic treatment [11, 16, 33]. Hence, establishing a comparative (control group) is an adequate strategy to assess OM outcomes at the same phase of the antineoplastic treatment – although there might be losses in terms of comparability, once the patients differ between groups. Two studies included in this review had a control group which, albeit unmatched, showed homogeneity in relation to the experimental group [7, 12]. One study presented a matched control group and assessed OM outcomes at the same phase of the antineoplastic treatment, which rendered data comparability significantly feasible [28].

As the studies included in this systematic review have a moderate risk of bias [34], generalization of the results should be regarded carefully due to methodological issues (*e.g.*, lack of information about the effect size and statistical power). Despite these shortcomings, the educational interventions carried out in all selected studies were significantly associated with a lower incidence and severity of OM in pediatric cancer patients.

Highly motivated patients commonly present reduced levels of bacterial plaque accumulation and gingival inflammation [14]. Although the actual role of the oral microbiome on the course of OM remains inconclusive [35], some studies have shown an association between oral health status and good OM management [1, 36, 37]. Bacterial colonization of oral tissues, especially of disrupted mucosal surfaces, stimulates macrophages to produce cytokines, which may amplify the pro-inflammatory cascade and cell apoptosis [6, 35]. Accordingly, it is possible that the oral microbiome is mostly related to the severity of OM than to its incidence, once OM is an expected event during the course of antineoplastic treatment, with multifactorial etiology. Patient education could lower OM grading by reducing the stimulation of the inflammatory response due to lesser activation of TLRs [5]. This hypothesis is consistent with the meta-analysis performed in this review, which showed that educational interventions might reduce the occurrence of OM severe lesions.

Killing oral microorganisms with the administration of antimicrobial mouthwashes (*e.g.*, chlorhexidine) to prevent the onset of OM is not recommended. Instead, the administration of mouth rinses able to symbiotically

control biofilm accumulation is preferred, there by cleansing debris, maintaining oral hygiene and enhancing patient wellbeing [8]. There is evidence supporting the use of sodium bicarbonate solution because it has been shown to reduce the healing time of OM lesions [38]. Most of the protocols in the included studies contained the recommendation for participants to rinse their mouth using bland solutions [7, 11, 12, 15, 16], in accordance with the most recent MASCC's guidelines. Two studies prescribed the use of chlorhexidine for 30 min after each meal, which is not supported by recent evidence [7, 12].

The success of educational interventions depends on participant compliance with the study protocol. Patients with a low compliance with oral care have an increased risk of developing oral complications during the antineoplastic treatment [39]. However, encouraging children to have good hygiene habits and manage self-care is a complex task, which demands pedagogical procedures. Ludic strategies were found to effectively improve learning, change habits, and promote health [40]. The literature also recommends the use of visual and written materials to reinforce the verbal instructions [41]. Nevertheless, there is no evidence to support a specific one-to-one oral hygiene advice yet, so it is suggested that it be made individually based on the peculiarities of each patient [42, 43].

In this regard, all included studies provided oral hygiene instructions individually to meet the participants' needs. To ensure that caregivers and patients would not forget the recommendations, written explanations were also given in all studies. Three studies made use of an educational video [7, 12, 28], and one used a computer presentation [16]. Audiovisual resources are valuable to attract the attention of children, in addition to being a well-accepted approach, with fast return, low cost, and ease of access [44]. Despite the cultural differences between the selected studies, which were carried out in five different countries, substantial patient compliance was globally obtained. The method for verifying patient compliance with the oral health protocol was by a diary of practices, which was an useful tool to establish a routine and encourage discipline.

Cancer patients are not always under direct professional supervision, because period of the treatment is spent at home. One study showed an association between at-home oral care practice and the incidence of OM in acute lymphoid leukemia pediatric patients [24]. Hence, it is utterly important to train patients and their caregivers' autonomy to monitor and self-manage oral complications. Training a patient on how to recognize the first signs of OM allows for an early diagnosis of this comorbidity and an appropriate clinical management [23]. All the studies selected in this review presented an oral health education protocol that made patients aware of cancer related oral comorbidities. Moreover, instructing patients on how to use validated scales to measure OM lesions may enhance the communication with the oral health care

team. One included study guided parents on how to use the OAG scale to assess their children's oral cavity and how to document each assessment [11].

The assessment of OM by a valid instrument contributes to better data reliability and evidence-based clinical practice. Besides it makes surveillance possible in order to minimize injuries. Multiples scales have been used worldwide to diagnose and measure the severity of OM. The most used and disseminated one is the WHO scale, which combines subjective and objective simplified measures [45]. Only one article included in this review used the WHO scale, which is also valuable in terms of comparability with the international literature [16] and for multi-professional communication. However, this scale has an important limitation to consider – that it classifies as severe only the most extreme cases.

The OAG scale considers as severe any ulcerative lesion, allowing for an early identification of complications and intervention by the oral healthcare team. This scale is simple and fast to use in children, who normally cannot spend much time with the mouth open [11, 46]. Four studies in this review measured OM outcomes with the OAG scale [7, 11, 12, 28]. One study trained participants on how to use the OAG to support the measurement of their quality of life [33]. However, such study used an adapted version of the WCNR scale to measure the severity of OM, which also considers visual OM signs, functional skills, and the presence of infection [47].

