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Original Article

The effects of honey supplementation on Egyptian children with hepatitis A: A randomized double blinded placebo controlled pilot study

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ABSTRACT

Background/Aim: Based on the observations that honey, as a natural substance, produced by the honeybees, has anti-oxidant, anti-microbial, anti-inflammatory and immune-modulator effects, we tried in this study to test the effects of honey ingestion on children with hepatitis A. **Methods:** This study is a randomized, placebo controlled double-blind study, which included 75 previously healthy children of both sexes, aged 2 to 12 years, who developed hepatitis A. They were randomly assigned to either honey or a placebo group with a ratio of 2:1, respectively. Patients in the honey group ingested 2ml honey/kg twice weekly for four weeks, whereas patients in the placebo group ingested molasses in the same dose and for the same duration as honey. The main outcome measure was the percentage of children, who recovered completely from hepatitis A by the end of the 4th week. **Results:** 92% of children in the honey group vs. 72% in the placebo group showed complete recovery by the end of the 4th week ($p = 0.03$), with a statistical power of 62.1%. However, the positive effects of honey were more evident on the symptoms; appetite, fever and abdominal pain, which showed significant improvement by the end of the 2nd week ($p < 0.001$) with statistical powers of 100%, 98.8% and 93.7%, respectively. **Conclusion:** Honey in the doses prescribed improved the symptoms and sped the recovery of hepatitis A. Honey may thus be recommended as a dietary supplement to children during the course hepatitis A.

KEY WORDS: Honey; Hepatitis A; Liver enzymes; Children; Dietary supplement

INTRODUCTION

The use of honey in treating liver diseases dates since time immemorial. Epidemic jaundice and fulminant hepatitis were described by Hippocrates (460 to 375 BC) in De Morbus Internis. He recommended a special diet of 'melikraton' which is honey and water, which is still an acceptable complementary-alternative medicine for many people [1]. In Ayurvedic medicine, a system of Hindu traditional medicine, honey is one of the main formulations used in treating liver diseases [2].

Honey is a natural substance produced by honeybees. Besides glucose and fructose, the major constituents of honey, honey also contains other bioactive constituents such as phenolic compounds, flavonoids, organic acids, carotenoid-derived compounds, nitric oxide metabolites, ascorbic acid, Maillard reaction products, aromatic compounds, trace elements, vitamins, amino acids and proteins [3-5]. Several *in vitro* and animal studies have shown that honey has hepatoprotective effects [6-10]. In humans, only a few studies have been done to evaluate the effects of honey on hepatitis A, and they showed positive effects [11, 12].

Unlike hepatitis B and C, hepatitis A virus (HAV) does not cause chronic liver disease, but it can lead to fulminant hepatitis, which may be associated with high mortality.

Hepatitis A is highly endemic in Egypt. An Egyptian sentinel surveillance for patients with acute hepatitis done between 2001 and 2004 found that 1684 (40.2%) of 4189 patients with positive serology for viral hepatitis markers had HAV- related acute hepatitis [13].

In this study, the effects of honey ingestion on children suffering from hepatitis were evaluated. Honey was chosen because it is a nutraceutical agent with both nutritional and therapeutic benefits, and hepatitis A was chosen because it usually presents as an uncomplicated acute illness, in which the effects of an intervention can be more easily evaluated over a short time. Further, there is still a controversy about the food plans to be followed during the course of hepatitis A. In Egypt, for example, cane molasses, is commonly prescribed for these patients as a rich source of carbohydrates, whereas the honey, produced by the honey bees, is not commonly prescribed. For this reason, molasses was chosen as a placebo to be compared with honey.

