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The efficacy of honey or olive oil on the severity of oral mucositis and pain compared to placebo (standard care) in children with leukemia receiving intensive chemotherapy: A randomized controlled trial (RCT)

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ABSTRACT

Background: Oral mucositis (OM) is a significant complication occurring in approximately 40 to 80% of patients receiving chemotherapy regimens. Although a wide variety of agents have been tested to prevent OM or reduce its severity, none have provided conclusive evidence.

Objectives: To determine the efficacy of honey or olive oil on the severity and OM pain in children with leukemia and suffering from OM compared to placebo (standard care) and, to assess which of the two interventions is more beneficial.

Methods: A single blind randomized controlled study (RCT) was used to evaluate the effect of Manuka honey or olive oil, in the treatment of chemotherapy-related OM in 42 children with leukemia. The *primary outcome* was the severity of mucositis, using the World Health Organization (WHO) scale and the *secondary outcome* was the pain assessed using the Visual analogue scale (VAS).

Results: Children who received the honey had less severe OM (assessed on the (WHO) scale), $p = 0.00$ and less pain (assessed on the VAS scale), $p = 0.00$, compared to the control group. Children who received the olive oil had less pain than the control group, $p = 0.00$, although not lower than the honey group.

Conclusion: Manuka honey or olive oil can be used as alternative therapies by nurses to children with leukemia and suffering from OM, especially in low and middle-income countries where more expensive therapies may not be available or economical.

Practice implications: Pediatric nurses may recommend Manuka honey to treat OM in children with leukemia as it is safe and inexpensive compared to other treatment modalities.

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Introduction

Oral mucositis (OM), is an inflammatory condition of the oral and oropharyngeal mucosa that occurs in the majority of patients on chemotherapy and/or radiotherapy (Lalla et al., 2014; Münstedt et al., 2019). It can be mild or severe, however in severe OM, patients present with deep ulcerations and severe pain, which requires opioid analgesics.

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Due to the severe pain, nutritional intake is compromised leading to weight loss, systemic infectious and decreased quality of life (Kusiak et al., 2020). Severe OM may also lead to reductions or interruptions in chemotherapy which increases length of stay and may negatively affect survival (Curra et al., 2018; Kusiak et al., 2020).

The incidence of OM varies depending on the type of cancer and how it is treated. For example, it affects 20–40% of patients receiving conventional chemotherapy and close to 80% of patients undergoing hematopoietic stem cell transplantation and receiving high doses of chemotherapy (Miranzadeh et al., 2015; Lalla et al., 2014; Sant Ana et al., 2020). Furthermore, OM is affected by several risk factors, such

as age, malnutrition, gender, pre-existing medical conditions, genetic and ethnic differences, poor dental health, and mucosal trauma (Al-Ansari et al., 2015; Peterson et al., 2015).

Although many treatment options are available to prevent and treat OM, none of them can completely prevent or adequately treat mucositis (Münstedt et al., 2019; Pulito et al., 2020). A recent systematic review of 1197 publications by the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) (Elad et al., 2020) recommended 24 evidence-based guidelines for treating OM. However, the authors of this review suggested that there are many clinical settings and geographic areas where there may be no recommended intervention. Also, the results of this review have shown that further research is required to document the benefits and risks expected from using different treatment methods.

Interventions that have been evaluated with the aim of reducing the severity of OM include, but are not limited to: oral hygiene care with mouth rinses and antimicrobial agents, sodium bicarbonate rinses, chlorhexidine rinses, the use of anti-inflammatory drugs, topical and systemic analgesics, topical antioxidants; mucosal-coating agents; ice chips, cryotherapy, herbal compounds, saliva stimulants/inhibitors, probiotics, and honey (Elad et al., 2020; Peterson et al., 2015; Yarom et al., 2020).

The purpose of this study was to assess the benefits of Manuka honey or olive oil in children with leukemia, receiving chemotherapy and suffering from OM. Studies to date have not provided conclusive evidence for the benefits of Manuka honey or olive oil in the prevention and treatment of mucositis in children. The primary objective of this study was to assess the efficacy of Manuka honey or olive oil compared to placebo (standard care) on the severity of OM in children and to determine which of the two interventions was more beneficial. The secondary objective was to assess the efficacy of Manuka honey or olive oil compared to placebo (standard care) on the pain from OM in children and to determine which of the two interventions was more beneficial in decreasing pain.