The latest reference manual of the American Academy of Pediatric Dentistry (AAPD), which guides evidence-based clinical practice to patients receiving immunosuppressive therapies, advocates that oral health prevention is necessary in all phases of the antineoplastic treatment. Contrasting with what was suggested in the past, the AAPD strongly recommends toothbrushing two to three times a day to patients able to perform it without bleeding, even those with different platelet counts. The AAPD guidelines do not recommend a specific technique, but the use of soft bristle toothbrushes – which are less probable to induce trauma – is strongly recommended [48].

The AAPD also advises on the use of fluoridated toothpaste and dental floss, which was not reported in any of the selected studies as a recommendation for patients. There is a concern about the possibility of trauma with inadvertent use, but the AAPD supports a professional guidance so that the proper use of dental floss provides preventive benefits that overcome the risks [48]. Another recommendation concerns the use of lip balms with lanolin-based ointments, which are more efficient than petrolatum-based products, such as petroleum jelly, which was prescribed in one the studies [11].

Dentists are some of the best trained professionals to deliver oral health education. Nevertheless, in five of the six studies included in this review [7, 11, 12, 15, 16], the intervention were performed by nurses, whom might experience

work overload. These findings may indicate the absence of dentists in hospital settings or their overload with elective procedures. While there are many dental demands in hospitals [2], preventive and educational practices should be one of the top priorities to prevent oral complications. Educational interventions should be performed at diagnosis as well as before and throughout the antineoplastic treatment [48].

Taken altogether, this systematic review emphasizes the value of oral health education strategies to children and adolescents undergoing cancer therapy. Positive findings suggest that educational interventions have a significant impact on the incidence and severity of OM, but it was not possible to establish a protocol because of the heterogeneity of the studies available in the literature. Study limitations, such as sample size and group comparability, may undermine the strength of the evidence presented herein. New studies with more methodological rigor are suggested. The literature compilation presented in this review may guide further research to standardize educational protocols in oral health for pediatric cancer patients. Collectively, this systematic review provides evidence to support evidence-based clinical practice.

Conclusions

In summary, this study reports that oral health education may be beneficial to pediatric cancer patients. The meta-analysis showed a favorable outcome for the educational intervention. The likelihood of patients attending oral health education activities to manifest OM lesions was significantly lower than that of the control.

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3. CAPÍTULO 2

O manuscrito a seguir será submetido para publicação no periódico *Supportive Care in Cancer*.

The effectiveness of an oral health education and prevention program on the incidence and severity of oral mucositis in pediatric cancer patients: a non-randomized controlled study

Abstract

In this study, we investigated the effectiveness of an Oral Health Education and Prevention Program (OHEPP) on the incidence and severity of oral mucositis (OM) in pediatric cancer patients. The OHEEP was a ludic strategy for promoting oral health and monitoring the oral health condition of these patients. In this historically controlled cohort study, we compared the incidence and severity of OM in patients who attended an OHEPP (experimental) against those under similar conditions who did not receive any type of educational intervention (comparative). Both groups were examined for 6 weeks by previously calibrated examiners ($k > 0.8$) using the modified Oral Assessment Guide (OAG). Fourteen patients aged 2 to 18 years were included in each group and matched for sex, age, tumor type, and treatment modality. The incidence and severity of OM were compared using the Chi-square test ($\alpha = 5\%$), and the relative risk and effectiveness of the OHEPP were calculated, with a statistical power of 0.97. Differences in total OAG scores between the groups were determined by the Mann-Whitney test ($\alpha = 5\%$). There was a higher incidence of OM in patients who did not attend the OHEPP ($P = 0.005$), and the relative risk of developing OM was significantly lower in OHEPP attendants (RR: 0.73; CI 0.60 - 0.92). However, no difference in the occurrence of severe OM was observed between the groups. The educational intervention reduced the risk of developing OM by 1.4-fold, with an effectiveness of 27%. There was a significant difference in total OAG scores between the groups ($P = 0.041$). To conclude, participation in an oral health education program was an effective measure to reduce the incidence of OM in pediatric cancer patients. Similar strategies may be implemented in pediatric oncology centers to improve these patients' quality of life.

Keywords: Mucositis, Patient Education as Topic, Oral Health, Pediatric Dentistry.

Introduction

Childhood cancer is a rare condition which accounts for 2.8% of all neoplasms. In the decade of 2001–2010, 62 countries reported a total of 385,509 cancer cases in children aged 0 to 19 years [1]. According to the

Brazilian Hospital Cancer Database, childhood cancer is the main cause of death by disease in Brazilian children and adolescents aged 0 to 19 years [2]. Antineoplastic treatments may cause clinically relevant oral comorbidities, such as oral mucositis (OM), which can drastically affect the patient's quality of life[3]. Due to pain and dysfunction, OM is one of the most debilitating cancer-related comorbidities, whose incidence rates in pediatric patients may be as high as 75% [3, 4]. The presence of OM increases the risk of infection and extends hospital stays, thereby impacting the patients' quality of life and hospital costs [5, 6].

The Multinational Association of Supportive Care in Cancer (MASCC) suggests that appropriate oral hygiene practice and health education are important measures to prevent the occurrence of OM [7]. These practices consist mostly of instructing patients and caregivers on how to perform oral hygiene. However, verbal education has been proven ineffective [6, 8] and further strategies are needed to obtain better outcomes [9]. Some techniques used to motivate children regarding their oral care include games, video presentations, and positive reinforcement rewards [8].

