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Effect of Honey Supplementation on Clostridium Difficile Infection in Childhood Cancer

Mohsen Saleh El Alfy, Iman Ahmed Ragab, Sally Mohamed Saber, Yasmin Gamal El Gendy, Zahia Shahat El Sayed

Pediatric Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

*Corresponding author: Mohsen Saleh El ALFY, E-Mail:elalfym@hotmail.com, Mobile: 01000864343 and Iman Ahmed Ragab , E- Mail : hragab68@hotmail.com,Mobile :01002550680

ABSTRACT

Background: the treatment of cancer is associated with nausea and vomiting, oral mucositis, constipation, xerostomia and diarrhea and weight loss, additionally; chemotherapeutic agents promote inflammatory changes in the gut, intestinal necrosis, and anaerobic conditions, allowing proliferation of Clostridium Difficile. Honey, as a natural honeybee product, has antioxidant, antimicrobial, immunomodulatory and anticancer effects. Honey can fight microbial infection by its immuno-activating, anti-inflammatory and prebiotic activity.

Objectives: the aim of this study was to evaluate the effect of honey supplementation on frequency of Clostridium Difficile infection (CDI) and gastrointestinal complications in pediatric patients undergoing chemotherapy.

Design: a cross sectional study conducted on 40 patients with malignancy recruited from Children's Hospital, Ain Shams University, Oncology Unit and Clinic, Cairo, Egypt in the period from December 2015 to December 2016. Patients were divided into two groups; group I (25 patients) received honey in the dose of 2gm/kg 3 times dailyfor 1month) while group II (15 patients) did not receive honey. All the studied patients were subjected to medical history and clinical examination, with special emphasis on gastrointestinal complication including oral mucositis, vomiting, diarrhea, constipation, and abdominal pain. Follow up was done for weight, height z score, gastrointestinal complications and any adverse events. Stool analysis, culture, C difficle toxin A, B by ELISA was done to all patients at baseline and repeated to patients receiving honey at week 4 of supplementation. Main outcome measure frequency of CDI, gastrointestinal complication, febrile neutropenia .

Results: the frequency of C difficle was 8% (2), the first case was 9 years old patient with ALL (50%) and the other 11 years old patient with Burkitts lymphoma both were diagnosed by positive stool culture and positive stool ELISA for toxin A, B. gastrointestinal complications were significantly less and improved in the supplemented group and mean of hemoglobin significant increase in group 1.

Conclusion: the frequency of CDI in children with cancer 8% diagnosed by stool culture and toxin A, B study in stool. Honey improved the oral mucositis and different GIT complications associated with chemotherapy.

Keywords: Honey, Clostridium difficle, Childhood cancer, chemotherapy.

INTRODUCTION

The treatment of cancer is associated with nausea and vomiting, oral mucositis, constipation, xerostomia and food aversion and it thus play an important role in decreased food intake, nutrient loss, energy expenditure alterations and weight loss, particularly lean body mass [(1)] .

Clostridium difficile is a spore-forming, Gram-positive anaerobic bacillus that produces two toxins: toxin A and toxin B. It is a common cause of antibiotic-associated diarrhea (AAD). It accounts for 15-25% of all episodes of AAD [(2)]

Cancer patients have a higher risk for *C. difficile* infection as compared to noncancer patients [(3)]. Traditional chemotherapy agents have been shown to perturb fecal microbiota, leading to conditionsthat promote the incidence and severity of CDAD and simultaneously hinder its resolution [(4)].

Honey is natural substance formed from nectar by honeybees. It is composed primarily of sugars glucose, fructose and its greatest component is water. Honey also contains numerous other types of sugar as well as acids, proteins, vitamins and minerals [(5)]. Honey can fight microbial infection by its immuno-activating, anti-inflammatory and prebiotic activity. Honey inhibits the growth of microorganisms and fungi.