MATERIALS AND METHODS

This study is a randomized, placebo controlled, double-blinded clinical trial, which was conducted at the Children's Hospital of Ain Shams University during the period from November 2013 to October 2015. This hospital is a big referral hospital in Cairo, Egypt. Eligible patients were previously healthy children of both sexes, aged 2 to 12

years, who developed manifestations of acute hepatitis. The exclusion criteria included patients with diabetes mellitus, chronic liver diseases, autoimmune disorders, renal disorders, neurologic diseases, malignancies, or patients who had positive HBsAg or HCV-Ab. Also, patients, who required hospitalization during the acute illness, or developed complications, including the extrahepatic manifestations of hepatitis A, were excluded.

Complete recovery from hepatitis A usually occurs before the end of the 8th week of illness [14]. Assuming the percentage of children, who recovered completely from hepatitis A by the end of the 4th week is 90 and 50% in either the honey or the placebo group, then a total sample size of 50 patients (25 for each group) is required to have a statistical power of 90% (alpha=0. 05).

One hundred thirty eligible patients were recruited from the outpatient clinic during the period from November 2013 to October 2015. All of the patients were subjected to the routine work up of acute hepatitis, including history taking, physical examination and laboratory investigations in the form of serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum gamma gultamyltransferase (GGT), serum bilirubin (total and direct) and assay for Hepatitis A Virus IgM (HAV IgM), HBsAg and HCV-Ab. Only the patients who had positive HAV IgM were candidates for this study; they were randomly assigned following a simple randomization procedure (computerized random numbers) to the honey or the placebo group with a 2:1 allocation ratio.

Each patient in the intervention group (honey group) took oral honey in a dose of 2ml/kg twice weekly for four weeks. The dose of honey was empirical because there is no a scientific basis for identification of a particular dose of honey in earlier clinical trials [15-20]. Also, recommended honey doses are not required for safety purposes [120]. The calculated dose of honey was dissolved in water with a ratio of 1: 3, respectively, and then ingested by the patient before breakfast. Dissolving honey in water enhances its anti-microbial properties [21], facilitates swallowing and helps adjusting the dose. The honey used in this study was a raw, unprocessed (not heated or irradiated) clover honey supplied directly from an apiary located in Al Mahala-Gharbia Governorate, Egypt. The honey was kept in dark containers and at room temperature for use in the study.

In the placebo group, each patient took cane molasses in a dose of 2ml/kg twice weekly. Also, similarly as with honey, each dose of molasses was dissolved in water before being ingested by the patient before breakfast.

Physicochemical analysis of the honey and molasses was done in the Chemical Analysis Laboratory of Honey Bee Products, Beekeeping Research Center, Plant Protection Research Institute, Agriculture Research Center, Giza, Egypt. The 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/100g, with a fructose to glucose ratio of 1.2: 0.8, respectively, and a non-reducing sugar content of 3.4g/100g. The Hydroxymethylfurfuraldehyde (HMF) content was 1.6 mg/kg. Values of HMF less than 15 mg/kg indicate fresh honey not exposed to heat [22]. Microscopic examination of samples from honey confirmed the presence of pollen grains, which were mainly of clover (*Trifolium alexandrinum*). The molasses had a pH of 5.0; moisture content of 21.8%; and carbohydrate content of 53g/100g, with a reducing to a non-reducing sugar ratio of 1:1.8..

Each participant was provided by 4 containers for each two weeks of the 4-weeks intervention period. Each container contained the calculated dose of undiluted honey or molasses; to be dissolved in water just before being ingested before breakfast. We requested the caregivers to return all the containers by the end of the 2nd and 4th week. In our country, we refer the word "honey" to either molasses or bee honey. This study was a double blind trial where both the investigators and the participants did not know the exact type of "honey" used. One investigator was responsible for either group, and was provided by containers labeled "A" containing the bee honey or "B" containing the molasses. The two types of honeys have nearly the same taste, color and consistency. The parents were instructed not to give any drug, including antipyretics and anti-emetics, to their children during the study period. Also, in the honey group, the parents were instructed not to give molasses to their children, whereas in the placebo group, they were instructed not to give bee honey to their children.