These approaches have been shown to decrease the occurrence and severity of OM in pediatric patients and, thereby, to reduce the length of hospital stay and related costs [10–13]. Nevertheless, in most studies, the effectiveness of oral health education strategies has been determined by comparing the same group of patients in different moments, or by comparing different unpaired groups, since a randomized study would be unethical - considering that if a group of patients receives oral health instructions, the comparative group should not be deprived of this benefit. Therefore, developing evidence-based strategies may be a complex task, particularly because only a few studies have addressed these aspects in children and adolescents with cancer [10–15].

In our study, we used existing data to compare two groups of pediatric cancer patients. The first group included children and adolescents submitted to an Oral Health Education and Prevention Program (OHEPP). The second group included patients from a previous time point during which the OHEPP had not been implemented yet. By analyzing paired historical groups undergoing the same phase of the antineoplastic treatment, we tested the hypothesis that oral health education strategies may reduce the incidence and severity of OM in children and adolescents with cancer.

Methods

Data source and design

This quasi-experimental study was designed as a historically controlled cohort study [16]. The data were collected at the Napoleão Laureano Hospital (NLH), which is a reference oncology facility located in the city of João Pessoa, Paraíba State, northeastern Brazil.

A total of 105 pediatric cancer patients were monitored from April 2013 to July 2015 for their oral health status and OM-related factors [17]. Later, from April to October 2018, the same variables were assessed in 27 new pediatric cancer patients, who then attended the OHEPP [13].

At both time points, children and adolescents were assisted by the oral health team at diagnosis, before starting treatment, and over 10 weeks after the beginning of the antineoplastic treatment. Intraoral clinical examination was performed weekly using the modified Oral Assessment Guide (OAG) [4]. Satisfactory interexaminer kappa values were obtained in the first (0.87) and second (0.80) time points. Sociodemographic data, hematological parameters, and information regarding the antineoplastic treatment were also collected on a weekly basis [17].

The OHEPP tested in our study consisted of strategies to motivate patients to improve their oral health condition, such as games, video presentations, and positive reinforcement rewards, which were systematically applied for 10 weeks alongside verbal education and weekly oral assessments (Figure 1) [13]. The OHEEP aimed to promote oral health and prevent the onset and progression of OM in children and adolescents with cancer.

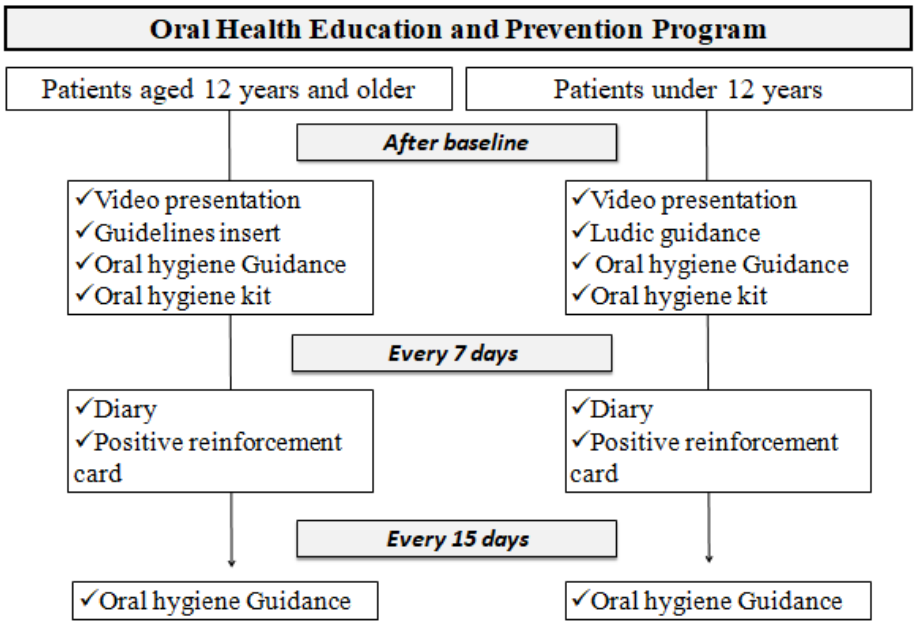

Figure 1. Flow diagram of the Oral Health Education and Prevention Program (OHEPP) applied to pediatric patients undergoing antineoplastic treatment. Adapted from Sampaio, 2019 [13].

In both time points, an overall sample size of 132 patients aged 0 to 19 years, undergoing antineoplastic treatment, was included. The effectiveness of the OHEPP in reducing the incidence and severity of OM was determined by comparing data from attendants [13] versus non-attendants [17].

Sample selection and pairing

Sample selection was carried out by pairing the groups. First, patients attending the OHEPP were selected to compose the intervention group if their oral assessments were available over six uninterrupted weeks. The number of six weeks was established because it comprises a period of cancer treatment when patients are more prone to develop oral comorbidities [18] and also because interrupted oral assessment could result in significant data loss (Figure 2).

Following these criteria, 14 patients were selected for the intervention group. They were matched for sex, age, tumor type (hematological or solid tumor), and treatment modality (exclusive chemotherapy or chemotherapy combined with radiotherapy) with other 14 patients who had not attended the OHEPP (comparative group).

