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Global Health Journal Club:
Is honey effective as a treatment for chemotherapy induced mucositis in paediatric oncology patients?

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Scenario

You are currently working at a large paediatric oncology centre in Tanzania. You have noticed that treatment has had to be delayed in several patients with severe mucositis; these patients have also experienced significant pain with a decrease in intake of oral nutrition and fluids. You have heard that honey has been trialled to treat mucositis and you therefore wonder whether this would be useful for your patients without a compromise in safety.

What's already known?

Oral mucositis (OM) is an inflammatory response of mucosal epithelial cells to the cytotoxic effects of chemotherapy and radiation therapy with the main symptom being severe debilitating oral pain, which may greatly complicate the management of cancer and compromise cure rates (1). Symptoms include soreness, erythema and ulcers. In extreme cases (e.g. WHO stage 4) it will lead to an inability to take fluids and solids orally (2). OM occurs in 20-40% of patients receiving conventional dose cytotoxic chemotherapy (3–5). Multiple factors may influence the extent and severity of OM, including the drug used, dose, route, frequency and patient's individual tolerance (6). The mucosal lesions often resolve within several days and are usually completely healed within two weeks after treatment (7). In severe cases, oral mucositis can lead to malnutrition and local and systemic infections (8).

A number of grading systems have been designed to grade the severity of mucositis, including the Children's International Mucositis Evaluation Scale (ChIMES) (9), National Cancer Institute Common Terminology Criteria (10) and the university of Nebraska Oral Assessment Score (11) and the WHO oral toxicity scale (2). The pediatric specific ChIMES tool was not used in any of the below studies, with the WHO scale being used most frequently.

The Mucositis Prevention Guideline Development Group have developed an international guideline for the prevention of mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation (HSCT). The preventative strategies with moderate evidence from randomised trials include cryotherapy, low level light therapy (LLLT) and keratinocyte growth factor (12). However, these strategies are often not available in resource-poor settings. Once mucositis is established potential treatments include basic oral care (tooth brushing and oral saline rinses etc), analgesia and mucosal coating agents. In resource-poor settings, use of ice chips as cryotherapy may be an option, however much of the evidence for its use comes from adult studies (12). There is also the limiting step of having ice available which in many settings is not feasible due to the lack of resources and lack of regular electrical supply.

Honey is known to have anti-inflammatory, antioxidant, and antimicrobial effects. The main components of honey are glucose and fructose but it also contains acids, proteins, and minerals. The antioxidant power of honey is attributed to its content of polyphenols (1). These properties, along with it's low cost, make honey an attractive potential therapy for oral mucositis.

Structured Clinical Question

In a child with chemotherapy related mucositis [Patient] can honey [Intervention] in addition to standard mouth care [Control] reduce duration and severity of symptoms [Primary outcome] and reduce chemotherapy interruptions [Secondary outcome]?

Optimal study design:
With this question, we are interested to know whether a novel treatment is more effective than standard conservative care alone (i.e. tooth-brushing). Ideally, this would be best studied using a double-blind, randomised controlled trial. However, honey has a distinctive taste and it would therefore be difficult to "blind" patients who were taking it orally. This means that we expect most studies into this intervention to be single blind.

Full search description:
A literature search was performed using eleven databases using the search terms in Table 1. The search was limited to studies in humans, children (0-18 years), and those available in the English language. We carried out the search on 09/08/2016 and looked for all papers published up to this date. This revealed no relevant papers. The "developing country" search string was therefore removed and the searches repeated. Once duplicates were removed a total of 44 papers were found of which four were relevant (see Table 2). We undertook a search of reference lists of the relevant papers and found no further relevant papers.

Insert "Table 1: Search terms" here

Insert “Table 2: Evidence Summary Table” here

Ask a statistician:
Allenidekania (16) described using a "double-blind approach". What is this? A "double-blind" trial refers to a research method where neither the participants nor those assessing them clinically are aware of which arm of the trial they are in. This is relatively straightforward in some trials (e.g. a trial comparing two oral medications where participants can be given either an active or placebo form which look and taste identical), but is more complicated in others (e.g. a trial comparing intravenous versus an oral therapy). In some trials, multiple arms comparing combinations of therapies are used and these can again be fully blinded. We would anticipate that blinding participants to whether they received oral honey (which is known for it's distinctive sweet taste) or chlorhexidine (which can sting and also has a distinctly non-sweet taste) would be difficult if not impossible. In theory, if patients had never experienced either honey or chlorhexidine before, they may be unaware of this, but this is relatively unlikely. However, it is relatively easy to ensure "single-blind" assessment by ensuring that the clinicians/researchers assessing mucositis severity are unaware of which treatment the participants have been assigned to. Although "double-blind" trials are considered the gold standard in research, this is mostly to counter the placebo effect and so long as independent assessors are truly blinded, a good quality scientific study can still be carried out.

Commentary:
Subtleties such as the broad spectrum of pediatric oncological conditions requiring different lengths of treatment and therefore chemotherapy exposure make a universal conclusion on the use of honey for OM challenging. You have found evidence from three RCTs and one non-randomised study combining a total of 229 paediatric patients. Honey was used as both a prophylactic intervention and as a treatment option. These four papers together demonstrate that honey reduces the frequency, duration and stage of mucositis in children receiving chemotherapy. Abdulrhman (1) found that in grade 2 and 3 mucositis, honey improved recovery time by nearly 2 days (6.10 versus 4.25 days) compared to standard care alone. Al Jaouni (14,15) found that children given regular honey had fever episodes of OM and that length of hospitalisation was shorter in the honey group (7 versus 13 days). Kobya Bulut (16) found an even more dramatic improvement in recovery time, although their baseline of 19 days seems unusually long. They also report lower use of other mucositis treatments in the group treated with honey. These studies have all demonstrated positive effects from honey use, however, you do worry about positive-results publication bias as you are concerned that researchers who did not find positive results may have chosen to not submit their findings for publication.

You didn't include infection rates as a secondary outcome in your PICO question, however you note that Al Jaouni (14) reported the rate of candida and bacterial positive blood cultures reduced markedly in patients who were prophylactically given oral honey. However, the culture positive rates in the control group were alarmingly high and may question this result.

None of the included studies made an assessment on the number of treatment interruptions caused by mucositis and therefore you are unable to comment on this outcome of our PICO question.

You work in a Low-income Economy (LIE) and note that this evidence is based on studies from two LMIE and one HIE country. Honey is a low-technology intervention that is widely available and therefore practical application to a new environment should not be difficult. In resource-poor settings where the recommended, high-cost, options for prevention and treatment of mucositis (12) are frequently unavailable, our search shows that honey may be beneficial and did not show any adverse effects.

At the bedside: applying the evidence

1. Honey may be effective for both preventing and treating oral mucositis in paediatric oncology patients in the resource-poor setting [GRADE C]
2. There is no evidence to compare if honey is equally or more effective than established treatments

What next:

1. Larger studies are needed to assess use of honey to prevent mucositis and specifically leading to a reduction in chemotherapy interruptions.
2. A study using ice-chips as cryotherapy in resource-poor settings.

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