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Coenzyme Q_{10} 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.
Objectives: This study aimed to assess the efficacy of adjunctive coenzyme Q_{10} (CoQ_{10}) in the treatment of elderly CAP.
Patients and Methods: Hospitalized elderly patients with CAP (diagnosed by using defined clinical and radiological criteria) were randomized to receive oral CoQ10 (200 mg/d) or placebo for 14 days, along with antibiotics. Primary and secondary outcomes on days 3, 7, and 14 were measured. Disease severity was scored using CURB-65 index. Statistical analysis was performed using SPSS and P value < 0.05 was considered significant.
Results: We enrolled 150 patients for this research. Then, 141 patients, including 70 patients in the trial group and 71 patients in the control group were analyzed. Mean age of the trial and control groups were 67.6 ± 7.2 years and 68.7 ± 7.9 years, respectively. Clinical cure at days 3 and 7 were 24 (34.3%) and 62 (88.6%) in the trial group (P value = 0.6745) and 22 (31%) and 52 (73.2%) in the placebo group (P value = 0.0209). Patients on CoQ10 had faster defervescence (P value = 0.0206) and shorter hospital stay (P value = 0.0144) compared with the placebo group. The subgroup analysis of the patients with severe pneumonia showed differences in clinical cure at day 14. Treatment failure was less in 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 outcome in hospitalized elderly CAP; therefore, we recommend it as an adjunctive treatment in elderly patients.

Keywords: Coenzyme Q_{10}; 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 $4800 million, compared with $3600 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 $7166, whereas for a young (8r patient the corresponding values were 5.8 days and $6042.

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 population 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).

CoQ_{10} 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. CoQ_{10} 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). CoQ_{10} 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 CoQ_{10} with antibiotic treatment may improve outcome of CAP in old patients.

2. Objectives

This study aimed to assess the efficacy of adjunctive coenzyme Q_{10} (CoQ_{10}) 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 CoQ_{10} within 1 month before study entry , hypersensitivity to CoQ_{10}, 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 CoQ_{10} or placebo. Those randomized to placebo received matching inactive tablets administered in a dosing regimen identical to the active treatment. Both CoQ_{10} 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 CoQ_{10} (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 O_2 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 $\geq 90\%$ (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;

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

Where p_1 = %3.5, p_2 = %18 (p_1 = proportion of death in vitamin C group and p_2 = proportion of death in placebo group). With a power of 80% and α 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

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

	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	4 (5.7)	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 (26.8)	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 (25.4.0%) patients in the 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 4 shows the subgroup analysis of the primary and secondary outcome parameters in patients with severe CAP (CURB-65 > 2). The length of stay and time to clinical stability in the trial group were 7.8 ± 5.7 d and 5.6 ± 3.9 d, respectively and in the control group were 10.6 ± 7.6 d and 7.1 ± 4.6 d, respectively. Resolution of fever was faster in the trial group. Median (± interquartile range) day of defervescence was day 2 ± 1 in the trial group and day 3 ± 2 in the control group (P value = 0.0206). The decline in CRP levels of two groups was not significantly different (P value = 0.6157).

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

	Trial Group (n = 70)	Control Group (n = 71)	P Value
Patients with increased CRP	64 (91.4)	66 (93)	0.7350
WBC, x 10^2/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

[a] 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 [a]

	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 (0.15-2.82)	0.5267
Mortality	1 (1.4)	2 (2.8)	0.50 (0.02-2.73)	0.5676

[a] 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 [a]

	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

[a] Data are presented as No. (%)