Figure 2. Uninterrupted oral assessment follow-up per week of experimental and comparative groups over 10 weeks. Adapted from Ribeiro, 2015 [17] and Sampaio, 2019 [13].

Data analysis

A total of 168 oral assessments from both groups over six weeks (14 assessments / week per group) were analyzed, which corresponded to 84 oral assessments per group. The data analysis was performed in the Statistical Package for the Social Sciences program version 20.0 (SPSS Inc. IBM, Armonk, NY, USA).

Since each oral assessment was considered a unit of analysis, the Chi-square test was applied to both groups to determine any weekly differences regarding the use of methotrexate, doxorubicin, and cytarabine, which are stomatotoxic chemotherapy drugs [19, 20]. The occurrence of thrombocytopenia and leukopenia in both groups before each oral assessment was analyzed by the Chi-square test. The mean age data of study participants showed a normal distribution according to the Shapiro-Wilk test and any difference between the groups regarding this aspect was estimated by the *t*-test.

Differences in the incidence and severity of OM were determined by the Chi-square test, and the relative risk of developing OM and the protective effects of the OHEPP were further estimated. The relationship between the use of stomatotoxic chemotherapy drugs and the presence of leukopenia and thrombocytopenia was determined in both groups by the Chi-square test.

The Kolmogorov-Smirnov test indicated non-normal distribution of the OAG data. Therefore, the Mann-Whitney test was used to compare total OAG scores between the groups. For this analysis, a single-tailed test was considered. A 5% significance level was used in all the data analysis.

Ethical aspects

This study was previously approved by the Research Ethics Committee at the Center for Health Sciences, Federal University of Paraíba, under protocol number: 29855220.7.0000.5188, and is in full accordance with the ethical standards of the 1964 Declaration of Helsinki.

Results

The groups were homogeneous for sex, age, tumor type, and treatment modality ($P > 0.05$), as shown in Table 1. Both groups had an age range between 2 and 18 years, with a mean age of 9.14 ± 5.0 in the intervention group and 8.28 ± 5.2 in the comparative group. There was a predominance of males in both groups (57.15%). Hematologic tumors were the most frequent tumor

type, with eight cases in each group (57.15%). Most patients (78.57%) underwent exclusive chemotherapy.

The intervention and comparative groups showed no differences as to the use of methotrexate and cytarabine (*P*> 0.05) (Table 1). Nevertheless, the administration of doxorubicin was more frequent in the intervention group (*P*=0.001). Hematological data was incomplete in the intervention group for some weeks, which might have rendered intergroup comparisons inaccurate regarding the occurrence of thrombocytopenia and leukopenia. Seventy-two hematological exams were analyzed in both groups and did not show any difference concerning the occurrence of thrombocytopenia. However, leukopenia episodes were more frequent in intervention patients than were in the comparative group (*P*=0.018).

Table 1. Descriptive analysis of pediatric cancer patients who attended (or not) an oral health education and prevention program (OHEPP).

	Intervention	**Comparative**	**P-value**
Age	9.14 (±5.00)	8.28 (±5.20)	*0.661**
Sex			
Male	8 (57.15)	8 (57.15)	*1.000*
Female	6 (42.85)	6 (42.85)	
Tumor type			
Hematologic	8 (57.15)	8 (57.15)	*1.000*
Solid	6 (42.85)	6 (42.85)	
Treatment modality			
Chemotherapy	11 (78.57)	11 (78.57)	*1.000*
Chemotherapy + radiotherapy	3 (21.43)	3 (21.43)	
Methotrexate			
Yes	16 (19.04)	27 (32.14)	*0.076*
No	68 (80.96)	57 (67.86)	
Cytarabine			
Yes	8 (9.52)	11 (13.09)	*0.627*
No	76 (90.48)	73 (86.91)	
Doxorubicin			
Yes	21 (25.00)	5 (5.95)	*0.001*
No	63 (75.00)	79 (94.05)	
Thrombocytopenia			
Yes	36 (50.00)	26 (36.11)	*0.130*
No	36 (50.00)	46 (63.89)	
Leukopenia			
Yes	48 (66,66)	33 (45.83)	*0.018*
No	24 (33.34)	39 (54.17)	

*Note: Categorical data were tested by the Chi-square test; *t-test.*

Table 2 shows the total oral assessments of both groups over a period of six weeks. Our findings indicated that there were more OM episodes in the

comparative group, with a statistical power of 0.97 calculated *a posteriori* (Table 2).

Table 2. The incidence and severity of oral mucositis in pediatric cancer patients who attended (or not) an oral health education and prevention program (OHEPP), according to six-week oral health assessments.

	Oral Mucositis			**Total**	
	Absent	Mild/Moderate	Severe		*P*-value
Intervention	35 (41.70)	27 (32.11)	22 (26.19)	84 (100.00)	
Comparative	18 (21.40)	46 (54.80)	20 (23.80)	84 (100.00)	*0.0053 3 casas*
Total	53	73	42	168	

Note: The data were analyzed by the Chi-square test.

The likelihood of developing OM was higher in the comparative group than in the intervention group. A relative risk of 0.73 (CI 0.60 - 0.92) was estimated, suggesting that the OHEPP reduced by 1.4-fold the risk of developing OM, with an effectiveness of 27%. However, participation in the OHEPP did not significantly affect the severity of OM in pediatric cancer patients (Table 3).

