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Research Article

A Pilot Study Examining the Effect of Kelulut Honey in Dengue Infected Patients by Examining Clinical, Hemodynamic and Biochemical Parameters

Muhamad NAN[1*], Roslan AF[1], Boon YW[2], Abidin SA[3], and Yusoff YA[3]

[1]Department of Emergency Medicine, HCTM-Universiti Kebangsaan Malaysia

[2]Diagnostic and Applied Health Science, Faculty of Health Science-Universiti Kebangsaan, Malaysia

[3]Department of Biochemistry, Universiti Kebangsaan Malaysia

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***Corresponding author:**

Nik Azlan Nik Muhamad, Department of Emergency Medicine, HCTM-Universiti Kebangsaan, Malaysia, Tel: 0123956197, E-mail: nikazlanmuhamad@hotmail.com

1. Abstract

1.1. Background: To examine the effects of low dose Kelulut honey administration in dengue patients on the outcome of clinical, haematological and hemodynamic parameters.

1.2. Methods: 47 serological positive dengue patients (age 33±11 year) were included in this double-blinded randomized control trial. Twenty-four patients were given low dose of Kelulut honey (0.2 mg/kg/day) for 3 days, while 23 patients were given corn syrup in the placebo group. Daily clinical condition, blood investigation and haemodynamic parameters were monitored for 3 days. Overall improvement of warning signs was recorded.

1.3. Results: Although insignificant, average overall day 1, 2 and3warningsignsimprovementwere64.5%±13.5% vs.61.3%±10.5%,42.6% ± 19% vs. 34.4%± 18% and 38.2%± 20.7% vs. 30%± 27% (honey vs. control respectively). At day 3 of administration, average white blood cell count tends to slightly increase with honey after day 3 compared to prior intervention (+0.1±0.37 vs.-0.7±0.32x10^3/mL). Average day 3 hematocrit showed decrease in both of the groups, but a higher decrease in honey (-5.2±2.45% vs. -3.7±1.4%). However overall platelet has been seen decreasing more in the honey group compared to control (-36.0±17.36 vs. -23.5±12.87x10^3/mL). Other parameters measured (BP, RR, renal profile, liver profile) did not show difference between two groups.

1.4. Conclusions: Low dose Kelulut honey administration to dengue patients had non-significant improvement; nevertheless it did not exhibit any detrimental effects on clinical, hemodynamic and biochemical parameters.

2. Keywords: Honey; Dengue Fever; Platelet; Hematocrit; White blood cell

3. Introduction

In dengue fever, interaction between virulent factors and heightened host immune system response may produce a cytokine storm which results in increased vascular permeability, organ damage and abnormal homeostasis. It was demonstrated that inflammatory endothelial cell activation induced by anti-Dengue Virus (anti DV) NS1 antibody via the transcription factor NF-ƙB-regulated pathway [1, 2] Research is intensively ongoing to search f or a cure to dengue fever. Treatment is mainly supportive and symptomatic.

Honey bees produce antimicrobial peptide and antiviral defence in response to viral infection. These peptides are effector molecules of Toll, Imd and JNK pathways which expression is increased in virus infected bees [3].The pathways mentioned are important in producing trans membrane signal

transducing proteins that play critical roles in both immunity and development (Figure 1). Interestingly enough, Toll pathway is also implicated in antiviral defence of *Aedes aegypty* [4]. It is also documented that honey produced also contains antimicrobial peptide, which provide its anti microbial property [5]. However, role in antiviral defence in honey and honey bees is not yet understood [3]. Several clinical studies proven topical honey has significant antiviral properties, against *herpes zoster* and *varicella zoster virus* [6-8]. *Trigona spp*., known as the 'Kelulut' is the stingless bee species native to tropical and subtropical where dengue is epidemic [9-11]. Hence it is postulated that the immunity developed by *trigona* spp can produce antiviral defence and peptides secreted in honey that can reduce dengue viral load, however this is still yet to be proven (Figure 2).

