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Effectiveness Combination of Ginger Extract *(Zingiber officinale)* and Ranitidine Compared with Combination of Ranitidine and Placebo against Severity of Functional Dyspepsia

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ABSTRACT

Background: Efficacy ranitidine as dyspepsia functional treatment was 8-35 % and ginger extracts as a traditional recipe in various countries for generations could be used as a therapy dyspepsia, antinausea, spasm, colic, and other stomach complaints. Ginger therapeutic effectiveness could reach 68-77% in vivo studies (animal models).
Objective: To determined how much influence combination of ginger extract and ranitidine could improve severity of dyspepsia compared with combination of ranitidine and placebo in patients with functional dyspepsia.
Method: This study was a quasi experimental. The research was conducted from December 2015 until April 2016 with 26 participants.
Results: After getting therapy for 2 weeks in group I, mean SODA score in the pain scale decreased (8.4 %) of 29.07 ± 7.29 to 25.08 ± 8.22, statistically significant (p <0.046). Mean SODA score in the pain scale group II decreased (7.2%) of 25.38 ± 6.19 to 24 ± 6.01 (p=0.302). Mean SODA score in the non pain scale in group I decreased (7.7%) of 16.84 ± 2.44 to 15.15 ± 2.64 (p=0.074), while in the group II decreased (1.6%) of 15.77 ± 2.71 to 15.23 ± 2.94 (p=0.470). Mean SODA score in the satisfaction scale in group I increased (19.9%) of 7.77 ± 3.63 to 10.08 ± 3.59 (p=0.053) while in the group II increased (8.4%) of 9.62 ± 2.72 to 10.92 ± 2.46 (p=0.072). Comparison decline of SODA score in the pain scale between group I was 4.31 ± 6.3 and in group II is 1.23 ± 4.91, greater in group I but not significantly (p=0.178) at baseline to week 2nd. Comparison decline of SODA score in the non pain scale between group I was 1.69 ± 3.11 and in group II was 0.54 ± 2.6, greater in group I but not significantly (p=0.316) at baseline to week 2nd. Comparison increasing of SODA score in the satisfaction scale between group I was – 2.31 ± 3.88 and in group II was -1.31 ± 2.39, greater in group I but not significantly (p=0.437).
Conclusion: Combination of ginger extract and ranitidine could decrease pain scale, non pain scale and increase satisfaction scale more effective clinically than plasebo and ranitidine for functional dyspepsia patient, but not statistic significantly
Keywords: ginger extract, severity of dyspepsia, and functional dyspepsia

Background

The actual prevalence of dyspepsia in the general population was unknown, but it estimated 25-40% of adults had experienced these symptoms. According to Indonesian Department of Health, ddyspepsia ranks 15th of the 50 diseases with the highest inpatients hospital. Reports outpatient of Sardjito Hospital explained that patients who present with dyspeptic complaints reached 40% of cases per year[1]. Dyspepsia patient was quite annoying not to be able to perform normal activities[2]. Approximately 50% of patients with functional dyspepsia still complained of gastrointestinal symptoms during follow-up of 5 years even though it was normal endoscopic [3].

One consideration why therapy of functional dyspepsia was necessary more developed was that the long-term use of PPIs could cause side effects. Some reports suspected cases of PPI induced carcinoma of the stomach[4]. Ranitidine use in the community was still relatively high and relatively safe [5] and the effectiveness of ranitidine for functional dyspepsia was only about 8-35% [6], so it needed to be combined with other agents. Another reason for therapies with complementary agents were often used by patients for several reasons such as ease of use, safer than pharmacological agents, the perception of their appeal more to use natural ingredients rather than drugs[6].

WHO monograph on ginger extract based farmakopoia and traditional systems of various countries used for the treatment of dyspepsia, flatulence, spasm, colic, vomiting and other stomach complaints. Only little published research on the effects of ginger extract in functional dyspepsia patients.

Methods

Method of this study was quasi-experimental to determine influence ginger extract combined with ranitidine may improve the severity of dyspepsia compared the combination of ranitidine and placebo in patients with dyspepsia. Research conducted in the endoscopy unit, medical record unit (medical record installation) and outpatient department of internal medicine Dr. Sardjito hospital, from December 2015 until April 2016. Subjects were functional dyspepsia patients who had undergone endoscopy between January 2013 and April 2015 and meet the inclusion and exclusion criteria. Demographic data were collected in the beginning of study. The subjects filled in a SODA questionnaire at weeks 0,1, and 2 to assess the severity of dyspepsia.

Inclusion criteria were functional dyspepsia patients with ≥ 18 years of age, meet the ROME III criteria and underwent endoscopy, and were willing to sign a informed consent. Exclution criteria were consumed products that contain ginger, suffered from organic disease or systemic, consumed drugs such as anticoagulants (warfarin, heparin) or patients with blood clotting disorders because it could increase the risk of

bleeding, and when using the drug salicylates, NSAIDs, glucocorticoids because it increased the risk of organic dyspepsia and could cause overlapping.

