การป้องกันการเกิดภาวะเยื่อบุช่องปากอักเสบในผู้ป่วยเด็กที่ได้รับเคมีบำบัด: การทบทวนอย่างเป็นระบบ

Prevention of Oral Mucositis in Pediatric Patients Receiving Chemotherapy: A Systematic Review

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บทคัดย่อ

การทบทวนอย่างเป็นระบบครั้งนี้ มีวัตถุประสงค์เพื่อศึกษาเกี่ยวกับแนวทางการให้การดูแลเพื่อป้องกันการเกิดภาวะเยื่อบุช่องปากอักเสบในเด็ก การศึกษานี้สืบค้นงานวิจัยจากฐานข้อมูลเผยแพร่ในสื่ออิเล็คโทรนิคส์และสื่อสิ่งพิมพ์ คัดเลือกกลุ่มตัวอย่างตามเกณฑ์คัดเข้าและคัดออก ได้ผลงานวิจัยที่เกี่ยวข้องจำนวน 5 เรื่อง ผลการทบทวนอย่างเป็นระบบพบว่า มีแนวทางการป้องกันการเกิดเยื่อบุช่องปากอักเสบจากงานวิจัยโดยการใช้ข้อกำหนดการดูแลสุขภาพช่องปากด้วยตนเอง จำนวน 1 เรื่อง และการดูแลสุขภาพช่องปากโดยการใช้น้ำยาบ้วนปากชนิดแตกต่างกัน จำนวน 4 เรื่อง ในกลุ่มผู้ป่วยเด็กอายุระหว่าง 1 ถึง 17 ปี และผลการวิจัยทั้ง 5 เรื่องรายงานว่าสามารถลดอุบัติการณ์การเกิดภาวะเยื่อบุช่องปากอักเสบได้อย่างมีนัยสำคัญทางสถิติ และมาตรฐานในการป้องกันการเกิดภาวะเยื่อบุช่องปากอักเสบในเด็กที่ได้รับเคมีบำบัดทุกคน สิ่งสำคัญอันดับแรกคือ การดูแลสุขอนามัยช่องปากให้สะอาด จากผลการศึกษาเสนอแนะว่า แนวทางการป้องกันการเกิดภาวะเยื่อบุช่องปากอักเสบควรพิจารณาแนวทางที่มีประสิทธิภาพ มีความเป็นไปได้ สามารถซื้อ/จัดหาได้ง่าย การใช้หลักฐานเชิงประจักษ์เกี่ยวกับการใช้น้ำยาบ้วนปากเพื่อป้องกันการเกิดภาวะเยื่อบุช่องปากอักเสบควรต้องมีการศึกษาเพิ่มเติม และไม่แนะนำให้ใช้ในการป้องกันการเกิดภาวะเยื่อบุช่องปากอักเสบในเด็ก

คำสำคัญ: การป้องกันภาวะเยื่อบุช่องปากอักเสบ, โรคมะเร็งในเด็ก, การรักษาด้วยเคมีบำบัดในเด็ก, การทบทวนอย่างเป็นระบบ

Abstract

This systematic review sets out to investigate and critically appraise and rate the evidence on different nursing care preventative agents used to prevent oral mucositis in children. Systematic literature searches were made in electronic and manual searches, assessed based on the inclusion and exclusion criteria. A total of 5 articles published were included in this study. The results found that the different preventative regimens/agents were: one articles on oral self-care protocols intervention, four articles focus on oral care protocol by using different mouth-wash rinsing. All articles involved children ranging in age from 1 to 17 years and reported statistically significant reduction in the rates of occurrence of oral mucositis. Moreover, a standard first step to preventing mucosal injury is the implementation of good oral hygiene and the use of a standardized oral care protocol for all children undergoing chemotherapy. This systematic review suggests that: Oral care protocols should be considered as efficacious, feasible and affordable mean to prevent oral mucositis in children.

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The evidence on the use of mouthwash to prevent oral mucositis needs further investigation and should not be considered in the prevention of oral mucositis in children.

