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Does honey provide therapeutic relief to patients with chemotherapy induced oral mucositis?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "does honey provide therapeutic relief to patients with chemotherapy induced oral mucositis?"

STUDY DESIGN: Review of one double-blind randomized control trial (RCT), one RCT, and one cohort study.

DATA SOURCES: All articles were published in English and taken from peer-reviewed journals using PubMed. All articles were published between 2012-2019.

OUTCOMES MEASURED: The outcomes measured included decreased severity of oral mucositis measured in one study using the WHO Oral Toxicity Scale and another using WHO-STC (Stomatitis Toxicity Criteria). Another outcome measured was recovery time, which was defined as the number of days from the start of treatment to when complete healing of every ulcer occurred.

RESULTS: The double-blind RCT performed by Raeessi et al. showed a statistically significant difference (p-value<0.001) after treatment with honey when compared to the steroid group. The mean severity of oral mucositis (OM) was 1.43± 0.75 after treatment with the steroid compared to 0.90 ± 0.65 after treatment with honey. The mean difference between the honey and control group was 0.51. Abdulrhman et al. conducted a RCT that showed a statistically significant difference (p-value <0.005) between the mean recovery time (days) of children with OM in the benzocaine group vs. the honey group. For the benzocaine group, the recovery time mean was 6.10±2.47. The honey group recovery time mean was 4.25±1.25. The mean difference between the two groups was 1.85. The cohort study performed by Singh et al. showed a statistically significant reduction (p-value<0.01) in the severity of OM by day 7 between the control group and the experimental honey group. By day 7, 27 (54%) children had Grade 0 OM in the control group, while 46 (92%) children had Grade 0 OM in the honey group. The calculated NNT was 3, the ABI was 0.38, and the RBI was 0.70.

CONCLUSION: All three studies demonstrated that honey provides a statistically significant decrease in severity of OM and recovery time, demonstrating the therapeutic relief honey provides to patients with chemotherapy induced OM.

KEY WORDS: honey, oral mucositis

INTRODUCTION

Oral mucositis (OM) is one of the most common and recurrent side effects of chemotherapy treatment. OM results from breakdown of the oral mucosal lining, leading to ulcer formation. Before ulcer formation occurs, endothelial cells become damaged and inflammatory cytokines and reactive oxygen species are activated at the mucosal level.[1,2] Between 40-80% of chemotherapy patients suffer from OM, which can adversely affect speech and nutrition and result in malnutrition and dehydration.[1,2] Patients who develop OM can also develop infections that require prolonged hospital stays. This increases treatment costs and may require clinicians to modify chemotherapy treatment protocols and doses for their patients.

Unfortunately, this common side effect of chemotherapy is often overlooked by clinical treatment teams who are capable of preventing and treating this condition.[1,2] Studies show that the estimated incremental cost of OM per cycle of chemotherapy is $3,700.[3] While it is unknown how many healthcare visits are associated with this condition each year, one study showed that in a population of cancer patients receiving chemotherapy, the average rate of hospitalization was one admission per year with 40% of admissions identified as being related to a chemotherapy issue.[4]

Often appearing 7-14 days after initiation of chemotherapy, OM results in erythema, edema, an ulceration that creates a burning sensation, or the development of painful ulcers that can impact oral function. OM usually resolves in 2-3 weeks after a chemotherapy infusion.[1,2] OM has a complex pathobiology on how oral mucosa damage occurs as a result of chemotherapy. Risk factors for the development of OM include younger age, poor oral hygiene, and the nutritional status of a patient.[2] Chemotherapy drugs that commonly cause OM include methotrexate, etoposide, cytarabine, fluorouracil, and doxorubicin.[2] Some of the usual methods

used to treat OM include oral hygiene protocols (frequent brushing/flossing), antimicrobial agents (chlorhexidine), local anesthetics (benzocaine), and steroids (betamethasone).[1,2,5,6] More recently oral cryotherapy, where ice chips are used to cool mucous membranes during infusions, is a readily available treatment intervention.[7]

While methods exist to address this condition, few efficacious interventions are available for management of chemotherapy induced OM. There is currently no specific, single standard method to prevent and treat OM.[1] As a result, research has been investigating the impact of honey on OM. Honey, which is produced by honeybees (*Apis mellifera*), has H_2O_2, which is produced by glucose oxidase and attributes to honey's antimicrobial property.[5] Honey can reduce inflammation and accelerate tissue regeneration, which explains its therapeutic use in treating conditions such as gingivitis and periodontal disorders.[5] This paper analyzes one double-blind RCT, one RCT, and one cohort study to evaluate the therapeutic relief honey provides for chemotherapy induced OM.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "does honey provide therapeutic relief to patients with chemotherapy induced oral mucositis?"

