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Serum Trace Elements in Coronary Artery Bypass Graft Surgery: The Relationship Between Trace Element Supplementation and Period of Mechanical Ventilation in a Randomized Double-Blind Placebo-Controlled Trial

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Abstract

Background: Coronary artery bypass graft surgery (CABG) may cause a substantial decrease in trace elements of whole blood during the operation, as well as increased oxidative stress and result in lung damage.
Objectives: This study aimed to evaluate the effect of Addamel, as a complete mixture of trace elements, in reducing the period of mechanical ventilation following the cardiac surgery.
Methods: In this randomized, double-blind, placebo-controlled trial, two hundred patients receiving CABG were randomized to receive three doses of either Addamel or normal saline. Selenium, zinc, copper, ferrous, and manganese serum levels were measured before the operation, on days one and two in all groups. Besides, the effects of Addamel on the mechanical ventilation period were evaluated.
Results: The mean length of stay on the mechanical ventilator was lower in the supplemented patients (21.98 $\pm$ 8.4 days) than the control patients (25.16 $\pm$ 8.44 days), and the difference was statistically significant (P = 0.009).
Conclusions: A substantial number of patients undergoing CABG may benefit from supplementation with Addamel, as a source of trace elements.

Keywords: Cardiac Surgery, Addamel, Trace Elements, Lung Injury, Mechanical Ventilation

1. Background

Coronary artery bypass graft surgery (CABG) may provoke unpleasant systemic inflammatory responses (1, 2). These procedures may cause a substantial decrease in trace elements of whole blood during the operation. Besides, the release of reactive oxygen species increases oxidative stress and inflammation may occur during CABG (3, 4). As a result, the temporary dysfunction of nearly every organ throughout the body would be expected (5). Unfortunately, pharmacological efforts with glucocorticoids and anti-inflammatory drugs were ineffective in attenuating these responses associated with CABG and cannot be recommended as routine therapeutic options (6, 7).

On the other hand, an increase in free radicals and oxidative stress may deteriorate organ dysfunction, especially the lung and produce a need for respiratory support with mechanical ventilation (8-10). Ventilation support itself is an independent predictor of hospital mortality (11). Nevertheless, in normal conditions, lungs have a well-organized anti-oxidative defense system, using antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase to neutralize these noxious agents (12-14). The trace elements are essential for oxidative balance by playing the role of an important cofactor for these antioxidant enzymes in small concentration (15, 16).

Oxidative stress is deteriorated in deficiencies of trace elements. Several studies showed that supplementation of critically ill patients with trace elements emphasizes the key role of these agents in oxidative balance and declines the morbidity rate (5, 17).

2. Objectives

Addamel, a pharmaceutical product, is a mixture of trace elements, including zinc (6.5 mg), copper (1.3 mg), manganese (0.27 mg), chromium (10 mcg), selenium (32 mcg), iron (1.1 mg), molybdenum (19 mcg), iodine (13 mg), and fluorine (95 mg) in each 10 mL vial. This is the first randomized study of Addamel, evaluating the serum levels of copper, manganese, ferrous, and zinc in patients underwent CABG and the serum changes of these elements after administration of three doses of Addamel. This study also evaluated the hypothesis that the administration of this supplement, as a complete mixture of trace element, would reduce the period of mechanical ventilation following the cardiac surgery.

3. Methods

This clinical trial was registered by Iranian Registry of Clinical Trials with the code number IRCT2015110924975N1. After obtaining approval from the Ethics Committee of Mazandaran University of Medical Sciences (ethics code: IR.MAZUMS.REC.95.2468.), this clinical trial was carried out in the cardiac surgery intensive care unit (ICU) of Fatemeh Zahra Cardiac Center in Sari, Iran. All patients signed written informed consent before the enrolment and on admission to the ICU.

3.1. Study Design

From September 2015 to December 2016, 200 eligible patients were enrolled in the study. Patients received either Addamel or normal saline, prospectively. The study was designed as a randomized, double-blind, placebo-controlled trial to evaluate the effects of the administration of trace elements during mechanical ventilation period following the cardiac surgery. The patients, clinicians, and other healthcare providers, and the investigator of clinical responses were all blinded to the randomization allocation.

3.2. Subjects

3.2.1. Eligibility Criteria

Two hundred subjects with the following criteria were included in the study: all patients having cardiopulmonary pump during the operation and aged 20 to 75 who signed the informed consent form and also were candidate for non-emergency CABG with a stable hemodynamic (mean arterial pressure 70 - 110 mmHg and heartbeat 50 - 110 per minute). Moreover, the subjects did not have a history of any type of tachycardia, including atrial fibrillation at baseline.