The main outcome measure was the percentage of children, who recovered completely from hepatitis A by the end of the 4th week of illness. Complete recovery is defined as the disappearance of all the symptoms and signs of hepatitis A and the return of the levels of serum bilirubin and liver enzymes to their normal levels.

During the study, the symptoms of hepatitis A analyzed were the decreased appetite, vomiting, abdominal pain, dark urine, light colored stool and fever. All these symptoms were assessed by questions with a yes or no response; and we gave sheets to the caregivers of each child to keep a diary of symptoms. The signs of hepatitis A were the jaundice and the sizes of the liver and spleen, which were measured by the abdominal ultrasound [23].

For all the patients the laboratory tests included complete blood count (CBC), ALT, AST, GGT and total and direct serum bilirubin. Measurements of ALT and AST were done by kinetic method according to the International Federation of Clinical Chemistry using Spectrum Diagnostics Liquizyme ALT and AST reagent kits, respectively. The normal levels ALT and AST were <60 and <40 IU/L, respectively. Measurement of GGT was done by kinetic colorometric Szasz method using Spectrum Diagnostics Liquizyme GGT reagent kit. The normal level of GGT was < 30 IU/L. Measurements of total and direct bilirubin levels were done by colorimetric Diazo method using Spectrum Diagnostics bilirubin reagent kit. The normal levels of total and direct bilirubin were <1.4 and <0.4 mg/dl, respectively. All Spectrum kits were supplied

by the Egyptian Company for Biotechnology. In addition, assay of Anti-HAV IgM was done by ELISA using VIDAS HAV IgM kits supplied by Biomerieux.

The data of patients of both groups were analyzed and compared at baseline (0), 2nd week and 4th week (end of the intervention).

All the caregivers were asked to stop the dietary intervention and to seek medical advice in the case the child developed any side effect that might probably be related to the ingestion of honey or molasses such as vomiting, diarrhea, skin rash, or dyspnea.

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). Assent tips from the child participants and permission from their parents were obtained before the research. Also, the study was approved by the local Ethics Committee of the Pediatric Department of Ain Shams University Hospitals.

Statistical analysis

Standard computer program SPSS for Windows, release 13.0 (SPSS Inc, USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD). Comparison of different variables in various groups was done using independent samples t test and Mann Whitney U test for normal and nonparametric variables, respectively. Fridman test was used to compare multiple readings of the same variable at various timings of the study. Chi-square ($\chi 2$) test was used to compare frequency of qualitative variables among the different groups. McNemar test was used to compare frequency of qualitative variables at different timings of therapy. For all tests, a probability (p) less than 0.05 was considered as significant [24]. The post-hoc test was used to calculate the power of the study.

RESULTS

Of the 130 patients enrolled, 87 patients had HAV-IgM positive. A total of 75 patients completed the study protocol and included in the final analysis, whereas 12 patients were not included; 10 patients lost to follow-up and 2 patients required intravenous fluids because of recurrent vomiting (figure 1; Flow chart).

Table 1 shows the baseline characteristics of the patients at baseline, 2nd week and end of the study (4th week).