Honey is one of the oldest known natural remedies regarded as a health-giving substance (Abdulrhman et al., 2012; Singh & Singh, 2020). Its medical use is recorded from around 3000 BCE onward and is addressed as a curative substance in the holy Bible. According to some studies, honey has antibacterial properties as well as antioxidants that can increase cytokine release which can cure wounds and ulcers (Maiti et al., 2012; Singh & Singh, 2020). A recent systematic review by Yarom et al. (2020) of 49 studies including 12 RCTs, concluded that honey used as a topical application or combined with systemic administration is beneficial in preventing the incidence, or limiting the progression of OM (Yarom et al., 2020). The main limitation mentioned by Yarom et al. (2020) is that the source of the honey varied between these studies. Four intervention studies were found that used local honey to treat OM in children with cancer. These studies were conducted in Egypt (Abdulrhman et al., 2012), in Saudi Arabia (Al Jaouni et al., 2017), in Turkey (Kobyta Bulut & Güdücü Tüfekci, 2016) and in India. (Singh et al., 2019). All four studies reported the beneficial effect of the local honey in reducing pain and limiting the progression of OM. While the above mentioned studies used local honey, we used Manuka honey imported from New Zealand that has the registered trade mark Unique Manuka Factor (UMF) which is a guarantee that the honey has the special antibacterial activity and is manufactured in accordance with rigorous quality standards. <https://manukahoney.co.uk/info/faqs.html>.

Manuka pollen is collected by honey bees from the manuka tree (*Leptospermum scoparium*) and has potent antibacterial effects attributed to the phytochemical component methylglyoxal. It grows abundantly throughout New Zealand and has been a part of traditional medicine since the earliest times. It has been used by the indigenous populations of New Zealand and Australia as topical preparations for wounds, cuts, sores and skin diseases and as inhalations for colds and (Bucekova et al., 2019; Hawley et al., 2014; Mathew et al., 2020).

Two studies using Manuka honey in adults found that it was effective in reducing plaque and gingivitis (English et al., 2004) and in

delaying the deployment of OM (Maddocks-Jennings et al., 2009). In contrast, four studies (Bardy et al., 2012; Fogh et al., 2017; Hawley et al., 2014; Parsons et al., 2012) studying the topical application of Manuka honey did not show positive effects on OM. Yarom and colleagues (2019) argue that "it is unclear if a combined topical and systemic application of Manuka honey will be effective in preventing OM" (p. 2468). Only three studies in the past decade used Manuka honey in children (Elsass, 2017; Rupesh et al., 2014; Singhal et al., 2018). In a randomized clinical trial with 135 children, Singhal et al. (2018) concluded that mouthwashes using manuka honey, raw honey or chlorhexidine were all effective in reducing oral plaque and gingivitis. Rupesh et al. (2014) found that children who used manuka honey had less salivary levels of mutans of streptococci. Elsass (2017) used manuka honey on 10 pediatric oncology patients between the ages of 9 months and 17 years and noted that children who used the honey paste had healing of the OM within 3 days.

Olive oil is derived from the fruit of the olive tree (*Olea europaea*), which grows in the east Mediterranean region and is one of the earliest botanicals used by mankind. The unique molecule that provides olive oil with its health benefits is "oleuropein" which is produced abundantly in the leaves as well as in the olive fruit itself (Abdulrhman et al., 2012). Three studies were found in the literature that used olive oil or olive oil products for treating OM (Abdulrhman et al., 2012; Ahmed et al., 2013; Alkhouli et al., 2021). One study in Egypt (Abdulrhman et al., 2012) noted that olive oil reduced the severity of OM in 90 children with ALL compared to the control group. However, in this latter study olive oil was mixed with honey and beeswax precluding its sole efficacy. Another study in Iraq assessed the benefits of olive leaf extract in 54 adults and children undergoing cancer treatment (Ahmed et al., 2013). Although the authors do not provide the number so children or adults in this study, they did report that the application of topical olive leaf extract was effective in treating OM and in decreasing pain compared to the benzydamine HCl and placebo groups. A third RCT in Syria (Alkhouli et al., 2021) with 36 children with acute lymphoblastic leukemia aged between 6 and 9 years and suffering from grade 3 or 4 oral mucositis, were randomly divided into three groups. The results indicated that both *Aloe Vera* and olive oil applied topically resulted in a significant decrease in OM grades compared to the standard sodium bicarbonate (Alkhouli et al., 2021).

