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Coenzyme Q₁₀ Administration in Community-Acquired Pneumonia in the Elderly

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Background: Community-acquired pneumonia (CAP) is generally considered a major cause of morbidity and mortality in the elderly. This study aimed to assess the efficacy of adjunctive coenzyme Q₁₀ (CoQ₁₀) in the treatment of elderly CAP.

Objectives: The objective of this study was to evaluate the efficacy of adjunctive CoQ₁₀ in elderly patients with CAP.

Methods: This was a randomized controlled clinical trial. Enrolled patients were randomized into two groups: CoQ₁₀ and placebo. CoQ₁₀ was administered orally at a dose of 200 mg/day for 14 days.

Results: Of the 150 patients enrolled, 141 were included in the analysis. The trial group had a shorter hospital stay (P = 0.0144) and faster defervescence (P = 0.0206) compared to the control group. The subgroup analysis showed differences in clinical cure at day 14. Treatment failure was less in the CoQ₁₀ group than in the placebo group (10% versus 22.5% and P value = 0.0440). Adverse events in two groups were few and similar.

Conclusions: CoQ₁₀ administration has no serious side effects and can improve outcomes in hospitalized elderly CAP; therefore, we recommend it as an adjunctive treatment in elderly patients.

Keywords: Coenzyme Q₁₀; Elderly; Pneumonia

1. Background

Community-acquired pneumonia (CAP) is a relatively frequent infectious disease, which causes serious morbidity worldwide (1). The reported annual incidence of CAP in different populations ranges from 1.3 to 11.6 cases per 1,000 people (2, 3), with the highest rate in older adults (4, 5). CAP in the elderly is rising due to the increased elderly population (6). Management of pneumonia in an elderly patient requires an appreciation of many aspects of the geriatric medicine such as demographics of aging population (7) and the effect of the pneumonia on the general health of the elderly. Most patients who require hospitalization for the treatment of community-acquired pneumonia (CAP) are old, and mostly treated by non-specialists. Thomas (8) calculated the annual treatment cost of pneumonia in patients aged > 65 years to be $48,000 million, compared with $36,000 million for those patients aged < 65 years. They also noted that the average hospital stay for an elderly person with pneumonia was 7.8 days, at a cost of $7,166, whereas for a young (8y) patient the corresponding values were 5.8 days and $6,042.

In developed countries, about 50% of total hospitalizations for pneumonia occur in patients over 65 years and pneumonia is the main reason of death among them (9, 10). However, despite the importance of CAP in the elderly, the information regarding its epidemiology in elderly populations is scarce and the true burden of the disease is not clear, as the incidence and mortality rates in elderly populations are variable in different studies. It has been reported that the incidence rate of elderly person-years varies between 0.2% and 4% and case-fatality rate ranges from 7% to 35% for elderly patients in Europe and North America during the last two decades (11-14).

CoQ₁₀ is a naturally occurring fat-soluble vitamin-like quinone. Quinone or ubiquinone exists in all eukaryotic cells. It exerts its action at the cellular level and improves some of the basic deficiencies causing certain diseases. These actions include correction of the energetic pathways and oxidant stresses in some conditions. CoQ₁₀ plays a key role in mitochondrial oxidative phosphorylation and ATP production. It participates in electron transfer in the mitochondrial oxidative respiratory chain, producing adenosine triphosphate (ATP) (15-19). In addition,
it is a potent antioxidant that prevents oxidative injury by free radicals, including lipids oxidation within the mitochondrial membrane (20, 21). CoQ₁₀ also serves as an antioxidant by activating and enhancing mitochondrial uncoupling proteins, an effect, which is anti-apoptotic and leads to a reduction in free radical generation (22). There is also emerging evidence for its pleiotropic effects. It has also been shown to inhibit interleukin-6, tumor necrosis factor-α, and nuclear factor-κB expression, thus exerting an anti-inflammatory role (23, 24). This adjunct also improves cardiac function, scavenger’s free radical, has antioxidant effects, improves endothelial function, vasodilatory effect, as well as membrane stabilization. Our hypothesis was that adjunctive treatment of CoQ₁₀ with antibiotic treatment may improve outcome of CAP in old patients.