The participants were randomly divided into two equal groups: the first group received 3 doses of trace elements intravenously. As for the Addamel group, a day before the operation and a day after it. The third dose was administrated on the second day after the operation. The second group received normal saline based on the same schedule as the control group.

3.2.2. Exclusion Criteria

The exclusion criteria were as follows: ejection fraction of less than 40%, a history of chronic obstructive pulmonary disease (COPD) or hyperthyroidism, recent myocardial infarction in less than 6 months, the need for pacemaker therapy, previous heart surgery, and the need for further surgery for all reasons.

In order to eliminate confounding variables that may influence clinical outcome, the use of drugs, including salicylates, steroids, and bronchodilators were standardized in both arms of the study. In addition, patients using trace element-containing supplements were excluded and all the participants were receiving the same pharmacological schedule with the only difference of receiving trace elements or not.

3.3. Calculation of Sample Size and Randomization

Calculation of sample size was according to the pilot study. The power was set at 80% for the calculation of sample size. With an allowance of 10% lost to follow-up rate, we allocated 100 people to the control group and 100 people to the treatment group.

Patients who met the eligibility criteria were assigned to one of the intervention groups by using a permuted block randomization method. Blocks of four were used for this purpose. Each participant was given a six-digit number by the principal investigator. The patients, the treatment group, and the investigator of the clinical trial were unaware of the types of the assigned interventions. At the end of the study, the principal investigator decoded the numbers and assigned each to the appropriate group correctly.

3.4. Supplement Administration and Sample Assessment

The patients were randomly divided within 24 h before the operation to receive trace element supplements by a central intravenous line together with the standard pharmacological therapy. The trace elements were provided as

sodium selenite (Na_2SeO_3) 69.0 μg/day, zinc 13.6 mg/day (available as Zinc Chloride), copper 3.4 mg/day (available as Copper Chloride), manganese 0.99 mg/day (available as Manganese Chloride), chromium 53.3 μg/day (available as Chromic Chloride), ferrous 5.4 mg/day (available as Ferric Chloride), molybdenum 48.5 μg/day (available as Sodium Molybdate), iodide 0.17 mg/day (available as Potassium Iodide), fluoride 2.1 μg/day (available as Potassium Fluoride), supplied by the product Addamel N 10 mL. The second group received only normal saline in addition to the standard pharmacological therapy, without any extra trace elements intravenously.

Venous blood (6 mL) was withdrawn from all of the participants in plain vacutainers and separated sera were stored at -80°C for trace element determination with flame atomic absorption spectrophotometry by Perkin Elmer (Perkin, AAnalyst 100, USA).

3.5. The Study Outcome

The endpoint with respect to the effect of trace elements on patients undergoing CABG was the difference in duration of remaining on the mechanical ventilator after intravenous administration of the tested trace elements.

3.6. Statistical Analysis

Qualitative variables were reported by frequency and percent and quantitative variables by mean $\pm$ SD (standard deviation). The statistical analysis was carried out using the chi-square test. Mann-Whitney and Fisher's exact test were used for comparing the quantitative and quantitative variables, respectively, in the two groups of the study. All statistical analyses were conducted using SSPS software version 19 and differences with a P value of < 0.05 were considered to be significant.

4. Results

Out of enrolled patients, eighty-seven female and 113 male subjects, with mean age of 62.45 years, were divided into two groups (100 subjects per group). The first group received trace elements during the operation and the second group did not receive Addamel and instead, normal saline was administrated as the control. The serum trace element levels (Se, Fe, Cu, Mn, and Zn) of CABG patients and their effects on the mechanical ventilation period were evaluated. None of the patients were excluded from the study during the research. The analysis involved all patients who were randomly assigned to both groups.

The enrollment flowchart of the patients is displayed in Figure 1. Demographic and baseline clinical characteristics of patients are summarized in Table 1. As indicated, there was no significant difference between the two groups in demographic and clinical characteristics (age, gender ratio, body mass index, surgery duration, bypass period, cross clump, diabetes, hypertension, and smoking history).

Changes in plasma values of selenium, zinc, copper, ferrous, and manganese are summarized in Tables 2-4. The baseline levels of trace elements were at the normal range and did not show significant differences between the two groups (Table 2). After receiving the second dose, only the level of ferrous concentration elevated significantly (Table 3). As illustrated, the means of trace element concentrations of Cu, Fe, and Mn tested in the Addamel group patients were significantly higher after the third dose of Addamel on day 2 (Table 4).

To investigate the importance of these changes of trace elements' serum level on the patient's clinical outcome, the period that patients spent on mechanical ventilation was investigated. Remarkably, the mean length of stay was lower in the supplemented patients (21.98 $\pm$ 8.4 days) than control patients (25.16 $\pm$ 8.44 days), and the difference did in fact achieve statistical significance (P = 0.009).

In addition, none of the patients in the Addamel group experienced any adverse effects due to the intervention.