Although, the benefits of both honey and olive oil are in general promising, the data are limited with insufficient evidence to recommend a 'magic bullet' for oncology nurses. In addition, there is a need for well-designed trials to arrive at a consensus for the benefits and harms of natural products in reducing OM. No study to date compared the benefits of olive oil or Manuka honey when swallowed in children with leukemia and suffering from OM. Olive oil in particular grows abundantly in the Mediterranean region, is used in the majority of Mediterranean dishes, and is relatively inexpensive. Thus, the use of honey and olive oil in this study was expected to be easy.

The hypotheses were as follows:

- 1) Children who receive honey (group 1) or olive oil (group 2) will have less severe OM assessed by the World Health Organization assessment scale (WHO) scale compared to the control group (*the primary outcome*)
- 2) Children who receive Manuka honey (group 1) or olive oil (group 2) will have less pain assessed by the Visual analogue 10 cm scale (VAS) than the control group (*pain is the secondary outcome*).

Materials and methods

Design

This was a single blinded randomized controlled clinical trial phase II (RCT) according to the CONSORT statement with three

parallel-groups conducted on 46 children with leukemia receiving high dose chemotherapy.

Setting

Participants were recruited from two university hospitals in the Middle East. Data were collected from July 2017 to December 2020.

Sample

Based on a significant difference between honey and placebo in a previous study (Maddocks-Jennings et al., 2009), a power of 80%, significance level of <0.05 and an attrition rate of 5%, the sample size was calculated to be 20 in each group. The inclusion criteria were based on previous similar studies (eg. Abdulrhman et al., 2012; Al Jaouni et al., 2017; Kobya Bulut & Gdc Tfekci, 2016). The following were the inclusion criteria:

1. Children with Acute Lymphocytic Leukemia (ALL) receiving intensive (high dose) chemotherapy treatment such as myeloablative, doxorubicin or methotrexate during induction, consolidation and re-induction therapy.
2. Children between the ages of 5–17 years
3. Absence of any home remedy for mucositis
4. Children with grades 1–4 OM based on the WHO grading system.

Children were excluded if, they had advanced or severe periodontitis (patients with periodontal pockets of 6 mm or more) if they had a

cognitive disability which may not enable them to assess their pain, and if they had a history of allergy to honey or olive oil. A summary of recruitment and interventions in this trial are shown in Fig. 1. Although we aimed at having 20 children in each group, we reached significance with 42 children.

Ethical considerations

Either parent signed a consent form while children signed an assent form. The study was approved by the IRB of the university (NU04) and registered in clinicaltrials.gov (NCT03399331). The IRB committee recommended the use of Manuka oil compared to the standard honey used locally in order to prevent possible botulism in immunocompromised children.

Procedure

Potential subjects were identified through reviewing daily census in the units. Participants were screened for eligibility and were excluded if they have any condition that may affect the efficacy of treatment as listed in the exclusion criteria. After approval from their attending physician, and if interested in participating, parents and children were approached directly by one of the investigators in this study during their hospital stay. The investigator(s) explained the study, answered all their questions and concerns and informed them about the study benefits/potential risks. If either parent approved to participate in the study, he/she signed an informed consent and children older than 7

