Original article

# RANDOMIZED CLINICAL TRIAL OF OMEPRAZOLE AND RANITIDINE USING INDONESIAN TRANSLATED NEPEAN DYSPEPSIA INDEX

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ABSTRACT

In patients with dyspepsia, a common initial management strategy in primary care is to prescribe a course of empiric antisecretory therapy. Ranitidin and omeprazole as antisecretory agents have been proven effective for treatment of dyspepsia. This research was aimed to evaluate the effect of omeprazole and ranitidine by using Nepean Dyspepsia Index (NDI) which was translated and validated in Indonesian language. Fifty healthy persons were asked to complete the Indonesia translated NDI(NDII) and Short Form(SF)- 36, which was previously validated. Cronbach' s alpha and test-retest were performed for reliability analysis. Spearman's rank correlation was used to assess validity. P -value <0.03 was considered statistically significant. The results concluded that NDIl can be used in dyspepsia patients who understand Indonesian language. The number of 104 subjects with a clinical diagnosis of dyspepsia according to the inclusion and exclusion criteria were recruited and randomized to receive ranitidine 150 mg twice daily and omeprazole 20 mg twice daily. Symptoms of dyspepsia were evaluated by using NDIl at baseline one week after treatment. The outcomes of omeprazole and ranitidine were evaluated by comparing improved NDIl score in 5 domains (tension, activities, eating/drinking, knowledge/control and work/study). The mean of age in the subjects was 47 years old that consisted of 36% male. After one week treatment, the NDIl dyspepsia patients score in omeprazole treated group was not significantly different from that in ranitidine treated group. The effect of omeprazole was not better than ranitidine when it was given as empirical treatment for dyspepsia patients in primary care.

Keywords: randomized clinical trial, dyspepsia, NDI, NDIl, omeprazole, ranitidine.

## BACKGROUND

Nowadays, dyspepsia achieves special attention in clinic and research better than other gastrointestinal problems.' Dyspepsia has become a main health problem in societies because of its high cost burden and result in decreasing quality of life.[2] The high cost burden is due to the high prevalence of dyspepsia among 15-20% [M] and the symptoms of dyspepsia are chronic and recurrent[4"6] The burden consists of investigation cost, medications, and decreased daily activities result in increased work lost[7]

Dyspepsia may influence the patient's quality of life including physical function, somatic sensation, psychology, and social interaction.[8] The treatment was aimed to eliminate the symptoms of dyspepsia, improved quality of life and cured the cause. Several researchers had proposed guidelines to manage dyspepsia.[9] The guidelines given by the American college of physicians in 1985: management of dyspepsia with empirical treatment. Empirical treatment was done by giving antisecretory drugs to dyspepsia patients without alarm signs.[10] Till nowadays, empirical treatment is often conducted in primary care.[11,12] Moreover,

many dyspepsia patients for the first time consume sold freely without recipe.[13]

The antisecretory drugs that are available in our hospital are omeprazole and ranitidine. Many researches reported that omeprazole was better than ranitidine,[14-19] but Parente, et al[20] reported that the most used antisecretory drugs in hospital was ranitidine (44.4%), then pantoprazole (31.5%), and omeprazole (23.0%). About 70% clinical practitioner make approach for converting proton pump inhibitors to receptor H2 antagonist to lower the cost for treatment without watching the symptoms of the patients.[21] In several countries, prescribing proton pump inhibitors make higher cost than other antisecretory drugs.[22] Beside that, the choice of antisecretory drugs was based on earlier treatment and the historical previous recipe. Usually, the first drugs taken by dyspepsia patients are receptor H2 antagonists which are sold freely without recipe.[23]

Dyspepsia is a complex of symptoms, it is not a diagnosis, and there is no objective guideline to evaluate dyspepsia.[24] In order to evaluate the results of treatment in dyspepsia, an quality of life instrument is used in the form of questioner related to the score of symptoms and improvements in quality of life.[25] The questioner will fail to function iflhe written language is not understood by the respondents.[26] The quality of life instrument related to specific disease for dyspepsia was available in many languages,[27-32] but it is not available in Indonesian. Among the quality of life instruments, it is Nepean dyspepsia index (NDI)[33] written in Australian English that had been translated and validated in German, Italian, Dutch, American English, French,[34] Arab,[35] Norwegia,[36] and Korea.[37]

In this research, the instrument to evaluate the effect of omeprazole and ranitidine was done by using Nepean dyspepsia index translated in Indonesian (NDII).