2. Objectives
This study aimed to assess the efficacy of adjunctive co-enzyme Q₁₀ (CoQ₁₀) in the treatment of elderly CAP.

3. Patients and Methods

3.1. Patients
This study recruited its participants from patients referring prospectively at the infectious diseases ward of Valiasr Hospital, a general teaching hospital in Arak City of Iran from August 2012 to September 2013. Patients with the following criteria were enrolled: signed written informed consent; having clinical symptoms suggestive of CAP such as cough (with or without sputum), fever (> 38.5°C), pleuritic chest pain or dyspnea, new consolidations on chest radiograph; aged 60 years or older. Patients were excluded from the study having the following criteria: presence of severe immunosuppression (HIV infection, use of immune-suppressants), malignancy, taking antibiotics before hospital admission for more than 24 hours, use of corticosteroids for any reason, other concurrent infections, obstruction pneumonia (e.g. because of lung cancer), pneumonia that developed within two weeks after hospital discharge, use of CoQ₁₀ within 1 month before study entry, hypersensitivity to CoQ₁₀, taking drugs or compounds with anticoagulants or antioxidants such as warfarin, vitamin C, vitamin E, or vitamin A, as well as indications that patients were unable to follow the protocol.

3.2. Study Design
We designed a clinical randomized placebo-controlled trial in elderly hospitalized patients with CAP. Primary outcomes were clinical cure at days 3 and 7. Secondary outcomes were clinical cure at Day 14, length of stay, time to clinical stability, defervescence, and serum C-reactive protein (CRP). Participants were assigned using computer-generated randomization to receive either CoQ₁₀ or placebo. Those randomized to placebo received matching inactive tablets administered in a dosing regimen identical to the active treatment. Both CoQ₁₀ and placebo capsules were identical in appearance. All laboratory tests were measured in one laboratory with the same personnel and calibrated equipment and all clinical signs and symptoms were measured by one person. The study was carried out in accordance with the Helsinki declaration. Written informed consent was obtained in all cases from patients. The study was approved by the Medical Ethics Committee of our institution. The trial has also been registered with www.irct.ir (IRCT201305159855N3).

3.3. Treatment and Outcomes
All patients were treated with antibiotics according to the latest recommendations of the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) guidelines [1]. In general, patients were treated with ceftriaxone plus azithromycin. Patients received 100 mg of CoQ₁₀ (Capsule 100 mg, Product of Nutri Century, Canada) twice daily or placebo for a total of 14 days. The selected antimicrobial regimen should not be changed during this time unless progressive deterioration was noted or initial microbiologic studies dictated so. The duration of antibiotic treatment was dictated by the patient’s response to therapy with a recommended minimum duration of 7-day therapy and all patients were followed for 30 days. Most patients treated with 7-10 days of antibiotic treatment, although longer courses may be necessary in patients with complications or certain pathogens such as Pseudomonas aeruginosa.

Standard laboratory assessment was performed on presentation and included renal and liver functions, O₂ saturation, hematology, glucose, CRP, and electrolytes analysis. Serum samples were drawn on the day of hospitalization, day 3, day 7, and day 14 for the assessment of CRP (latex agglutination tests), WBC (hematology analyzer Sysmex K1000), BUN (AutoAnalyzer Cobas Mira), and O₂ saturation (pulse oximeter Beurer PO30).

Clinical cure was defined as the resolution or improvement of the symptoms and clinical signs of pneumonia without the need for additional or alternative therapy. Clinical stability was defined with slight modification of Halm’s criteria (25, 26), as the condition when the following values were achieved for all parameters: temperature ≤ 37.2°C, heart rate ≤ 100 beats/min, respiratory rate ≤ 24 breaths/min, systolic blood pressure ≥ 90 mmHg, and oxygen saturation ≥ 90% (when the patient was not receiving supplemental oxygen).