The antibacterial effect of honey is mostly against gram-positive bacteria [(6)]. Important honey effects on human digestion have been linked to honey oligosaccharides. These honey constituents has a prebiotic effect, similar to that of

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fructooligosaccharides (FOS) [7]**.** FOS may help in the prevention and treatment of C. difficle infections by aiding in the restoration of microbiota and the strengthening of intestinal barrier integrity [8]**.** Honey affect on biofilms of clostridium difficle [9]**.**

Aim: the aim of this study was to evaluate the effect of honey supplementation on frequency of Clostridium Difficile infection (CDI) and gastrointestinal complications in pediatric patients undergoing chemotherapy.

SUBJECTS AND METHODS

This was across sectional study conducted on 40 patients with pediatric malignancy in the period from December 2015 to December 2016. They were recruited from oncology unit and clinic, Children's Hospital, Ain Shams University, Cairo, Egypt. Patients were chosen according to the following inclusion criteria: Children less than 18 years, Diagnosed with childhood malignancy and Receiving systemic chemotherapy. Patients off chemotherapy or during periods of radiotherapy with no combined chemotherapy were excluded from the study . **The study was approved by the Ethics Board of Ain Shams University.**

Patients were divided into two groups; group I (25 patients) who received honeysupplementation in the dose of 2gm/kg daily for 1month) while group II (15 patients) did not receive honey.

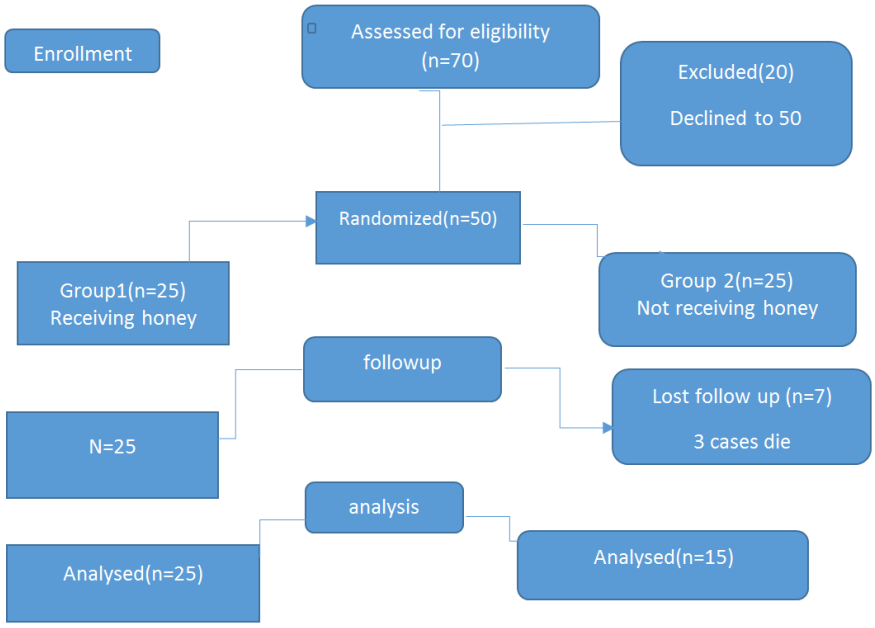
All the studied patients were subjected to medical history and clinical examination, with special emphasis on oral mucositis and different gastrointestinal complication, routine laboratory tests. Follow up was done for weight, height z score, gastrointestinal complications and any adverse events. Stool analysis, culture, C difficle toxin A, B by ELISA was done to all patients at baseline and repeated to patients receiving honey at week 4 of supplementation.

The included patients were subjected to the following:

Initial phase: Complete history taking revising from hospital records including sex, age at time of diagnosis, age at time of study, type of malignancy, stage of malignancy, and protocol of chemotherapy. Any hospital admission for febrile neutropenia was documented with stress on: Duration and frequency of hospital stay, concurrent treatment, number & type of antibiotic used and anti fungal.

