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Original Article

Early thrombolysis is associated with decreased operative mortality in postinfarction ventricular septal rupture

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ABSTRACT

Background: Post myocardial infarction ventricular septal rupture (PMI-VSR) is a dreaded mechanical complication of acute coronary syndromes. Given that surgical mortality approaches 50%, it is pragmatic that the risk factors for mortality and outcomes after surgical correction of PMI- VSR are carefully scrutinized.

Methods: We performed a single-center, retrospective cohort study of 35 patients presenting for surgical closure of post myocardial infarction ventricular septal rupture over six years. We reviewed patient characteristics, clinical, echocardiographic, angiographic and perioperative risk factors which may affect mortality after surgical repair of PMIVSR and 30 day and one year mortality rates of these patients. Univariate and multivariate logistic and cox proportional hazard regression analysis was used to identify predictors of operative and overall mortality. Long term survival was presented with Kaplan-Meier Survival Curve.

Results: Sixteen patients (46%) were in cardiogenic shock. Concomitant coronary artery bypass grafting (CABG) was done in 22 patients (63%) but did not influence survival. Preoperative thrombolysis was done in 12 patients (34%) out of which 10 (53%) survived Operative mortality was 46% and one-year mortality was 49%. Multivariate analysis identified preoperative thrombolysis: Hazards ratio, 0.12; 95% CI, 0.02-0.61; p value of 0.01, as significant independent predictor of survival in PMIVSR cohort.

Conclusions: Preoperative thrombolysis is associated with decreased odds of operative and overall mortality after surgical repair in PMIVSR patients.

1. Introduction

Post–myocardial infarction ventricular septal rupture (PMI-VSR) is a rare but potentially lethal complication of acute coronary syndromes, with current literature reporting an incidence between 0.17 and 0.31%.[1] While the outcomes of patients with acute coronary syndrome have improved drastically, the outcome in this subset remains distinctively poor, with 30-day mortality approaching 100% with medical management[2] and close to 50% with surgical repair.[3]

Operative mortality for PMI-VSR is not randomly distributed, instead it can be predicted with clinical and perioperative risk factors. Predictors of poor outcomes in this subset include cardiogenic shock at presentation, early surgical repair, posterior VSRs, right ventricular dysfunction, and inferior wall myocardial infarction.[3]

In this single-center, retrospective study of consecutive cohort of patients undergoing PMI-VSR repair, we describe risk factors for operative mortality and outcome analysis. The results provided by this study will enable clinicians to have an appreciation of modifiable risk factors that may improve outcomes in this cohort.

2. Methods

2.1. Subject selection

This retrospective cohort study was approved by the institutional review board (NK/4270), and written informed consent was

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waived. We collected clinical and perioperative data of a cohort of 41 consecutive adult patients (aged >18 years) with PMI-VSR presenting between January 2012 and February 2018 for surgical repair at a tertiary care north Indian cardiac center. The subjects included those who primarily presented to our tertiary cardiac center and those who were referred from local hospitals without cardiac care facilities and regional centers where cardiac catheterization facilities exist without surgical backup. Eligible patients who underwent concomitant coronary revascularization (thrombolysis/percutaneous coronary intervention/coronary artery bypass grafting) or other valvular procedures along with surgical closure of PMI-VSR were also included. Patients with congenital heart disease and incomplete data set were excluded. Management strategy for VSR was consistently (1) urgent 2-dimensional echocardiography and preoperative angiography and (2) subsequent urgent or elective VSR repair depending on hemodynamic stability with complete revascularization over the study period. This article adheres to the applicable Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Outcomes

The primary outcome was identification of risk factors for mortality after surgical repair of PMI-VSR. Secondary outcomes included 30-day and 1-year mortality after surgical repair.

2.3. Definitions

Acute myocardial infarction (AMI) was defined as per the Third Universal Definition of Myocardial Infarction.[4] Cardiogenic shock/postoperative low cardiac output syndrome was defined as mean arterial pressure $\leq$60 mm Hg or cardiac index <1.8 L/min/m^2 with evidence of end-organ hypoperfusion (decreased urinary output $\leq$ 0.5 ml/kg/hr, anuria, acutely rising urea/creatinine levels with serum creatinine >2.2 mg/dl in the absence of chronic renal failure) despite maximal treatment (use of inotropes or intraaortic balloon counter pulsation/extracorporeal membrane oxygenator or both).[5] Operative mortality was defined as death in hospital or after discharge but within 30 days of index surgery. Pulmonary hypertension was defined as resting mean pulmonary artery pressure $\geq$25 mm Hg. Right ventricular failure was defined as the clinical syndrome resulting from the inability of the right ventricle to fill or eject to provide adequate blood flow to the pulmonary circulation at a normal central venous filling pressure, leading to low cardiac output or atrial/ventricular arrhythmias.[6] Renal impairment was defined as documented oliguria of <0.5 ml/kg/h for >6 h.[7]

2.4. Study protocol

This retrospective observational study included 41 patients from January 2012 to February 2018. Hospital medical records, electronic and hard copies of patients' charts, were used to abstract prescribed data elements for analysis. Detailed demographic, medical, clinical, echocardiographic, angiographic, and perioperative data variables that may affect mortality after surgical repair of PMI-VSR were collected from an advanced cardiac center database. The database presents a limited data set originally collected for nonresearch purposes. The data for survivors and nonsurvivors after PMI-VSR were analyzed with respect to the primary and secondary outcomes after deidentification.