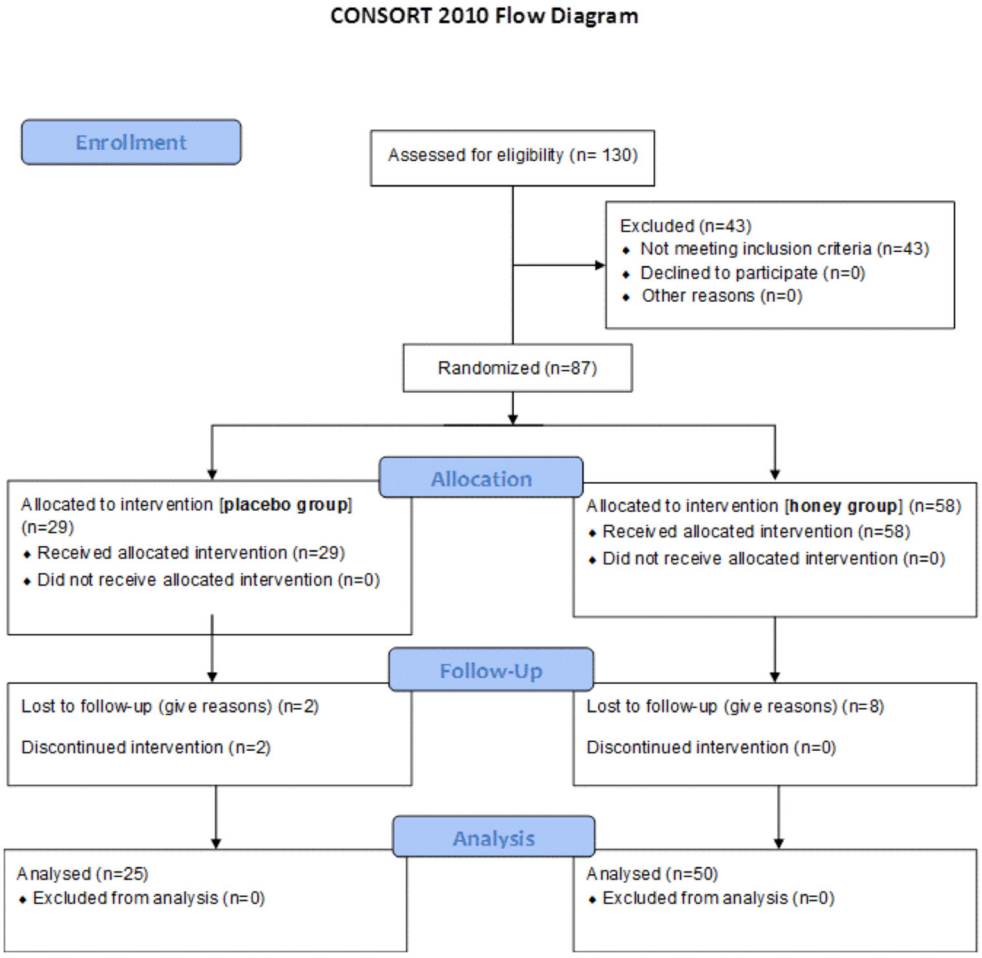

Figure 1. Flow chart

Table 1. Characteristics of patients at baseline (0), 2nd week and 4th week

Characteristic	Honey [50 patients]			Placebo (molasses) [25 patients]		
	0	2nd wk.	4th wk.	0	2nd wk.	4th wk.
Age (year) No. (%)		6.50 (6)			8.00 (6)	
Males%		52.0			44.0	
Females%		48.0			56.0	
Duration of illness before the intervention (days)		7.00 (3)			6.00 (4)	
Decreased appetite	48 (96%)	16 (32%)	2 (4%)	23 (92%)	23 (92%) **	13 (52%) **
Vomiting	48 (96%)	4 (8%)	0	23 (92%)	5 (20%)	0
Abdominal pain	48 (96%)	12 (24%)	0	24 (96%)	18 (72%) **	0
Liver tenderness	46 (92%)	12 (24%)	0	23 (92%)	18 (72%) **	1 (4%)
Dark urine	48 (96%)	6 (12%)	0	23 (92%)	11 (44%)*	1 (4%)
Light colored stool	44 (88%)	0	0	21 (84%)	8%	0
Fever	48 (96%)	4 (8%)	0	24 (96%)	11 (44%) **	0
Jaundice	50 (100%)	30 (60%)	2 (4%)	25 (100%)	22 (88%)*	5 (20%)*
Liver length (cm)	13.02±2.61	12.4±2.45	11.50 (3)	13.8±2.3	13.1±2.1	13.00 (4)
Spleen length (cm)	8.5 (3.5)	8.0 (2.3)	7.50 (2)	10.00 (2)	9.50 (1.8)*	9.00 (3)*
Hepatomegaly	26 (52%)	12 (24%)	2 (4%)	14 (56%)	9 (36%)	4 (16%)
Splenomegaly	20 (40%)	8 (16%)	0	9 (36%)	5 (20%)	1 (4%)
Serum bilirubin (mg/dl)						
Total	6.35±2.27	2.64±1.11	1.07 (.1)	6.38±1.57	3.45±1.12	1.09 (.9)
Direct	3.30 (1.6)	.78±0.44	.11 (.06)	3.10 (1)	1.39±0.40	.40 (.50)**
ALT (U/L)	970 (555)	87 (66)	29 (10)	816 (526)	275 (228)**	36 (36)**
AST (U/L)	891 (510)	232 (323)	37 (7)	778 (500)	297 (363)	39 (27)
GGT (U/L)	120 (200)	77 (60)	18 (12)	134 (113)	89 (55)	30 (35)**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma gultamyltransferase
Values are expressed as median (IQR), percentage or mean ± SD
The characteristics of the patients of both groups were compared at baseline (0), 2nd week and 4th week
*P < 0.05; **P < 0.001