Statistical Analysis

Results were presented as mean ± standard deviation. Shapiro-Wilk test is to determine if the variable distribution was normal or not. Variables with normal distribution were tested by paired t-test to compare SODA scores before and after treatment. Independent t-test or the Mann Whitney test to compared SODA scores in group I (treatment) and group II (control). We used the Chi Square test or Fisher's exact test or the Kolmogorov-Smirnov Z test to analyze categorial variables. $p < 0.05$ regarded as significant[7].

Results

This study was to determine whether the extract of ginger combined with ranitidine may improve the severity dyspepsia compared with placebo combined with ranitidine in functional dyspepsia patients? Before the main research, questionnaires severity of dyspepsia assestment (SODA) were validated using α-Cronbach with the results: first reliability of the questionnaire of each scale showed the pain scale r = 0,917 (good), the non pain scale r = 0,809 (good), a satisfaction scale r = 0,371 (less), and second reliability of each scale shows the pain scale r = 0,923 (good), non pain scale r = 0,843 (good), and the satisfaction scale r = 0,6 (sufficient). During January 2013 until May 2015 there were 198 functional dyspepsia patientd who have endoscopy at Dr. Sardjito hospital. We gave invitation to 140 patients and were willing to participate in the study as many as 34 people. Exclusion performed on two patients due to anemia, so the overall functional dyspepsia patients who met the inclusion criteria study was 32 patients. Group I (ranitidine and ginger extract) as many as 18 people, and group II (ranitidine and placebo) for 14 people. In the course of time there were 2 people who did not continue the study because of persistent pain, and 3 people dropped out because of abdominal pain advancing. Group II there was 1 person whose loss of follow-up. A total of 26 patients with functional dyspepsia were included analysis until the end of the study, groups I and II respectively 13 people. Characteristic data are presented in table 1.

Table 1 Characteristic of pasient at baseline

Characteristic	Total (%)
Sex :	
- Female	11 (42)
- Male	15 (58)
Age (year) :	

- 20 – 30	3 (11)
- 31- 40	9 (35)
- More than 40	14 (54)
Marital status :	
- Married	21 (81)
- Not married	5 (19)
Level of education :	
- Primary school	1 (4)
- Secondary school	12 (46)
- university	13 (50)
occupation	
- Work at home	11 (42)
- Goverment employees	6 (23)
- Others	9 (34)

Table 2 Comparison characteristic of patients at baseline

Characteristic	Group I (n=13) n (%)	Group II (n=13) n (%)	p value 95 % CI
Sex :			0,691*
- Female	5(38)	6(46)	
- Male	8(62)	7(54)	
Age (year) :			0,570***
- 20 – 30	2(15)	1(8)	
- 31- 40	6(46)	3(23)	
- More than 40	5(39)	9(69)	
Marital status :			0,500**
- Married	10 (77)	11(85)	
- Not married	3(23)	2(15)	
Level of education :			0,584*
- Primary school	1(8)	0	
- Secondary school	6(46)	6(46)	
- university	6(46)	7(54)	
Occupation:			0,879***
- Work at home	7 (54)	4(31)	
- Goverment employees	3(23)	3(23)	
- Others	3(23)	6(46)	

$p < 0,05$ regarded as significant, * *Chi square test,* ** *Fisher's exact test,* *** *Kolmogorov-Smirnov Z test*

Table 3 Mean SODA score for pain scale and p value for mean changes between I (group treatment) and II (group placebo)

	Baseline	Week 1st	Week 2nd	p		
I	29.07 ± 7.29	25.61 ± 9.31	25.08 ± 8.22	0.056*	0.658**	0.046***
II	25.38 ± 6.19	26 ± 7.82	24 ± 6.01	0.572*	0.050**	0.302***

Table 4 Mean SODA score for non pain scale and p value for mean changes between I (group treatment) and II (group placebo)

	Baseline	Week 1st	Week 2nd	p		
I	16.84 ± 2.44	14.84 ± 3.62	15.15 ± 2.64	0.069*	0.711**	0.074***
II	15.7 ± 2.713	16.08 ± 3.25	15.23 ± 2.94	0.527*	0.217 **	0.470***

Table 5 Mean SODA score for satisfacion scale and p value for mean changes between I (group treatment) and II (group placebo)

	Baseline	Week 1st	Week 2nd	p		
I	7.77 ± 3.63	8.69 ± 2.95	10.08 ± 3.59	0.381*	0.053**	0.053***
II	9.62 ± 2.72	10.15 ± 3.64	10.92 ± 2.46	0.464*	0.352**	0.072***

p < 0.05 regarded as significant, paired t test

information : * mean *baseline*-week 1st *** mean *baseline*-week 2nd
** mean week 1st-week 2nd

Table 6 Comparison delta SODA score in the week 0,1,2 between group I and group II