GIT complications of chemotherapy including; oral mucositis, vomiting, diarrhea, constipation, and abdominal pain were recorded. Oral mucositis: was assessed by assigning a modified ulcerative mucositis score according to the WHO [10]**.** Full detailed clinical examination; laying stress on anthropometric measurements including: weight, height z score for age, BMI,MAC Z score, weight height-for-age was calculated according to the center for disease control and prevention growth charts, created by the National Center for Health Statistics [11]**.** Laboratory investigations: Including: Complete blood count, Stool culture and stool analysis, Detection of clostridium difficle toxin A, B in stool by ELISA.

The diagnosis of C difficile disease is based on the presence of watery diarrhea (defined as ≥3 loose stools in 24 hours) and C difficile toxins in a diarrheal stool specimen [12]**.**



Enrollment flow chart (figure 1)

Total number of eligible patients was 70, however 20 patients refused the study either because they didn't hear about the effect of honey in treatment of cancer or they feared to try while others refused to sign the written consent. Enrollment was shown in Figure 1 flow chart.

50 patients accepted the study and were enrolled in it and divided randomly into 2 groups:
Group 1: 25 patient who completed course of honey but there were 3 patients completed course of honey but we couldn't get sample stool because they died.
Group 2: 25 patients we missed 10 patients, 3 patients died and 7 patients refused follow up.

Intervention phase

Patients were divided into 2 groups:
Group 1: 25 children with cancer on chemotherapy who received Egyptian clover honey. The honey was given with dose 2 g/kg daily three times for one month. Honey dose was calibrated for mother using graduated cup diluted in water three times daily.
Group 2: 15 children with cancer on chemotherapy who did not receive honey.
After obtaining the approval of ethical committee of the children's hospital, Ain Shams University, the nature of study was explained to the parents or legal guardian and a written consent was signed.

Honey
They received Egyptian clover honey (Trifoliumalxandrinum). The honey used in this study was a raw, unprocessed. The origin of honey was El MahalaGharbia Governorate, Egypt.
It was supplied directly from abeekeeper and stored in dark containers at room temperature for use in study.The dose of honey was estimated according to the patient weight by multiplying the child weight by 2(2 gm/kg three times daily for 1 month), then the dose of honey was calibrated for the mothers using a graduated cup then the honey was dissolved in water and given orally to the patient.
Physicochemical analysis of the honey was done 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. Microscopic examination of samples from honey confirmed the presence of pollen grains, which were mainly of clover (Tri-folium alexandrinum).

Follow up phase
The honey was given regularly through complete 1 month then reevaluation was done which included:

History and Clinical examination weekly regarding GIT symptoms (diarrhea, vomiting, colics and oral mucositis) and fever. Antimicrobial therapy.

Side effects (related to disease, treatment or Honey supplementation Follow up for weight and height by using z score for age.

Laboratory assessment in the form of complete blood count (CBC) initially and after one month for estimation of values of Hb, TLC, NE and PLT counts,stool culture Detection of clostridium difficle toxin A,B in stool by ELISA (Enzyme Linked Immuno Assay in group 1, Follow up for clinical response of diarrhea: symptoms resolution, partial response (50% reducation in frequency of diarrhea episodes), no response worsening (megacolon and or perforation) and if there was relapse within 30 day.

Microbiological procedures: The ELISA method (Ridascreen-Biopharm, Germany) was used to identify C. difficile toxins A/B in stool. Tests were performed according to the manufacturers' instructions.

Statistical analysis

Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non parametric distribution. ***Chi-square test*** was used in the comparison between two groups with qualitative data and ***Fisher exact test*** was used instead of the Chi-square test when the expected count in any cell found less than 5. ***Independent t-test*** was used in the comparison between two groups with quantitative data and parametric distribution and ***Mann-Whitney test*** was used in the comparison between two groups with quantitative data and non parametric distribution. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P > 0.05: Non significant (NS), P < 0.05: Significant (S), P < 0.01: Highly significant (HS).