At baseline, both groups were comparable as regards the age, sex, the duration of the illness before the intervention, the frequency of symptoms and signs, and the levels of liver enzymes (ALT, AST and GGT) and the total and direct serum bilirubin.

By the end of the 2nd week, the patients of both groups showed improvement, but the improvement was significantly better in the honey group with regard to appetite, fever, abdominal pain, liver tenderness and ALT levels ($p<0.001$). Also, there was a significant improvement of the jaundice and spleen length ($p<0.05$) in the honey group, as compared with placebo. However, the size of the liver, the serum bilirubin and the levels of AST and GGT did not show significant difference between two groups.

By the end of the 4th week, a more significant improvement was observed in the honey group with regard to appetite, jaundice, spleen length and levels of ALT. Moreover, there was a significant decrease in the levels of direct bilirubin and GGT ($p<0.001$). However, the improvement in the other parameters did not show significant difference between the honey group and placebo.

Complete recovery from hepatitis A is defined as the disappearance of all the symptoms and signs of hepatitis A and the return of the levels of serum bilirubin and liver enzymes to their normal levels. By the end of the 2nd week of illness 4(8%) of the 50 patients of the honey group completely recovered from hepatitis A, whereas all the patients of the placebo group still had manifestations of hepatitis A. This difference was not statically significant. On the other hand, 46 (92%) of the honey group and 18 (72%) of the placebo group showed complete recovery by the end of the 4th week. This difference was statistically significant (Table 2).

Table 2. Number and percent of patients recovered from hepatitis A during the study

Group	End of 2nd week	End of 4th week
Honey (50 patients)	4 (8%)	46 (92%)
Placebo (25 patients)	0	18 (72%)
†P	0.19	0.03

† Chi square test

During the study period, no patient from either the honey or the placebo group developed significant adverse effect as a result of the intervention.

DISCUSSION

The positive effects of honey on hepatitis A were more evident on the symptoms of the disease; anorexia, fever and abdominal pain, which showed significant improvement by the end of the 2nd week of illness. Using the post-hoc test to calculate the power of study; the positive effects of honey on the appetite, fever and abdominal pain had the powers of 100%, 98.8% and 93.7%, respectively. However, the subjective survey used in this study to assess the frequency and severity of symptoms may be considered as a limitation, but clinicians and parents often make decisions based on subjective assessment. In terms of complete recovery, on the other hand, 92% of the honey group vs. 72% of the placebo group showed complete recovery by the end of the 4th week, with a statistical power of only 62.1%, probably because of the small sample size of the study.

Despite this study was done on a relatively benign disorder, the positive effects of honey observed in speeding the recovery from hepatitis A might be of help when a food plan is prescribed for children suffering from hepatitis A.