Figure 1-6: Change in warning signs in intervention (honey) vs. control group

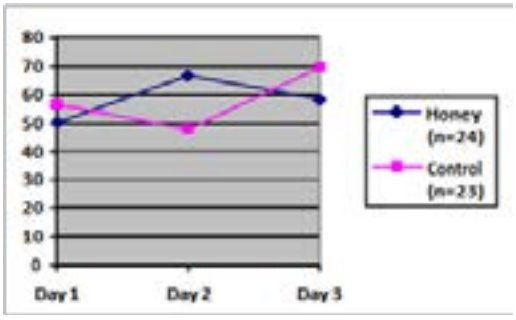

Figure 1: Percentage improvement in general condition

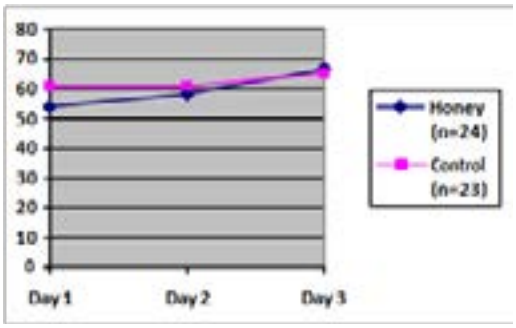

Figure 2: Percentage improvement in oral intake

Kelulut honey has been reported to have relatively higher phenolic content [10]. This is important in its ability to modulate excessive immune response though anti-inflammatory and anti-oxidant properties [12-17]. Animal studies has shown that honey produced from stingless bees has a protective role against systemic damaged induced by sepsis by modulating the cytokine response via down-regulating nuclear factor –kappa B (NF-kB) pathway [18]. The modulation of this pathway is to moderate the dysregulation of host immune response which can be translated by improvement of warning signs, hematology and hemodynamic parameters. Compliance towards honey is acceptable due to its medicinal value, not only in Western world but also as an adjuvant in traditional Chinese medicine [19]. In Islamic medicine; it is mentioned in the Holy Quran as a remedial material [20]. To our knowledge this is the f irst randomized controlled study on human subjects. It is not to replace the current modern practice in managing dengue, but act as an adjuvant complementary therapy. This study also assesses the safety profile of Kelulut honey in severe infections such as dengue.

4. Materials and Methods

This is a double blind randomized control trial. Prior to sample collection, an agreement with the head of department of both Emergency and Medical unit will be attained (Figure 3). A written approval has been given by the Head of Department of Medical Unit for assessing patient in their medical ward. Ethical clearance is obtained from National University of Malaysia ethical board, FF-2017-453

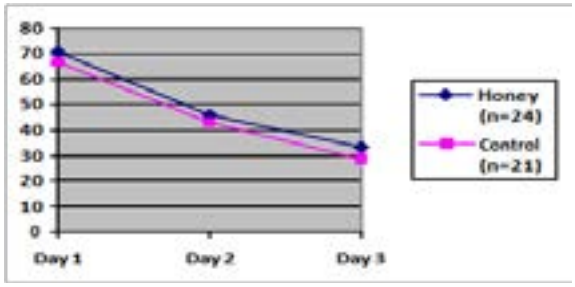

Figure 3: Percentage improvement in headache

This study was conducted in the Hospital Canselor Tuanku Muhriz (HCTM), Cheras, and Kuala Lumpur, Malaysia from July 2017 to June 2019. A written consent from the patients was obtained to be part of the study. Only patients above the age of 18 years were selected for the study. The inclusion criteria were patients diagnosed with dengue fever based on clinical warning signs, hematological results and positive dengue serology. Excluded were high risk dengue patients, dengue hemorrhagic shock, dengue septic shock, underlying coagulopathy, need of ICU care, ischemic heart disease, pregnant / lactating mothers, underlying diabetic mellitus, incapable of giving consent (altered mental status / psychiatric conditions), allergic to honey, received transfusion of blood or blood product during current stay, already taking honey as a supplement (any type of honey) and known to be taking other types of Complementary Alternative Medicine (CAM) (Figure 4).