Scale	Treatment		p value
	Group I	Group II	
Pain intensity (2-47)			
Baseline	29.07 ± 7.29	25.38 ± 6.19	0.177
Change in week 0-1	3.38 ± 5.92	-0.62 ± 3.82	0.052
Change in week 1-2	0.62 ± 4.17	2 ± 3.31	0.358
Change in week 0-2	4.31 ± 6.3	1.23 ± 4.91	0.178
Not pain symptoms (7-35)			
Baseline	16.84 ± 2,44	15.77 ± 2.71	0.298
Change in week 0-1	2 ± 3,60	-0.31 ± 1.7	0.048
Change in week 1-2	-0.31 ± 2,92	0.85 ± 2.34	0.278
Change in week 0-2	1.69 ± 3,11	0.54 ± 2.6	0.316
Satisfaction (2-23)			
Baseline	7.77 ± 3.63	9.62 ± 2.72	0.156
Change in week 0-1	-0.92 ± 3.662	-0.54 ± 2.57	0.759
Change in week 1-2	-1.38 ± 2.32	-0.85 ± 2.88	0.448*
Change in week 0-2	-1.23 ± 4.26	-1.31 ± 2.39	0.955

p < 0,05 regarded as significant, unpaired *t-test*, * Mann-Whitney test

Discussion

This study showed the addition of ginger extract in the treatment group reduced mean of pain scale SODA scores and this significant reduction obtained after receiving ginger extract for 2 weeks. In table 2 above, we could see a decrease in mean of pain scale SODA score of 29.07 ± 7.29 to 25.08 ± 8.22 in the second week and this reduction was significant (p = 0.046), while the decline in 1st week was not significant (p = 0.056). In the control group there is also a decrease in pain scale SODA score, but the decline was not significant (p = 0.302). The mean of non pain scale SODA score in giving ginger extract for 2 weeks decreased greater symptoms (7.7%) compared with placebo (1.6%) but a decrease in

the symptoms were not significant (p = 0.074).

The results were matching with research Drozdov about the effect of ginger (treatment) or diclofenac sodium (positive control) to gastrointestinal health in the population, which showed a significant slight decrease in pain scale SODA score, but there was no change in the non pain scale SODA score in the ginger group[8]. This study also showed that the levels of prostaglandin (PG) gastric mucosa in the group receiving ginger extract showed elevated levels of PGE1, PGE2, PGF2α and gastrin-17 serum (stimulator PG) compared to the control group which was increasing the potential protective mucous.

The declines in mean pain scale SODA score were statistically significant after 2 weeks of ginger extract. This was consistent with *Attilio* research who received efficacy short-term treatment of functional dyspepsia with supplementation of ginger extract and artichoke[9]. The effect was statistically significant compared to placebo. Treatment efficacy appears when day 14th. The treatment group demonstrated the efficacy of therapy in 86.2% of cases after receiving supplementation for 28 days.

The addition of ginger extract in this treatment group was different from Attilio research which the addition did not have a significant effect[9]. In Table 10 showed that after two weeks treatment the mean difference in pain score decrease SODA scale higher in the treatment group compared with the control group (4.31 ± 6.3 vs. 1.23 ± 4.91), although this difference was statistically not significant (p = 0.178). The mean difference in reduction non pain scale SODA score higher in the treatment group compared with the control group (1.69 ± 3.11 vs. 0.54 ± 2.6), also not statistically significant (p = 0.316). This may be due to relatively small sample size and treatment time was not long enough, and cannot be ascertained whether the patient actually already taking capsules as instructed. Results in table 5 shows that the group I, addition ginger extract after two weeks, the level of satisfaction with the health-related dyspepsia were higher percentage (19.9%) compared with the placebo group (8.4%) despite the increasing in satisfaction was not statistically significant in both groups. The higher increasing delta SODA score for satisfaction also could be seen in table 6 where in the group I, the satisfaction scale changes in the second week compared to baseline was -2.31 ± 3.88, while the second group -1.31 ± 2.39 (p = 0.437). Satisfaction scale SODA questionnaire of this language when translated into Indonesian results were difficult to understand by the respondent, and the results of the validation analysis of questionnaire results α-Cronbach r = 0.6 (sufficient) that might affect the significantly results. Nunnally recommended a minimum standard level of reliability was 0.7 for the group. Lately alpha 0.8 ten cited as the minimum[10].

Limitations of this study were not controlled for confounding factors such as dietary intake, lifestyle and psychosocial factors. The absence of evaluation of the treatment was given by the supervisor, with a record time of drug administration schedule and records the rest of medicine. The process of translating the questionnaire SODA at the time of validation was not up to standard. Ideally the questionnaire translated 2 times by linguists (2 different translators) from an officionale institution (eg, Language Training Center), and then sent back to the Department of Veterans Affairs Health Services Research and Development Field Program, the agency that compiled the questionnaire SODA, for rated is already in line with the original questionnaire. Another limitation was the lack of power research, for each scale was about 37.94 %, 25.66 %, and 19.1 %, indicating that the study did not have sufficient power to prove the differences were obtained significant statistically, due to the sample size calculation was based only one the scale and time for follow-up study was less long. To reached power about 80 %, sample had to added be 129 samples for every group.

Conclutions

The combination of ginger extract and ranitidine could decrease pain scale, non pain scale and increased satisfaction with the health-related scale of SODA score more effective clinically than the combination of ranitidine and placebo in patients with functional dyspepsia, but was not statistically significant.

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