METHODS

The population targeted for this review included patients with chemotherapy induced oral mucositis (OM). The intervention being investigated for therapeutic relief of oral mucositis is honey in comparison to benzocaine gel, betamethasone steroid, and analgesic/antiseptic gel (choline salicylate 8.7% w/w + benzalkonium 0.01% w/w + lignocaine HCL 2.0% w/w). The outcomes being measured are decreased severity of oral mucositis and recovery time. All articles were published in English in peer-reviewed journals between 2012-2019 and obtained from PubMed. The articles were selected based on relevance and if they included patient oriented

outcomes. Keywords used to obtain the articles included “honey” and “oral mucositis”. Inclusion criteria were articles published in the last 10 years in English that involved humans. Exclusion criteria included systematic reviews and research published before 2012. A summary of statistics reported includes p-values, NNT, RBI, and ABI. The studies included in this EBM review include a double blind RCT, a RCT, and a cohort study. Table 1 includes demographics and characteristics of the included studies.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion	Exclusion	W/D	Interventions
Raeessi (2014)[5]	Double Blind RCT	75	15-80	Patients 15-80 years old with oral mucositis after chemotherapy	Patients with other systemic disease and/or abnormal laboratory tests	13	Oral Honey Regimen (600 g solution contained 300 g of honey), 3 tsp every 3 hours for 1 week
Abdulrhman (2012)[6]	RCT	90	2-18	Children 2-18 years old with acute lymphoblastic leukemia and chemotherapy-related oral mucositis grade 2 and 3	Patients with coexisting Diabetes Mellitus, presence of neutropenia, presence of severe periodontitis, previous treatment for oral mucositis, administration of antiviral or antifungal therapy	0	Topical Honey, received 0.5 g honey/kg (maximum 15 g) applied to affected oral mucosa 3 times daily until healing or for 10 days
Singh (2019)[1]	Cohort Study	100	<18	Children <18 who developed Grade I and II oral mucositis after chemotherapy	Adults, Children with Diabetes Mellitus	0	Topical Honey 1-2 ml 4 times daily until cure of oral mucositis

OUTCOMES MEASURED

The outcomes measured in this EBM review included decreased severity of oral mucositis measured using the WHO Oral Toxicity Scale and the WHO-STC (Stomatitis Toxicity Criteria), as well as recovery time that was defined as the number of days from the start of treatment to when complete healing of all ulcers occurred.[6] The WHO scales grade OM in the following manner: Grade 0 (none) None, Grade 1 (mild) oral soreness, erythema, Grade 2 (moderate) erythema, ulcers, solid diet tolerated, Grade 3 (severe) oral ulcers, liquid diet only, Grade 4 (life-threatening) oral feeding is impossible, requires parental nutrition.[1,5]

RESULTS

Raeessi et al. conducted a double-blind RCT that compared the effects of oral honey and betamethasone in adults with chemotherapy induced OM. A total of 75 participants (15-80 years old) with chemotherapy induced OM during a period of three years at Baqiyatallah University Hospital in Tehran, Iran were selected for this study between 2012-2013.[5] Individuals were chosen based on specific inclusion and exclusion criteria noted in Table 1. Participants were randomized using an online statistical computing web programming into two groups-one group receiving the steroid betamethasone and another group receiving oral honey.[5] In order to keep consistency between all three studies, this review will not discuss the third comparison intervention measured in this study. The treatments for each group were encoded confidentially and distributed randomly to participants. Participants were instructed to sip and swallow 3 teaspoons of their prescribed treatment and were asked to repeat this process every three hours for one week.[5] There were 13 participants who were lost to follow up or discontinued the intervention, leaving 62 participants left to be analyzed at completion of the study. The losses were equal across each studied group.[5]

