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Multimicronutrient supplementation and asymptomatic urinary tract infections in the elderly

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ABSTRACT

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As human life expectancy continues to increase, developing countries are reporting higher percentages of elderly in their respective populations. The defense mechanisms of the elderly are reduced due to several factors, such as increased susceptibility to infection, specifically urinary tract infection (UTI). A randomised, placebo-controlled, double-blind trial was conducted to assess whether multimicronutrient supplementation is effective in reducing UTIs in older people in the community. A total of 261 elderly who lived in Mampang Prapatan district, South Jakarta, were randomised to daily multimicronutrient supplementation or control groups. The primary outcomes were the incidence of asymptomatic UTI, the organisms responsible for UTIs and the results of sensitivity tests on UTI microorganisms. UTI was defined as culture-positive urine yielding a single species of organisms in numbers greater than 10^4 cfu/mL urine specimen. At base-line 19.5% of the elderly had UTI, namely 23.7% patients in the MMN group and 16.7% in the control group, but the difference was not statistically significant (p=0.158). *Escherichia coli* was the most common microorganism, isolated in 20.7% of the MMN group and 17.5% of the control group. After six months of supplementation, UTI in the MMN group decreased by 40.6% compared with only 14.4% in the control group. The numbers of *E. coli* also declined by 64.3% in the MMN group compared to 37.8% in the control group. This study has confirmed the beneficial effect of multimicronutrient supplementation on UTI in the elderly.

Keywords: Multimicronutrients, urinary tract infection, resistance, elderly

INTRODUCTION

In 2004 the number of elderly in Indonesia was 5.8% of the general population and will continue to increase.[(1)] From the year 2000 up to 2050, the elderly population throughout the world will experience a two to fourfold increase.[(2)] Infection is among the most common of disorders in older Americans, and elderly individuals are 2–10 fold more likely to die of a variety of infections than are young adults.[(3)] Urinary tract infection (UTI) is very common in older people, being the most frequent bacterial infection recorded in older people, followed by pneumonia and skin/soft tissue infections.[4] The majority of UTI in elderly over 65 years of age in the urology department of RSCM hospital occurred in men (95.0%), in whom the proportion of UTI was 14.4%. The most frequent etiological organism was *E.coli* (38.6%).[5]

A study in the UK showed a UTI prevalence of 5.6% in the elderly.[6] The causes of the increased susceptibility to UTI in older people are multiple: decline in cell-mediated immunity, altered bladder defenses due to obstructive uropathy, neurogenic bladder dysfunction, increased bacterial receptivity of uroepithelial cells, increased risk of contamination due to faecal and urinary incontinence as well as urethral instrumentation and catheterization, and decrease in prostatic and vaginal antibacterial factors associated with changes in zinc levels, urinary and vaginal pH, and hormones, especially lack of estrogens. Men become more susceptible to UTIs after 50 years of age, when they begin to develop prostate problems. Benign prostatic hyperplasia (BPH) can produce obstruction in the urinary tract and increase the risk for infection. In men, recurrent UTIs are also associated with prostatitis caused by *E. coli*.[7] Although only about 20% of UTIs occur in men, these infections can cause more serious problems than they do in women. Men with UTIs are far more likely to be hospitalized than women.[8] Bacterial UTIs can be classified according to localization as urethritis (urethra), cystitis (bladder), or pyelonephritis (kidney). In men, prostatitis may mimic or complicate UTI. Alternatively, UTI can be classified by the presence or absence of symptoms (as symptomatic or asymptomatic), the frequency of its occurrence, the presence or absence of complications, and especially important in the elderly whether UTI is associated with catheter use. Older people are more likely to have adverse reactions to drugs. Up to the present time older women with uncomplicated UTI were treated longer than younger patients without any scientific evidence and with an increased risk of adverse drug reactions.[9]

Older adults are at risk for malnutrition, which may contribute to their increased risk of infection. UTI is defined when the number of bacteria on urinary culture is more than 100,000 colony forming units per mL.[10] If not promptly and appropriately managed, UTI may lead to infection of the kidneys and renal failure. Urine was the most common specimen of *E.coli* inactive isolated.[11] The etiology of UTI in the elderly is mainly *E.coli* (50%).[12] Studies on the prevalence of bacteriuria in Indonesian elderly are few in number. The effects of multimicronutrient supplementation on bacteriuria and microbial antibiotic resistance in the elderly are still not clearly understood, and will be the subject of the current study.

