Complementary Therapies in Medicine 25 (2016) 98–103

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevierhealth.com/journals/ctim

Effect of honey on febrile neutropenia in children with acute lymphoblastic leukemia: A randomized crossover open-labeled study

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ARTICLE INFO

Article history:
Received 14 March 2015
Received in revised form 27 January 2016
Accepted 29 January 2016
Available online 2 February 2016

Keywords:
Honey
Febrile neutropenia
Leukemia
Chemotherapy

ABSTRACT

Objectives: Febrile neutropenia (FN) is a common adverse effect of chemotherapy. Current management of FN is expensive and may induce side effects. Honey, as a natural honeybee product, has antioxidant, antimicrobial, immunomodulator and anticancer effects. Additionally, honey is not expensive. The aim of this study is to test the effects of a 12-week honey consumption on children with acute lymphoblastic leukemia (ALL) particularly with regard to FN.
Design: A randomized crossover clinical trial. Forty patients of both sexes, aged 2.5–10 years, were randomized into two equal groups [intervention to control (I/C) and control to intervention (C/I)].
Setting: Children Hospital of Ain Shams University-Cairo-Egypt. The dietary intervention consisted of honey in a dose of 2.5 g//kg body weight per dose twice weekly for 12 weeks.
Main outcome measure: Febrile neutropenia in terms of frequency and duration of hospital admission.
Results: The intervention resulted in a significant decrease of FN episodes, the number of patients admitted with FN and the duration of hospital stay. Also, honey consumption improved the levels of hemoglobin and did not produce any serious side effect. As a possible effect of honey withdrawal in the I/C group, the Hb%, the absolute neutrophil count and the platelet count decreased.
Conclusion: Honey intervention in a group of children with ALL resulted in positive effects on FN and hematologic parameters. Further studies that include a larger number of patients are recommended to confirm that honey, has beneficial effects, as a complementary agent, in children with ALL.

1. Introduction

Children with acute lymphoblastic leukemia (ALL) are at high risk of sepsis during the neutropenic phase following chemotherapy. In developing countries, sepsis is a major obstacle toward improving survival of affected children.[1] Febrile neutropenia (FN) is defined as fever ≥38.3 °C (101 °F) or ≥38.0 °C (100.4 °F) for ≥1 h; and neutropenia is defined as a neutrophil count <500 cells/mm^3; or <1000 cells/mm^3 with a predicted decrease to <500 cells/mm^3.[2] Despite advances in cancer treatment with chemotherapy and supportive care, FN remains a common complication after chemotherapy.[3] Although FN-related morbidity and mortality have been reduced, the currently available management strategies might induce side effects, including promoting microbial resistance against antibiotics, decreasing the patient's quality of life, and increasing treatment costs.[4,5]

In ALL, the immune defects and the immunosuppressive effects of chemotherapy increase the risk for infections. The chemotherapy not only induces neutropenia, but also results in chemotactic and phagocytic defects.[6,7] Based on the observations that honey, as a natural, inexpensive substance produced by honey bees, has antimicrobial,[8–12] antioxidant,[13–15] immunomodulator[16] and anticancer effects,[17–19] we tried in the present study to test the effects of honey on a group of children with ALL particularly with regard to FN episodes. Furthermore, honey can stimulate monocytes in cell cultures to produce tumor necrosis factor (TNF)-α and interleukin (IL)-1.[20] These inflammatory mediators can stimulate tissues to produce Granulocyte Colony Stimulating Factor (G-CSF) which induces the production of neutrophils in chemotherapy-induced bone marrow suppression.[21]

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http://dx.doi.org/10.1016/j.ctim.2016.01.009
0965-2299/

2. Patients and methods

2.1. Patients

This was a crossover randomized study that took place at the Children Hospital of Ain Shams University-Cairo-Egypt, from March 2011 to August 2013. Patients with ALL were recruited from the Outpatient Hematology-Oncology Clinic of the hospital. All patients >2 years of age with ALL, treated according to the Modified CCG 1991 protocol for standard- risk ALL and on maintenance therapy, were candidates for this study. All patients were receiving trimethoprim/sulfamethoxazole as a prophylactic antibiotic. Patients with diabetes mellitus (DM) and patients who had FN at the time enrollment were excluded from the study.

