A Double-Blind, Randomized Clinical Trial Comparing Cardioprotective Effects of N-acetylcysteine and Glucose-Insulin-Potassium as an Additive to Cardioplegia during Coronary Artery Bypass Grafting

Mohammad Reza Habibi [1], Shervin Ziabakhsh-Tabari [2], Alireza Khalilian [3], Samira Rahemi [4], Rozita Jalalian [5]

[1.] Department of Anesthesiology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[2.] Department of Cardiac Surgery, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[3.] Department of Biostatistics, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[4.] Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[5.] Department of Cardiology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
Corresponding author: Dr. Mohammad Reza Habibi
Mazandaran Heart Center, Artesh Boulevard, Mazandaran Province, Sari, Iran.
Email: contactroute@yahoo.com

Abstract: Optimum conditions for many coronary artery bypass graft surgeries (CABG) necessitate the heart to be prevented from beating. Cardioplegic solution and its ingredients are thus of utmost importance in cardioprotection. An ideal protection will help the heart return into its normal function after CABG. This research compared the cardioprotective effects of adding either N-acetylcysteine (NAC) to Cardioplegic solution with infusion of glucose-insulin-potassium (GIK) in patients with low ejection fraction (EF). In a double-blind randomized clinical trial, 60 elective CABG patients with EF < 50% were evaluated. The patients were numbered according to their reference to the Heart Center of Mazandaran (Iran) and their arrangements in the operation list. They were randomly allocated to 2 groups of 30 by a computer program to receive either GIK (group G) or NAC (group N). Compared to group G, group N had significantly lower incidence of arrhythmia during and after the operation (p = 0.041). They also needed lower doses of inotropic medications after the termination of cardiopulmonary bypass (CPB) (p = 0.041). The 2 groups were not significantly different in the need for shock or pacemaker after CPB and using pacemakers and inotropic drugs in the intensive care unit. Changes in mean EF from before to after the operation were 0.87 ± 0.85% in group N and -2.24 ± 1.02% in group G (p = 0.012). The mean troponin I levels were 0.406±0.316, 0.41 ± 0.512 in groups N and G, respectively (p = 0.41). NAC seems to be more beneficial than GIK for protecting myocardial cells, decreasing threatening signs of patients, especially arrhythmia, and increasing EF after CABG. It would probably decrease the mortality risk associated with arrhythmias.

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1. Introduction

Optimum conditions for many coronary artery bypass graft surgeries (CABG) necessitate the heart to be prevented from beating. On the other hand, the heart would not survive without an appropriate blood circulation. Since cardiac ischemia and reperfusion can produce free radicals and thus damage cardiac myositis and coronary artery endothelial cells, cardioplegia should be performed according to scientific and guaranteed principles to prevent ischemic incidences and irreversible complications (1,2). In addition, overproduction of free radicals causes macromolecular injuries, lipid peroxidation, and tissue deterioration (3) as a result of changes in cell membrane permeability and arrangement of membrane proteins following reperfusion and ischemic injury. Therefore, the composition of cardioplegic solution plays a vital role in protecting the heart. In fact, using an ideal protection, the heart will return to its normal function after the termination of cardiopulmonary bypass. Previous studies have employed different kinds of cardioplegic solutions such as crystalloid, blood, and L-arginine cardioplegic solutions (4,5). Research has also shown that adding factors to inhibit oxygen free radicals to the primary solution of cardiopulmonary bypass pump or to the cardioplegic solution can improve the heart function (6). On the other hand, patients with an ejection fraction (EF) lower than normal need to benefit from precise and specific medical supports or else their heart will not be able to function properly despite the conducted surgical procedures. In such cases, supportive measures are taken before, during, and after the surgery to decrease the complications of myocardial ischemia. Among these measures is using glucose-insulin-potassium (GIK) before operation and cold blood cardioplegia during the surgery. Being a branched-chain, low

molecular weight thiol compound with antioxidant properties, N-acetylcysteine (NAC) improves microcirculation and suppresses neutrophil aggregation. It can also be transferred into myocardial cells and increase intracellular glutathione concentration. Since cellular glutathione has antioxidant effects, it can decrease the risk of ischemia (7-9).

This research hence compared the clinical effects of adding NAC to cardioplegic solution with those of GIK administration on heart protection in patients with low EF. Since the mentioned clinical methods have not previously been compared, this study tried to shorten hospitalization period and reduce treatment expenditures. It also attempted to present more scientific and functional solutions for decreasing complications of myocardial ischemia during CABG.

2. Material and Methods

In a double-blinded randomized clinical trial, 60 elective CABG patients with an EF lower than 50% and an age of 35-75 years old were evaluated. The patients were numbered according to their reference to the Heart Center of Mazandaran (Iran) and their arrangements in the operation list. On the other hand, subjects were excluded in case of requiring intra-aortic balloon pump during the operation, prolonged cross-clamp period of 1.5 hours or more, and sensitivity to NAC.