METHODS

Research design

A randomized, placebo-controlled, double-blind trial was conducted to assess whether multimicronutrient supplementation is effective in reducing UTIs in older people.

Study population

The target population were the elderly residents of Mampang Prapatan district, South Jakarta. The inclusion criteria were: male and female elderly aged 60 years and over, mobile, healthy, able to communicate and willing to participate in the study. Terminally ill persons and those currently receiving antibiotic therapy for infections were excluded. Written informed consent was obtained from the participants and the study was approved by the Ethics Committee, Medical Faculty, Trisakti University. A total of 261 subjects were enrolled using cluster and simple random sampling.

Randomization

Participants were randomized to receive multi-micronutrients (MMN) consisting of 40 mg elemental zinc (as zinc gluconate), 120 mg ascorbic acid, 6 mg â-carotene, 15 mg á-tocopherol (d-á-tocopheryl acid succinate) and 400 μg folic acid. The control group received daily oral tablets containing 400 mg calcium carbonate. Randomization was performed using a blocks-of-six design in a numbered sequence prepared from computer-generated random numbers (Microsoft Excel) by an individual not otherwise involved in the study.

Intervention

The supplementation was given every day for 6 months by the field workers at their home visits. Participants in the treatment group received a daily oral tablet containing the amounts of vitamins and minerals stated above, except that on Saturdays they received two tablets. Participants in the control group received a daily oral tablet containing calcium. Both supplements were identical in color, size and taste, and would cause similar changes in the color of the participants' urine. PT Ikapharmindo Pharmaceutical prepared the supplement and control tablets specifically for this study, according to the specifications of the investigators. All participants were required to take the tablets daily for 6 months. At the home visits, the field workers recorded all occurring side effects and at the end of the month noted the number of supplements taken. The subjects were designated as withdrawals when they had not taken the supplements for two weeks consecutively.

Collection of specimens

After the elderly stated their willingness for participation in the study by signing the informed consent form, the examining physician filled out the forms on personal data and clinical information for each participant. Collection of early morning mid-stream urine was done on the fasting subject to avoid dilution of the urine. For female elderly, before voiding urine the external genital area was cleansed with soap and water and rinsed with clean water. The first portion of the urine was discarded, and only 20 mL of the mid-stream portion was collected in a sterile container. Collection of urine samples was conducted before and after the 6 months of MMN supplementation.

Transport of urine samples

The containers with the urine samples labeled with the subject's identification number were put in an ice-box for transport to the Microbiological Laboratory, Medical Faculty, Trisakti University within 4 hours after collection. The urine samples that could not be sent on time were put in refrigerators at the study location and were sent to the laboratory within 24 hours. On arrival at the Microbiological Laboratory the specimens were recorded in a logbook.

Bacteriological examination

On arrival at the laboratory, the urine specimens were promptly processed according to standard methods.(4) Direct microscopy was performed on a Gram smear of uncentrifuged urine. The number of bacteria per high-power field was counted and the presence of leucocytes was recorded. A volume of 10 mL urine was centrifuged at 2500 rpm for 5 minutes. The supernatant was discarded and one drop of the sediment was placed on a glass slide, a cover slip was put on top, and the preparation was examined under a microscope. The mean of three high-power field readings was taken as the outcome. Pyuria was diagnosed when more than 5 leucocytes per high-power field were found.

Urine culture methods

The urine sample of elderly with pyuria was cultured for assessment of bacterial colony count. Volumes of 0.01 mL and 0.001 mL of uncentrifuged urine were taken from the container by means of a calibrated loop, which was inserted vertically into the urine sample. The urine sample was streaked evenly on blood agar and McConkey agar plates, using the same loop. The agar plates were subsequently incubated aerobically at 35^0-37^0 C for 24-48 hours, after which the colonies were counted. From the results the mean was taken to obtain the number of colonies per milliliter of urine. Identification of isolates was performed according to standard methods.(4) A subject with a colony count of < 10,000 cfu/mL on blood agar plate was not considered to be suffering from bacteriuria. A count of 10,000-100,000 cfu/mL might be due to contamination, but a count of >100,000 cfu/mL was considered indicative of bacteriuria.(4)