RESULTS

Table (1): Comparison between studied groups as regards demographic data

	Patients receiving honey (No.=25)		**Patients not receiving honey (No.=15)**		**Chi square test**	
	N	**(%)**	**N**	**(%)**	**t/X^2**	**p**
Sex						
Male	15	(60.0%)	8	(53.3%)	0.171*	0.680
Female	10	(40.0%)	7	(46.7%)		
Age (months)						
Mean ± SD	74.00 ± 36.22	95.93 ±58.03			-1.476	0.148
Range	18 - 156	18 - 180				

Table 1 shows no statistically significant difference in age and sex in the studied groups.

Table (2): Comparison between studied groups as regards diagnosis

		Patients receiving honey (No.=25)		**Patients not receiving honey (No.=15)**		**Chi square test**	
		No.	**%**	**No.**	**%**	**X^2**	**P-value**
Diagnosis	ALL	22	88.0%	10	66.7%	5.689	0.338
	AML	1	4.0%	1	6.7%		
	NHL	1	4.0%	2	13.3%		
	solid tumor	1	4.0%	2	13.3%		

ALL= Acute lymphoblastic leukemia,AML= Acute myeloid leukemia,,NHL= Non hodgkins lymphoma

Table 2 Shows no statistically significant difference in diagnosis in the studied groups.

In group 1 males were 60%(15), female were 40%(10).The age of patients of group 1 ranged from 18 to 156 month, in group 2 male 53.35%(8),females46.7%(7) The age of patients of group 2 ranged from 18 to 180 month. And there is no significance difference regarding age, sex in studied groupsas shown in table 1.

The frequency of cl difficle infection in our study was 8% and associated significant with using antibiotics cephalosporins and quinolones.

In our study the frequency of cl difficle was 8%(2 female patients),one patient 9 years old diagnosed with ALL (50%) and the other 11 years old with Burkitts lymphoma, both were diagnosed by positive stool culture and positive stool ELISA for toxin A, B. The 2 patients had CDI, one of them was using antibiotics cephalosporin, quinolones, carbapenems, pencillin, vancomycin metronidazole and the other was using cephalosporin, quinolones, aminoglycosides, vancomycin, metronidazole.

Table (3): Comparison between studied groups regarding some Gitsymptoms(diarrhea ,abdominal pain ,vomiting, constipation) initially

		Group 1	**group 2**	**Test value**	**P-value**	**Sig.**
		No. = 25	**No. = 15**			
Diarrhea No of episodes	Median (IQR) Range	3 (3 – 4) 2 – 6	4 (2 – 6) 2 – 6	-0.117ǂ	0.907	NS
Constipation No ofepisodes	Median (IQR) Range	1 (1 – 1) 1 – 1	1 (1 – 1) 1 – 1	0.000ǂ	1.000	NS
Abdominal pain No of episodes	Median (IQR) Range	1 (1 – 2) 1 – 3	2 (2 – 2) 1 – 3	-1.884ǂ	0.060	NS
Vomiting No of episodes	Median (IQR)	3 (3 – 4) 2 – 5	4 (3 – 4) 3 – 5	-0.856ǂ	0.392	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; ǂ: Mann-Whitney test

Table (4): Comparison between studied groups regarding some Git symptoms in follow up and total days of febrile neutropenia

		Group 1	**Group2**	**Test value**	**P-value**	**Sig.**
		No. = 25	**No. = 15**			
Diarrhea No of episodes	Median (IQR) Range	0 (0 – 0) 0 – 0	4 (4 – 4) 4 – 4	-5.196ǂ	<0.001	HS
Constipation No of episodes	Median (IQR) Range	0 (0 – 0) 0 – 0	1 (1 – 1) 1 – 1	-5.000ǂ	<0.001	HS
Abdominal pain No of episodes	Median (IQR) Range	0 (0 – 0) 0 – 0	1 (1 – 1) 1 – 2	-5.936ǂ	<0.001	HS
Vomiting No of episodes	Median (IQR) Range	0 (0 – 0) 0 – 0	3 (2 – 4) 2 – 4	-5.186ǂ	<0.001	HS
Total days of febrile neutropenia	Median (IQR) Range	10 (7 – 14) 4 – 21	30 (21 – 30) 14 – 30	-3.246ǂ	0.001	HS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; ǂ: Mann-Whitney test