Table 3. Absolute and relative risk of developing OM and severe OM in pediatric cancer patients who attended (or not) an oral health education and prevention program (OHEPP).

	Oral Mucositis		**Total**	**Absolute Risk**	***Relative Risk***	***P*-value**
	Present	Absent				
Intervention	49 (58.30)	35 (41.70)	84 (100.00)	0.58		
Comparative	66 (78.60)	18 (21.40)	84 (100.00)	0.79	0.73	*0.005*
Total	115	53	168	0.68		
	Severe Oral Mucositis*					
	Present	Absent				
Intervention	22 (26.19)	35 (41.70)	57 (67.89)	0.38		
Comparative	20 (23.80)	18 (21.40)	38 (45.20)	052	0.73	*0.158*
Total	42	53	95	0.44		

*Note: The data were analyzed by the Chi-square test; *Mild/moderate OM cases were not considered in this analysis.*

When comparing total OAG scores between the groups (Figure 3), the group of patients who did not receive any educational intervention had higher scores than those who did (*P*=0.041), in a single-tailed test. In the intervention group, OAG scores ranged from 8 (normal tissue condition) to 22, with a median of 9 and an interquartile range of 3. In the comparative group, OAG scores ranged from 8 to 18, with a median of 9 and an interquartile range of 1.

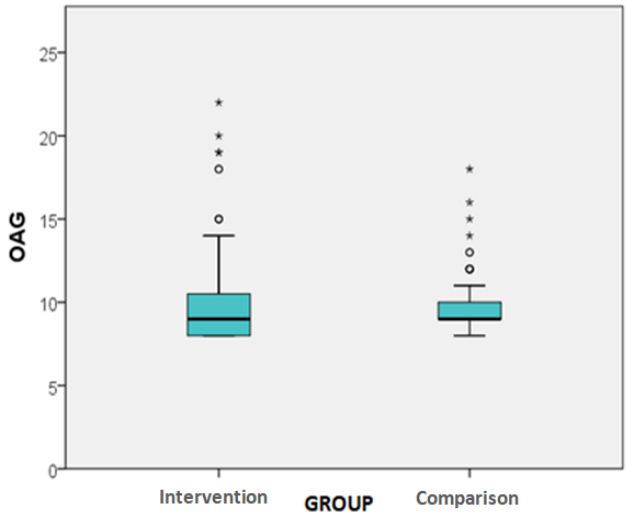

Figure 3. Distribution of total OAG scores among pediatric cancer patients who attended (or not) an oral health education and prevention program (OHEPP).

Discussion

This is the first study comparing the incidence and severity of OM in matched historical groups in the same phase of antineoplastic treatment. The historical design of our study mitigates the interference of confounding factors [16]. Comparing groups at different timelines - but in the same phase of the antineoplastic treatment - seems to be a useful strategy to determine the impact of an educational intervention on the incidence and severity of OM [16]. The first weeks of anticancer therapy correspond to the induction phase, a critical moment when patients are submitted to higher doses of chemotherapy drugs. Hence, promoting oral health in this phase of the antineoplastic treatment is critical to prevent the development of OM lesions [21].

Matching groups for sex, age, and tumor type, was performed to attenuate some important biological conditioners that possibly affect cell turnover[17, 19, 22]. In other words, patients who attended the OHEPP were compared against non-attendees under similar circumstances other than the educational intervention. The lack of difference between the groups regarding tumor type was an important outcome to consider, because hematological tumors are more frequently associated with oral mucosal alterations [23]. The groups were also comparable as for treatment modality, which consisted of radiotherapy combined with chemotherapy. Importantly, head and neck radiotherapy is known to significantly damage oral tissues and to increase the likelihood of developing OM [24]. As the groups were matched for tumor type, radiotherapy regions did not differ between the groups too. Thus, concerning these factors, the groups had similar exposition to OM.

While selected patients were matched for treatment modality and tumor type, it is possible that protocol adjustments might have been incorporated into

the antineoplastic treatment over time or that drug suppliers might have been changed, or even that the hospital might have lacked some chemotherapy drugs. To ensure that such possibilities did not affect the patients‘exposure to the stomatotoxic drugs, the groups were also analyzed as to the use of methotrexate, doxorubicin, and cytarabine. Methotrexate is one of the most harmful drugs to oral tissues and is commonly used to treat children with hematological tumors - who corresponded to the majority of our study sample [25]. Both groups were similarly exposed to methotrexate and cytarabine - whose stomatotoxic potential is remarkable at high doses [20]. Intervention patients were more exposed to doxorubicin, which is known to damage the DNA of oral cells [17, 19] and thereby increase the patient’s risk of developing OM.

Our findings revealed that while both study groups did not differ with respect to thrombocytopenia, the intervention group showed more leukopenia episodes over the course of six weeks. Counting blood components is an effective approach to measure the patients' systemic condition and, indirectly, their body defense and tissue regeneration functions. Leukopenia episodes may aggravate OM lesions and neutropenic patients who develop OM have a 4-fold higher risk of sepsis [26]. Thus, in our study, children and adolescents in the intervention group were more likely to have severe OM lesions.

Yet, patients in the comparative group experienced more frequent OM episodes, even though they had a better hematological condition and were less exposed to stomatotoxic drugs. The fact that they did not attend the oral health education program strongly suggests that it increased their probability of developing OM. Accordingly, this program may be considered a protective factor by improving the patient’s oral condition, reducing plaque accumulation, and promoting periodontal health. Moreover, the oral assessment carried out during the follow-up period may have raised awareness of patients and caregivers towards an early identification of oral conditions [13].