5. Discussion

The production of oxidative stress results in lung injury through oxidizing polyunsaturated fatty acids in the cellular membrane (10). Lungs have an antioxidant system to protect against these noxious agents by the function of detoxifying enzymes (18). Small concentrations of trace elements are essential for the proper function of these enzymes (3). Thus, in this research, Se, Fe, Cu, Mn, and Zn concentrations were measured before and after the administration of Addamel and also during the period that patients spent on mechanical ventilation following the cardiac surgery in the hospital.

Lower levels of trace elements have a direct relationship with some lung diseases e.g. COPD (8, 19). They are also lower in critically ill patients (17). Selenium is the essential cofactor for the function of glutathione peroxidase, a metalloenzyme needed for oxidant/antioxidant balance (15). It plays an important role in protecting against oxygen radical-initiated cell injury. The serum levels of selenium are lower in COPD and asthma patients (8). Some studies suggested that patients supplementing with selenium results in better clinical outcome and decrease in mortality of ICU patients (20). Although the patients in this study received three doses of Addamel, selenium serum level did not rise significantly. Possibly, the higher doses of selenium were needed. In a similar study evaluating the effect of trace elements on mechanical ventilation period

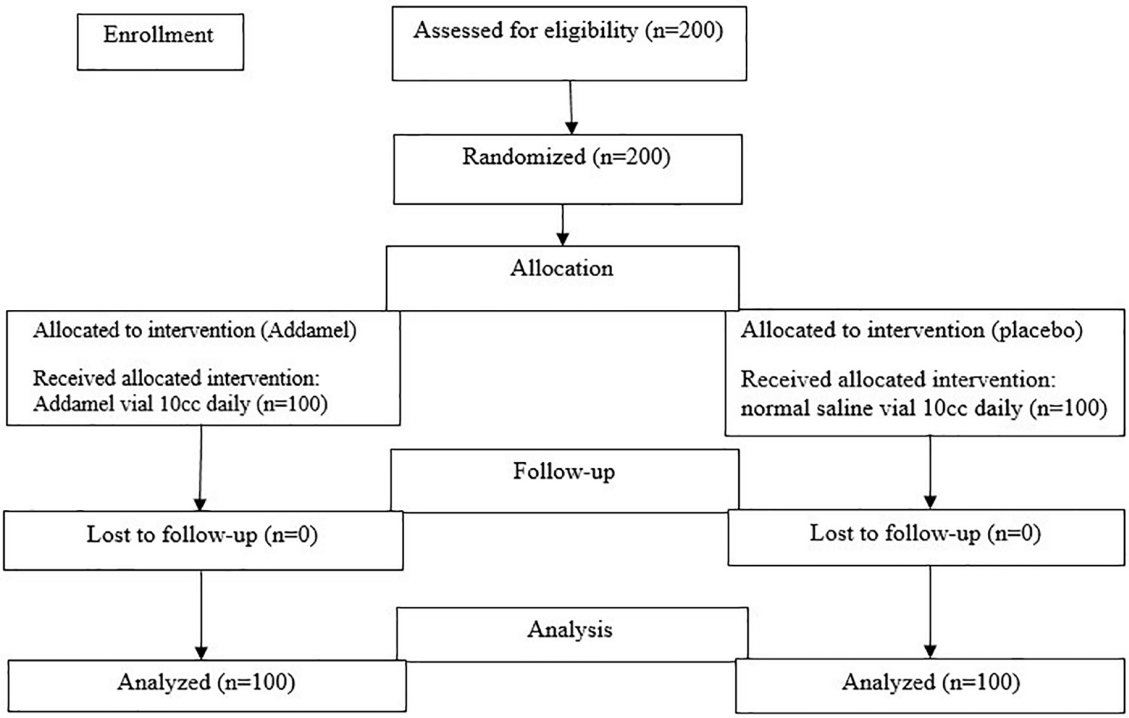

Figure 1. The flowchart of enrollment of the patients

Table 1. Demographic and Basic Clinical Characteristics

Variable	Control (N = 100)	Addamel (N = 100)	Statistics	P Value
Age, y	63.42 ± 7.601	61.49 ± 9.407	T-test	0.112
Gender, No. (%)				
Male	61	52	Chi-square	
Female	39	48		
BMI, kg/m^2	26.88 ± 3.767	26.53 ± 5.017	T-test	0.576
Co morbidity, %				
Diabetes,	59	52	Chi-square	0.319
Hypertension	40	45	Chi-square	0.474
Hyperlipidemia	63	59	Chi-square	0.562
Smoking history	42	38	Chi-square	0.564
EURO score	2.74 ± 1.51	2.75 ± 1.51	Mann-Whitney	0.96

Abbreviations: BMI, body mass index; Euroscor, European system cardiac risk evaluation

in COPD patients, the higher doses of selenium (sodium selenite 100 mg/day) were used (8).