Table (5): Comparison between initial and follow up as regards vomiting, abdominal pain, constipation, , diarrhea in group 1

		Group 1		Test value	P-value	Sig.
		Initial	Follow up			
Diarrhea No of episodes	Median (IQR) Range	3 (3 – 4) 2 – 6	0 (0 – 0) 0 – 0	-3.207	0.001	HS
Constipation No of episodes	Median (IQR) Range	1 (1 – 1) 1 – 1	0 (0 – 0) 0 – 0	-1.414	0.157	NS
Abdominal pain No of episodes	Median (IQR) Range	1 (1 – 2) 1 – 3	0 (0 – 0) 0 – 0	-4.338	<0.001	HS
Vomiting No of episodes	Median (IQR) Range	3 (3 – 4)	0 (0 – 0)	-3.114	0.002	HS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test.

Diarrhea was reported in 52.0% (13) out of 25 patients in group 1 and 26.7% (4) out of 15 in group 2 had diarrhea before honey supplementation, after honey supplementation for 4 weeks there was significant decrease and improvement in consistency and frequency of diarrhea in group 1(0.0%) compared with group 2(20.0%) p =. 02. A significant decrease of diarrhea in group 1 after honey supplementation (P-value=0.001) as shown in tables (3,4,5).

Vomiting was reported in 48% (12) out of 25 patients in group 1and 5 patients (28.6%) out of 15 patients in group 2 before honey supplementation A significant decrease and improvement the frequency of vomiting in group 1(0.0%) compared with group 2(20.0%) after honey supplementation for 4 weeks p =. 02. A significant decrease in frequency of vomiting in group 1 after honey supplementation P =0.001as shown in tables (3,4,5).

24 patients (96%) out of 25 patients had abdominal pain in group 1 and 15 patients (100%) out of 15 patients in group 2, A significant decrease in frequency of abdominal pain in group 1 (0.0%) compared with group 2(80%) after honey supplementation during week 1, week 2and week 3 and 4 week of the study duration p value=(0.064, 0.001, <0.001, <0.001). and a significant decrease in frequency of abdominal pain in group 1 after honey supplementation p =0.001as shown in tables (3,4,5)..

In our study we found 10 patients (40%) out of 25 patients with oral mucositis in group 1(according to WHO grading grade 1(28%) and grade 2(12%)) and 9 patients (60%) out of 15 in group 2 had oral ulcers (grade 1(40%) and grade 2 (20%))before honey supplementation, after honey supplementation a significant decrease and improvement in degree of oral mucositis in group 1(0.0%) as compared with group 2(26.70%) (grade 1 (20.00%) and grade 2(6.70%)) during week 1, week 2 and week 3 and 4 week of the study duration (p value =0.021, 0.042,0.025 and. 025 respectively). With a significant decrease of oral mucositis in group 1 after honey supplementation **(**P=0.008) as shown in table (6).