The eligible subjects were randomly allocated to 2 groups of 30 individuals by a computer program to receive either GIK (group G) or NAC (group N). In group G, 10 cc/h of GIK solution was infused constantly during the surgery. Group N was injected with a cardioplegic solution containing 200 mg NAC. Normal saline was used as placebo in both groups (injected in group G and infused constantly in group N) to prevent the surgical team form identifying the drugs. A cardiopulmonary bypass pump was used for all cases in both groups. In order to ensure blinding, an anesthesia technician numbered the medicines and placebos (n = 30 for each). The cardiologist and anesthesiologist were not aware of the numbering and the kind of used drug during the surgery. The code of the administered medication was recorded in each patient's follow-up form. After decoding at the end of the survey, the kinds of drugs were recorded in patient forms.

Echocardiograms were ordered and performed by the same specialist before and 3-5 days after CABG to compare EFs. Frequency of arrhythmia, need for inotropic drugs during and after the operation, need for shock and pacemaker, commencement of normal heart rhythm, postoperative levels of cardiac enzymes, ECG changes, central venous pressure (CVP), and duration of hospital and intensive care unit (ICU) stay were also recorded and compared between the 2 groups.
Ethical considerations were taken into account by describing the aims and quality of the study to the patients and obtaining written consents from all participants. Besides, the questionnaires were filled out anonymously and the results were surveyed generally. The patients were also allowed to withdraw from the study at their wish. This survey did not impose any extra costs on either patients or insurance companies.

Quantitative and qualitative variables were analyzed by t-test and chi- square test, respectively. In all statistical analyses, p values less than 0.05 were considered as significant.

3. Results

The mean age of the participants (n = 60) was 62.5 ± 7.2 years old. Males and females constituted 58.3% (n = 35) and 41.7% (n = 25) of the whole population, respectively. The mean age of patients was 63.2 ± 6.1 (range: 44-74) years old in group N and 61.4 ± 5.9 (range: 45-71) years old in group G. There was no significant difference between the 2 groups in terms of age and sex distribution (p = 0.68). A history of myocardial infarction was reported by 8 patients of group N (26.6%) and 6 patients of group G (20%) (p = 0.84).

Groups N and G were not significantly different in the mean duration of pumping (78.3±17.6 minutes vs. 74.1 ± 21 minutes; p = 0.73). The mean duration of aortic cross-clamping was 42.35±14.27 minutes in group N and 44.6±19.61 minutes in group G (p = 0.56). The normal rhythm of the heart started 2.5 ± 2.4 minutes and 2.2 ± 1.1 minutes after aortic cross-clamp removal in groups N and G, respectively (p = 0.37). The mean EF before surgery was 45.4 ± 4.2% in group N and 47.3 ± 2.9% in group G (p = 0.17). However, the mean EFs of groups N and G were significantly different 5 days after the surgery (52.3 ± 8.0% vs. 45.1 ± 10.0%; p = 0.01). The changes in mean EF from before to after the operation were 0.87 ± 0.85% and -2.24 ± 1.02% in groups N and G, respectively (p = 0.01).

After the surgery, the mean level of troponin I was 0.4 ± 0.3 in group N and 0.4 ± 0.5 in group G. As mentioned earlier, NAC can increase intracellular glutathione concentration by moving into myocardial cells. In addition, its antioxidant effects are expected to change the levels of cardiac enzymes. Nevertheless, troponin I levels were not significantly different between the 2 groups.

The mean duration of hospitalization was 7.4 ± 1.9 days in group N and 8.2 ± 1.8 days in group G (p > 0.05). The mean ICU stay was 45.6 ± 3.1

hours in group N and 48.2 ± 5.2 hours in Group G ($p > 0.05$).

The incidence of arrhythmia during and after operation in group N was significantly lower than that in group G ($p < 0.05$). However, there were no significant differences between the 2 groups in requiring shock after separating the patients from the pump, placing pacemaker after pumping and in ICU, and in prescribing an inotropic in ICU ($p > 0.05$). Moreover, none of the patients needed shocking in ICU (Table 1).

Table 1. Relative frequency of some incidences in glucose-insulin-potassium group (group G) and N-acetylcysteine (group N) after cardiopulmonary bypass (CPB) termination and during intensive care unit (ICU) stay

		Group N	Group G	P
After CPB termination	Arrhythmia	3 (10.0%)	8 (26.6%)	0.08
	Shock	3 (10.0%)	7 (23.3%)	0.15
	Pacemaker	2 (6.6%)	3 (10.0%)	0.56
	Inotropic drug	4 (13.3%)	12 (40%)	0.04
During ICU stay	Arrhythmia	5 (16.6%)	14 (46.6%)	0.03
	Shock	0	0	0.99
	Pacemaker	0	1 (3.3%)	0.56
	Inotropic drug	5 (12.6%)	13 (42.3%)	0.12

Values are expressed as n (%).

