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Prognostic Relevance of Intra-aortic Balloon Pump in Patients with Acute Myocardial Infarction Complicated by Cardiogenic Shock: Nationwide Population Study in Taiwan

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Objectives: Intra-aortic balloon pump (IABP) is the most widely-used form of mechanical hemodynamic support in patients with cardiogenic shock. However, usefulness of IABP in the high-risk patient population is conflicting. We examined whether the patient prognosis in Taiwan for those treated with IABP has improved in recent years. **Methods:** We used Taiwan's National Health Insurance Research Database to retrospectively review 3145 (2358 men, 75% of cases) cardiogenic shock patients who were treated with primary percutaneous coronary intervention (PCI) due to acute myocardial infarction (AMI) between 2000 and 2012. The primary outcome was all-cause mortality and secondary outcome was heart failure. **Results:** A total of 1417 patients who received IABP therapy and 1728 patients who did not receive non-IABP were selected in this study. During the follow-up period, the adjusted hazard ratio for overall mortality was 1.22 (CI 95%: 1.10-1.35, p <0.0001) and for overall heart failure was 1.24 (CI 95%: 1.08-1.41, p <0.001). Risk factors for all-cause mortality were previous heart failure, diabetes, chronic kidney disease and hypertension. **Conclusion:** In this nationwide, population-based, retrospective cohort study in Taiwan, we found that mortality rate and heart failure rate did not decline in cardiogenic shock patients who underwent primary PCI plus IABP therapy.

Keywords: Intra-Aortic Balloon Pumping; Shock, Cardiogenic; Myocardial Infarction; Percutaneous Coronary Intervention; Prognosis

Introduction

Cardiogenic shock complicates 5 to 10% of cases with acute myocardial infarction (AMI) and remains the leading cause of death in patients hospitalized with AMI [1, 2]. Intra-aortic balloon pump (IABP) is the most widely-used form of mechanical hemodynamic support in patients with cardiogenic shock, but data on the usefulness of IABP in this setting are conflicting.

Using IABP with thrombolytic therapy increases survival rate in patients with AMI [3, 4]. The National Registry of Myocardial Infarction 2 study also demonstrated that patients with AMI complicated by cardiogenic shock may have substantial benefit

from IABP when used in combination with thrombolytic therapy [5]. Meta-analysis of IABP therapy also showed that IABP therapy is adjunctive to thrombolysis during ST elevation myocardial infarction (STEMI) complicated by cardiogenic shock [6].

However, the CRISP-AMI randomized controlled trial showed that among patients with acute anterior STEMI without shock, IABP plus primary PCI compared with PCI alone did not reduce infarct size [7]. Also, the IABP-SHOCK II randomized controlled trial showed that IABP did not significantly reduce 30-day and 1-year mortality in patients with cardiogenic shock complicating AMI with an early revascularization strategy [8].

Taiwan's National Health Insurance Research Database (NHIRD) is a large dataset that allows for investigative cohort studies using propensity score matched groups derived from Taiwan's population. NHIRD contains data of patients who received NHI coverage and therefore, it is close to real world circumstances. In this study we aimed to reveal long-term prognostic relevance of IABP in patients with cardiogenic shock complicating AMI using NHIRD. We examined whether the patient prognosis in Taiwan treated with IABP has improved in recent years.

Materials and Methods

1. Ethics statement

Study approval was originally obtained by the National Health Research Institutes in Taiwan. To avoid the potential for ethical violations related to the data, the privacy of each individual's information was protected by de-identifying the data. Thus, informed consent was not required.

2. Data source

Data were extracted from Taiwan's NHIRD, which contains anonymized secondary data released for research purposes. Taiwan's NHI program, launched in 1995, currently covers 99% of the population of 23 million people [9]. The database includes all registry and claims data from the NHI system, ranging from demographic data to detailed orders for ambulatory and inpatient care. Disease diagnoses are coded according to the "International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)."