Severity of OM was clinically evaluated before treatment and one week after the intervention began. Five physicians categorized participants on the basis of the WHO Oral Toxicity Scale for grading OM. Grading was assigned on a scale of 0-3 (0=no OM, 1=mild, 2=moderate, 3=severe), and was used as the main outcome measurement to compare the effectiveness of the interventions.[5] Table 2 depicts the changes in the mean of OM severity and standard deviation (± STD) before and after treatment for each intervention. A statistically significant difference after treatment was measured as a p-value <0.001 between interventions.[5] For the steroid group, the mean severity of OM was 2.52 ± 0.51 before treatment and 1.43± 0.75 after treatment, with a mean difference of 1.09.[5] For the honey group, the mean severity of OM was 2.50 ±0.51 before treatment and 0.90 ± 0.65 after treatment, with a mean difference of 1.60.[5] The mean difference between the honey and control group was 0.51.[5] This study did not discuss adverse events, safety concerns, or tolerability among its participants.

Table 2. WHO Oral Toxicity Scale Mean± STD Change in Severity of OM Before and After Treatment and Statistical Significance[5]

	Before Treatment (Mean±STD)	After Treatment (Mean± STD)	Mean Change from Baseline (Calculated)	P-value
Steroid Group	2.52± 0.51	1.43± 0.75	1.09	0.001
Honey Group	2.50± 0.51	0.90± 0.65	1.60	
Both groups			0.51	

Abdulrhman et al. conducted a RCT that compared the effects of topical honey and benzocaine gel in children with chemotherapy induced OM. A total of 90 children (2-18 years old) with acute lymphoblastic leukemia (ALL) and chemotherapy induced OM (grade 2 and 3) were selected for this study. Children were recruited from the Hematology-Oncology Unit of Children's Hospital of Ain Shams University in Egypt from 2010-2011.[6] Children were chosen

based on the inclusion and exclusion criteria noted in Table 1. Children were admitted to the hospital during the study period to avoid follow-up loss and ensure compliance. Children were randomized into two groups-one group received benzocaine 7.5% gel three times daily and another group received 0.5g honey/kg applied topically to the oral mucosa three times daily until healing occurred or for 10 days, which is usually the maximum healing time frame for OM.[6] In order to keep consistency between all three studies, this review will not discuss the third comparison intervention measured in this study. All children received routine oral care (tooth brushing followed by a saline rinse three times daily) and were followed up daily.[6] Application of both treatments was applied by a resident or nursing staff member under researcher supervision.[6] The outcome measured was recovery time, which was defined as the number of days from the start of treatment to when complete healing of OM occurred.[6] No children were lost to follow up for this study and all topical treatments were tolerated with no gastrointestinal adverse effects or hypersensitivity reaction.[6]

Table 3 depicts the mean recovery time (days) and standard deviation (± STD) for both interventions for children with grade 2 and 3 OM. A statistically significant difference was measured as a p-value <0.005 between interventions.[6] For the benzocaine group, the recovery time mean was 6.10±2.47. The honey group had a recovery time mean of 4.25±1.25. The mean difference between the two groups was 1.85.[6]

Table 3. Recovery Time Mean± STD in Children with Chemotherapy Induced OM and Statistical Significance[6]

	Recovery time (days) Mean ± STD	Mean difference (calculated)	P-value
Benzocaine Group	6.10±2.47		0.005
Honey Group	4.25±1.25		
Both Groups		1.85	

Singh et al. was a cohort study that compared topical honey to a routine practice of analgesic and antiseptic gel in children with chemotherapy induced OM. A total of 100 children from the Hematology-Oncology Unit at APC, PGIMER, Chandigarh were selected for this study in India.[1] Children were selected based on specific inclusion and exclusion noted in Table 1. Two groups (experimental and control) with 50 children in each were identified, with the outcome of the study assessed by a blinded observer who assessed the severity of OM using the WHO-STC scale every other day until cure in both groups.[1] The experimental group received topical honey while the control group received a routine practice of analgesic and antiseptic gel. Caregivers of the children were trained through demonstration on how to apply topical honey on OM.[1] Caregivers applied 1-2mL of honey four times daily from the start of the study until cure of OM.[1] The control group only received the analgesic and antiseptic gel. No children were lost to follow up.