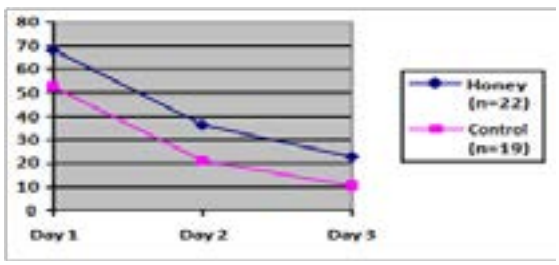

Figure 4: Percentage improvement in vomiting

Patients were given briefing regarding invasive procedures such as blood taking, which would be done routinely in dengue patients. Baseline values for all parameters were taken on Day 1 of admission before initiating the intervention. They were also instructed on methods of consumption of the honey or placebo. Subsequent blood samples will be taken afterwards in accordance to the normal protocol of dengue management. Their clinical progress was observed daily alongside other blood parameters as well as their vital signs.

Blood parameters including Platelet count, hemoglobin, white blood cell count, hematocrit, Liver Function Test, Renal Profile were taken. A total of 5 ml of blood will be required at each sampling according to the table below. Patients were randomly given a package which was indistinguishable from one or another as they are individually covered. The packages contained 12 sachets of 8 ml of either Kelulut Honey or corn syrup. Each has a label which would be recorded together with the patient's information (Figure 5).

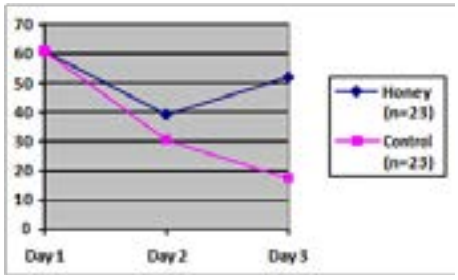

Figure 5: Percentage improvement in lethargy

Patients were required to take honey or control twice daily; every morning and evening, 15 minutes after breakfast and dinner respectively for 3 consecutive days. During their stay, they will receive the standard management as per the National Clinical Practice Guidelines for the Management of Dengue. Clinical progression was assessed daily for 3 days by the medical team assigned to the ward. Daily visits were done to assess patient's warning signs. Haematological and biochemical test were taken daily for the next 3 days and was processed respectively in the laboratories of hematology and biochemical department. All the data gathered were validated, traced and analyzed. Mean and standard deviation of the blood parameters were calculated. In the event where patients are discharged before the completion of clinical trial of 3 days, they were required to continue the administration of honey at home and called back for blood taking and clinical review, as stated in the information sheet and consent (Figure 6).

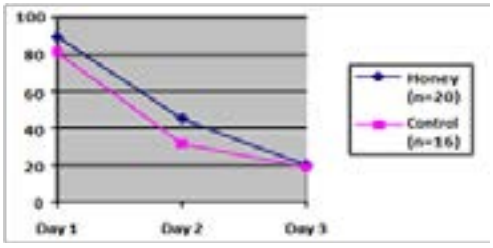

Figure 6: Percentage improvement in abdominal pain

In case of allergic or anaphylaxis reaction to the control or kelulut honey, allergic or anaphylaxis protocol will be implemented. Patients will be given hydrocortisone and adrenaline as per protocol.

4.1. Kelulut Honey

Kelulut Honey was obtained from Syamille Agro Farm and Resort, a private plantation certified by the Ministry of Agriculture in Perak. They were certified for Malaysian Technology Development Corporation (MTDC) Centre in UKM, Bangi. They were pre- packaged into 4 ml sachets of pure Kelulut (Trigona) Honey, without being diluted (3.5 g/sachet). Two sachets were given daily, with the total amount of 7g/day. The dose was on average 0.2g/kg/day for a normal adult, an average of one tablespoon per day. This less than experimented in previous studies 1.5g/kg [17]. This is designed that the amount of honey is palatable and affordable to most patients, which measures to approximately two teaspoon twice a day (1 teaspoon =5 mL)

The control consists of corn syrup which is the regular type (100% glucose). It was obtained from conventional supermarket and widely used food and beverage sweetener.