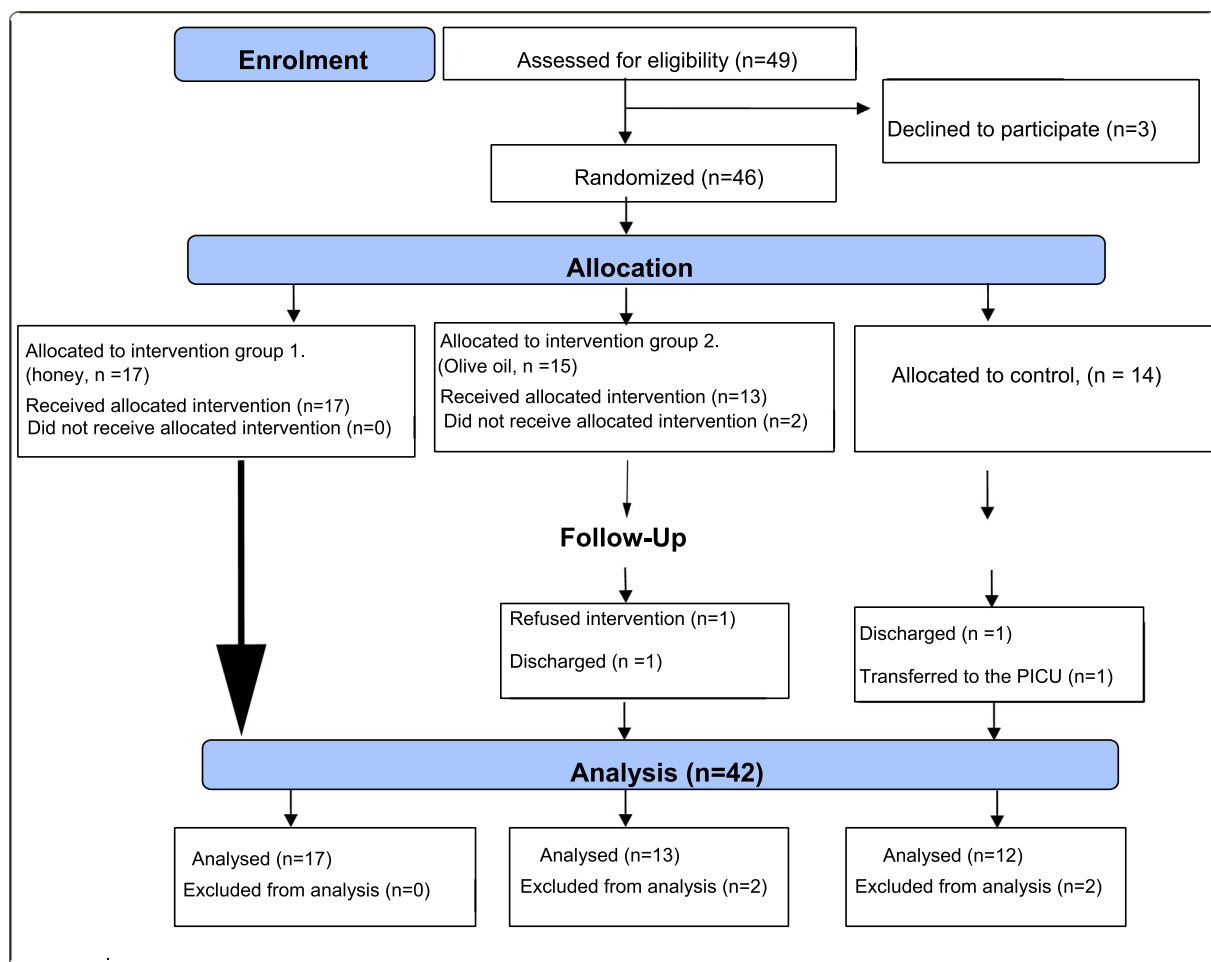


Fig. 1. Flow diagram of the study: recruitment and final analysis of participants.

children signed an assent form. Children were randomly assigned to 1 of 3 groups, using a paper list-generated random assignment sequence by a statistician not involved in the trial. The numbers for each group assignment were placed in an opaque envelope which was to be opened when parents and their children signed the consent and assent forms. Based on group assignment, participants received a different compound applied to the oral mucosa 3 times daily by their assigned nurse until healing, or for 7 days, whichever comes first. All children were treated based on the standard St. Jude protocol for leukemia.

Group 1 received 2.5 cc of Manuka honey imported from New Zealand which is certified and. For every participant in the study, the honey was drawn in syringes and kept in a dark cool place.

Group 2 received 2.5 cc of extra virgin olive oil directly from a local distributor in south Lebanon. The olive oil is made by pressing the olives in the old traditional methods that preserve most of the biological benefits of the olives. It was drawn in syringes for every participant and stored in a dark cool place.

Group 3 served as control, which at our institution is 5 cc of 3% sodium bicarbonate and 5 cc Rinsidin. Children in groups 1 and 2 were instructed to slowly swish the honey or olive oil in their mouths for one minute then swallow it 3 times a day. This was in order for the honey or olive oil to contact the oral mucosa and the pharyngeal mucosa. For group 3, children were instructed to swish the mixture then spit it out 3 times a day. The attending physician wrote the order for the different solution in each medical record and the nurse caring for the child observed the child taking the solution and documented it on the flowsheet. Routine oral care was performed for all children in the three groups and consisted of tooth brushing using a soft toothbrush followed by oral normal saline rinse 3 times daily. At the time of enrollment, all patients had the following recorded:

- (1) Pain assessment by the nurses.
- (2) Physical examination with oral and dental assessment (normal/abnormal)
- (3) Grading of oral mucositis using the World Health Organization Mucositis Assessment Index (WHO) scale.
- (4) Results of their blood analysis found in their medical records (ANC levels).
- (5) Use of antibiotics (yes/ no).
- (6) Risk category of risk of leukemia.
- (7) Height and weight (BMI).