This EBM review will focus on the results of day 7. On the 7th day there was a statistically significant reduction in the severity of OM with a measured p-value<0.01.[1] As shown in Table 4, by day 7, 27 (54%) children had Grade 0 OM in the control group, while 46 (92%) children had Grade 0 OM in the experimental honey group. The calculated NNT was 3, which showed a large treatment effect that implies clinical significance. The ABI was 0.38 and the RBI was 0.70 as shown in Table 5. No adverse effects, tolerability, or safety concerns were mentioned in this study.

Table 4. Number of Children with Grade 0 OM on Day 7 in Both Groups and Statistical Significance[1]

Control group n (%)	Experimental group n (%)	P-value
27(54)	46(92)	0.01

Table 5. Calculations for Treatment from Singh et al.[1]

Study	CER	EER	RBI	ABI	NNT
Singh et al.	0.54	0.92	0.70	0.38	3

DISCUSSION

OM can be a debilitating condition for those who are battling cancer. The goal of this systematic review was to determine if honey provided therapeutic relief to patients with chemotherapy induced OM. All three articles reviewed demonstrated a significant improvement of OM with the use of honey. For Raeessi et al. there was a significant difference ($p<0.001$) in the mean severity of OM between the steroid group (2.52 ± 0.51 before treatment and 1.43± 0.75 after treatment) and the honey group (2.50 ±0.51 before treatment and 0.90 ± 0.65 after treatment), meaning that honey reduced the severity of OM in adults more than the use of the steroid.[5] The mean change from baseline difference between both groups was 0.51, demonstrating a large treatment effect in favor of honey.

Singh et al. and Abdulrhman et al. both demonstrated the positive impact of honey on OM in children. Abdulrhman et al. demonstrated that there was a statistically significant difference ($p<0.005$) between interventions in their mean recovery time. The mean recovery time for the benzocaine group was 6.10 days, while the honey group had a recovery time mean of 4.25 days. The mean difference was 1.85 days, which shows that honey produced faster healing of Grade 2 and 3 OM than the use of benzocaine.[6] Singh et al. focused on children with Grade 1 and 2 OM. By day 7, 54% of children in the control group had Grade 0 OM compared to 92% from the experimental honey group, demonstrating a statistical significant difference ($p<0.01$) between both groups in terms of decreased severity of OM with honey providing the most improvement.[1] The treatment effect of honey was large, with NNT=3.

One limitation for Singh et al. was there was no intention-to-treat analysis and the children were not blinded to their treatment or randomized. The study also excluded children with DM.[1] There was also a disparity between the control and experimental group on the 1st day

of enrollment. In the experimental group, 96% of children had grade II OM compared to 78% in the control group, demonstrating that from the first day of enrollment there were children with a more severe grade of OM in the experimental group compared to the control group.[1] Limitations for Abdulrhman et al. and Raeessi et al. also existed due to the exclusion of participants with certain preexisting conditions as noted in Table 1. Abdulrhman et al. also states that the better distribution and amount of honey used in the oral cavity could have contributed to its outcome.[6] The benefit to this intervention is that honey is widely available to all at any local grocery store and is cost-effective. The one drawback to this intervention would be that it would not be recommend to those who have had allergic reactions to honey in the past.

CONCLUSION

All three studies in this EBM review demonstrated that honey provides therapeutic relief to patients with chemotherapy induced OM. Future studies could include incorporating more patients who have concurrent systemic diseases to assess if the impact of honey differs for those who also suffer from additional co-existing medical conditions and enhance generalizability. Future studies can be designed to include stratified random sampling to ensure both groups being studied have a more equal, comparable severity grade of OM at baseline to further strengthen the significance of the results. A more recent study has demonstrated that not only can use of a honey mouthwash decrease OM severity, but it can also reduce the possibility of weight loss and encourage weight gain amongst cancer patients.[8]

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