Clinical Trial/Experimental Study

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Beneficial effect of polaprezinc on cardiac function post-myocardial infarction

A prospective and randomized clinical trial

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Abstract

Background: Polaprezinc is clinically used for the treatment of gastric ulcers. It induces the mobilization of mesenchymal stem cells and the mRNA expression of insulin-like growth factor-1 in vascular endothelial cells in order to protect injured gastric tissue or skin.

Methods: The current study population included 50 patients with primary acute myocardial infarction (AMI). After percutaneous coronary intervention, the subjects were randomly divided into 2 groups, namely, the nonpolaprezinc and polaprezinc groups. Peripheral blood and urinary samples were collected in a specific time to analyze zinc concentration, cardiac enzymes, and the levels of the inflammation marker interleukin-6. To evaluate the cardiac function, echocardiography was performed upon admission to the hospital and at 9 months post-AMI.

Results: The urine and blood zinc levels of the polaprezinc group were higher compared with those of the non-polaprezinc group at 8 days after percutaneous coronary intervention. The mean interleukin-6/maximal creatine phosphokinase level was significantly reduced in the polaprezinc group (0.024 [0.003–0.066] vs. 0.076 [0.015–0.212], respectively; $P = .045$). In addition, echocardiography revealed that the ejection fraction of the nonpolaprezinc group was not significantly increased between day 3 and 9 months post-AMI (53 [49–60.8] vs. 59.5 [52–69.3], respectively; $P = .015$). However, a significant increase was detected in the ejection fraction of the polaprezinc group at the 2 time points (54 [51–57] vs. 62 [55–71], respectively; $P < .01$).

Conclusions: The results of the present study suggest that polaprezinc has an anti-inflammatory effect and improves cardiac function after AMI.

Abbreviations: AMI = acute myocardial infarction, BMI = body mass index, BMS = bare metal stent, CPK = creatine phosphokinase, CRP = C-reactive protein, DES = drug eluting stent, DM = diabetes mellitus, EF = ejection fraction, hsCRP = high-sensitive C-reactive protein, IGF-1 = insulin-like growth factor 1, IL-6 = interleukin-6, LVDd = left ventricular end-diastolic dimension, LVDs = left ventricular end-systolic dimension, mRNA = messenger ribonucleic acid, PCI = percutaneous coronary intervention, WBC = white blood cell.

Keywords: acute myocardial infarction, cardiac function, inflammation, polaprezinc

1. Introduction

Zinc is an essential trace element for humans, animals, and plants.[1,2] It is vital for several biological functions and plays a crucial role in more than 300 enzymes in the human body.[3,4] Zinc also functions as an antioxidant and can stabilize cell membranes.[5,6] Cardiovascular diseases, including acute myocardial infarction (AMI), are the leading cause of mortality worldwide.[7,8] Pro-inflammatory cytokines, such as interleukin-6 (IL-6), and acute-phase proteins, such as C-reactive protein (CRP), are upregulated in patients with AMI, and high blood IL-6 level has been reported in these patients.[9] The involvement of inflammation is regarded as an important mechanism in the onset of acute coronary syndrome, including arteriosclerosis-related lesion and AMI.[10]

In addition, zinc is involved in the regulation of inflammation. Although zinc deficiency contributes to and results in chronic inflammation, zinc supplementation has been reported to protect against chronic cardiomyopathy in a rat model of type 2 diabetes.[11–13] Polaprezinc (Zeria Pharmaceutical Co., Ltd., Tokyo, Japan) is a drug clinically used for the treatment of gastric ulcers and is a chelate compound consisting of a zinc ion, L-carnosine, β-alanine dipeptide, and L-histidine.[14] Its mechanism of action is believed to involve oxygen radical scavenging, antioxidation, and acceleration of wound healing.[14–16] Accumulating evidence suggests that polaprezinc exerts gastric mucosal cytoprotection and promotes ulcer healing through multiple mechanisms including antioxidant activity.[17–19] Fur-

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thermore, it has recently been reported that the zinc derivative, polaprezinc, induces the mobilization of mesenchymal stem cells and the mRNA expression of insulin-like growth factor (IGF) 1 in vascular endothelial cells to protect injured gastric tissue or skin.[20] Zinc has been shown to have an effect on myocardial ischemia/reperfusion;[21] therefore, the present study examined the effect of polaprezinc on cardiac function subsequent to AMI.