3. Study design

This nationwide, population-based, retrospective cohort study was conducted to determine the association between IABP treatment and subsequent mortality and heart failure. The study populations extracted from the entire original NHIRD consisted of patients with an admission diagnosis of AMI (ICD-9-CM code 410, including both STEMI and NSTEMI) complicated by cardiogenic shock (ICD-9-CM code 785.51) who received primary percutaneous coronary intervention (PCI, ICD-9-CM operation code 36.06 and 36.07) between January 2000 and December 2012. The patients managed by thrombolytic therapy were excluded. After patients were selected, they were divided into two groups according to IABP treatment. Patients who received IABP treatment were defined as a case cohort (or IABP group) and patients who did not receive IABP were defined as a control cohort (or non-IABP group). The index date was defined as the date of AMI.

4. Outcomes

The primary outcome was all-cause mortality within 30 days, 6 months and during follow-up. The secondary outcome was hospitalization and principal diagnosis of heart failure (ICD-9-CM 428.0-428.2) during follow-up. All subjects were followed up until death, loss of follow-up, or December 31, 2012.

5. Baseline characteristics

Baseline characteristics between the IABP and non-IABP groups were estimated for each of the following covariates: age, gender, previous myocardial infarction (ICD-9-CM 412), previous heart failure (ICD-9-CM 428), diabetes (ICD-9-CM 250), chronic kidney disease (ICD-9-CM 582 and 585), hypertension (ICD-9-CM 401-402) and previous coronary atherosclerosis (ICD-9-CM 414.0). All covariates were defined before the AMI date.

6. Statistical analysis

Baseline characteristics were separately estimated in the IABP group (case cohort) and non-IABP group (control cohort). Normally distributed continuous variables were analyzed by independent sample t-test and presented by the mean and standard deviation. Categorical variables were analyzed by Pearson Chi-square test and presented by frequency and percentage. Cox regression models with a conditional approach using stratification were used to calculate adjusted hazard

ratios (HRs) and 95% confidence intervals (CIs) for the all-cause mortality and heart failure in each group. The survival and heart failure-free rate was estimated by use of the Kaplan-Meier method and differences between cohorts were evaluated with the log-rank test. Finally, univariate and multivariate Cox regression models were used to identify potential predictors of all-cause mortality and heart failure among the study population. All of the statistical analyses were conducted with STATA statistical software (version 12.0; StataCorp, TX). Statistical significance was defined as $p < 0.05$.

Results

1. Baseline characteristics

In this study, a total of 3145 (2358 men, 75%) cardiogenic shock patients treated with primary PCI due to AMI were selected. A total of 1417 (45%) were treated by primary PCI plus IABP (IABP group) and 1728 (55%) were treated by only PCI (non-IABP). The mean age of the IABP group and non-IABP group was 68.1 ±13.1 years and 67.0 ±13.3 years, respectively ($p = 0.02$). The percentage of elderly patients (≥70 years old) was 45.1% in the IABP group and 51.3% in the non-IABP group ($p = 0.007$). For each cohort, the majority of patients were men. The frequency of comorbidities was comparable between two cohorts except for chronic kidney disease (131 patients (7.58%) in non-IABP group and 78 patients (5.5%) in IABP group, $p = 0.02$). Therefore, age and chronic kidney disease adjusted Cox proportional hazard analysis were used. Detailed characteristics of both cohorts are provided in Table 1.