4. Discussions

One of the traditional and acceptable methods for stopping the heart during CABG is using a cardioplegic solution along with a cardiopulmonary bypass machine. Previous studies have evaluated the toxicity of adding different compounds such as glucose-aspartate-insulin to cardioplegic solutions (10-12). According to research, the antioxidant effects of intracellular glutathione make it useful in establishing the cellular perfusion which decreases during ischemia (13,14). NAC is a medication containing thiol groups. It can cause increase intracellular glutathione concentration by transferring into myocardial cells. In the present research, 60 elective CABG patients were evaluated to compare the cardioprotective effects of cardioplegic solutions containing either NAC or GIK. Similar to the findings of Davudi and Rasuli (15), we could not establish any significant differences between the 2 groups in demographic specifications, the mean pumping duration, aortic cross-clamp duration, and the mean EF before surgery.

On the other hand, statistically significant differences between the 2 groups were found in terms of the incidence of arrhythmia and the need for an inotropic drug after the termination of cardiopulmonary bypass machine, the incidence of arrhythmia in ICU, the mean EF after the operation, and the mean changes of EF from before to after the surgery.

As mentioned before, arrhythmia is one of the acute and prevalent complications after CABG which can occasionally lead to death. In our study, patients who were received GIK developed a significantly higher incidence of arrhythmia after the operation. Curvnes et al. stated that patients suffering from atrial fibrillation have lower glutathione content in their left atrial cells (14). Using NAC in the present research could have elevated glutathione concentration in heart cells and thus reduced the rate of arrhythmia caused by ischemia. Adding insulin to a cardioplegic solution to improve the aerobic myocardial metabolism has not been found to be more effective than placebo in decreasing the rate of atrial fibrillation after operation (16). Therefore, using NAC in cardioplegic solutions seems more efficient than using GIK (17-20). Likewise, Bruemmer-Smith et al. showed that using GIK solution did not decrease myocardial cells injuries. GIK was not hence superior to other additive materials in eliminating arrhythmia (18).

After the operation, we detected lower, but not significantly, levels of troponin enzyme in group N compared to group G. Rorrigus et al. assessed the administration of cardioplegic solutions containing NAC, aspartate, and glucose. They reported NAC to significantly decrease cardiac enzymes after the surgery in comparison with the other 2 compounds (11). The difference between the 2 studies might have been caused by different dosages and methods of drug administration. As declared by Hammasy et al., compared to placebo, the oral administration of NAC before operation did not make any significant changes in the rate of clinical parameters and levels of enzymes (21). To our surprise, some clinical parameters, such as the need for shock and pacemaker after separating the patients from cardiopulmonary bypass machine, the need for

pacemaker and inotropic drugs in ICU, dosage of inotropic drugs during and after the operation, the mean hospital and ICU stay, and the level of troponin enzyme, were not significantly different between the 2 groups of the present study. The low number of cases requiring shock or pacemaker and the strict guidelines about how and when to discharge patients from the ICU could have been responsible for the absence of significant statistical differences between the 2 groups. Nevertheless, the clinical need for inotropic drugs in the ICU was lower in group N. In addition, group N received lower dosages of inotropic drugs after the surgery than they did during the surgery. In contrast, Koromaz et al. could not establish any significant differences in clinical efficacy of cardioplegic solutions with or without NAC after the operation (8).

According to the results of comparisons between NAC and GIK in the present study and previous research, adding NAC to a cardioplegic solution not only improves the enzymatic effects of the solution in cellular level, but also has clinical effects on decreasing the incidence of some complications such as arrhythmia and the need for inotropic drugs during the surgery and after separating patients from the cardiopulmonary machine. On the other hand, despite the favorable clinical effects of adding GIK to a cardioplegic solution, high incidence of arrhythmia limits the use of this compound. However, Vento et al. reported NAC to reduce the levels of myeloperoxidase and myocardial glutathione while no hemodynamic differences were observed between the 2 groups of NAC and glucose-magnesium receivers. Moreover, arrhythmia was detected in neither group (22).

Most previous studies have compared the myocardial protective effects of NAC and other compounds including normal saline at the molecular level (11,20). The present study thus employed a practical innovation since it showed the beneficial effects of NAC over GIK in decreasing the incidence of some signs and complications like arrhythmia and improving heart function. These findings are consistent with the antioxidant properties of NAC and the laboratory results obtained by other studies. Overall, NAC seems to be superior to GIK in protection of myocardial cells during open heart surgery due to its ability in reducing the rate of threatening signs, especially arrhythmia, and increasing EF after operation. It would also decrease the risk of mortality caused by arrhythmia after operation.

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