A planned mouth care education program to prevent OM in pediatric cancer patients was conducted in Turkey. Similar to the OHEPP, 16 eligible children attended oral health education sessions and were given soft-bristle toothbrushes, trained on how to brush their teeth, and followed up for 21 days. The presence of OM lesions and oral pain was compared before and after the intervention in the same group of patients. The authors concluded that both outcomes (presence of OM and pain) were significantly reduced after the intervention [10].

Another oral care protocol was applied to 21 pediatric cancer patients in Hong Kong, who were followed-up before starting chemotherapy and twice a week for 3 weeks during the treatment course. Patients were invited to watch an educational video and were given informative handouts and a diary to record oral hygiene practices. The experimental group was compared against an

unpaired control group. The authors observed that patients submitted to the new protocol had 38% less OM episodes compared to those in the control group [12]. This is in agreement with our findings showing that the educational intervention was highly effective (27%) and with data published elsewhere showing that educational and preventive measures have a positive impact on the incidence of OM [4, 11, 27].

The literature demonstrates that despite some cultural differences, oral health education programs increase patient compliance and improve their oral health condition, which may ultimately translate into reducing the occurrence of OM. Preventive and educational strategies may ameliorate OM outcomes by indirectly preventing biofilm accumulation through oral care. Metabolic products of oral pathogens, such as endotoxins, amplify the proinflammatory cascade and the damage to oral tissues [28]. Thus, simply improving the oral hygiene routine may delay or prevent the onset of ulcerative lesions [12].

The role of the oral microbiome in the pathogenesis of OM goes beyond a passive contributor in the ulceration phase [29]. OM is an expected side effect of the antineoplastic treatment which has multifactorial etiology, and microorganisms are known to significantly affect all phases of lesion development [29]. The pathogen-associated molecular pattern (PAMP) expressed by oral bacteria interacts with toll-like receptors (TLR) on the surface of inflammatory cells. In turn, inflammatory cells produce interleukins (IL-1β and IL-6) and tumor necrosis factor (TNF), which escalate the inflammatory cascade [30]. Microorganisms found in oral biofilms, such as *Porphyromonas gingivalis, Fusobacterium nucleatum,* and *Streptococcus gordonii*, may also amplify the inflammatory cascade via the mitogen-activated protein kinase (MAPK) pathway [31, 32]. The subclinical oral mucosal damage caused by the administration of stomatotoxic agents combined with microbial-induced proinflammatory responses may contribute to the development of clinically moderate or severe lesions.

Improvements in oral hygiene are possible if patients and caregivers are compliant with the educational program. Lack of adherence to dental treatments by pediatric cancer patients was found to increase their risk of developing oral complications during the antineoplastic treatment [9]. Therefore, it is strongly recommended to develop specific strategies for the children and adolescent population which should be compelling and have an accessible language. To date, there is still insufficient high-quality evidence to support any specific type of one-to-one oral hygiene advice. Hence, oral health education should be individualized according to the patient's needs [8].

Implementing oral health protocols is one of the most important demands in the hospital setting [33]. The presence of a dentist in the multi-professional team is important to guarantee comprehensive assistance to admitted patients.

A systematically organized participation of the dentist in preventive and educational practices is needed to hold patients and caregivers responsible for their oral care and to encourage self-management [10]. While undergoing antineoplastic treatment, patients stay most of the time at home. A previous study showed a relationship between oral health care practice at home and the incidence of OM in children with acute lymphoblastic leukemia [34].

Oral health professionals play an important educational role in care delivery. Here, patients who received an educational intervention were more neutropenic and more exposed to stomatotoxic drugs, but they experienced OM episodes less frequently than those who did not attend the educational program. Patients in the comparative group were assisted by dentists once a week, whereas those in the intervention group were additionally delivered oral health education and positive reinforcement, which probably protected them from developing OM.

The evidence presented herein strongly suggest that oral health-promoting strategies may reduce the incidence of OM. Some of the strengths of the present study include the homogeneity (matching) of sample groups; the 6-week follow-up period; the use of a validated scale (OAG) that allows for an early identification of oral conditions; and the comparison of groups in the same phase of the antineoplastic treatment. We provided evidence showing that patients who attended the OHEPP had significantly less OM episodes, despite their leukopenic condition and higher exposure to stomatotoxic drugs. More importantly, the OHEPP was found to be effective for approximately half of the follow-up period, which can be considered highly beneficial.

The implementation of oral health education programs in pediatric oncology facilities is a relatively easy and inexpensive maneuver, especially in healthcare services that include a dentist in the multi-professional team. Educational interventions may contribute to an early identification of oral comorbidities and self-management of patients and caregivers while substantially improving their quality of life.

Limitations

This study has some limitations to consider, which include the relatively small sample size, the assessment of OM in patients with solid and hematologic tumors together, the time gap between the two study periods (experimental and comparative), and the absence of hematological data for all follow-up weeks. Moreover, the drug dosage and peculiarities of the antineoplastic protocol for each patient were not considered in this study. Individual genetic variations, which can differentially predispose patients to develop OM, were also not considered in this study.