Treatment failure was defined as development of all or each one of the following conditions: the persistence or progression of all signs and symptoms that developed during the acute disease episode after random allocation, the development of a new pulmonary or extrapulmonary infection, the deterioration of chest radiography, death due to pneumonia, or the inability to complete the study owing to adverse events (27). Defervescence was defined
as a temperature less than 37.5°C.

3.4. Statistics

Sample size was calculated based on the published data of a resembling trial on vitamin C (28). The formula of calculating sample size was:

\[
(n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times (p_1(1-p_1)+p_2(1-p_2))}{(p_1-p_2)^2}),
\]

Where \( p_1 = 0.30 \) and \( p_2 = 0.15 \) (\( p_1 \) = proportion of death in vitamin C group and \( p_2 \) = proportion of death in placebo group). With a power of 80% and \( \alpha \) level of 0.05, the sample size was calculated to be 68 for each group and taking into account 10% drop-out, a total of 150 patients were enrolled in two groups of case and control. An intention-to-treat analysis of the primary study outcomes was performed for all randomized patients. The data were summarized as frequencies or percentages for categorical variables and as means and standard deviations for continuous variables. Differences between the groups were compared by the chi-square or Fisher exact test for categorical variables and t test or Mann–Whitney test for continuous variables depending on the result of the Kolmogorov-Smirnov test for normality of distributions. Differences in the length of stay and time to clinical stability between treatment groups were compared by a log-rank test and the Kaplan-Meier method was used to analyze time from admission to discharge and time to clinical stability and repeated-measures analysis of variance (ANOVA) was used to test for difference between group means over time. Subgroup analysis of the patients was planned with severe CAP (CURB-65 > 2). Odds ratios are reported with 95% confidence intervals. Statistical Package of SPSS (version 16.0) was used for the statistical analysis and data management. \( P < 0.05 \) was considered to be statistically significant.

4. Results

A total of 150 patients were enrolled in the study. During the follow up, 9 patients were excluded from the study (4 patients withdrew from therapy because of their discharge, one patient with pulmonary embolism, one patient with diagnosis of tuberculosis during hospitalization, one patient because of chronic liver disease).

Table 1. Demographic Features and Clinical Characteristics of the Two Groups of Hospitalized Patients With Community Acquired Pneumonia at the Day of Admission

|                        | Trial Group (n = 70) | Control Group (n = 71) | P Value |
|------------------------|---------------------|------------------------|---------|
| Age, y                 | 67.6 ± 7.2          | 68.7 ± 7.9             | 0.3892  |
| Gender, Male           | 37 (52.9)           | 39 (54.9)              | 0.8050  |
| Current smoker         | 15 (21.4)           | 18 (25.4)              | 0.5822  |
| Comorbidities          |                     |                        |         |
| Cardiovascular disease | 27 (38.6)           | 26 (36.6)              | 0.8111  |
| Diabetes mellitus      | 15 (21.4)           | 14 (19.7)              | 0.8018  |
| COPD                   | 12 (17.1)           | 14 (19.7)              | 0.6936  |
| Neurological disease   | 17 (24.3)           | 19 (26.8)              | 0.7361  |
| Renal disease          | 5 (7.1)             | 3 (4.2)                | 0.7125  |
| Liver disease          | 3 (4.3)             | 3 (4.2)                | 0.9858  |
| Temperature, °C        | 38.4 ± 1.1          | 38.6 ± 1.2             | 0.3044  |
| Heart rate, b/m        | 102.7 ± 20.3        | 98.5 ± 18.6            | 0.2018  |
| Respiratory rate, br/m | 26.8 ± 6.6          | 25.4 ± 7.5             | 0.240   |
| Systolic blood pressure, mmHg | 129.3 ± 22.2 | 131.4 ± 21.2          | 0.5690  |
| Hg                     | 55 (78.6)           | 54 (73.2)              | 0.7188  |
| Dyspnea                | 55 (78.6)           | 57 (80.3)              | 0.8018  |
| Cough                  | 51 (72.9)           | 52 (68.6)              | 0.9592  |
| Purulent sputum        | 27 (38.6)           | 32 (45.1)              | 0.4341  |
| Pleuritic chest pain   | 66 (94.3)           | 64 (90.1)              | 0.3589  |
| Rales                  | 64 (91.4)           | 61 (85.9)              | 0.3021  |
| Abnormal body temperature |                     |                        |         |
| Severity (CURB-65)     |                     |                        |         |
| Score 0                | 12 (17.1)           | 15 (21.3)              | 0.5485  |
| Score 1                | 21 (30)             | 19 (26.8)              | 0.6696  |
| Score 2                | 25 (35.7)           | 23 (32.4)              | 0.6774  |
| Score 3                | 9 (12.9)            | 11 (15.5)              | 0.6527  |
| Score 4                | 3 (4.3)             | 2 (2.8)                | 0.6384  |
| Score 5                | 0                   | 1 (1.4)                | 0.3190  |