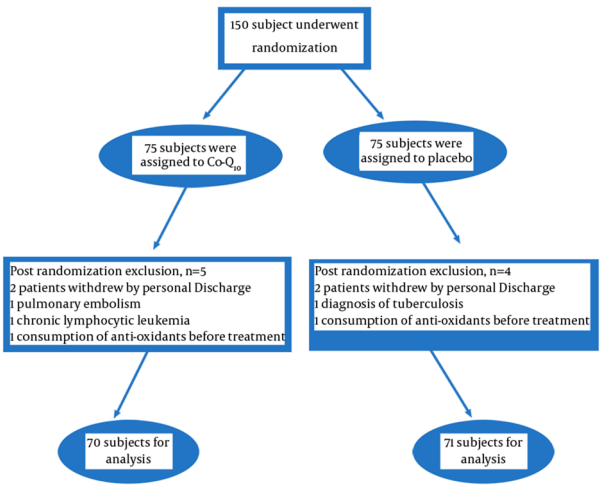

Figure 1. Study Flow Chart

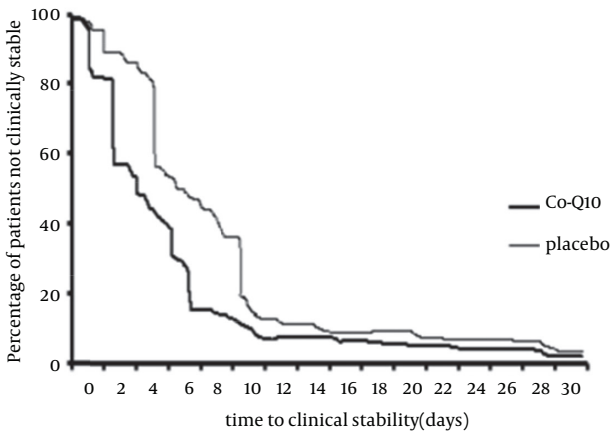

Figure 3. Kaplan-Meier curves Showing the Effect of the Intervention on Time to Clinical Stability in the Intention-to-Treat Population

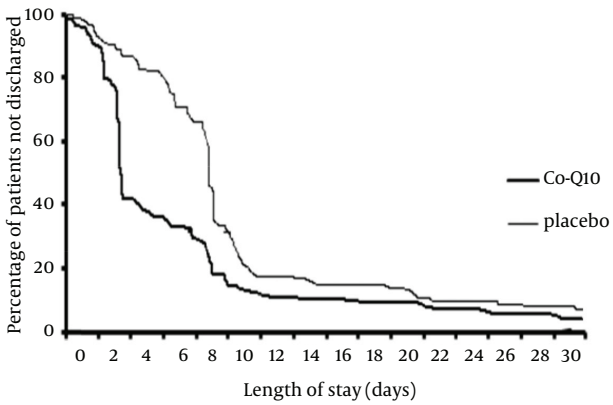

Figure 2. Kaplan-Meier Curves Showing the Effect of the Intervention on Length of Stay in the Intention-to-Treat Population

5. Discussion

This is the first randomized double-blinded placebo-controlled trial of CoQ_{10} in hospitalized elderly patients with CAP. We found beneficial effects of adjunctive CoQ_{10} 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 CoQ_{10} has been found in combi-

nation with the main treatment. In randomized, multicenter studies, it was found that CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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. CoQ_{10} has been considered for improving glycemic control through different mechanisms, especially via lowering oxidative stress. In a recent clinical trial, administration of CoQ_{10} (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 CoQ_{10}, 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 CoQ_{10}, however, reliable information about its use in pregnant or breastfeeding mothers or young children is not available. In general, manufacturers have recommended doses of CoQ_{10} ranging from 22 to 400 mg. Adverse effects with CoQ_{10} 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 CoQ_{10} over four weeks, showed no significant change in prothrombin time and INR levels (39). Because CoQ_{10} 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 CoQ_{10} was well tolerated by the patients. We concluded that adjuvant CoQ_{10} in elderly patients with CAP hastens symptom resolution and shortens the duration of treatment with antibiotics. CoQ_{10} 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 CoQ_{10} require further investigation. Although CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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 CoQ_{10} 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. CoQ_{10} 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

All authors participated in revising the paper.

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