## MATERIALS AND METHODS

### Steps of study

This study was done in 5 steps. The first step, NDI and SF-36 were translated in Indonesian and consulted to a person that was expert in Indonesian. The second step, the translated SF-36 was tested in 50 healthy persons and retested at interval 7 days, the third step was done for internal consistency. The forth step, NDU was test for validation. The last step, randomized clinical trial of omeprazole and ranitidine was performed. The steps of this study are shown in figure 1.

### Population Study

The samples of this study are dyspepsia patients who came for treatment in primary care at Department of Internal Medicine, Faculty of Medicine, University of Jenderal Soedirman/Margono Soekarjo Hospital, Purwokerto that fulfill research criteria. The inclusive criteria were patients with more man 18 years of age with dyspepsia symptoms, sign agreement of informed consents, and able to understand Indonesian language. The exclusive criteria were patients with alarm signs (history of upper gastrointestinal cancer in the family, decreased body weight with unknown cause, gastrointestinal bleeding, progressive dysphagia, odynophagia, iron deficient anemia without known cause, persistent vomiting, lymphadenophaty, and hyperbilirubinemia), gastroesophageal reflucs, consuming proton pump inhibitors or receptor H2 antagoniit, non steroid anti inflamation drugs regularly, antibiotics in 4 weeks previously, history of surgery in upper gastrointestinal tract, and pregnancy.

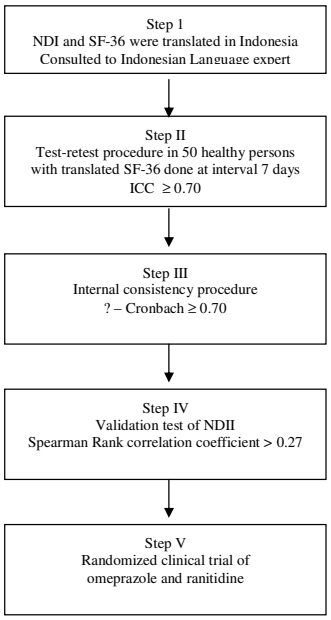


Figure 1. Steps of study

**Sample Size**

Sample Size was determined by comparing the proportion of 2 samples. The healing proportion of omeprazole = 61%, the healing proportion of ranitidine = 41%[38], $\alpha$ = 0.05, and $\beta$ = 0.20. Using Medicalc in 8.2 version, it required 94 persons as the sample size. With the assumption that 10% dropout, so it required 104 persons.

**The Nepean Dyspepsia Index**

NDI was developed by the Sydney research teamwork consisted of 42 questions with 17 aspects.[30] The questioner was further developed to be shorter, easier, and more sensitive to the changes in clinical appearances. The patients can fill the questioner alone. The short form of NDI consisted of 10 questions with 5 aspects (tensions, interferences with daily activities, eating/drinking, knowledge/control, and work/study).[36]

**Interventions**

Subjects for this research were randomized to be treated with 20 mg omeprazole twice daily or 150 mg ranitidine twice daily. At the first day and after 7 days of treatment, interview was done with the NDII.

**Data analyze**

The mean was compared using independent T test and categorial data was tested using $X^2$. The mean difference is significant at the $p < 0.05$. Validation of NDII by using reliability and validity. Reliability was tested with internal consistency and reproducebility. Internal consistency was measured with $\alpha$-Cronbach, it was valid if the a value > 0.70. Reproducibility was evaluated with test-retest procedure (intra-class correlation). The minimal standar of intra-class correlation coefficient was 0.70.[39] NDII validation was analyzed by correlating the NDII score with SF-36 score using Spearman's non-parametric coefficient test at >0.27.[40] Statistic analyzes were done with SPSS program for Windows version 14.