\(^a\) Data are presented as Mean ± SD or No. (%).
lymphocytic leukemia and 2 patients due to consumption of anti-oxidants before treatment) and finally 141 patients, including 70 patients in the trial group and 71 patients in the control group were analyzed. Figure 1 shows the study flow chart. The mean age of the trial group was 67.6 ± 7.2 y and median was 65 years. In the control group, the mean age was 68.7 ± 7.9 y and the median was 65 years. Demographic characteristics of the patients showed that 28.4% of them belonged to the rural areas while 71.6% were from the urban sector.

Patients with severe pneumonia (CURB-65 score > 2) were evenly distributed among the two groups, 12 (17.2%) patients in the case group and 14 (19.7%) in control group (P value = 0.6965). Baseline patient characteristics and comparison of serum mean level of BUN, CRP, WBC, oxygen saturation in two groups are shown in Tables 1 and 2. Antimicrobial treatment was similar in both study groups. Seventeen (24.3%) patients in the trial group and 18 (25.4%) patients in control group were using antibiotics for less than 24 hours before admission.

The clinical cure rate at days 3, 7, and 14 of treatment was reached by 24, 62, and 68 patients in the trial group and 22, 52, and 62 patients in control group. Table 3 shows the differences between groups. One patient in the trial group and two patients in control group died during hospitalization. Four patients in the trial group and 6 patients in control group were admitted to ICU. In the trial group, 7 (10%) patients with treatment failure needed an additional course of antibiotics, and 6 (8.6%) patients developed a pleural effusion or empyema necessitating additional therapy. In the control group, 16 (22.5%) patients with treatment failure needed additional antibiotics, and 7 (9.9%) patient developed a pleural effusion requiring additional therapy. Kaplan-Meier plots of length of stay and time to stability are shown in Figure 2 and 3. The percentage of censored data was 2.1.

Table 2. Laboratory and Radiological Features of the Two Groups of Hospitalized Patients With Community-Acquired Pneumonia at the Day of Admission

|                          | Trial Group (n = 70) | Control Group (n = 71) | P Value |
|--------------------------|---------------------|------------------------|---------|
| Patients with increased CRP | 64 (91.4)          | 66 (93)                | 0.7350  |
| WBC, x 10^9/L            | 14.2 ± 6.5          | 13.9 ± 5.8             | 0.7736  |
| O2 saturation            | 64.6 ± 13.7         | 62.5 ± 11.8            | 0.3304  |
| BUN, mg/dL               | 39.4 ± 8.3          | 41.3 ± 7.8             | 0.1640  |
| Chest radiography        |                     |                        |         |
| Interstitial             | 3 (4.3)             | 5 (7)                  | 0.4793  |
| Alveolar infiltrates     | 54 (77.1)           | 57 (80.3)              | 0.6489  |
| Mixed alveolar + interstitial | 13 (18.6)      | 9 (12.7)               | 0.3348  |
| Multilobed infiltrates   | 14 (20)             | 11 (15.5)              | 0.4835  |
| Pleural effusion         | 6 (8.6)             | 7 (9.9)                | 0.7948  |