Microbial susceptibility to antibiotics

Antibiotic sensitivity tests were conducted on antimicrobial drugs commonly used for treatment of bacteriuria, such as ciprofloxacin, norfloxacin, nalidixate, tetracycline, ampicillin, and chloramphenicol. The sensitivity tests were performed according to the Kirby-Bauer disk diffusion method and the minimal inhibitory concentration (MIC) were assessed using the National Committee for Clinical Laboratory Standards. (8,9)

Statistical methods

Sample size

Based on a study by Achmad(6) on UTI, it was predicted that a final sample of 260 participants would be required to have a power of 80% at P<0.05 for detecting a 50% reduction in the incidence of subjects having at least one episode of UTI in the MMN group.

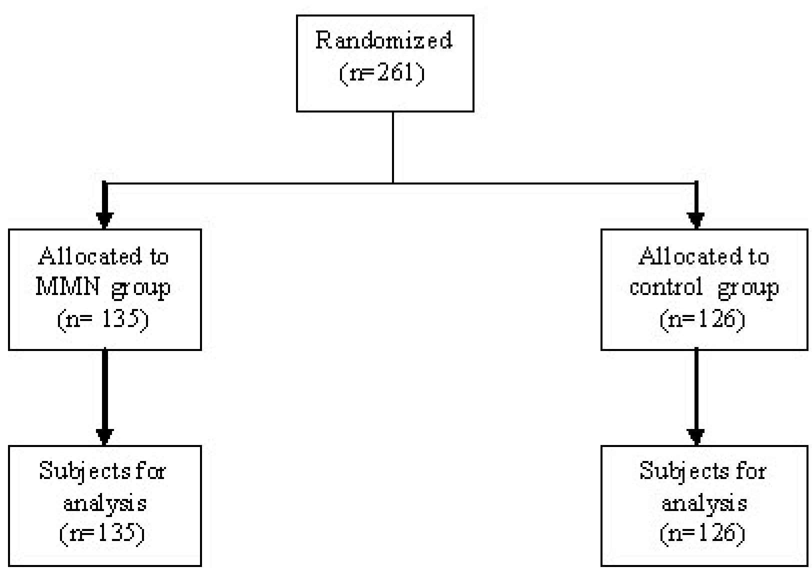

Figure 1. Participant recruitment and follow-up

Statistical analysis

Data were entered onto Excel database and analyzed using SPSS version 15.0. Full statistical analysis was performed prior to breaking the treatment code. Between-group comparisons were made using the unpaired t-test for normally distributed variables. Categorical variables were compared using the chi squared test.

RESULTS

Figure 1 outlines the results of the trial selection process. A total of 261 elderly were enrolled and randomized into MMN (n=135) and control (n=126) groups.

Participant characteristics

Table 1 summarizes the characteristics of the study participants at baseline. Participants were similar at baseline with no significant differences between the two groups (Table 1). The overall sample was predominately female (62.8%), and between the ages of 60 and 78 years. A total of 19.5% (53/261) had at least one UTI, consisting of 32/135 (23.7%) subjects in the MMN group and 21/126 (16.7%) in the control group, but the numbers were not significantly different (p=0.158). *E. coli* was the most common microorganism, being isolated in 20.7% of the MMN group and in 17.5% of the control group, but the difference in frequencies was not statistically significant (p=0.181). Another isolated microorganism was *Klebsiella*, found only in the MMN group (2.2%).

Antimicrobial sensitivity tests at baseline

The results of several antimicrobial sensitivity tests on 50 *E.coli* isolates indicated that there were no significant differences in sensitivity tests between the MMN and control groups for ciprofloxacin, norfloxacin, tetracycline, ampicillin and chloramphenicol (p > 0.05). However, antimicrobial sensitivity tests for nalidixate on *E.coli* isolates showed a significant difference between the MMN and control groups, antimicrobial resistance being higher in the control group compared with the MMN group (p = 0.037) (Table 2).