## RESULTS

**Population Study**

This study was conducted from January 2006 till August 2006. Subjects found are 442 dyspepsia patients and 50 healthy persons. Of 442 dyspepsia patients, the 104 persons were categorized as subjects for research. Then, the whole data were got from 154 persons. Characteristic of subjects for research was presented in table 1.

Table 1. Characteristic of subjects for research

| Characteristic | Normal N = 50 | Dyspepsia n = 104 |
|---|---|---|
| Male n(%) | | |
| Age (years) | 19(38) | 37(36) |
| Range | 21-28 | 14-80 |
| mean | 23 | 47 |
| SD | 1.28 | 15.48 |
| BMI (kg/m2) | | |
| range | 17.30-28.60 | 13.32-34.13 |
| mean | 21.98 | 21.95 |
| SD | 3.13 | 3.93 |
| Occupation n(%) | 0(0) | 46(44) |
| Education | | |
| ≥ high school n(%) | 50(100) | 39(37) |

Characteristic of subjects was 64% female dyspepsia patients. The interval of age in dyspepsia patients were 14-80 years with mean 46.81. The body mass index intervals were 13.32-34.13 with mean 21.95. About 56% dyspepsia patients had no occupation, 63% dyspepsia patients were educated under high school.

**Validation test of NDII**

The NDII reliability test was presented in table 2.

Table 2. Reliability of NDII

| | Mean (SD) | Test-retest | | P value |
|---|---|---|---|---|
| | | Cronbach Alpha | Correlation coefficient | |
| Tension | 5.3(2.1) | 0.84 | 0.72 | 0.00 |
| Decreased daily activity | 5.5(2.1) | 0.95 | 0.94 | 0.00 |
| Eating/drinking | 5.0(2.4) | 0.96 | 0.95 | 0.00 |
| Knowledge/control | 5.3(2.1) | 0.95 | 0.94 | 0.00 |
| Work/Study | 5.3(2.1) | 0.84 | 0.98 | 0.00 |

From the 5 domains of NDII, the value of internal consistency α-Croncbanch > 0.70 with p< 0.05 which proved that the relationship among domains in NDII were consistent. The reproducibility of NDII with ICC > 0.70 with p < 0.05 which proved that using repeated NDII in dyspepsia had the same results.

**Validity test for NDII**

Each domain of NDII correlated with all domains of SF-36 with coefficient correlation (r) > 0.27 with p < 0.05 (table 3).

**Table 3. Correlation between NDII and SF-36**

| NDII domains | SF-36 domains | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Physical Function | Role-physical | Bodily pain | General health | Vitality | Social function | Role-emotion | Mental health |
| Tension | 0.450 | 0.036 | 0.440 | 0.638 | 0.424 | 0.286 | 0.350 | 0288 |
| Interference with daily activities | 0.291 | 0.291 | 0.403 | 0.474 | 0.405 | 0.368 | 0.353 | 0.280 |
| Eating/drinking | 0.426 | 0.373 | 0.363 | 0.388 | 0.301 | 0.291 | 0.436 | 0.379 |
| Konwledge/ control | 0.378 | 0.381 | 0.348 | 0.424 | 0.318 | 0.364 | 0.295 | 0.370 |
| Work/study | 0.313 | 0.358 | 0.430 | 0.399 | 0.391 | 0.332 | 0.341 | 0.306 |
| Average NDH | 0.535 | 0.302 | 0.392 | 0.485 | 0.393 | 0. 344 | 0.296 | 0.291 |

**Homogenity test in omeprazole and ranitidine groups**

Homogenity test in groups of subject treated with omeprazole and ranitidine was presented in table 4 and table 5.

Table 4. Data from patients

| | Ranitidin (n=52) | Omperasol (n=52) | P=value |
|---|---|---|---|
| Sex | 1.630 (0.49) | 1.65 (0.48) | 0.686 |
| Age | 47.6 (16.5) | 46 (14.4) | 0.403 |
| BMI | 21.93 (3.6) | 21.94 (4.2) | 0.267 |

Table 5. Data score NDII before treatment

| | Ranitidin (n=52) | Omperasol (n=52) | P=value |
|---|---|---|---|
| Tension | 5.2 (2.2) | 2.7 (1.9) | 0.03 |
| Activities | 5.4 (2.6) | 5.6 (1.8) | 0.07 |
| Eating/drinking | 5.2 (2.1) | 5.4 (2.0) | 0.30 |
| Konwledge/control | 4.9 (2.0) | 5.5 (1.8) | 0.08 |
| Work/study | 5.4 (2.0) | 5.5 (1.8) | 0.24 |

The homogenity test was analyzed for sex, age, body mass index and ND1I before the treatments. It was found that sex, age, and body mass index had $p > 0.05$. Among 5 items of ND1I only tension that was significantly different ($p < 0.05$). The results concluded that the effect of omeprazole and ranitidine could be tested without tension item.