2. Methods

This prospective, open-label, and randomized clinical study was approved by the Ethics Committee of Kuwana City Medical Center in November 16, 2011 (application number #38), and all patients provided written informed consent post-percutaneous coronary intervention (PCI). The study population included 50 patients with initial ST elevation myocardial infarction between September 2011 and July 2014. The patients underwent PCI successfully within 12 h from the onset of AMI. After PCI, they were randomly divided into 2 groups, namely, a nonpolaprezinc group, serving as the control (C) group (n = 26), and a polaprezinc group (P group; n = 24), in which patients were administered 75 mg of polaprezinc twice a day. Patients started to take polaprezinc on the day of PCI or on the following morning after PCI at the latest. All patients of the P group continue to take polaprezinc for 9 months. Randomization was based on computer-generated codes. Peripheral blood and urinary samples were collected in a specific time to analyze the zinc concentration, cardiac enzymes, and the level of inflammation markers (including high-sensitive CRP and IL-6) at 8 days after administration of polaprezinc. To evaluate the cardiac function in terms of the ejection fraction (EF), left ventricular end-diastolic dimension (LVDd), and left ventricular end-systolic dimension (LVDs), echocardiography was performed upon admission to the hospital and at 9 months post-AMI. The LVDd and LVDs were determined according to the guidelines of the American Society of Echocardiography. The EF was estimated using the modified Simpson method. Patients were excluded from this study if they were diagnosed with cardiogenic shock (systolic blood pressure of less than 90 mm Hg), were already taking polaprezinc, or were diagnosed with cancer or an inflammation disease. All patients were administered 100 mg aspirin and 75 mg clopidogrel as dual antiplatelet therapy and 4 mg candesartan basically post-PCI. At 8 days after PCI, statin was administered to all patients.

2.1. Percutaneous coronary interventions

All patients received a single dose of 300 mg clopidogrel and 200 mg aspirin pre-PCI. Heparin was also administered in the catheterization laboratory. After PCI, patients continued to take 100 mg aspirin and 75 mg clopidogrel daily until the follow-up study. The PCI was performed according to the transfemoral, transradial, and transbrachial approaches, and the puncture was performed using 6 F or 7 F sheaths, as shown in Table 1. If necessary, an aspirator was used during PCI, such as TVAC (Nipro, Japan, n = 19) and Thrombuster (Kaneka, Japan, n = 21). The bare metal stents used included Driver (Medtronic, Ireland, n = 2), Liberte (Boston Scientific, USA, n = 1), Coroflex (B. Braun Melsungen AG, Germany, n = 1), S-Stent (St. Jude Medical, USA, n = 2), and Integrity (Medtronic, n = 7). The drug eluting stents used included Nobori (Terumo, Japan, n = 16), Endeavor (Medtronic, n = 4), Resolute (Medtronic, n = 3), Xience (Abbott, USA, n = 6), and Promus (Boston Scientific, n = 7). Significant differences were not detected in the number of responsible branches for AMI (Table 1).

Table 1

Patient characteristics.