* Data are presented as No. (%)

Table 3. Clinical Outcome of the Two Groups of Hospitalized Patients With Community-Acquired Pneumonia by Intention-to-Treat Analysis

|                          | Trial Group (n = 70) | Control Group (n = 71) | OR (95%CI) | P Value |
|--------------------------|---------------------|------------------------|------------|---------|
| Clinical cure at day 3    | 24 (34.3)           | 22 (31)                | 1.16 (0.54-2.50) | 0.6745  |
| Clinical cure at day 7    | 62 (88.6)           | 52 (73.2)              | 2.83 (1.15-6.99) | 0.0209  |
| Clinical cure at day 14   | 68 (97.1)           | 62 (88.7)              | 4.94 (1.03-7.64) | 0.0370  |
| length of stay, day       | 7.8 + 5.7           | 10.6 + 7.6             | -2.8 (-5.06 to -0.59) | 0.0144  |
| Time to clinical stability day | 5.6 ± 3.9         | 7.1 ± 4.6              | -1.5 (-2.91 to -0.09) | 0.0384  |
| Treatment failure         | 7 (10)              | 16 (22.5)              | 2.62 (1.12-7.64) | 0.0440  |
| ICU admission             | 4 (5.7)             | 6 (8.5)                | 0.66 (0.35-2.82) | 0.5267  |
| Mortality                | 1 (1.4)             | 2 (2.8)                | 0.50 (0.02-2.73) | 0.5676  |

* Data are presented as No. (%)
Table 4. Clinical Outcome of Severe Pneumonia as Defined by CURB-65 Score Greater Than 2 of the Two Groups of Hospitalized Patients With Community-Acquired Pneumonia by Intention-to-Treat Analysis

| Clinical Outcome                          | Trial Group (n = 12) | Control Group (n = 14) | OR (95% CI) | P Value |
|------------------------------------------|----------------------|------------------------|-------------|---------|
| Clinical cure at day 3                   | 2 (16.7)             | 1 (7.1)                | 0.39 (0.03-2.83) | 0.4410  |
| Clinical cure at day 7                   | 5 (41.7)             | 3 (21.4)               | 0.38 (0.07-2.12) | 0.2458  |
| Clinical cure at day 14                  | 10 (83.3)            | 6 (42.9)               | 6.67 (1.05-42.43) | 0.0424  |
| Length of stay, day                      | 15.2 ± 8.4           | 18.6 ± 10.1            | -2.9 (-6.47 to -0.34) | 0.3867  |
| Time to clinical stability day           | 9.5 ± 6.7            | 12.4 ± 8.9             | -2.9 (-9.60 to 3.80) | 0.8991  |
| Treatment failure                        | 5 (41.7)             | 10 (71.4)              | 0.56 (0.11-2.56) | 0.6358  |
| ICU admission                            | 4 (33.3)             | 5 (35.7)               | 0.90 (013-3.06) | 0.4090  |
| Mortality                                | 1 (8.3)              | 2 (14.3)               | 0.55 (0.02-2.67) | 0.4126  |

Data are presented as No. (%).

5. Discussion

This is the first randomized double-blinded placebo-controlled trial of CoQ10 in hospitalized elderly patients with CAP. We found beneficial effects of adjunctive CoQ10 in patients hospitalized with CAP; clinical cure was similar in both groups at day 3, but at days 7 (P value = 0.0209) and 14 (P value = 0.0370) a higher clinical cure rate was observed in the trial group. Treatment failure (P value = 0.0440) and time to clinical stability (P value = 0.0384) in the trial group was significantly lower than the control group. Length of stay was lower in the trial group (P Value = 0.0144), but ICU admission (P value = 0.5267) and mortality rate was not significantly different (P value = 0.5676).