It would be packaged similarly as the Kelulut honey. It has the same consistency, colour, and a comparable taste to Kelulut Honey. Each box would then be wrapped analogously, to achieve randomization. They were labeled individually, together with the patient's information.

A form consisting of detailed information of patients together with a record of their clinical progression and blood parameters was attached to each patient record. Each form was labeled with a corresponding package during the start of the study for every patient. The patients were reviewed every day with his clinical progression recorded and hematological parameters measured. The statistic calculation is based on intention to treat basis. Statistical analyses were performed using IBM SPSS version 22.0.0.

Ethic approval was attained from HCTM Ethical Board. (FF-210-453). Study was conducted in line with the standards provided by the Malaysian Good Clinical Practice

Privacy and Confidentiality: All data collection from the patients was classified as confidential from public view. Data collection sheet of patient was kept separately in different envelopes and stored in a specific folder only accessible to individuals involved in the study. Data will be kept up to end of duration of the research.

5. Results

A total of 47 patients included in this study. None developed any allergies or deterioration of clinical conditions during the trial.

5.1. Demographics

The demographic of the patient enrolled is as shown in (Table 1). Note that day of fever describes at what day of fever that the patient first presented to emergency department f or enrolment in this study.

Table 1: Day of fever describes at what day of fever that the patient first presented to emergency department f or enrolment in this study.

Demographics			
Variables	Honey N=24(%)	Control N=23(%)	p-value
Mean age of patient	32.5 (15.3)	31.0 (14.0)	0.655[a]
Gender			0.106[b]
Male	10 (41.7)	15 (65.2)	
Female	14 (58.3)	8 (34.8)	
Ethnic			0.829[c]
Malay	18 (75.0)	16 (69.6)	
Chinese	3 (12.5)	2 (8.7)	
Indian	2 (8.3)	2 (8.7)	
Others	1 (4.2)	3 (13.0)	
Day of fever			0.384[b]
Day 3	5 (20.8)	6 (26.1)	
Day 4	7 (29.2)	10 (43.5)	
Day 5	12 (50.0)	7 (30.4)	

Note :
[a]Mann-Whitney test;
[b]Pearson Chi-square test;
[c]Fisher's Exact test.

5.2. Hematological parameters

(Table 2) shows the adjusted mean changes of the hematological parameters of patients in both group as well as comparison between them. Day 1 denotes the initial day in which the patient enrolls in this study and not day 1 of fever.

Table 2: Adjusted mean changes of the hematological parameters of patients in both group as well as comparison between them. Day 1 denotes the initial day in which the patient enrolls in this study and not day 1 of fever.