	P group	C group	*P*
Patients' character			
Age	61.7 ± 13.1	69.2 ± 14.6	0.077
Male rates	96%	69%	0.014*
Smoking rates	54%	32%	0.151
Height (cm)	166.8 ± 8.9	161.3 ± 10.0	0.038*
Weight (kg)	69.9 ± 11.4	60.5 ± 13.8	0.008†
BMI	25.1 ± 2.8	23.3 ± 3.6	0.020*
Sys. pressure (mm Hg)	121.5 ± 19.1	123.2 ± 22.1	0.968
Dias. pressure (mm Hg)	72.3 ± 11.7	68.3 ± 13.1	0.199
HbA1c (%)	5.9 ± 0.8	5.5 ± 0.5	0.062
LDL-cho (mg/dL)	119.7 ± 41.4	118.3 ± 34.3	0.952
HDL-cho (mg/dL)	52.0 ± 19.9	48.7 ± 16.8	0.616
Creatinine (mg/dL)	0.88 ± 0.24	1.19 ± 1.25	0.129
UA (mg/dL)	5.3 ± 1.6	5.6 ± 1.3	0.876
Medication of DM	13%	16%	1.000
Medication of HT	50%	58%	0.776
Responsible branches for AMI			0.733
LAD	45.8%	50.0%	
LCX	8.3%	15.4%	
RCA	45.8%	34.6%	
Sheath size			0.248
6Fr	50%	30.8%	
7Fr	50%	69.2%	
Approach site			0.246
TFA	79.2%	61.5%	
TRA	20.8%	26.9%	
TBA	0%	11.5%	
Aspiration catheter			
TVAC/Thrombuster	83.3%	76.9%	0.727
Stent/POBA			1.000
BMS	25.0%	26.9%	
DES	66.7%	61.5%	
POBA	8.3%	11.5%	

AMI = acute myocardial infarction, BMI = body mass index, BMS = bare metal stent, DES = drug eluting stents, DM = diabetes mellitus, HDL = high-density lipoprotein, HT = hypertension, LAD = left anterior descending artery, LCX = left circumflex coronary artery, LDL = low-density lipoprotein, POBA = percutaneous old balloon angioplasty, RCA = right coronary artery, TBA = transbrachial approach; TFA = Transfemoral approach, TRA = transradial approach, UA = uric acid.

* $P < .05$.

† $P < .01$.

2.2. Statistical analysis

Continuous data are presented as the median with interquartile range, and categorical data are presented as the number (percentage). The present study had a small sample size, and thus nonparametric statistical analysis methods were employed. Differences between continuous variables were analyzed using Mann–Whitney *U* test. Categorical data were compared using Fisher's exact test. Mann–Whitney *U* test was used to compare the EF, LVDd, and LVDs detected by echocardiography during the follow-up. A *P* value of $< .05$ or .01 was considered to indicate a statistically significant difference. We used a *P* value of $< .01$ in the improvement of EF to demonstrate precisely. We used a *P* value of $< .05$ in other measurements. All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[22]

3. Results

Statistically significant differences in the clinical characteristics at the baseline were detected between patients in the P and C groups