Keywords: Prevention of oral mucositis, Children with cancer, Pediatric patients receiving chemotherapy, Systematic review

Introduction

Cancer is one of the most fatal of death in pediatrics following infection and trauma. The most common pediatric cancer is leukemia, the second one is neuroblastoma, and the third one is lymphoma. Nowadays, treatment of pediatric cancer is more advance, and most of them be completely cured.[1] Because of the histologic knowledge for through classification, the multidisciplinary clinical trial for comparison between the new regimen and standard regimen has set up "the Risk-adapted therapy" with low-risk patient should be given appropriate, not-too-intensive drug regimen, and high-risk patient should receive the more intensive regimen at the beginning does of treatment.[2] Although pediatric cancer can be completely cured at the moment, 10-25% of patients die from complications of disease and treatment instead of cancer.[3] The most common cause of death in pediatric cancer is opportunistic to infection in patients who have neutropenia from chemotherapy.[4] By the way, chemotherapy agents target rapidly growing cells at a certain time in the cell's developmental cycle and do not discriminate between healthy and cancerous cells in that same developmental cycle.4 The result is that rapidly growing cells, including hair follicles, mucous membranes, and blood cells, will experience the effects of the agent aimed at the cancer cells. Oral mucositis is a distressing toxic effect of systemic chemotherapy with many commonly utilized drugs and of head and neck irradiation in patients with cancer. Due to severe painfulness, oral mucositis interferes with the patient's quality of life and nutrition. It also increases the risk of systemic infections in immune com-promised patients due to disrupted barriers and often is the dose-limiting factor interfering with the intensification of anticancer therapy.[3]

It is defined as the painful inflammation and ulceration of oral mucous membranes. This painful inflammation and ulceration causes discomfort that makes it difficult for affected patients to eat, swallow, speak, or perform oral hygiene measures. These effects in turn might result in weight loss, dehydration, and risk of oral infections. Oral mucositis may also limit the dosages and interfere with the timing of cancer treatment cycles that have to be postponed until the patient becomes well enough to eat and drink and thus cope with further cancer treatments. Oral mucositis also impacts on patients 'quality of life and their mood status. These complications result in extended hospital stay which poses financial and staffing constrains on hospitals and health care systems.

Children and adolescents are more prone to develop oral mucositis with incidence rates ranging between 50% and 54%. Although their risk of developing oral mucositis is higher than that of adults, the mucositis heal more rapidly in a child than in an adult. This phenomenon can be related to the rapid epithelial mitotic rate in the pediatric population. Several systematic reviews and meta-analyses were published on the prevention of oral mucositis. However, these reviews were not specific for the nursing care prevention of oral mucositis in the pediatric population, probably due to the low

incidence of childhood cancer as compared to that of the adult population. Pediatric cancer patients differ from adults in many aspects including compliance, acceptance and response to different preventative agents. They are also unique in their dependence on consenting parents/care givers, thus adding another level of compliance and consenting issues. This systematic review sets out to investigate and critically appraise and rate the evidence on different nursing care preventative agents used to prevent oral mucositis in children.[2]

Materials and methods

A comprehensive search was carried out on the literature. 6 databases were searched including: CU database, CINAHL with full text, Cochrane Library, Google scholar, Ovid MEDLINE, PubMed, The keywords that were used to search the different databases were obtain edusing the PICO (Population, Intervention, Comparator, and Outcome) criteria and using all possible subject headings and synonyms from the databases as shown in Table 1. Search commands were created by joining the different keywords according to the appropriate specifications of each database. In addition to the electronic searches, manual searches were performed on reference lists of the included articles, systematic reviews, and related literature. Relevant articles were included according to the following inclusion criteria: all clinical trials published in English and Thai, clinical trials involving children aged 0–18 years, clinical trials involving a mixture of age groups including children and adults, clinical trials on the prevention of oral mucositis among patients receiving cancer treatments (chemotherapy), and clinical trials on the prevention of oral and gastrointestinal mucositis among patients receiving cancer treatments.

Table 1: Keywords used for searching databases

Population		Intervention	Outcome
Pediatric	Cancer chemotherapy	Prevention	Mucosittis
Children	Chemotherapy	Prevent	Stomatitis
Adolescents			Oral Infection
Boy			Oral inflammation
Girl			Mouth inflammation

Irrelevant articles were excluded at different levels (title, abstractor full article) based on the following exclusion criteria: animal trials, clinical trials that only involved adults, clinical trials on the treatment of mucositis, case studied and case series, clinical guidelines on the prevention of oral mucositis, and letters to the editors and commentaries. Articles were also excluded if the age group of participants was not specified, if there was no distinction in the results between oral and gastrointestinal mucositis, or the trial was published only as an abstract.