Each participant was assessed daily for signs of healing or progression to a more severe grade of mucositis. When a participant deteriorated, or was transferred to the Intensive Care Unit, due to a worsening medical condition, the treatment was interrupted upon discretion of the attending physician.

Outcomes

The primary outcome was the severity of OM measured by the severity of the OM from the day the first treatment began until healing or day 7 assessed by four trained nurses on a daily basis and who are blinded to the study group using the scale designed by the World Health Organization. The WHO scale assesses OM development, and recovery. Scale measurements are: 0 indicated (no mucositis), 1 slight degree of mucositis, 2 moderate degree of mucositis, 3–4 (severe mucositis). The WHO scale is widely used for cancer patients to assess the degree of OM (Ahmed et al., 2013; Kobya Bulut & Gdc Tfekci, 2016; Peterson et al., 2015). The WHO scale is based upon the ability to eat and drink combined with objective signs of mucositis, namely erythema and ulceration which was recorded daily by visualization of the oral cavity. Although the WHO scale is routinely used in most of our hospitals, the Co-Principal investigator [Co-PI] (RS) established inter-rater reliability with the four nurses before the study began by assessing patients on

the WHO scale. Each nurse conducted the assessment and compared her/his results with the PI, until a reliability of $r \geq 0.80$ was achieved.

The secondary outcome was pain assessed as per the institution's policy using the Visual analogue 10 cm scale (VAS). A score of 1 on the VAS indicates no mouth or throat pain and 10 indicates the most severe mouth or throat pain. The construct, convergent and predictive validity of the VAS has been widely published (Wewes & Lowe, 1990) and has been used in several studies and countries worldwide (Tahmasebi et al., 2009; Erdogan & Aytekin Ozdemir 2021).

Pain scores of the OM were conducted twice a daily for study purposes by nurses blinded to group assignment and which was documented in the patient charts twice per day at 8 am and at 8 pm (even in the absence of pain).

Statistical analysis

The characteristics of the three subject groups were described using means and standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables. Baseline differences between the two groups were tested using ANOVA for continuous data, and the Chi-square for categorical data. The three groups were compared based on the initial treatment assignment and not on the treatment eventually received. ANOVA tests were used to find the association between group assignment and the pain scores on the VAS scale as well as the association between group assignment and the severity of OM on the WHO scale. This was followed by post hoc Tukey-Kramer tests, to assess which of the three treatment was the most effective (McDonald, 2014). For ease of analysis, days 1, 3 and 7 were compared. Data were analyzed on 42 children (23 males and 19 females) out of the 46 randomized ones, as two children were discharged three days after being in the study and could not be followed up, one refused to take the olive and was dropped from the study and one child was transferred to the pediatric intensive care unit (PICU), two days after the treatment was initiated.

Results

On enrollment, there were no significant differences between groups in terms of age, gender, BMI, Pain level, blood values, OM grading, severity of leukemia and antibiotics received. Table 1 provides the characteristics of children in each group. Honey was well accepted by all children in group 1 without any complaint while children in group 2 did not like the taste of olive oil. None of the children, developed any gastrointestinal adverse effects or an allergic reaction as a result of swallowing the compound.

For hypothesis one or the primary outcome, at day 7 children who received honey (group 1) or olive oil (group 2) had less severe OM, based on the WHO scale, compared to the control group on, $F = 5.18$, $p = 0.01$. The result of the Tukey post hoc test indicated that group 1 (honey group) was significantly lower than group 3 (control group), $p = 0.00$, and group 2 (olive oil) was significantly lower than group 3 (the control group), $p = 0.00$. Table 2 shows the results for days 1, 3 and 7.