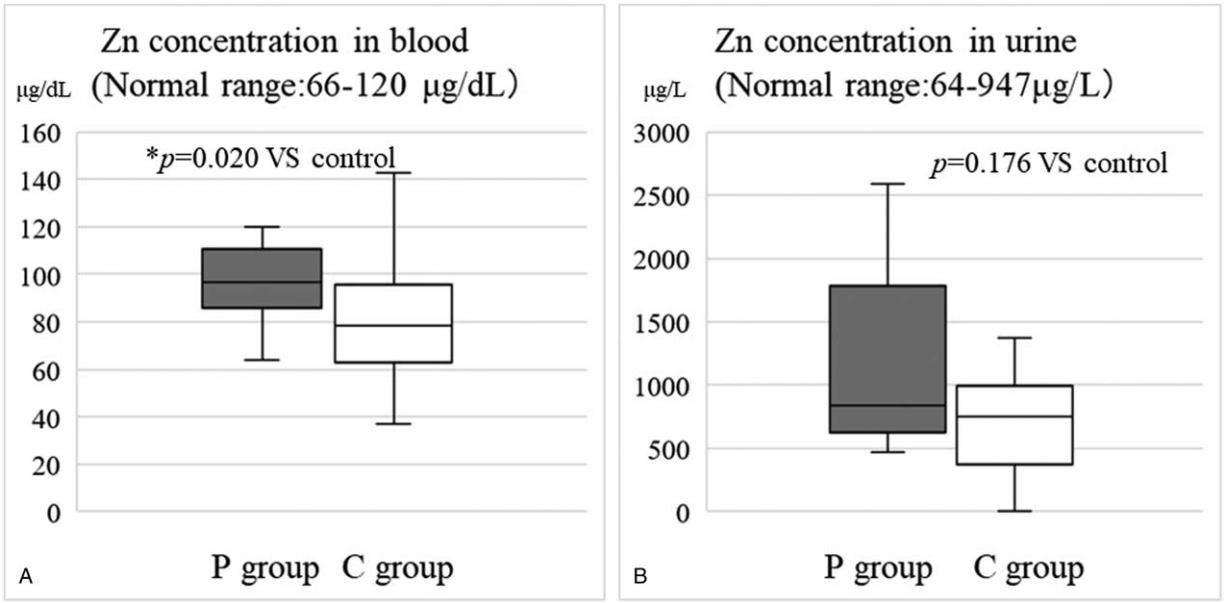

Figure 1. Zinc concentration in the blood and urine. Serum zinc concentration (1A) and urine zinc level (1B) in patients were measured 8 days after administration of polaprezinc.

(Table 1). A higher number of male patients ($P = .014$) and higher body mass index (BMI; $P = .020$) were observed in the P group. There was no difference between the 2 groups in terms of the total number of patients taking diabetes mellitus drugs or hypertension drugs (Table 1).

The serum zinc concentration and the urine zinc level were first measured to evaluate the metabolism of polaprezinc. While the serum level of zinc in the peripheral blood was within the normal range (66~120 μg/dL) in both groups at baseline, the zinc concentration was significantly augmented in the P group compared to that in the C group (96.5 [85.75–110.5] vs. 80 [65.25–97.75]μg/dL, respectively; $P = .020$) at 8 days after administration of polaprezinc (Fig. 1AA). This elevated serum level persisted throughout the study period (data not shown). The urine zinc level of the P group was also higher in comparison to that of the C group, without a significant difference detected (843 [623–1780] vs. 763 [510–1030]μg/L, respectively; $P = .176$) (Fig. 1B). This shows that administration of polaprezinc increased zinc concentration in the patients.

It is well-known that creatine phosphokinase (CPK) is the standard assessment for myocardial infarct size.[23–25] In the present study, the maximal CPK was measured to evaluate the infarct size. Given that the maximal CPK in the P group was higher than that in the C group (843 [623–1780] vs. 763 [510–1030]U/L, respectively; $P = .041$) (Fig. 2AA), the results suggest that the infarct size of the P group was larger when compared with that of the C group biochemically.

Recent studies have shown that inflammatory markers, such as CRP and IL-6, are more important than maximal CPK as prognostic factors of MI.[26,27] Thus, IL-6 level and white blood cell were also measured. Since a previous clinical study showed that the plasma IL-6 reached peak levels at approximately 3 days