2. Long-term risk analysis

Median follow-up time until death was 1.51 years in the non-IABP group and 1.07 years in the IABP group ($p < 0.0001$). Median follow-up time for heart failure was 0.28 years in the

Table 1. Baseline characteristics between non-IABP group (n = 1728) and IABP group (n = 1417)

Variable	All		Non-IABP		IABP		p-value
	n	%	n	%	n	%	
Age (years)							0.007[a]
<50	335	10.7	174	10.1	161	11.4	
50-59	640	20.4	338	19.6	302	21.3	
60-69	645	20.5	330	19.1	315	22.2	
≥70	1525	48.5	886	51.3	639	45.1	
Mean (SD)	67.6	(13.2)	68.1	(13.1)	67.0	(13.3)	0.02[b]
Gender							0.17[a]
Women	787	25.0	449	26.0	338	23.9	
Men	2358	75.0	1279	74.0	1079	76.2	
Comorbidity							
Previous myocardial infarction	109	3.47	56	3.95	53	3.07	0.18[a]
Previous heart failure	333	10.6	192	11.1	141	9.95	0.29[a]
Diabetes	872	27.7	485	28.1	387	27.3	0.64[a]
Chronic kidney disease	209	6.65	131	7.58	78	5.50	0.02[a]
Hypertension	1172	37.3	662	38.3	510	36.0	0.18[a]
Previous coronary atherosclerosis	615	19.6	352	20.4	263	18.6	0.20[a]
Mean follow-up duration (median (IQR))							
Death	1.28	(3.14)	1.51	(3.54)	1.07	(2.78)	<0.0001[c]
Heart failure	0.15	(2.18)	0.28	(2.68)	0.09	(1.77)	<0.0001[c]

[a] Chi-square test [b] t-test [c] Wilcoxon rank sum test

non-IABP group and 0.09 years in the IABP group (p <0.0001). During the follow-up period, adjusted HRs were 1.22 (CI 95%: 1.10-1.35, p <0.0001) for overall mortality and 1.24 (CI 95%: 1.08-1.41, p <0.001) for overall heart failure. The maximum value of adjusted HRs at 1.67 (CI 95%: 1.27-2.20, p <0.0001) for all-cause mortality and 1.70 (CI 95%: 1.25-2.30, p <0.0001) for heart failure were observed in patients aged 50-59 years old. The HRs corresponding to age group and gender are showed in Table 2. Most of the episodes of all-cause mortality occurred within 30 days. Within 30 days, 512 patients died in the non-IABP group and 472 patients died in the IABP group and HR for all-cause mortality was 1.20 (CI 95%: 1.06-1.36, p <0.001). After six months, HR for all-cause mortality was 1.42 (CI 95%: 1.12-1.80, p <0.001). The risk of all-cause mortality had still increased at the one-year follow-up (HR: 1.43, CI 95%: 0.92-2.22) and stabilized after that (HR: 1.03, CI 95%: 0.77-1.37). Also, the risk of heart failure was high within 30 days (HR: 1.17, CI 95%: 0.98-1.39) and 6 months (HR: 1.31, CI 95%: 0.97-1.78), however, these results are not statistically significant. The HRs stratified by follow-up duration is showed in Table 3.

Table 2. Rate and HR for death and heart failure by age group and gender in Cox proportional hazard regression

Variable	Non-IABP			IABP			IABP vs. non-IABP HR (95% CI)	
	n	Person-years	Rate[d]	n	Person-years	Rate[d]	Crude	Adjusted
Death								
Overall[a]	821	3593	22.9	722	2351	30.7	1.16 (1.05-1.28)[g]	1.22 (1.10-1.35)[g]
Age (years)[b]								
<50	36	534	6.74	38	413	9.20	1.22 (0.77-1.93)	1.21 (0.77-1.92)
50-59	96	943	10.2	116	596	19.5	1.57 (1.20-2.06)[f]	1.67 (1.27-2.20)[g]
60-69	135	804	16.8	154	596	25.9	1.30 (1.03-1.64)[e]	1.31 (1.04-1.66)[e]
≥70	554	1312	42.2	414	747	55.5	1.12 (0.99-1.27)	1.14 (1.00-1.29)
Gender[c]								
Women	274	695	39.4	210	440	47.7	1.11 (0.92-1.33)	1.21 (1.01-1.45)[e]
Men	547	2898	18.9	512	1911	26.8	1.21 (1.07-1.36)[f]	1.24 (1.09-1.39)[g]
Heart failure								
Overall[a]	471	2647	17.8	415	1559	26.6	1.21 (1.06-1.38)[f]	1.24 (1.08-1.41)[f]
Age (years)[b]								
<50	40	422	9.47	35	328	10.7	0.99 (0.63-1.55)	0.98 (0.63-1.55)
50-59	49	739	10.7	94	379	24.8	1.67 (1.23-2.26)[g]	1.70 (1.25-2.30)[g]
60-74	86	612	14.1	91	393	23.2	1.28 (0.96-1.73)	1.28 (0.96-1.73)
≥75	266	874	30.4	195	459	42.5	1.14 (0.94-1.36)	1.14 (0.95-1.37)
Gender[c]								
Women	130	485	26.8	94	242	38.9	1.10 (0.84-1.43)	1.13 (0.86-1.48)
Men	341	2162	15.8	321	1317	24.4	1.25 (1.08-1.46)[f]	1.27 (1.09-1.48)[f]