Urinary tract infections after supplementation

After 6 months of multi-micronutrient supplementation, the proportions of the elderly with UTI were 12.6% in the intervention group and 14.3% in the control group, the difference

Table 1. Baseline demographic characteristics and urinary tract infections in the elderly according to study group at baseline

Variable	MMN group (n=135)	Control group (n=126)	P value
Age (yrs)	65.8 ± 4.5	65.7 ± 4.6	0.839
Gender			
Male	55 (40.7%)	42 (33.3%)	0.115
Female	80 (59.3%)	84 (66.7%)	
Sediment			
Abnormal	32 (23.7%)	21 (16.7%)	0.158
Colony count			
≥ 100.000	32 (23.7%)	21 (16.7%)	0.158
Bacterial identification			
E.coli	28 (20.7%)	22 (17.5%)	0.181
Klebsiella	3 (2.2%)	0 (0.0%)	

Tabel 2. Antimicrobial sensitivity tests on 50 *E.coli* isolates in the elderly by study group at baseline

Antimicrobial	MMN group (n=28)	Control group (n=22)	P value
Ciprofloxacin			
Sensitive	24 (85.7%)	22 (100.0%)	0.065
Resistant	4 (14.3%)	0 (0.0%)	
Norfloxacin			
Sensitive	27 (96.4%)	21 (95.5%)	0.861
Resistant	1 (3.6%)	1 (4.5%)	
Nalidixate			
Sensitive	11 (39.3%)	11 (50.0%)	0.037 *
Resistant	16 (12.7%)	6 (27.3%)	
Intermediate	1 (3.6%)	5 (22.7%)	
Tetracycline			
Sensitive	18 (64.3%)	10 (45.5%)	0.183
Resistant	10 (35.7%)	12 (54.5%)	
Ampicillin			
Sensitive	4 (14.3%)	6 (27.3%)	0.253
Resistant	24 (85.7%)	16 (72.7%)	
Chloramphenicol			
Sensitive	19 (67.9%)	15 (68.2%)	0.661
Resistant	8 (28.6%)	7 (31.8%)	
Intermediate	1 (3.5%)	0 (0.0%)	

being statistically not significant (p=0.719). However, when compared with baseline values, UTI in the MMN group after supplementation was reduced by 40.6% (11.1%/27.3%), whilst in the control group the reduction in UTI was only 14.4% (2.4%/16.7%). The proportions of *E.coli* and *Klebsiella* after 6 months of supplementation were respectively 7.4% and 4.4% in the intervention group and respectively 12.7% and 0.8% in the control group, these figures being statistically also not significant (p=0.078). The proportion of *E.coli* was also decreased by 64.3%% {(20.7% - 7.4%)/20.7%} in the intervention group after 6 months of supplementation, compared with the proportion at baseline. In the control group the proprtion of *E.coli* decreased by 37.8%{(17.5% - 12.7%)/ 17.5%}.

Table 3. Urinary tract infection in the elderly after 6 months of supplementation by study group

Urinary tract infection	MMN group (n=135)	Control group (n=126)	P value
Sediment			
abnormal	17 (12.6%)	18 (14.3%)	0.719
Colony count			
≥ 100.000	17 (12.6%)	18 (14.3%)	0.719
Genus/species of bacterium			
E.coli	10 (7.4%)	16 (12.7%)	0.078
Klebsiella	6 (4.4%)	1 (0.8%)	

Table 4. Antimicrobial sensitivity tests on 25 *E.coli* isolates in elderly by study group after supplementation

Antimicrobial	MMN group (n=9)	Control group (n=16)	P value
Ciprofloxacin			
Sensitive	9 (100.0%)	15 (93.8%)	0.444
Resistant	0 (0.0%)	1 (6.2%)	
Norfloxacin			
Sensitive	9 (100.0%)	15 (93.8%)	0.444
Resistant	0 (0.0%)	1 (6.2%)	
Nalidixate			
Sensitive	9 (100.0%)	14 (87.5%)	0.269
Resistant	0 (0%)	2 (12.5%)	
Tetracycline			
Sensitive	6 (66.7%)	12 (75.0%)	0.569
Resistant	3 (33.3%)	3 (18.8%)	
Intermediate	0 (0.0%)	1 (6.2%)	
Ampicillin			
Sensitive	2 (22.2%)	4 (25.0%)	0.724
Resistant	7 (77.8%)	11 (68.8%)	
Intermediate	0 (0.0%)	1 (6.2%)	
Chloramphenicol			
Sensitive	8 (88.9%)	15 (93.8%)	0.667
Resistant	1 (11.1%)	1 (6.2%)	

Antimicrobial sensitivity tests on *E.coli* after supplementation

Sensitivity tests for several antimicrobials on *E. coli* after 6 months of MMN supplementation indicated that *E. coli* was sensitive (100%) to ciprofloxacin, norfloxacin and nalidixate in the intervention group, compared with the control group, where 87.5% - 93.8% of the bacteria was sensitive. However, the difference was statistically not significant (p> 0.05) (Table 4).