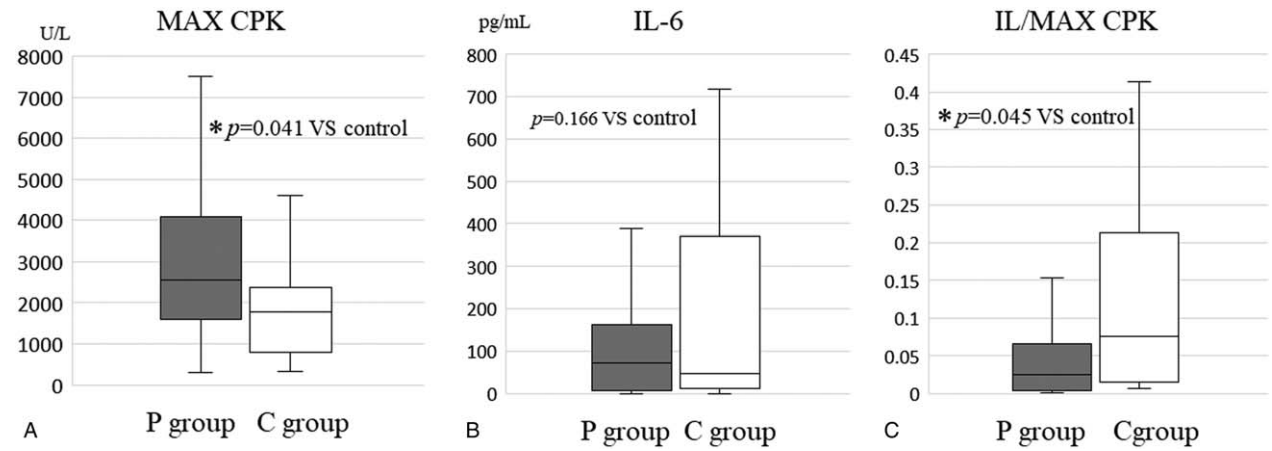

Figure 2. Evaluation of inflammation. The Max (maximal) CPK level was measured post-AMI (2A) and IL-6 was measured 8 days after administration of polaprezinc (2B). The IL-6 value divided by the Max CPK value was calculated in each patient as a new index (2C). AMI = acute myocardial infarction, CPK = creatine phosphokinase, IL-6 = interleukin-6.

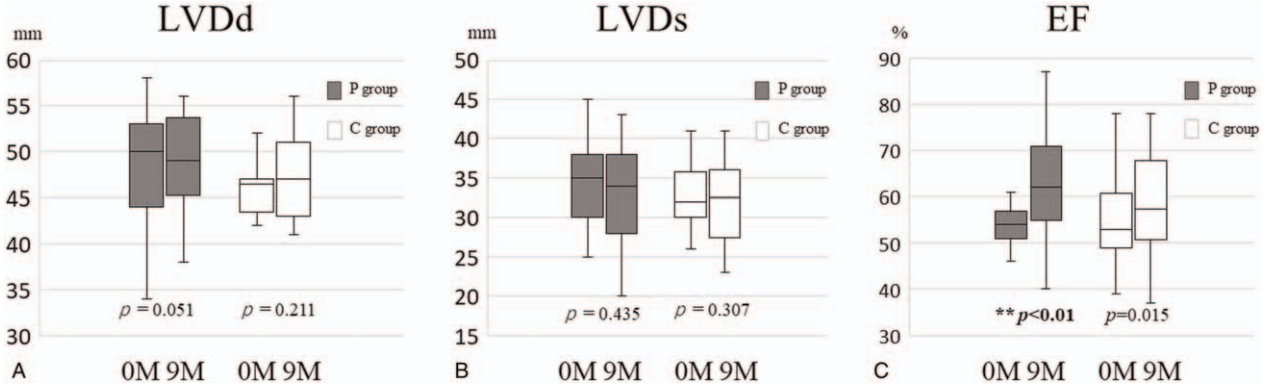

Figure 3. Changes in the data of echocardiography. Changes in LVDd (3A), LVDs (3B) and in EF (3C) from day 3 to 9 months post-AMI are shown. AMI = acute myocardial infarction, EF = ejection fraction, LVDd = left ventricular end-diastolic dimension, LVDs = left ventricular end-systolic dimension.

and 1 week after AMI,[28] IL-6 was measured 8 days after AMI in the current study. Significant differences were not observed in the IL-6 level (Fig. 2B) and white blood cell recovery rates (data not shown) in the 2 groups.

It is natural that a large infarction induces high levels of both CPK and IL-6 in the serum of the patients. In addition, it has been reported that IL-6 exhibits a positive correlation with maximal CPK after AMI.[29,30] In the present study, there was a positive correlation between max CPK and IL-6 in both groups (C group: $y = 0.0488X + 155.57$; P group: $y = 0.0029x + 104.67$). Thus, the IL-6 values were corrected due to the significant difference of the maximal CPK in the 2 groups. To evaluate the actual inflammatory reaction post-MI, the IL-6/maximal CPK in each patient was calculated as a new index. IL-6/maximal CPK was significantly lower in the P group 8 days after administration of polaprezinc compared with that in the C group, as shown in Figure 2C (0.024 [0.003–0.066] vs. 0.076 [0.015–0.212], respectively; $P = .045$). Although there was no difference in LVDd (Fig. 3AA) and LVDs (Fig. 3B), echocardiography showed that the EF of patients in the C group was not significantly increased between day 3 and 9 months post-AMI (53 [49–60.8] vs. 59.5 [52–69.3]%, respectively; $P = .015$), as shown in Figure 3C. By contrast, echocardiography indicated that the EF of the P group was significantly increased between day 3 and 9 months post-MI (54 [51–57] vs. 62 [55–71]%, respectively; $P < .01$) (Fig. 3C). By 9 months post-AMI, 1 patient was lost to follow-up in the P group and 2 patients were lost to follow-up in the C group, since these 3 patients were followed up by other hospitals after moving.