[a]Adjusted for age and chronic kidney disease [b]Adjusted for chronic kidney disease [c]Adjusted for age and chronic kidney disease [d]Per 100 person-years [e]p <0.01 [f]p <0.001 [g]p <0.0001

Table 3. Rate and HR for death and heart failure stratified by follow-up duration in Cox proportional hazard regression

Follow-up duration (days)	Non-IABP			IABP			IABP vs. non-IABP HR (95% CI)
	n	Person-years	Rate[b]	n	Person-years	Rate[b]	
Death[a]							
1-30	512	108	473.2	472	84	561.5	1.20 (1.06-1.36)[c]
31-180	139	452	30.8	137	335	40.9	1.42 (1.12-1.80)[c]
181-360	42	504	8.33	39	365	10.7	1.43 (0.92-2.22)
>360	128	2529	5.06	74	1567	4.72	1.03 (0.77-1.37)
Heart failure[a]							
1-30	265	93	285.9	248	68	362.2	1.17 (0.98-1.39)
30-180	90	360	25.0	78	247	31.5	1.31 (0.97-1.78)
180-360	40	382	10.5	36	253	14.2	1.42 (0.91-2.24)
>360	76	1813	4.19	53	990	5.35	1.33 (0.93-1.89)

[a]Adjusted for age and chronic kidney disease [b]Per 100 person-years [c]p <0.001

Survival rate and heart failure-free rate between the IABP group and the non-IABP group was examined by the Kaplan-Meier method and differences between cohorts were evaluated with the log-rank test (Figure 1). According to the Kaplan-Meier analyses, survival and heart failure-free rate were significantly lower in cardiogenic shock patients who were treated by IABP.

3. Potential predictors for all-cause mortality

The NHIRD study allows for subgroup analysis to be conducted because it has a large data resource. According to the multivariable analysis of covariates, patients with previous heart failure (HR: 1.20, CI 95%: 1.02-1.41, p <0.01), diabetes (HR: 1.28, CI 95%: 1.14-1.44, p <0.0001), chronic kidney disease (HR: 1.39, CI 95%: 1.17-1.65, p <0.0001) and hypertension (HR: 1.25, CI 95%: 1.11-1.40, p <0.0001) are associated with increased risk of all-cause mortality (Table 4).