Table (6): Comparison between studied groups as regards oral mucositis according WHO

Oral mucositis		Patients receiving honey (No.=25)		Patients not receiving (No.=15)		Chi square test	
		No.	%	No.	%	X^2	p
Initial	Grading 1	7	28.00%	6	40.00%	1.530	0.465
	Grading 2	3	12.00%	3	20.00%		
1week	Grading 1	6	24.0%	6	40.0%	7.744	0.021
	Grading 2	0	0.0%	3	20.0%		
2 weeks	Grading 1	3	12.0%	3	20.0%	6.348	0.042
	Grading 2	0	0.0%	3	20.0%		
3 weeks	Grading 1	0	0.0%	3	20.0%	7.407	0.025
	Grading 2	0	0.0%	1	6.7%		
4weeks	Grading 1	0	0.00%	3	20.00%	7.407	0.025
	Grading 2	0	0.00%	1	6.70%		

Table 6 shows statistically significant decrease in oral mucositis at 4 weeks evaluation after honey intake in group 1 compared to unsupplemented group.

In our study 12 patients (48.0%) out of 25 patients had febrile neutropenia in group 1 and 7(46.7%) out of 15 in group 2 had febrile neutropenia before honey supplementation. After honey supplementation a significant decrease of fever in 3 and 4 weeks in supplemented group (p =. 014,. 020) and total days of febrile neutropenia ranged from 4 to 21 days in group 1 and 14 to 30 day in group 2as shown in table(4).

The mean of hemoglobin was 9.87 gm /dl in group1 and 9.43gm/dl in group 2 before honey supplementation, and a significant increase of hemoglobin level 10.86 gm/dl in group 1 compared with group 2 (8.86) gm/dl P value =.000 after honey supplementation and a significant increase in mean of hemoglobin (9.87 gm/dl initial, 10.86gm/dl after 1 month), p value =.000 and neutrophil (1.58 initial, 2.18 after 1 month) p value=.009 post honey in group 1as shown in table(7).

There was no significant change regarding anthropometric (weight, height z score for age, BMI, MAC) in both groups. However, there was slight increase in weight among the supplemented group after 1 month (z-score was-0.208 initially, -0.03 after 1 month) with a slight decrease in weight among the unsupplemented group (z-score was-0.526 initially, -0.89 after 1 month) as shown in table (8).

Table (7): Comparison between studied groups as regards CBC

		Patients receiving honey (No.=25)				Patients not receiving (No.=15)				Independent t-test	
		Mean	SD	Min	Max	Mean	SD	Min	Max	t	p
HB g/dl	Initial	9.87	1.76	7.3	13.7	9.43	1.83	7	13.6	0.757	0.454
	Follow up	10.86	1.23	8.5	13.5	8.86	1.65	6	11.1	4.373	<0.001
TLC	Initial	3.00	1.90	0.9	8.2	4.23	2.02	1.1	7.5	-1.942	0.060
	Follow up	3.57	1.63	1.4	8.4	2.91	1.52	0.9	6	1.282	0.208
Ne	Initial	1.58	1.36	0.2	6	2.36	1.43	0.5	4.5	-1.727	0.092
	Follow up	2.18	1.18	1	5.6	1.46	1.04	0.2	3.5	1.956	0.058
PLT	Initial	260.64	138.94	57	580	228.20	146.99	49	631	0.700	0.488
	Follow up	297.96	197.85	19	935	192.80	119.51	16	463	1.859	0.071

Hb—hemoglobin; TLC—total leucocytic count; ANC—absolute neutrophil count; PLT—platelet count.

Shows no statistically significant difference in complete blood count (CBC) in initial phase in the studied groups but there was significant increase in hemoglobin level (Hb) after honey intake in group 1 compared with un supplemented group.

Table (8): Comparison between studied groups as regards anthropometric measures

		Patients receiving honey (No.=25)				Patients not receiving honey (No.=15)				Independent t-test	
		Mean	SD	Min	Max	Mean	SD	Min	Max	t	p
Height (Median &IQR)	Z score: initial	-0.62(-1.408-0.067)		-2.39	2.25	-0.073(-1.133-0.692)		-1.42	1.45	-1.299*	0.194
	Z score: follow up	-0.506(-1.378-0.067)		-2.27	2.25	-0.073(-1.133-0.816)		-1.42	1.45	-1.146*	0.252
Weight (Median &IQR)	Z score: initial	-0.208(-0.671-0.208)		-3.19	1.80	-0.526(-1.35-0.15)		-3.12	0.77	-0.782*	0.434
	Z score: follow up	-0.03(-0.49-0.48)		-2.68	1.89	-0.89(-1.35-0.15)		-3.12	0.62	-1.579*	0.114
BMI		16.30	1.98	11.8	21.5	16.15	3.21	12.8	22.7	0.192	0.848
MAC		18.00	2.42	13	22	18.67	3.04	14	24	-0.767	0.448