Some strategies were adopted to overcome these limitations, such as matching groups, limiting the study length to 6 weeks, and considering each oral assessment as a unit of analysis. Further research should focus on standardizing preventive and educational protocols for pediatric cancer patients.

Conclusions

Our study demonstrated that participation in an oral health education program was an effective measure to reduce the incidence of OM in pediatric cancer patients. Similar strategies may be implemented in pediatric oncology centers to improve these patients' quality of life.

Compliance with ethical standards: All procedures conducted in this research were in accordance with the ethical precepts of the Human Research Ethics Committee at the Center for Health Sciences, Federal University of Paraíba, under protocol number: 29855220.7.0000.5188.This study is in accordance with the 1964 Declaration of Helsinki and its subsequent amendments.

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4. CONSIDERAÇÕES GERAIS

O capítulo 1 desta dissertação foi idealizado durante o componente curricular de Tópicos em Revisão Sistemática, sob orientações dos docentes desta disciplina e das orientadoras desta pesquisa. A sua realização reiterou a necessidade de elaboração de estudos intervencionais, delineados sob critérios metodológicos rígidos, para evitar variáveis confundidoras e permitir menor risco de viés.

O delineamento do capítulo 2 foi realizado durante o primeiro ano deste curso de mestrado, seguindo critérios metodológicos rígidos, a fim de fornecer evidências científicas robustas acerca deste tema, mediante aprovação do Comitê de Ética em Pesquisa do Centro de Ciências da Saúde da UFPB (Anexo I). A pesquisa foi executada a partir de dados secundários oriundos de estudos previamente realizados no Hospital Napoleão Laureano (João Pessoa/PB), durante o segundo ano deste curso como requisito obrigatório para obtenção do título de Mestre em Odontologia.

O artigo produzido por esta pesquisa esteve compreendido nos critérios de elegibilidade da revisão sistemática e, por esta razão, foi selecionado por meio da busca manual para extração de dados, síntese qualitativa e quantitativa.

Sendo assim, as evidências reunidas por esta dissertação sugerem uma contribuição da educação em saúde bucal para o paciente oncopediátrico na redução da incidência e gravidade de mucosite oral. Constata-se, pois, que apesar da heterogeneidade metodológica dos estudos, é perceptível que pacientes submetidos a tais intervenções são menos acometidos pela referida comorbidade.

Ressalta-se, porém, o caráter multifatorial da mucosite oral e que se trata de um evento esperado, a depender do protocolo antineoplásico instituído. Não se almeja, portanto, inferir causalidade por meio deste estudo, mas demonstrar a contribuição das intervenções educativas em saúde bucal para o menor acometimento e gravidade de lesões de mucosite oral.

Padronizar protocolos educativos e preventivos em saúde bucal e aplicá-los em ensaios clínicos controlados e randomizados, constitui-se como as perspectivas futuras para o estudo desta temática.

5. CONCLUSÃO

Os estudos que compõem esta dissertação demonstram o impacto positivo da educação em saúde bucal na incidência e na gravidade da mucosite oral em pacientes oncológicos pediátricos.

A revisão sistemática da literatura demonstrou que pacientes que receberam educação em saúde bucal apresentaram significativamente menos lesões ulceradas de mucosite oral que pacientes não submetidos a tais intervenções.

O estudo quase-experimental demonstrou a efetividade de uma estratégia educativa, o Programa Educativo e Preventivo de Saúde Bucal, em reduzir a incidência de mucosite oral em pacientes pediátricos oncológicos. Os pacientes participantes do programa, embora com mais episódios de leucopenia em seis semanas e mais frequentemente submetidos a drogas estomatotóxicas, apresentaram risco diminuído de desenvolver a referida comorbidade em comparação com um grupo histórico pareado não submetido à educação em saúde bucal.

Sugere-se a implementação de estratégias similares em centros de oncologia pediátrica, a fim de proporcionar a redução da incidência e gravidade de mucosite oral para as crianças e adolescentes em tratamento oncológico.

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ANEXO I

APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA DO CENTRO DE CIÊNCIAS DA SAÚDE (CCS) – UFPB

UFPB - CENTRO DE CIÊNCIAS DA SAÚDE DA UNIVERSIDADE FEDERAL DA PARAÍBA

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Efetividade de estratégias de educação em saúde bucal na incidência e severidade de mucosite oral em pacientes oncopediátricos: coorte retrospectiva

Pesquisador: PAULA MARIA MARACAJÁ BEZERRA

Área Temática:

Versão: 1

CAAE: 29855220.7.0000.5188

Instituição Proponente: Centro De Ciências da Saúde

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.933.784

Apresentação do Projeto:

Trata-se de projeto de pesquisa apresentado ao Programa de Pós-Graduação em Odontologia da Universidade Federal da Paraíba como requisito de uma das disciplinas do curso (Disciplina de Seminários em Ciências Odontológicas). A proposta tem como pesquisadores a mestranda Paula Maracajá, e como orientadora a Profa Ana Maria Gondim Valença e a Profa Simone Alves de Sousa como co-orientadora. A principal hipótese desta pesquisa é que estratégias de educação em saúde bucal para crianças e adolescentes impactem na incidência e severidade da mucosite oral em grupos históricos pareados não concorrentes no mesmo período de tratamento antineoplásico.O objetivo do estudo é avaliar o impacto de um Programa Educativo e Preventivo de Saúde Bucal previamente instituído na incidência e severidade da mucosite oral em pacientes oncopediátricos, a partir da comparação com um grupo de crianças e adolescentes com câncer não beneficiados pelo Programa. A amostra será composta de participantes de trabalhos prévios e será composta de 28 indivíduos divididos em dois grupos:previamente beneficiados por um Programa Educativo e Preventivo de Saúde Bucal (Grupo Intervenção – G1) e não beneficiados (Grupo Comparação – G2). A partir da seleção dos pacientes de G1 (n=14), serão definidos pela técnica de pareamento os integrantes de G2 (n=14), totalizando assim, a amostra de 28 pacientes. Os dados do estudo são oriundos de planilhas previamente estruturadas pelas pesquisas citadas, das quais serão extraídas informações sobre a implementação do Programa Educativo e Preventivo de Saúde Bucal, além de variáveis de caracterização dos pacientes e

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sociodemográficas, relativas à sua neoplasia de base, bem como tratamento antineoplásico instituído e ocorrência de mucosite oral.

Objetivo da Pesquisa:

Objetivo Primário:Avaliar o impacto de um Programa Educativo e Preventivo de Saúde Bucal previamente instituído na incidência e severidade da mucosite oral em
pacientes oncopediátricos, a partir da comparação com um grupo de crianças e adolescentes com câncer não beneficiados pelo Programa.

Objetivo Secundário: Comparar a ocorrência da mucosite oral durante o período de acompanhamento nos pacientes beneficiados; Comparar a ocorrência da mucosite oral grave durante o período de acompanhamento nos pacientes beneficiados; Realizar análise de microcusteio de um programa educativo e preventivo em saúde bucal; Identificar experiência de cárie em cada grupo, mediante análise de prontuários odontológicos.

Avaliação dos Riscos e Benefícios:

As pesquisadores relatam quanto aos riscos:A pesquisa em questão oferece riscos mínimos aos indivíduos participantes, sendo eles: a exposição indevida de suas informações clínicas previamente coletadas, bem como dados sociodemográficos. Para minimização de tais riscos, os dados serão manipulados por apenas uma
pesquisadora que se compromete em zelar por sua confidencialidade e divulgação apenas dos resultados encontrados na pesquisa.

Benefícios: Atualizar a literatura acerca do impacto de um programa educativo e preventivo em saúde bucal na incidência e severidade de mucosite oral em
pacientes oncopediátricos, fornecendo dados que consolidem tal prática como um protocolo de baixo custo e eficaz de cuidados paliativos em
câncer.

Comentários e Considerações sobre a Pesquisa:

Trata-se de uma coorte retrospectiva, com técnica de abordagem indutiva, por meio de procedimentos comparativos estatísticos. A técnica de documentação será indireta e extensiva, por meio de dados secundários coletados em duas pesquisas previamente realizadas no Hospital Napoleão Laureano (HNL). A população do estudo serão todos pacientes oncopediátricos de 0 a 18 anos acompanhados por tais pesquisas (n=132). Destes, serão selecionados aqueles que receberam a intervenção ininterruptamente por 6 semanas para compor o Grupo Intervenção (G1;n=14). Cada paciente de G1 será pareado com um paciente não beneficiado pelo programa

educativo a partir de variáveis confundidoras, patologia de base, protocolo de tratamento antineoplásico, idade e sexo para compor o Grupo Comparação (G2; n=14). Os dados serão analisados por meio de estatística descritiva e inferencial, pelos programas Microsoft Excel e IBM SPSS 20. Testes de hipótese serão realizados, bem como tabelas de contingência e razão de chances. Os resultados desta pesquisa poderão reforçar a importância da implementação de programas educativos e preventivos de saúde bucal em unidades de oncologia hospitalar pediátrica.
A proposta tem boa fundamentação teórica e os objetivos estão em sintonia com a metodologias apresentadas.

Considerações sobre os Termos de apresentação obrigatória:
Termos de apresentação assinados e em conformidade.

Recomendações:
nada a declarar

Conclusões ou Pendências e Lista de Inadequações:
nada a declarar

Considerações Finais a critério do CEP:
Certifico que o Comitê de Ética em Pesquisa do Centro de Ciências da Saúde da Universidade Federal da Paraíba – CEP/CCS aprovou a execução do referido projeto de pesquisa. Outrossim, informo que a autorização para posterior publicação fica condicionada à submissão do Relatório Final na Plataforma Brasil, via Notificação, para fins de apreciação e aprovação por este egrégio Comitê.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1519335.pdf	11/03/2020 11:11:12		Aceito
Outros	planilhacomparacao.xlsx	11/03/2020 11:08:51	PAULA MARIA MARACAJÁ BEZERRA	Aceito
Outros	planilhaintervencao.xlsx	11/03/2020 11:07:45	PAULA MARIA MARACAJÁ	Aceito

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Outros	planilhaintervencao.xlsx	11/03/2020 11:07:45	BEZERRA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	solicitacao_dispensa_TCLE_assinada.pdf	11/03/2020 11:06:03	PAULA MARIA MARACAJÁ BEZERRA	Aceito
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Projeto Detalhado / Brochura Investigador	Projeto_de_dissertacao_paulamaracaja.pdf	05/03/2020 17:19:04	Paula Maracajá	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

JOAO PESSOA, 25 de Março de 2020

Assinado por:
Eliane Marques Duarte de Sousa
(Coordenador(a))