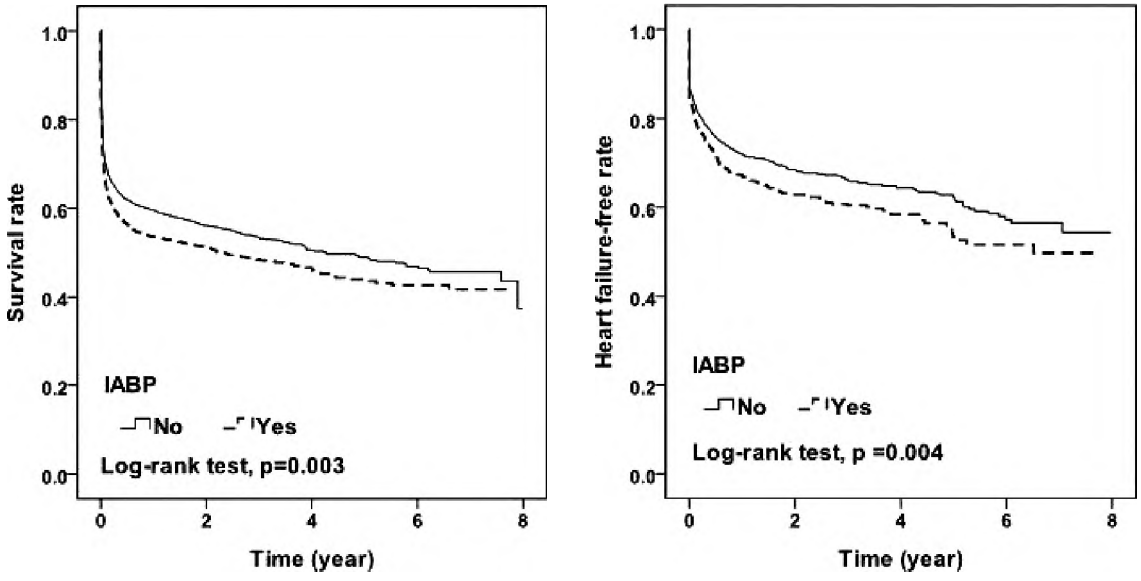

Figure 1. Survival and heart failure-free rate between non-IABP group and IABP group.

Table 4. HR for death and heart failure in multivariable Cox proportional hazard regression

	HR for death	HR for heart failure
Age group	1.03 (1.03-1.04)[c]	1.01 (1.01-1.02)[c]
Men vs. women	1.17 (1.04-1.31)[b]	1.00 (0.85-1.18)
IABP vs. non-IABP	1.25 (1.13-1.39)[c]	1.25 (1.09-1.43)[b]
Comorbidity (no vs. yes)		
Previous myocardial infarction	0.98 (0.76-1.27)	1.17 (0.86-1.60)
Previous heart failure	1.20 (1.02-1.41)[a]	1.70 (1.38-2.10)[c]
Diabetes	1.28 (1.14-1.44)[c]	1.10 (0.94-1.29)
Chronic kidney disease	1.39 (1.17-1.65)[c]	0.93 (0.71-1.21)
Hypertension	1.25 (1.11-1.40)[c]	1.16 (0.99-1.36)
Previous coronary atherosclerosis	0.98 (0.86-1.12)	1.26 (1.05-1.51)[a]

[a]p<0.01 [b]p<0.001 [c]p<0.0001

Discussion

The proportion of STEMI patients developing cardiogenic shock increased from 6.5% in 2003 to 10.1% in 2010 in the USA [10]. IABP is the most widely-used form of mechanical hemodynamic support in patients with cardiogenic shock. Previous studies demonstrated a significant increase in the overall IABP utilization rates, for example from 44.8% in 2003 to 54.5% in 2009 in the USA [10]. Despite increased usage of IABP in patients with cardiogenic shock, data on the usefulness of IABP in this setting are conflicting. A meta-analysis of seven randomized trials comparing IABP use with no IABP use in STEMI patients with cardiogenic shock showed neither a 30-day survival benefit nor improved left ventricular ejection fraction with IABP use, while being associated with significantly higher stroke and bleeding rates [6]. Similarly, in a meta-analysis of nine cohort studies, IABP was associated with a decrease in 30-day mortality in patients treated with thrombolysis but not in those treated with primary PCI [6]. Subsequently, the IABP SHOCK II trial showed that use of IABP in patients with cardiogenic shock complicating AMI who underwent early revascularization did not reduce 30-day mortality compared with medical therapy alone [8]. However, these studies focused on short-term patient prognosis and long-term prognostic information is still unknown.