A similar study has not been done so far, but in other studies, the benefit of CoQ10 has been found in combi-
nation with the main treatment. In randomized, multicenter studies, it was found that CoQ10 was associated with less functional decline, including daily activities in patients with Parkinson's disease, amyotrophic lateral sclerosis, and Friedreich's ataxia (29-33). A preliminary open label trial (34) on 32 patients taking 150 mg/d of CoQ10 demonstrated efficacy in reducing the frequency of migraine attacks. A number of randomized controlled trials (35) showed improvement in several clinical parameters of congestive heart failure such as dyspnea, edema, and frequency of hospitalization. These trials were weakened by small sample sizes (only 2 of 14 trials had more than 25 participants) and older techniques for calculating ejection fraction. A systematic review (36) of 8 trials using CoQ10 as adjuvant therapy, at various doses for essential hypertension, found a mean decrease of 16 and 10 mmHg, in systolic and diastolic blood pressure, respectively. CoQ10 has been considered for improving glycemic control through different mechanisms, especially via lowering oxidative stress. In a recent clinical trial, administration of CoQ10 (200 mg/d for 12 weeks) caused modest improvements in hemoglobin A1c levels (P value = 0.32)(37).

In our study, subgroup analysis of patients with severe CAP did not show any beneficial effect for CoQ10, also, the absolute numbers of patients who needed mechanical ventilation was low and clinical cure in day 14 was better in trial group patients with severe CAP. Alleviation of symptoms, shorter length of stay, and reduction of intravenous antibiotic therapy are also important clinical goals in the treatment of patients with CAP. In this study, patients had no side effects. No absolute contraindications are known for CoQ10; however, reliable information about its use in pregnant or breastfeeding mothers or young children is not available. In general, manufacturers have recommended doses of CoQ10 ranging from 22 to 400 mg. Adverse effects with CoQ10 are rare. On average, mild gastrointestinal discomfort is reported in less than 1% of patients in clinical trials (38). Potential interactions with warfarin causing decreased international normalized ratio (INR) have been reported in case studies. However, a prospective placebo controlled trial of 24 stable patients taking warfarin and 100 mg of CoQ10 over four weeks, showed no significant change in prothrombin time and INR levels (39). Because CoQ10 has potentially hypoglycemic and hypotensive effects, close monitoring of the patients is advised during its simultaneous use with other anti-diabetic medications. In our study, no side effects were seen and CoQ10 was well tolerated by the patients. We concluded that adjuvant CoQ10 in elderly patients with CAP hastens symptom resolution and shortens the duration of treatment with antibiotics. CoQ10 is a valuable adjuvant therapy due to its antioxidant effect, regulation of cell membrane channels, and beneficial effects on cellular bio-energy mechanisms. It may reduce cost of the treatment, lower morbidity, and finally improve the quality of life. Nevertheless, pharmacokinetic, pharmacodynamics, dosing, and clinical application of CoQ10 require further investigation. Although CoQ10 improves community-acquired pneumonia in elderly and its beneficial role is well established, especially on the ‘quality of life’ and reduction in length of hospitalizations, its benefits regarding mortality is not clearly seen. Also, its favorable effects have been observed in elderly patients of CAP with co-morbidity of cardiovascular diseases, diabetes mellitus, COPD, and neurological diseases. The present study has a potential limitation. The prevalence of CoQ10 deficiency in our study population was not directly assessed. In addition, bacterial pathogens (other than by Gram stain ones) were not identified; therefore, the effect of specific bacterial pathogens on the treatment effect of CoQ10 could not be explored. Taking clinical cure as the primary outcome is a subjective parameter, prone to bias. But in our opinion, this parameter reflects daily clinical practice and because of the randomized design, the introduction of bias was minimized. Finally, we used CoQ10 twice daily, for practical reasons, which may not be sufficient for establishing effective serum levels during 24 hours, although the limited sample size and short duration of the trial enforce the need for further research in this regard. CoQ10 administration may lead to a new era of cellular and biochemical treatment and complementing the existing approach of treating CAP in elderly patients.

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Authors’ Contributions
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