2.5. Statistical analysis

Continuous variables were tested for distribution normality using the Shapiro–Wilk test and expressed as mean ± standard deviation (SD) or median and interquartile range. Differences between groups were assessed using *t*-test for continuous variables and χ^2 test or Fisher exact test for categorical variables. Long-term survival was presented using a Kaplan–Meier curve. The impact of clinical, echocardiographic, angiographic, and perioperative variables on in-hospital and overall mortality was assessed using the Cox proportional-hazard regression model. Clinically relevant variables with a p value $\leq$0.2 on individual analysis were included in forward stepwise multivariable regression models. A p value $\leq$0.05 was considered statistically significant for the final result. SPSS, version 22.0, (SPSS Inc, Chicago, IL) was used for calculations.

3. Results

A total of 41 patients with PMI-VSR were examined for eligibility, out of whom 35 were confirmed eligible and were included in the study and their records were traced. Two patients had incomplete data documentation and four had no follow-up records and were thus excluded. Patients' characteristics and clinical variables are presented in Tables 1 and 2. The VSR was posterior in 17% of the population. The culprit vessel was left anterior descending artery in 83% of the patients. Sixteen patients (46%) were in cardiogenic shock with New York Heart Association (NYHA) IV status, with two of them (6%) presenting with right ventricular failure. Out of twelve patients who were thrombolyzed with streptokinase (<12 h of onset of AMI), ten survived. The perioperative variables are listed in Table 3. Twenty-six patients (74%) were operated by infarct exclusion technique, and concomitant coronary artery bypass grafting (CABG) was performed in 22 patients (63%).

Operative mortality was 46%, and one-year mortality was 49%. Mortality in posterior VSR group was 19%. Development of postoperative low cardiac output syndrome was the most common reason for mortality. Univariate and multivariate cox proportional-hazard regression analysis identified preoperative thrombolysis as an independent predictor of survival from in-hospital and overall mortality. Cardiogenic shock at presentation was associated with decreased odds of survival. Results from statistical analysis are presented in Table 4. Long-term survival after surgery is presented as a Kaplan–Meier survival curve for overall survival (Fig. 1), and the difference in survival between thrombolyzed and non-thrombolyzed patients is presented as a Kaplan–Meier survival curve for thrombolysis (Fig. 2). Most of the survivors (88%) are currently in NYHA grade I/II.

4. Discussion

The present study showed that preoperative thrombolysis, if received <12 h after AMI, is the single most important factor favoring survival from operative mortality in cox proportional-hazard regression analysis (hazards ratio, 0.12; 95% confidence interval [CI], 0.02–0.61; p value, 0.01), after controlling for other factors in multivariate analysis. Out of twelve patients who received early thrombolysis with streptokinase preoperatively, ten survived. Thrombolysis by virtue of restoring the flow through the occluded coronary vessels may limit the infarct size expansion, translating in survival benefit. In a resource-constrained country such as India, where after AMI, access to percutaneous or surgical coronary revascularization may not be universally available, combined with delay along the referral

Table 1
Patients' characteristics.

Variables	Survivors, $n = 19$ (%)	Nonsurvivors, $n = 16$ (%)	Total, $n = 35$	p value
Age	58 ± 11	64 ± 9	61 ± 10	0.138
Gender (female)	6 (32)	10 (63)	16 (46)	0.067
BMI	23 ± 2	25 ± 2	24 ± 2	0.031*
Diabetes mellitus II	7 (37)	8 (50)	15 (43)	0.433
Systemic hypertension	14 (74)	14 (88)	28 (80)	0.415
P/h/o CAD	5 (26)	1 (6)	6 (17)	0.187
P/h/o stroke	0 (0)	2 (13)	2 (6)	0.202
Renal impairment	1 (5)	1 (6)	2 (6)	1.00

BMI: body mass index; CAD: coronary artery disease; P/h/o: past history of.
* Statistically significant.

Table 2
Patients' clinical and angiographic data.