Haematological Parameters					
Outcome	**Overall Adjusted Mean (SE)**	**p-value**	**Honey Adjusted Mean (SE)**	**Control Adjusted Mean (SE)**	**p-value**
Total White Cell		0.166[b]			0.396[b]
Baseline	5.0 (0.30)		4.6 (0.43)	5.3 (0.44)	
Day 1	4.3 (0.32)		3.9 (0.44)	4.7 (0.45)	
Day 2	4.4 (0.40)		4.2 (0.55)	4.7 (0.56)	
Day 3	4.6 (0.43)		4.7 (0.60)	4.6 (0.62)	
Haemoglobin		0.696[b]			0.355[b]
Baseline	13.7 (0.29)		13.4 (0.40)	14.0 (0.41)	
Day 1	13.4 (0.30)		13.0 (0.42)	13.8 (0.43)	
Day 2	13.9 (0.72)		14.2 (1.00)	13.7 (1.02)	
Day 3	13.8 (0.74)		14.1 (1.04)	13.4 (1.06)	
Haematocrit		0.000[b]			0.367[b]
Baseline	47.0 (0.64)		46.4 (0.91)	47.6 (0.93)	
Day 1	45.0 (0.52)		44.0 (0.73)	45.8 (0.75)	
Day 2	43.1 (0.82)		41.7 (1.14)	44.7 (1.17)	
Day 3	42.5 (0.82)		41.0 (1.14)	43.9 (1.17)	
Platelet		0.000[b]			0.530[b]
Baseline	100.2 (6.11)		97.6 (8.55)	102.8 (8.73)	
Day 1	77.0 (5.15)		72.3 (7.20)	81.7 (7.36)	
Day 2	67.0 (6.13)		60.0 (8.57)	73.2 (8.76)	
Day 3	70.5 (7.53)		61.6 (10.53)	79.3 (10.76)	
Creatinine		0.003[b]			0.182[b]
Baseline	83.8 (3.23)		80.3 (4.45)	87.4 (4.69)	
Day 1	79.1 (2.39)		76.1 (3.29)	(82.0 (3.47))	
Day 2	75.8 (1.94)		75.6 (2.66)	76.0 (2.81)	
Day 3	75.8 (2.12)		76.1 (2.92)	75.6 (3.08)	
Urea		0.292[b]			0.370[b]
Baseline	4.1 (0.25)		3.7 (0.35)	4.5 (0.37)	
Day 1	3.8 (0.18)		3.4 (0.25)	4.1 (0.26)	
Day 2	4.2 (0.56)		3.5 (0.77)	4.9 (0.81)	
Day 3	3.5 (0.14)		3.5 (0.19)	3.5 (0.20)	
Albumin		0.073[b]			0.519[b]
Baseline	37.2 (0.61)		36.6 (0.84)	37.9 (0.87)	
Day 1	36.7 (0.61)		35.9 (0.85)	37.4 (0.87)	
Day 2	35.6 (0.56)		34.6 (0.78)	36.5 (0.81)	
Day 3	36.7 (0.46)		36.7 (0.64)	36.8 (0.66)	
Alanine Transaminase		0.105[b]			0.205[b]
Baseline	115.87 (22.6)		89.0 (31.44)	142.7 (32.47)	
Day 1	143.13 (29.71)		92.3 (41.34)	194 (42.70)	
Day 2	145.03 (27.8)		94.3 (38.67)	195.8 (39.94)	
Day 3	128.58 (21.09)		88.7 (29.34)	168.5 (30.30)	

Note :
[a]Sphericity assumed;
[b]Greenhouse Geisser.

6. Discussion

As visualized in the graph there has been minor overall improvement in symptoms, hematocrit and white cell count with honey intervention, however due to lack in sample size, the overall p value is insignificant. ($p>0.05$). No discrepancies were found in the hemodynamic and other parameters (Table 3 and 4), as patients with shock and severe dengue were excluded. Renal profile and other blood parameters also did not differ, as well as no adverse reactions were reported during this study, which can be concluded that the use of Kelulut honey in dengue is safe. This pilot study can act as a model for further multicentre study that can engage the usage of kelulut honey in treating dengue, as well as other infections.

Table 3: The adjusted mean changes of the haemodynamic parameters of patients in both group as well as comparison between them. Important vital signs in managing dengue fever are taken into account. Measurements were done at one point of time, usually during follow up by the investigator.