Our nationwide, population-based, retrospective cohort study in Taiwan found that IABP therapy does not add prognostic beneficial effects in cardiogenic shock patients treated by primary PCI during long-term follow-up. In our study, HR for 30-day mortality was 1.20 (CI 95%: 1.06-1.36, p <0.001), which means that cardiogenic shock patients treated by primary PCI plus IABP do not receive additional survival benefits compared with patients treated primary PCI alone. Furthermore, risk of all-cause mortality had still increased at the six-month and one-year follow-up and these results are consistent with other studies [8]. Therefore, we suggest at least one-year careful patient follow-up for patients with cardiogenic shock.

The IABP SHOCK II study demonstrated that younger patients (≤50 years old) have a trend toward benefits from IABP therapy [8]. However, our study demonstrated that all age groups, even younger patients, have no beneficial effect from IABP therapy (Table 2). Therefore, tight medical control should be considered not only for older patients but also younger patients.

IABP is designed to improve end-diastolic aortic pressure and subsequent coronary perfusion during diastole [11]. In this situation, dysfunctional or hibernating (not contracting but still viable) cardiomyocytes receive the highest benefit from IABP. However, different types of comorbidities are associated with poor left ventricular function caused by decrease in cardiomyocyte number. Therefore, previous comorbidities could decrease the effectiveness of IABP treatment. In our study, we conducted subgroup analysis for each covariate and found that previous heart failure, diabetes, chronic kidney disease and hypertension are potential predictors of all-cause mortality among the study population. These findings suggest that patients without previous comorbidities, as causes of decreased left ventricular function, benefit more from IABP therapy and physicians should consider previous disease condition in their practice of IABP treatment.

Heart failure is a major consideration after AMI and it is caused by loss of cardiomyocytes and extent of scar tissue. IABP is designated to increase cardiomyocyte survival through improved end-diastolic aortic pressure and subsequent coronary perfusion during diastole. Therefore, decreasing infarct size by using IABP therapy is reasonable. However, the CRISP-AMI trial showed that primary PCI plus IABP therapy does not decrease infarct size in AMI patients [7]. In our study, we tested the association between risk of heart failure and IABP therapy after AMI. After AMI, HR for heart failure was 1.24 (95% CI: 1.08-1.41, p <0.001). At the six-month and one-year follow-up, the HR for heart failure was 1.31 (95% CI: 0.97-1.78) and 1.42 (95% CI: 0.91-2.24), respectively (Table 3).

Finally, this study has some limitations. We could not take the patients' health and hemodynamic parameters, such as blood pressure, heart rate, respiratory rate, oxygen saturation, severity of disease, extension of ischemic zone, and time to intervention from the NHIRD. Therefore, final study results cannot be applied for all patient populations. Also, this study is susceptible to patient selection bias. However, we used the propensity score matching method to balance cohort groups and avoid this difficulty in this study.

Our study also has advantages. Any significant differences between the IABP group and non-IABP group provides evidence-based information about the effectiveness of IABP therapy during AMI complicated by cardiogenic shock and the results of the current study more likely indicate implications of

real-world practice of IABP based on a big population based database. Therefore, results from our study could be used for real-time clinical decision-making. Furthermore, health care policy makers can use results of the current study to make any conceptual decision in cardiovascular health care policy.

Our nationwide, population-based, retrospective cohort study described the trend of IABP usage in the general population of Taiwan. We agree that IABP is somewhat beneficial in certain clinical circumstances. The results from our study did not disapprove the benefit of IABP in special clinical condition, but we found that mortality rate and heart failure rate was not declined in cardiogenic shock patients who underwent primary PCI plus IABP therapy. Therefore, based on currently available evidences, we suggest that current practices of IABP usage in cardiogenic shock patients should be reconsidered. Future studies that clarify the effect of IABP in cardiogenic shock patients are needed.

Conflict of Interest

The authors state no conflict of interest.

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