For hypotheses two or the secondary objective, at day 3 children who received the honey (group) or the olive oil (group 2) had less pain than the control group, $F = 7.22$, $p = 0.002$. The results of the Tukey post hoc analysis showed that the honey group had significantly least pain, $p = 0.002$ than group 3 (the control group). At day 7 there was a significant difference between groups $F = 14.18$, $p = 0.00$. The results of the Tukey test indicated that group 1 (the honey group) had less pain than group 3 (the control group), $p = 0.00$ and that group 2 (the olive oil group) had less pain than group 3 (the control group), $p = 0.00$. Table 2 shows the results on days 1, 3 and 7.

Table 1
Characteristics of participants in the three groups.

Characteristics	Intervention group 1 Honey (N = 17)	Intervention group 2 Olive oil (N = 13)	Control group N = 12	Test result and p value
Gender (Male)	9 (53%)	8 (62%)	4 (33%)	$\chi^2 = 2.08, p = NS$
Age	10.89 ± 4.10	9.63 ± 4.17	9.03 ± 3.98	$F = 0.80, p = NS$
BMI	19.24 ± 6.36	18.78 ± 8.09	20.43 ± 10.04	$F = 0.14, p = NS$
Length of stay before allocation treatment	13.41 ± 9.65	15.57 ± 9.12	13.30 ± 8.95	$F = 0.16, p = NS$
Dental assessment (normal)	8 (47%)	9 (69%)	7 (58%)	$\chi^2 = 2.26, p = NS$
Category of Leukemia				
Stand risk	6 (35%)	4 (31%)	5 (42%)	$\chi^2 = 0.32, p = NS$
High risk	5 (29%)	5 (39%)	4 (33%)	$\chi^2 = 0.27, p = NS$
Remission	4 (24%)	2 (15%)	2 (17%)	$\chi^2 = 0.83, p = NS$
Relapse	2 (12%)	2 (15%)	1 (8%)	$\chi^2 = 0.86, p = NS$
Intensity of pain before allocation treatment	4.35 ± 2.44	5.71 ± 3.98	5.08 ± 2.87	$F = 0.73, p = NS$
WHO scale before allocation treatment	1.85 ± 1.14	2.32 ± 1.87	1.79 ± 1.24	$F = 0.69, p = NS$
Absolute neutrophil count (/mm ³)	1599.37 ± 2090.86	1233.14 ± 3030.77	1902.78 ± 2936.98	$F = 0.19, p = NS$

NS = non-significant.

Discussion

Discussion, limitations, conclusion, I still do not see practice implications in the discussion section

Because OM is an unwanted outcome of cancer chemotherapy resulting in pain, and inability to eat or drink in children, we conducted this RCT to assess the benefits of Manuka honey or olive oil in comparison to the standard treatment of 5 cc of 3% sodium bicarbonate and 5 cc Rinsidin. The results reveal that both Manuka honey and olive oil were superior to the standard treatment albeit children did not like the taste of olive oil. In contrast to previous studies, which assessed the benefits of Manuka honey or olive oil, in our study children were instructed to swish the solution in their mouth then swallow it allowing for increased contact with the oral mucosa and helping in the healing of the oral cavity lesions, and any mucosal inflammation in the oropharynx, and esophagus. This method may have been responsible for the positive results obtained. Of note is the fact that the children tolerated the Manuka honey probably due to the small amount (2.5 cc) they received which is unlike a previous study where the author indicated that patients did not tolerate the taste and texture of the product (Bardy et al., 2012). We found that Manuka honey was superior to both olive oil and the standard treatment. Our results are in contrast to four earlier studies, which showed little benefit to using Manuka honey with adults, receiving radiation therapy or chemotherapy (Bardy et al., 2012; Fogh et al., 2017; Hawley et al., 2014; Parsons et al., 2012). It is worth noting that in these four studies, the Manuka honey was either irradiated to sterilize it from known pathogens (Fogh et al., 2017; Hawley et al., 2014), was prepared specifically for the study (Bardy et al., 2012), or the study had a very small sample size (Parsons et al., 2012). No studies have been conducted in children suffering from OM and treated with

Table 2
Differences between the three groups in terms of OM grade and pain level.