4. Discussion

The present study suggested that polaprezinc administration significantly increased the serum level of zinc, reduced the IL-6/maximal CPK value, and increased the EF in post-AMI patients. Maximal CPK is known to be an effective marker for representing the myocardial infarct size,[23–25] while AMI is associated with a significant increase in IL-6 levels independent of the infarct size or myonecrosis.[31] It has already been reported that maximal CPK and EF are negatively correlated.[32] In the present study, IL-6/maximal CPK was significantly lower in the P group, indicating a suppressive effect of polaprezinc on the inflammatory process of post-AMI.

It is well known that statin drugs can reduce inflammation in AMI.[33] Statins also have antiatherosclerotic, anti-inflammatory, antioxidant, immunomodulatory, and antithrombotic effects.[34] Previously, it was reported that statin therapy significantly decreased the hazard ratio for 1-year mortality in patients with high CRP levels to approximately the same hazard ratio as that observed in patients with low CRP levels who did not receive statin therapy.[35] These "pleiotropic" effects stem from their inhibition of prenylation of the small GTP-binding proteins, Ras and Rho, and the disruption or depletion of cholesterol-rich membrane microdomains (membrane rafts).[34] It was difficult to administer statin therapy before evaluating the levels of the inflammatory markers IL-6 and CRP in the blood of patients in the present study. Furthermore, it is unclear why polaprezinc exerted an anti-inflammatory effect after MI. Polaprezinc has been demonstrated to increase IGF-1 production in both in vitro and in vivo studies.[20] Insulin and IGF-1 receptor signaling are known to be essential for cardiac development and function.[36,37] Guo et al[38] reported that IGF-1 pretreatment of mesenchymal stem cells may play antiapoptotic and anti-inflammatory roles in post-MI. In addition, O'Sullivan et al[39] demonstrated the prosurvival and antiapoptotic effects of IGF-1 in preclinical models of MI. Ellison et al[40] also reported that, in a pig model of AMI, intracoronary administration of IGF-1 was a practical and effective strategy for reducing pathological cardiac remodeling, inducing myocardial regeneration, and improving ventricular function. Therefore, the beneficial effects of polaprezinc in patients post-AMI may be through IGF-1.

Compared to the patients of the C group, the age of patients was lower, and the number of males and BMI values were greater in the P group. A higher BMI may negatively influence the recovery process, as it has been reported to suppress the secretion of adiponectin, which is known to exert anti-inflammatory effects.[41,42] In terms of cardiac remodeling, patients in the P group exhibited a better recovery of EF in comparison with those in the C group. These results also support that polaprezinc may inhibit the myocardial injury post-AMI through an anti-inflammatory effect.

It is worth nothing that, a patient in the C group was consuming daily a large amount of green tea containing high levels of zinc. Although this patient was in the C group, the zinc level in his peripheral blood and urine were higher than the average level in the P group (blood level, 143 μg/dL; urine level, 2540 μg/L). The patient showed a high recovery of EF (55–67%) between 3 days and 9 months post-MI. Therefore, it can be speculated that a reduction in myocardium damage may be induced by not only the administration of polaprezinc but also the intake of a zinc-rich drink.

4.1. Study limitations

The present study has several limitations. First, the sample size was fairly small. The limitations of this study also include the absence of a multicenter trial and significant differences in the percentage of BMI between the 2 groups. In addition, the study excluded patients with severe MI or inflammation disease. Furthermore, 3 patients were lost to follow-up during the study. Finally, the PCI procedures were performed by multiple doctors.

5. Conclusions

Polaprezinc, a drug commonly used in the treatment of chronic gastric ulcers, was reported to improve cardiac function post-AMI. This effect may be due to anti-inflammatory processes through the suppression of IL-6. However, further studies are required to clarify the suppressive effect of zinc on IL-6 production.

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