DISCUSSION

Infectious diseases are a common cause of increased morbidity and mortality in the elderly people. A number of health factors contribute to genitourinary infections. Comorbid diseases, functional status, and living environments each play a role in a patient's susceptibility to infection, and each may complicate an otherwise simple urinary infection. Among healthy elderly patients, these infections are usually benign; however, in patients with significant comorbidities, UTIs can ultimately lead to more serious complications.[12,13] Infections in the elderly are quite different from infections in a younger population. These differences are due to age-related alterations in immunity. There are multiple reasons for higher rates of infection when compared with younger patients. Anatomic variations during the aging process (such as changes in prostatic function in men and changes in vaginal flora associated with menopause in women) increase the risk of UTIs.[14] Incidence and bacterial spectrum depends on the site of infection and whether the patient is hospitalized, living in a nursing home or in the community. In this study, of 261 elderly in the community 19.5% had UTI. Our results showed a similar UTI prevalence when compared with a study in 520 elderly people in nursing home at Iran, where the UTI prevalence was 15.5%.[1] On the other hand, our study showed a higher UTI rate than that found in a study of 262 nursing home residents, where the UTI rate was 3.4%.[15] The reason for these differing figures may lie in the fact that in the present study the number of females was higher than that of males, and that males are less prone to UTI, possibly because of their longer urethra and the presence of antimicrobial substances in prostatic fluids.[16] Most UTI are asymptomatic, which is remarkable in view of the prevalence of bacteriuria in 15% - 50% of all residents of long-term care facilities.[17]

Diagnosis of UTI in confused elderly patients can be difficult because of the non-specific and frequently misleading symptoms and signs, and is therefore primarily based on microscopic examination of urine . [18] A study of institutionalized elderly persons demonstrating the benefits by means of clinical end points suggested that trace minerals, rather than vitamins, may be the key nutritional factor for preventing infection in older adults.[18]

Escherichia coli was the commonest organism isolated in our study, and is recognised as the most common urinary tract pathogen in elderly people.[10] We found significantly fewer infections with *E. coli* in the multi-micronutrient group than in the control group. An important reason for evaluating the effectiveness of multimicronutrients is because of their potential to improve immune responses to infection and thus prevent illness. Multi-micronutrient supplementation for older people increased their in-vitro lymphocyte response to mitogens.[20]

The use of antimicrobials for treatment of urinary infection is a part of the larger concern about appropriate antimicrobial use in the elderly and the impacts of the selective pressure of antimicrobials on colonization and infection with resistant organisms. Treatment of urinary infections in elderly patients should be conservative when compared with younger, healthier individuals. Higher rates of failure and relapse are more often associated with advanced age. Fluoroquinolones are the preferred first-line treatment when the pathogen is not known, as they have a wider spectrum of coverage and greater penetration of the prostate gland compared with other antibiotics.[11] In our study, after six months of multimicronutrient supplementation antimicrobial sensitivity tests showed that *E. coli* was 100% sensitive to ciprofloxacin and norfloxacin compared with the control group (sensitivity 87.5% – 93.8%), which figures were however not significantly different. The occurrence of interactions between host and numerous potential pathogens should be further investigated using a larger number of *E. coli* isolates. It should be of interest to explore whether multi-micronutrient supplementation might not be able to affect the host-pathogen balance, impacting on antimicrobial sensitivity of the pathogens.[21] Numerous micronutrients play a special role in human immune function. Should *Escherichia coli* after micronutrient supplementation of the host become more sensitive to the fluoroquinolones, by what amount, and how effective would the supplementation be. We propose a more integrated approach to investigate the actions of micronutrients in human beings on the interaction between host and pathogen biology and genomics.

CONCLUSIONS

A multi-micronutrient supplement reduced the incidence of UTI by 40.6% in the MMN group and only by 14.4% in the control group. Infections with *E. coli* were less frequent in the multi- micronutrient group than in the control group after six months of supplementation.

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