Variable	Honey group (1) Mean/SD	Olive oil group (2) Mean/SD	Control group Mean/SD	Fvalue/p level
OM grade				
Day 1	2.39 ± 1.53	2.13 ± 1.44	3.56 ± 2.71	1.98/0.16
Day 3	2.55 ± 0.93	3.00 ± 1.22	2.75 ± 1.03	0.67/0.52
Day 7	1.00 ± 0.63	1.47 ± 0.42	2.50 ± 0.71	5.81/0.019*
Pain				
Day 1	3.02 ± 1.34	3.56 ± 2.14	3.09 ± 2.33	0.32/0.72
Day 3	2.30 ± 1.89	3.80 ± 1.93	4.54 ± 0.70	7.22/0.002**
Day 7	1.19 ± 1.33	2.13 ± 1.23	3.75 ± 0.1.70	14.18/0.00***

* Group 1 vs Group 3: Diff = 1.16, 95% CI = 0.46 to 1.85, p = 0.00, Group 2 vs Group 3: Diff = 1.03, 95% CI = 0.29 to 1.76, p = 0.00.

** Group 1 vs Group 3: Diff = 2.24, 95% CI = 0.77 to 3.70, p = 0.0018.

*** Group 1 vs Group 3: Diff = 2.56, 95% CI = 1.38 to 3.73, p = 0.00, Group 2 vs Group 3: Diff = 1.62, 95% CI = 0.37 to 2.86, p = 0.00.

Manuka honey imported from New Zealand, which was not irradiated and was swallowed. It is thus necessary to conduct future studies with large samples to confirm the results of this study.

Although the exact mechanism of action of “honey” is not well established, osmolality, acidity, and the production of hydrogen peroxide have been proposed to be the main factors. Manuka honey specifically has natural antimicrobial, immuno-stimulant and wound healing properties due to a number of ingredients it contains mostly methylglyoxal (MGO) which is found in high concentrations and is a potent antimicrobial agent as compared to other honeys (Frydman et al., 2020).

Despite the fact that olive oil is a common household ingredient in the Middle East and used daily in cooking and in salads, children did not like the taste of it. The benefits of olive oil in helping heal OM is supported by earlier studies that have found that olive oil may have anti-inflammatory properties, and a substantial role in decreasing mucosal injury (Alkhouli et al., 2021; Dağdelen, 2016; Mahendran et al., 2018). Three previous studies by Abdurhman et al. (2012), Alkhouli et al. (2021) and Ahmed et al. (2013) reported that olive oil was effective in treating OM in children with leukemia albeit, the olive oil was applied topically. Thus, the benefits of olive oil applied topically or systemically is worth further research especially that the former mentioned studies did not assess pain.

Practice implications

Pediatric nurses working with children with cancer may recommend Manuka honey to treat OM in children with leukemia as it is safe and children liked its taste compared to other treatment modalities. While we used Manuka honey in this study which was imported from New Zealand at 99\$ per 100 cc, local honey which costs much less can be used and has been tested in studies in developing countries and found to be safe (Abdurhman et al., 2012; Al Jaouni et al., 2017; Singh et al., 2019). Local honey or olive oil are especially proposed in developing countries where the cost of alternative medications such as sodium bicarbonate and Rinsidin at a cost of around 30\$ per 100 cc, are either not available or expensive.

Limitations

Although this is the first study to report the benefits of Manuka honey or olive oil on OM in children with leukemia, there are limitations worth noting. First, the sample size was small especially in the olive oil group, which may have affected the results indicating the need for a larger controlled trial to confirm the effect of honey or olive oil on pain and the severity of OM. Second, the nurses taking care of the children and the treating physicians were not blinded to the study arm, which may have affected their decisions to report pain severity or to prescribe opioids. Finally, the Manuka oil used was imported from

New Zealand which makes it difficult for daily clinical use, local honey as documented in several previous studies could be more practical to use and less expensive.

Conclusion

Oral mucositis may be successfully treated by Manuka honey or olive oil. Albeit, children did not like the taste of olive oil. Compared to standard treatment, honey is economical, well tolerated by children and can be used as an alternative medicine especially in low and middle-income countries. Further RCTs are warranted to provide conclusive evidence to the efficacy of both Manuka honey and olive oil to treat OM in children receiving chemotherapy for leukemia.

CRediT authorship contribution statement

Lina Kurdahi Badr: Conceptualization. **Rebecca El Asmar:** Data curation, Supervision, Project administration. **Sarah Hakim:** Investigation. **Rima Saad:** Investigation, Supervision, Visualization. **Roni Merhi:** Investigation. **Ammar Zahreddine:** Investigation. **Samar Muwakkit:** Resources.

Conflict of interest

The authors of this study certify that they have no affiliations with, or involvement in, any organization or entity with any financial interest or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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