Results of the electronic and manual searches were assessed based on the inclusion/ exclusion criteria. After the removal of all duplicates, articles were included or excluded at different levels starting at the level of the title followed by inclusion/ exclusion at the level the abstract and finally at the level of the full article. Each of the included articles

was then critically appraised for validation and quality assessment using a checklist consisting of categories to assess and evaluate the evidence on the efficacy of the preventative agent (Table 2). The outcome measures that were regarded to be of interest, in our systematic review, when assessing the evidence on the prevention of oral mucositis included: rate of occurrence of oral mucositis, severity of oral mucositis, duration of oral mucositis, levels of pain, degree of discomfort, alteration of eating and/or drinking, loss of body weight, alteration of the ability to perform mouth care

Table 2 : Checklist to assess and criticize evidence of efficacy of therapy or prevention

Category description

1. Was the study ethical?
2. Was a strong design used to assess efficacy?
3. Were outcomes (benefits and harms) validly and reliably measured?
4. Were interventions validly and reliably measured?
5. Was the treatment effect large enough to be clinically important?
6. Was the estimate of the treatment effect beyond chance and relatively precise?
7. If the findings were ''no difference'', was the power of the study 80% or better?
8. Was the assignment of patients to treatments randomized?
9. Were all patients who entered the trial properly accounted for and attributed at its conclusion?
10. Was loss to follow-up less <20% and balanced between test and controls?
11. Were patients analyzed in the groups to which they were randomized?
12. Was the study of sufficient duration?
13. Were patients, health workers, and study personnel ''blind'' to treatment?
14. Were the groups similar at the start of the trial?
15. Aside from the experimental intervention, were the groups treated equally?
16. Was care received outside the study identified and controlled for?
17. Were all clinically important outcomes considered?
18. Are the likely benefits of treatment worth the potential harms and costs?

The results of the final critical appraisal process were then tabulated separately for each article with a comprehensive summary of the article, critical appraisal comments, and an evidence rating.

Results

The electronic and manual searches yielded a total of 980 articles. The details of these searches in the 6 different databases are shown in Table 3. The 980 articles were then transferred to the reference management software that removed duplicate articles to reduce the number to 240 articles. These articles were assessed by the inclusion/exclusion criteria at the different levels of exclusion and yielded a total of 5 articles. These 5 articles were critically appraised and tabulated in 5 tables of evidence summarizing and rating each of them separately. The breakdown of the 5 articles that reported the different preventative regimens/agents were: one articles on oral self-care protocols intervention, four articles focus n on oral

care protocol by using different mouth-wash such as chlorhexidine and benzydamine rinsing, All articles involved children ranging in age from 1 to 17 years.

All articles reported statistically significant reduction in the rates of occurrence of oral mucositis

Table 3: Details of databases search results.

Database	Number of Article
CU database	140
CINAHL with full text	46
Cochrane Library	263
Google scholar	347
Ovid MEDLINE	49
PubMed	135
Total	**980**

The four articles that investigated the efficacy of chlorhexidine mouthwash were ranging in their strength of evidence from fair in supporting the use of the mouthwash. Four articles reported significant reduction in the rates of occurrence of oral mucositis among those who used the mouthwash. The four articles support that with fair strength of evidence reported rates of reduction of oral mucositis.

A standard first step to preventing mucosal injury is the implementation of good oral hygiene and the use of a standardized oral care protocol for all children undergoing chemotherapy. A number of oral care protocols have been studied in the literature. Cheng et al[5] reported on the effectiveness of an oral care protocol for the prevention of chemotherapy-induced oral mucositis; the protocol was evaluated over an 8-month period in 42 pediatric cancer patients who ranged in age from 6 to 17 years. The experimental group consisted of 21 children who were instructed in the proper technique of tooth brushing; they were also given a 0.2% chlorhexidine mouth rinse, which was used twice a day, and a 0.9%

saline rinse, which was used in the morning, after each meal, and before going to bed. Another 21 patients made up the control group and did not receive the oral care protocol intervention or information concerning the importance of oral care. If oral lesions developed, these patients were treated with symptomatic measures, including the use of 0.9% sodium chloride solution and benzydamine hydrochloride rinse to control the pain. The results obtained from this study were significant and demonstrated a 38% reduction in the incidence of ulcerative mucositis in the experimental group (p = 0.01).Furthermore, the severity and related pain were considerably reduced in the experimental group throughout the study.

De Brito Costa et al6 evaluated 14 children, whose ages ranged from 2 to 10 years, who were receiving intensive chemotherapy for treatment of acute lymphoblastic leukemia. None of the children had any clinical signs of oral or esophageal candidiasis at the start of the study, and none had any other complications of the oral mucosa before beginning chemotherapy or the study's oral protocol.