*Mann- Whitney test/Mean -SD

Table 8 shows no statistically significant difference in weight for age and height for age z score, body mass index, and mid arm circumference in initial and follow up in the studied groups

DISCUSSION

Chemotherapy treatment results in shifts of the human microbiota associated with side-effects like diarrhea, constipation and malnutrition. The altered balance of the microbiota potentially leads to CDI, altered absorption and other intestinal functions involving the microbiota [13].

In the current study, we assessed the effect of honey supplementation on CDI and gastrointestinal complications in pediatric patients undergoing chemotherapy.

In our study the frequency of cl difficle was 8%(2),1 patient with ALL (50%) and the other had Burkitts lymphoma, both were diagnosed by positive stool culture and positive stool ELISA for toxin A, B.

Variable frequencies for CDI were reported in different centers, ***Fisher et al.*** [14] reported that (3.2%) of pediatric patients with ALL developed CDI within 180 days of ALL diagnosis . ***Price et al.*** [15] reported that 11% of pediatric patients with acute myeloid leukemia (AML) had CDI., While another study found nine (6%) out of 141 patients treated for solid tumours had C. difficile toxin A detected in their stools in the presence of abdominal symptoms including vomit, abdominal pain and diarrhea [16].

Chemotherapy induced GI complications are common in cancer patients undergoing chemotherapy [17]. Application of either fresh or old natural bee honey has been showed to be effective in managing vomiting, diarrhea, constipation, mucositis, or infectious states [18.].

Diarrhea was reported in 52.0% (13) out of 25 patients in group 1 and 26.7% (4) out of 15 in group 2 before honey supplementation, after honey supplementation for 4 weeks there was significant decrease and improvement in consistency and frequency of diarrhea in group 1(0.0%) compared with group 2(20.0%) p =. 02.,This agrees with a previous study of a combination of honey and ardew for at least 30 consecutive days in AML patients under chemotherapy improved diarrhea [19].

We found 12 patients (48%) out of 25 patients had vomiting in group 1and 5 patients (28.6%) out of 15 patients in group 2 had vomiting before honey supplementation A significant decrease and improvement the frequency of vomiting in group 1(0.0%) compared with group 2(20.0%) after honey supplementation for 4 weeks p =. 02. and a significant decrease in frequency of vomiting in group 1 after honey supplementation P =0.001 this agree with a previous work, reporting that nausea and vomiting, which is one of most prevalent and annoying complications induced by chemotherapy declined significantly after combination of 50 grams of honey and 150 grams of Ardew for at least 30 consecutive in AML patients under chemotherapy [19]. 24 patients (96%)out of 25 patients had abdominal pain in group 1 and 15 patients (100%) out of 15 patients had colic in group 2,A significant decrease in frequency of colic in group 1 (0.0%) compared with group 2(80%) after honey supplementation during week 1, week 2and week 3 and 4 week of the study duration p value=(0.064, 0.001, <0.001, <0.001). and a significant decrease in frequency of colics in group 1 after honey supplementation p =0.001. A similar finding to previous work [19]. Honey has long been known to have a soothing action on mucus membranes and recommended for the management of oral mucositis. Because of its high viscosity, acidic PH, hydrogen peroxide, high osmolarity, and rich nutritional properties [20]. In our study we found 10 patients (40%) out of 25 patients had oral mucositis in

group 1(according to WHO grading grade 1(28% and grade 2(12%)) and 9 patients (60%) out of 15 in group 2 had oral ulcers (grade 1(40%) and grade 2 (20%)) before honey supplementation.