Previous studies evaluating the effects of honey on hepatitis A are few [111, 112], and it showed positive effects on the duration of anorexia, the liver size and the levels of ALT and serum bilirubin, but the other clinical and laboratory measures of hepatitis A were not assessed as the case in our study.

The combined anti-oxidant [25-27], anti-microbial [21, 25, 28], anti-inflammatory [29-32] and immune modulator [33, 34] effects of honey are possible mechanisms underlying the beneficial effects of honey on hepatitis A. However, the well-known anti-oxidant power of honey might be the main contributing factor because several randomized clinical trials have demonstrated the beneficial effects of antioxidants in liver diseases [35, 36].

In developing countries, like Egypt, hepatitis A is endemic and it usually results in frequent school absences among children who are not routinely vaccinated against hepatitis A. Therefore, recommending honey, as a dietary supplement, during the course of hepatitis A might help speeding the recovery from this illness, and thus reducing the duration of school absence.

As a conclusion, the present study, despite limited by its small sample size, might offer help for children suffering from hepatitis A.

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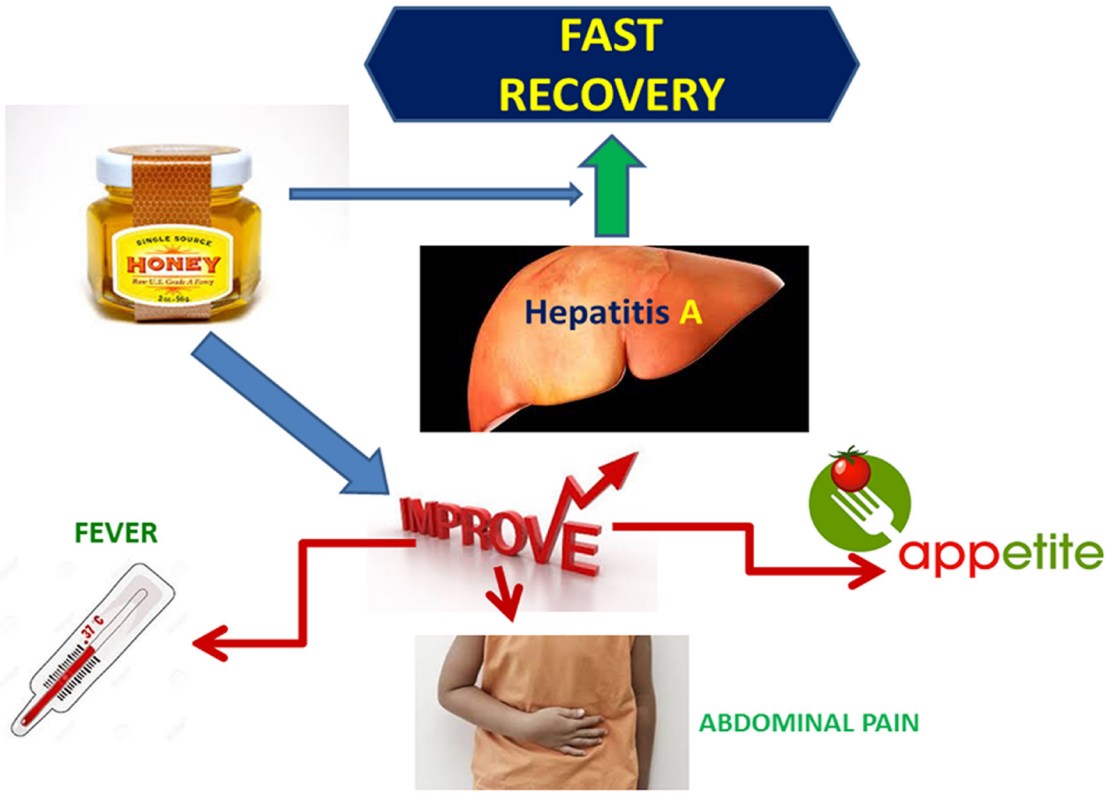
GRAPHICAL ABSTRACT



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