Haemodynamic Parameters					
Outcome	**Overall Adjusted Mean (SE)**	**p-value**	**Honey Adjusted Mean (SE)**	**Control Adjusted Mean (SE)**	**p-value**
Systolic BP		0.332[b]			0.571[b]
Baseline	124.0 (2.27)		123.7 (3.17)	124.3 (3.24)	
Day 1	125.0 (1.44)		124.8 (2.01)	125.1 (2.06)	
Day 2	125.9 (1.30)		127.0 (1.18)	124.8 (1.85)	
Day 3	126.6 (1.15)		126.0 (1.61)	127.2 (1.65)	
Diastolic BP		0.2730[b]			0.429[b]
Baseline	79.1 (1.67)		80.0 (2.33)	78.3 (2.83)	
Day 1	76.5 (0.68)		76.5 (0.95)	76.5 (0.97)	
Day 2	77.6 (0.71)		77.8 (0.99)	77.4 (1.02)	
Day 3	77.6 (0.58)		76.5 (0.81)	78.8 (0.83)	
Pulse Rate		0.000[b]			0.508[b]
Baseline	114.5 (2.96)		114.0 (4.14)	115.0 (4.22)	
Day 1	96.7 (1.60)		97.1 (2.24)	96.0 (2.28)	
Day 2	88.3 (1.07)		90.7 (1.49)	86.0 (1.52)	
Day 3	81.0 (1.15)		82.8 (1.60)	79.3 (1.663)	
Temperature		0.000[b]			0.547[b]
Baseline	38.3 (0.25)		38.2 (0.35)	38.4 (0.36)	
Day 1	37.5 (0.07)		37.6 (0.94)	37.4 (0.10)	
Day 2	37.1 (0.02)		37.3 (0.31)	37.1 (0.03)	
Day 3	37.0 (0.16)		37.0 (0.23)	37.0 (0.02)	

aSphericity assumed;
bGreenhouse Geisser.

Table 4: Clinical Condition

Outcome	**Intervention group**		**Control group**		**p-value Pearson's chi square**
General Condition	Improvement (n) Total N=24	Improvement (%)	Improvement (n) Total n=23	Improvement (%)	
Day 1	12	50%	13	56.50%	0.654
Day 2	16	66.70%	11	47.80%	
Day 3	14	58.30%	16	69.60%	
Oral intake	Improvement (n=24)	Improvement (%)	Improvement (n=23)	Improvement (%)	
Day 1	13	54.20%	14	60.90%	0.642
Day 2	14	58.30%	14	60.90%	
Day 3	16	66.70%	15	65.20%	
Headache	Improvement (n=24)	Improvement (%)	Improvement (n=21)	Improvement (%)	
Day 1	17	70.80%	14	66.70%	0.763
Day 2	11	45.80%	9	42.90%	
Day 3	8	33.30%	6	28.60%	
Vomiting	Improvement (n=22)	Improvement (%)	Improvement (n=19)	Improvement (%) ±sd	
Day 1	15	68.20%	10	52.60%	0.546
Day 2	8	36.30%	4	21.10%	
Day 3	5	22.70%	2	10.50%	
Lethargy	Improvement N=total with symptom=23	Improvement (%)	Improvement N=total with symptom =23	Improvement (%)	
Day 1	14	60.90%	14	60.90%	1
Day 2	9	39.10%	7	30.40%	
Day 3	12	52.10%	4	17.40%	
Abdominal Pain	Improvement (n) N=total with symptom=20	Improvement (%)	Improvement (n) N=total with symptom=16	Improvement (%)	
Day 1	18	90%	13	81.30%	0.451
Day 2	9	45%	5	31.50%	
Day 3	4	20%	3	18.80%	
Bleeding Tendency	Improvement (n=14)	Improvement (%)	Improvement (n=16)	Improvement (%)	
Day 1	8	57.10%	8	50%	0.696
Day 2	1	7.10%	1	6.30%	
Day 3	2	14.30%	0	0%	
Overall Mean clinical Improvement	**Interventional group±sd**		**Non-interventional group±sd**		**t-test variance of mean significance (p value)**
Day 1	64.46%±13.5%		61.27%±10.5%		0.474
Day 2	42.61%±19%		34.41±18%		0.423
Day 3	38.2%±20.7%		30.0%±27%		0.536