Some studies showed that selenium and zinc concentrations are lower in patients with chronic diseases. They interpreted that the main mechanism for this event is the redistribution of trace elements from plasma to tissue compartments during a strong inflammatory state. Also, the lower concentrations of trace elements are associated with a higher degree of tissue damage, presenting as organ failure, infection or increased mortality (4). However, the findings of the present study did not confirm these data. The levels of selenium and zinc did not increase signifi-

Table 2. Comparison of the Trace Element Levels Between the Control and Addamel Groups at the Baseline

Parameters	Control Group	Addamel Group	P Value*
Selenium, μg/mL	0.072 ± 0.014	0.069 ± 0.013	0.088
Zinc, μg/mL	1.234 ± 0.25	1.171 ± 0.24	0.080
Copper, μg/mL	1.153 ± 0.26	1.107 ± 0.24	0.199
Ferrous, μg/mL	1.03 ± .28	1.02 ± .20	0.842
Manganese, μg/mL	0.005 ± 0.003	0.005 ± 0.003	0.982

Table 3. Comparison of the Trace Element Levels Between the Control and Addamel Groups on Day 1 After the Operation

Parameters	Control Group	Addamel Group	P Value*
Selenium, μg/mL	0.070 ± 0.014	0.071 ± 0.015	0.725
Zinc, μg/mL	1.214 ± 0.29	1.198 ± 0.24	0.672
Copper, μg/mL	1.119 ± 0.23	1.170 ± 0.21	0.107
Ferrous, μg/mL	1.02 ± .23	1.09 ± .23	0.026
Manganese, μg/mL	0.006 ± 0.005	0.006 ± 0.001	0.878

Table 4. Comparison of the Trace Element Levels Between the Control and Addamel Groups on Day 2 After the Operation

Parameters	Control Group	Addamel Group	P Value*
Selenium, μg/mL	0.071 ± 0.15	0.073 ± 0.015	0.515
Zinc, μg/mL	1.223 ± 0.26	1.216 ± 0.23	0.854
Copper, μg/mL	1.134 ± 0.23	1.231 ± 0.19	0.002
Ferrous, μg/mL	1.05 ± .21	1.17 ± .14	0.000
Manganese, μg/mL	0.006 ± 0.001	0.007 ± 0.005	0.007

cantly after three doses of Addamel and it might be due to the fact that participants of this study had normal baseline levels of trace elements.

Moreover, manganese is essential for the proper action of superoxide dismutase, which is a metalloenzyme with antioxidant activity. Also, copper is needed for the function of proteins such as ceruloplasmin and superoxide dismutase, which protects the body against free radical damage. Zinc is another trace element, which is necessary for the immune system regulation. In COPD, the plasma concentration of zinc is reduced. Similar to Mn and Cu, zinc is essential for the function of superoxide dismutase, the major enzyme involved in detoxification of ROS (21).

This prospective clinical trial study on cardiac surgery patients showed that supplementation with Addamel significantly reduced the length of stay on mechanical ventilation. In a study by Berger et al., selenium supplement slowed down the inflammatory cascade and improved organ dysfunction, but did not reach a significant level ($P > 0.05$) (4). In another study by El-Attar et al., intravenous supplementation with Se, Mn, and Zn significantly reduced the period of mechanical ventilation that COPD patients spent on (8).

It should be declared that the current study had some major limitations. First, healthy volunteers were not included in this study and all of the participants were from CABG patients. So there was not a lucid basic vision on the possible difference in the concentration of trace elements in plasma between healthy or heart patients at the baseline. Second, the level of the glutathione peroxidase was not assessed in the present study. Therefore, the exact effect of supplementation on inverting the oxidative balance is yet imperceptible. Another limitation to this study was not obtaining biopsy specimens for determination of tissue trace elements' concentration to observe the exact effect of CABG on total body trace elements. Finally, the measurement of a systemic inflammatory factors such as CRP would be of a great value to determine the direct effect of supplementation on the general status of body. Although the results of this study were promising and it was performed in a randomized controlled prospective manner with predefined endpoints, these findings need to be confirmed in future studies with possibly a cellular approach since this is the first preliminary clinical trial of Addamel in patients undergoing CABG.

5.1. Conclusions

In conclusion, the result of the present study suggested that supplementation of the CABG cases with trace elements may lead to a reduction in the total time patients spent on mechanical ventilation.

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Footnotes

Conflict of Interests: We declare that there are no conflicts of interest associated with this publication.

Ethical Approval: Ethics code: IR.MAZUMS.REC.95.2468

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Patient Consent: All patients signed an informed consent form before enrolment and on admission to the ICU.

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