The oral protocol was used during the intensification period of the chemotherapy. It began at least 1 day before initiating the chemotherapy and ended 10 days after the end of this period. The average length of treatment was 8 weeks. The treatment group consisted of 7 patients who received a mouth rinse with a non-alcoholic solution of 0.12% chlorhexidine and oral hygiene care, including twice-daily tooth brushing (in the morning and evening) supervised by guardians. The control group followed the same protocol for brushing their teeth but was given a placebo mouth rinse. The results were considered statistically significant. Only 1 child from the treatment group, compared to 5 children in the control group, developed oral mucositis. The oral lesions were less severe and of a shorter duration in the children who received chlorhexidine mouth rinses compared to the control group, although the authors did not give specific values. The authors cited limited numbers of participants as a weakness; the results are nevertheless promising.

Levy-Polack et al7 evaluated a preventive protocol for oral complications associated with acute leukemia. A control group of 60 Caucasian children already undergoing chemotherapy who received only palliative treatment for complications was compared with a treatment group of 36 Caucasian children (ages 1 to 16) with newly diagnosed acute lymphoblastic leukemia receiving a daily mouth care protocol for a 13-month period. The protocol consisted of the following: a mouthwash with sodium bicarbonate and water after every meal; a mouthwash with a nonalcoholic solution of chlorhexidine (0.12%) twice a day; cleaning of mucosa with gauze soaked in iodopovidone 4 times a day prior to the use of nystatin; "swishing and swallowing" with nystatin (500,000 units oral suspension prepared with sorbitol) 4 times a day; and a daily rinse with sodium fluoride 0.05%. Post intervention, the control group showed a 68.2% incidence of poor oral hygiene versus 51.6% in the experimental group (p<0.001), shows that this protocol, while time consuming, may have been useful in limiting the incidence and severity of oral mucositis.

Aunkana Chiamchiraporn8 studies the effect of an oral self-care program on self-care behavior and mucositis of school-age children with cancer receiving chemotherapy. There were 30 Thai children age 6-12 with cancer separate to 15 were controlled group and 15 were experimental group. The experimental were received the oral self-care program included teaching and training self-care skill (Education: meaning, mechanism, symptom, early detect, diet avoidance, Training: oral care skill, self -examination tooth brushing, mouth rinsing, apply lib lubricant). The researcher provides oral self-care instruction and used Smart kid calendar. The result of the study find mean score of oral self-care behavior of children with cancer in the experimental group after program was significant higher than before enroll the program and the severity of oral mucositis in the experimental group was significant lower than in control group.

Discussion

This systematic review intended to shed some light on agents that may be used to prevent oral mucositis in children. In a recent study, health care professionals toward preventing oral mucositis in children receiving cancer treatment were investigated. While parents and health professionals believed similarly that mild oral mucositis is important, health care professionals rated severe oral mucositis as more important than what the parents believed. This latter study highlights the importance of preventing oral mucositis in children. It could also set the scale in favor of agents that could prevent oral mucositis and at the same time do not pose toxicity threats or jeopardize the life expectancy of

children e.g. oral care protocols.

We have included outcome measures that we thought are important in assessing an agent to prevent oral mucositis. The duration of oral mucositis can indicate a delay in the onset and rate of resolution of oral mucositis lesions and thus can be used to represent the efficacy of preventing oral mucositis as well as the efficacy of its treatment. Although the outcome measures that we chose to represent the prevention of oral mucositis were not all reported in the 5 selected articles, most of the articles reported on the rates of occurrence and the severity of oral mucositis. Few of them reported on the levels of pain and alteration to eating and drinking while some of them reported on the alteration to the ability to perform oral hygiene practices.

Most of the articles involved in this review examined the efficacy of preventative agents among patients who were receiving cancer treatments documented to cause oral mucositis. However, the reader should acknowledge the difficulties associated with standardizing all variables to conduct studies among the pediatric cancer population. These variables include many risk factors associated with the development of oral mucositis including genetic predisposition. This genetic predisposition along with other risk factors has not been studied in children due to the low incidence of childhood cancer and due to family sensitivity issues when it comes to clinical trials involving their children. These issues have left researchers and clinicians with more challenges to investigate. In conclusion and despite the limited number of articles on this age group and the drawbacks of the selected articles, oral mucositis in children remains an important topic that require further research to better understand it and reduce its complications.

This systematic review suggests that:

Oral care protocols should be considered as efficacious, feasible and affordable mean to prevent oral mucositis in children because of their strength of evidence that ranged from fair to good in favor of their efficacy.

The evidence on the use of mouthwash to prevent oral mucositis needs further investigation and should not be considered in the prevention of oral mucositis in children. This is because the current evidence is conflicting with some articles in favor of their use and others against their use.

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