It was noticed that there was a non-significant improvement in headache, lethargy and abdominal pain. According to a study by Schramm, phenolic antioxidant from honey increases the antioxidant activity of plasma [17]. This protects human from oxidative stress. Comparison was made with corn syrup treatment which contained 0.21 +/- 0.06 mg of phenolic antioxidants per gram, and the two buckwheat honey treatments which contained 0.79 +/- 0.02 and 1.71 +/- 0.21 mg of phenolic antioxidants per gram. This results in increasing plasma total-phenolic content and improved plasma antioxidant and reducing capacities. However this study uses higher dosage of honey which was 1.5 mg/kg of bodyweight, in comparison to this current study which administers only 0.2 mg/kg/day. The high

phenolic and flavinoid content which act as an oxidant scavenging and immune modulator [12-14].

There was a higher percentage of improvement in gastrointestinal symptoms (vomiting and abdominal pain) in the intervention group compared to the control group. This can be compared to previous study of honey on gastrointestinal symptoms, in which honey had caused a reduction in the duration of bacterial diarrhea, and acts as a substitute for glucose in an oral rehydration solution containing electrolytes. In nonbacterial gastroenteritis, honey had the same effect as glucose on the duration of the diarrhea. It has been suggested as a therapy various gastrointestinal disorders, from the periodontal region to the intestinal region and as a replacement for oral rehydration salts. It has been proven for the non-infective and the infective diarrhea for infants and children, as it provides anti-inflammatory and antibacterial properties [21].

Despite the data being insignificant, we can observe that in terms of overall outcome, patients administered with Kelulut Honey has a marginally faster hematological and hemodynamic improvement when compared to those receiving control. Perhaps this is due to the anti- inflammatory properties of honey [10]. Although the amount of cytokines and inflammatory mediators are not quantified in this study, they should translate to the blood parameters investigated and patient's vital signs. Thus, we can observe that there is a slight improvement of dengue patients receiving honey compared to those who do not.

In previous literature on honey bees, Toll pathway is also implicated in antiviral defense of *Aedes aegypty* [4]. It is also documented that honey produced also contains antimicrobial peptide, which provide its anti microbial property [5]. Since dengue viral load is not included in this study is difficult to determine the response of antiviral defense in the honey. White cell count did not change significantly between intervention and control subjects.

The purpose of recruiting dengue patients at day 3 to day 5 of fever is to start treating them during the critical phase. This is when the cytokine response is elevated and most notable changes in laboratory findings take place as well as

Organ dysfunction, if present, occurs [1, 6]. This is thought to provide the most noticeable hematological and hemodynamic changes when given honey or control. Patients with solitary IgG positivity in combo test are excluded as dengue IgG antibodies can persist in previously infected patients for months [1]. Avoidance of patient presented in recovery phase was done by screening from history and blood parameters. Dengues patients in recovery phase are mostly already well with resolution of warning signs and improving blood parameters as well as stable vital signs.

This study is the first to be done regarding administration of honey towards dengue patients. This study also introduced the usage of bedside dengue combo test to the Emergency Department, PPUKM. Previously, dengue serological testing is sent to the lab which takes time for dengue infection confirmation. This is only done if the FBC components are suspicious of dengue infection. By acquiring the combo test in the pursuit of faster patient recruitment, the emergency department also enjoy faster dengue infection verification and can start treatment quicker with earlier referrals to the medical department.

7. Future Directions

Additional investigation such as measurement of inflammatory markers such as interleukins and prostaglandins would procure better information in understanding the effect of honey in dengue fever.

8. Conclusion

There is no significant improvement in the hematological, hemodynamic and clinical conditions when giving honey to treat dengue patients. Supportive treatment with judicious amount of fluid in accordance to the clinical practice guideline in treating dengue patients remained to be the cornerstone in managing dengue fever.

Nevertheless, complementary alternative medicine remained to be a subset of treatment initiated pro-actively by patients themselves. Most of the patients would seek out a type of CAM during the study duration themselves (which caused them to be excluded) or after the study period has finished.

Lastly, though not significant, patients receiving honey claimed to feel better clinically at a faster rate compared to control receiving group.

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