2.2. Study protocol

A crossover design (two 12-week intervention periods) was used to measure honey effects. The subjects were randomized into either group A (control to intervention [C/I] group) or group B (intervention to control [I/C] group). Participants were randomly assigned following simple randomization procedure (computerized random numbers) to 1 of 2 groups with a 1:1 allocation ratio. Based on the results of the study of Zidan et al.[22] which showed that honey intervention resulted in a decrease in the frequency of severe FN by 40%; a total sample size of 32 patients (16 per group) is required to have a 90% chance of detecting, as significant at the 5% level, a decrease in the frequency of FN by 40% during the intervention period. The subjects in the I/C group B took 2 ml (2.5 g) honey/kg body weight/dose twice weekly during the first 12-week period (period 1), whereas the subjects in the C/I group A did not receive honey as a control in the period 1. All parents were instructed not to give any type of bee honey to their children during the control period. The study was open labeled, and the dose of honey was empirical because there was no identification of a particular dose of honey in earlier clinical trials using honey in various diseases. Furthermore, dose-related toxicity to honey has not been previously reported, except probably for patients with DM. Following period 1, the protocol was exchanged for each group for the following 12-week period (period 2). Because laboratory tests for measurement of honey levels in blood or tissues are not yet available, each patient took the dose of honey under visual supervision of the researcher to ensure adherence. For this reason, the patients were seen in the clinic twice weekly during the intervention periods, whereas during the control periods they were seen once weekly. Each calculated dose of honey was dissolved in water with a ratio of 1:3, respectively, and then ingested by the patient before meal. Dissolving honey in water enhances the anti-microbial properties of honey,[8,9] facilitates swallowing and helps adjusting the dose.

2.3. Honey

The honey used in this study was a raw, unprocessed (not heated or irradiated) clover honey collected from Al Mahala-Gharbia Governorate, Egypt. It was supplied directly from an apiary, and then kept in dark containers at room temperature for use in the study. Physicochemical analysis of the honey was done in the Chemical Analysis Laboratory of Honey Bee Products, Beekeeping Research Center, Plant Protection Research Institute, Agriculture Research Center, Giza, Egypt. This honey had a pH of 3.7; moisture content of 18.8%; electrical conductivity of 0.27 mS/cm; and a carbohydrate content of 78.4 g/100 g, with a fructose to glucose ratio of 1.2:0.8, respectively, and a non-reducing sugar content of 3.4 g/100 g. The Hydroxymethylfurfuraldehyde (HMF) content was 1.6 mg/kg. Values of HMF less than 15 mg/kg indicate fresh honey not exposed to heat.[23] Microscopic examination of samples from honey confirmed the presence of pollen grains, which were mainly of clover (*Trifolium alexandrinum*). The physicochemical characteristics of the honey used in the study are detailed in the Supplementary Table 1.[24]

2.4. Outcome measures

The primary outcome measure was febrile neutropenia in terms of frequency, the number of patients admitted and the duration of hospital stay. The secondary outcome measures were hemoglobin (Hb) level, total leucocytic count (TLC), absolute neutrophil count (ANC) and platelet count (PLT). Blood count was performed for all patients on a weekly basis. All measures were analyzed in participants at baseline (0 week), the end of the 12th week (crossover) and the end of the 24th week (end point).

All patients who developed FN during the study were admitted to the hospital and received an empirical combination of intravenous antibiotic therapy consisting of piperacillin (200 mg/kg/24 h, divided q 6 h) and amikacin (20 mg/kg q 24 h). Chemotherapy dose escalation was done when ANC exceeded 2000/mm^3 for more than 6 weeks.

All study procedures were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975 (as revised in 1983). An informed consent was obtained from at least one parent of each child before enrollment, and the study was approved by the local Ethics Committee of the Pediatric Department of Ain Shams University Hospitals.

2.5. Statistical analysis

The collected data were introduced to a PC using Statistical Package for Social Sciences (SPSS 15.0.1 for Windows; SPSS, Inc., 2001). Variables were expressed as mean (±SD) or median. Student's *t* test was used for normal variables. The paired *t*-test was used to assess the statistical significance of the difference between two means measured twice for the same study group. Independent sample *t*-test was used to assess the statistical significance of the difference between two study group means. The Mann–Whitney *U* and Wilcoxon Signed Ranks tests were used for non-parametric data. Chi-square (χ^2) test was used to measure the association between two qualitative variables. McNemar's test was used for paired nominal data. A value of $P < 0.05$ was considered significant.

3. Results

Fifty five patients were enrolled and assessed for eligibility. Eleven patients were excluded; 7 patients declined to participate, and 4 patients did not meet the inclusion criteria; one patient had DM and 3 had febrile neutropenia at baseline. Forty four eligible patients were thus randomized to either group A (C/I) or group B (I/C). One patient from group A lost follow-up, and 3 patients (one from group A and two from group B) discontinued the intervention because they developed undesirable effects following honey intake. Only 40 patients who completed the study protocol were included in the final statistical analysis (Fig. 1; flow chart). All enrolled patients were of low socioeconomic standard.

Throughout the periods of the study no patient relapsed and no patient required blood transfusion, colony-stimulating factor (CSF) or central venous line.