**Test for the effect of omeprazole and ranitidine**

The effect of omeprazole and ranitidine were evaluated by comparing unproved NDII score that was validated (table 6)

Table 6. Changed score in each domain after treatment

| | Ranitidin (n=52) | Omperasol (n=52) | P=value |
|---|---|---|---|
| Tension | -0.65 (1.95) | -0.58 (1.85) | 0.59 |
| Activities | -0.46 2.17) | -0.38 (2.05) | 0.75 |
| Eating/drinking | -0.40 (1.94) | -0.71 (1.96) | 0.67 |
| Konwledge/control | -0.45 (2.30) | -0.42 (1.85) | 0.60 |
| Work/study | -0.73 (1.81) | -0.63 (2.02) | 0.26 |

Based on the mean value, ranitidine was better than omeprazole in tension, activity, knowledge /control and work/study domains. For the 4 items, ranitidine produced improved symptoms better than omeprazole. However, it was not significantly different by statistic test ($p > 0.05$).

## DISCUSSIONS

Validation test for NDII was done to evaluate the results of treatment in dyspepsia patients given omeprazole or ranitidine which were gastric acid suppressive drugs. Validation test was consisted of reliability and validity tests. Reliability test was done for internal consistency and reproducibility of an instrument. Internal consistency was proposed that the question items in a questioner correlated each other and homogenous. One of the evaluation for internal consistency was counting a-Cronbach that was good at value > 0.070. Reproducibility was directly proven by the same value from an instrument if it was done repeatedly. Reproducibility was evaluated with test-retest procedure (intra-class correlation) for the different value at previous interview and die repeated value at another day. The minimal standar of intra-class correlation coefficient was 0.70.[39] This study showed that 5 Hems in NDII at internal consistency a-Cronbach > 0.070 with $p < 0.05$ concluded that the correlation among the question items in NDII were consistent. In this research, the value of ICC was > 0.070 with $p < 0.05$ which proved that using NDII repeatedly in dyspepsia produced die same result

Validity test was aimed to test an instrument that could be trusted to give outcome value acording to its function.[39] Validity test of an instrument was determined by finding the correlation in its item with one generic instrument like SF-36. The correlation was decided by using Pearson's product moment correlation with coefficient > 0.27.[40] In this study, the validity test results showed that all of the items in NDII > 0.27 proved that the NDII was valid. It was concluded that NDII could be used to evaluate treatment for dyspepsia patients who understood Indonesian language. Many researchers had reported the validity of NDI in various languages.[27-32]

In this research, omeprazole was not proven better than ranitidine. The result did not agreed with other researchers[18,19] [19] who concluded that omeprazole was better than ranitidine. Several researchers reported that omeprazole was better than ranitidine in dyspepsia patients who were also infected by *H. pylori* and ulcer-like dyspepsia.[41] Other researchers reported that omeprazole was not proven better than ranitidine. Ranitidine was better than omeprazole if the patients also suffered oesophagial reflux[43] and consumed together with drugs to eradicate *H. pylori.* It was better because gastric acid suppressive drugs strongly influenced the avaibility of anti H. *pylori* drugs.[44] This recent

research *did* not involved the data of *H. pylori* infection nor subgroups of dyspepsia.

Although many researchers reported that omeprazole was better than ranitidine[4-19], this research supported that ranitidine was the most frequently used drug in hospitals[21] with less cost.[22] This research concluded that NDII could be used to evaluate the treatment of dyspepsia patients and empirical treatment with omeprazole was not better than ranitidine for dyspepsia patients in primary care.

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