A significant decrease and improvement in degree of oral mucositis in group 1(0.0%) as compared with group 2(26.70%) (grade 1(20.00%) and grade 2(6.70%)) after honey supplementation during week 1, week 2and week 3 and 4 week of the study duration (p value =0.021, 0.042,0.025 and. 025 respectively). With a significant decrease of oral mucositis in group 1 after honey supplementation(P=0.008) and this agree with study by ***Al Jaouni et al.*** [21]showed that the honey treatment is effective in reducing and minimizing oral mucositis among pediatric cancer patients treated with chemo/radiotherapy and is cost-effective treatment

However ***Bardy et al*** .[22] found no significant difference between honey and golden syrup in their effects on oral mucositis. Active manuka honey did not improve mucositis, but both the honey and the syrup seemed to be associated with a reduction in bacterial infections .

In our study there was no significant difference in weight, height z score for age, BMI, MAC in both groups before honey supplementation. However, there was slight increase in weight among the supplemented group after 1 month (z-score was-0.208 initially, -0.03 after 1 month) with a slight decrease in weight among the unsupplemented group (z-score was-0.526 initially, -0.89 after 1 month). These findings can be attributed to the decreased incidence of gastrointestinal complications (including mainly anorexia, nausea and vomiting and oral ulcer and diarrhea) related to chemotherapy administration. The decreased incidence of these symptoms resulted in improvement of appetite and increased food intake.

This agree with the results of a comparative study on the evaluation of honey versus sucralfate for oral mucositis and the mean weight loss was more in sucralfate group as compared to honey and it was concluded that honey was more effective in increasing the weight as compared to sucralfate group [23]**.**

In our study 12 patients (48.0%) out of 25 patients had febrile neutropenia in group 1 and 7(46.7%) out of 15 in group 2 had febrile neutropenia before honey supplementation. With a significant decrease of fever in 3 and 4 weeks in supplemented group (p =.014, 020) respectively prove (48 %to 8%) compared with un supplemented (46.7% to 40.0%).

The mean of hemoglobin was 9.87 gm /dl in group1 and 9.43gm/dl in group 2 before honey supplementation, and a significant increase of hemoglobin level 10.86 gm/dl in group 1 compared with group 2 (8.86) gm/dl P value =.000 after honey supplementation and a significant increase in mean of hemoglobin (9.87 gm/dl initial, 10.86gm/dl after 1 month), p value =.000 and neutrophil (1.58 initial, 2.18 after 1 month) p value=.009 post honey in group 1.

Our study agrees with ***Zidan et al.*** [24] found with the addition 5 gm of LMH (Life Mel honey honey (Express Honey, Tzuf Globus, Israel)) for 5 days in patients with cancer, no recurrence of neutropenia after LMH intake and no need for treatment with CSFs in 40% of patients. Hemoglobin levels remained >11 g/dL during LMH intake in 64% of patients***).*** Another study found febrile period which is mostly a consequence of neutropenia in patients receiving chemotherapy, diminished significantly ($p<0.05$) [19]**.** Similarly was previously reported with honey consumption improved the levels of hemoglobi [25].

STUDY LIMITATIONS

The sample size is small. The total number of CDI cases is small. Although our patients had malignancy, they were on different stages of immune suppression and type of their underline disease was not similar. Follow up was limited to 1months and the study was not blinded. A washout period was not calculated in this study because there is not yet available test to measure honey or its components in blood, and hence the half-life of honey concentration in the blood cannot be known. Therefore, as a limitation to this study, the possible carry-over effects of honey may yield statistical bias.

CONCLUSION

The frequency of CDI in children with cancer was 8% diagnosed by stool culture and toxin A, B study in stool. Honey improved the oral mucositis and different GIT complications associated with chemotherapy.

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