Variables	Survivors, $n = 19$ (%)	Nonsurvivors, $n = 16$ (%)	Total, $n = 35$ (%)	p value
Time from AMI to VSR (days)	3 (2–4)	3 (2–5)	3 (2–5)	0.613
Time from AMI to VSR repair (days)	15 (4–35)	6 (1–18)	11 (1–26)	0.035*
Systolic blood pressure (mm Hg)	101 ± 17	101 ± 16	101 ± 16	1.00
Diastolic blood pressure (mm Hg)	69 ± 15	65 ± 13	67 ± 14	0.505
Heart rate (/min)	106 ± 16	108 ± 18	107 ± 17	0.668
NYHA class (IV)	5 (26)	11 (69)	16 (46)	0.018*
AMI location (inferior)	3 (16)	3 (19)	6 (17)	1.00
EF at presentation (%)	33 ± 7	33 ± 12	33 ± 9	0.776
Cardiogenic shock (CS)	5 (26)	10 (63)	15 (43)	0.067
Right ventricular dysfunction/failure	1 (5)	1 (6)	2 (6)	1.00
Pulmonary artery pressure (mmHg)	43 ± 5	50 ± 13	46 ± 10	0.035*
Mitral regurgitation (moderate to severe >2/4)	2 (11)	1 (6)	3 (9)	1.00
VSR location (posterior)	3 (16)	3 (19)	6 (17)	1.00
Angiographic data				
Culprit vessel LM	0	0	0	–
Culprit vessel LAD	16 (84)	13 (81)	29 (83)	1.00
Culprit vessel LCX	0	1 (6)	1 (3)	0.457
Culprit vessel RCA	2 (11)	3 (19)	5 (14)	0.64
No. Of diseased vessels	1 (1–2)	3 (1–3)	2 (1–3)	0.164
Total occlusion of culprit artery	12 (63)	14 (88)	26 (74)	0.135
Percent stenosis of culprit artery (%)	94 ± 10	98 ± 8	98 ± 9	0.225
Thrombolysis, <12 h from onset of AMI	10 (53)	2 (13)	12 (34)	0.030*
PCI of culprit vessel	3 (16)	5 (31)	8 (23)	0.424
IABP insertion				
Preoperatively	3 (16)	8 (50)	11 (31)	0.065*
Perioperatively	3 (16)	2 (13)	5 (14)	1.00
Postoperatively	0	0	0	0
ECMO support				
Preoperatively	0 (0)	1 (6)	1 (3)	0.457

AMI: acute myocardial infarction; VSR: ventricular septal rupture; NYHA: New York Heart Association; EF: ejection fraction; CS: cardiogenic shock; LM: left main; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; IABP: intraaortic balloon counter pulsation; ECMO: extracorporeal membrane oxygenator; PCI: percutanous coronary intervention.
* Statistically significant.

Table 3
Perioperative data.

Variables	Survivors, $n = 19$ (%)	Nonsurvivors, $n = 16$ (%)	Total, $n = 35$ (%)	p value
Technique of repair				
Direct closure	1 (5)	1 (6)	2 (6)	1.00
Septal patch	5 (26)	2 (13)	7 (20)	0.405
Infarct exclusion	13 (68)	13 (81)	26 (74)	0.460
Concomitant CABG	11 (58)	11 (69)	22 (63)	0.508
Concomitant LV repair done (free wall rupture/aneurysm)	4 (21)	3 (19)	7 (20)	1.00
Concomitant MV procedure (repair/replacement)	4 (21)	3 (19)	7 (20)	1.00
Aortic cross-clamp time	119 ± 36	113 ± 47	116 ± 41	0.673
Cardiopulmonary bypass time	172 ± 49	173 ± 57	172 ± 52	0.997
Duration of mechanical ventilation (hrs.)	19 (14–36)	72 (22.5–105)	26 (15–72)	0.041*
Length of ICU stay (days)	7 (6–10)	4.5 (3–8)	6 (5–9)	0.040*
Postoperative VIS	19 ± 5	35 ± 14	26 ± 13	<0.001*
Ventricular tachyarrhythmias	0	10 (63)	10 (27)	<0.001*
Postoperative low cardiac output syndrome	0	15 (94)	15 (43)	<0.001*
Stroke	1 (5)	0	1 (3)	1.00
Sepsis	0 (0)	5 (31)	5 (14)	0.013*

CABG: coronary artery bypass grafting; LV: left ventricle; MV: mitral valve; ICU: intensive care unit; VIS: Vasoactive-Inotropic Score; CS: cardiogenic shock.
* Statistically significant.

Table 4
Significant predictors of mortality in univariate and multivariate Cox proportional-hazard regression models.

Variable	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.04	0.97–1.12	0.29	–	–	–
Time from AMI to VSR repair	0.96	0.91–1.02	0.19	0.84	0.59–1.18	0.32
Cardiogenic shock at presentation	0.04	0.35–0.98	0.02*	0.54	0.31–0.93	0.02*
Posterior VSR	0.30	0.04–2.11	0.23	–	–	–
Thrombolysis	0.21	0.04–0.95	0.04*	0.12	0.02–0.61	0.01*
PCI of culprit vessel	3.33	0.72–15.46	0.12	1.27	0.34–4.71	0.71
Concomitant CABG	0.94	0.16–5.70	0.95	–	–	–
Aortic cross-clamp time	0.99	0.96–1.01	0.24	–	–	–

AMI: acute myocardial infarction; VSR: ventricular septal rupture; CABG: coronary artery bypass grafting; HR: hazard ratio; CI: confidence interval; PCI: percutanous coronary intervention.
* Statistically significant.

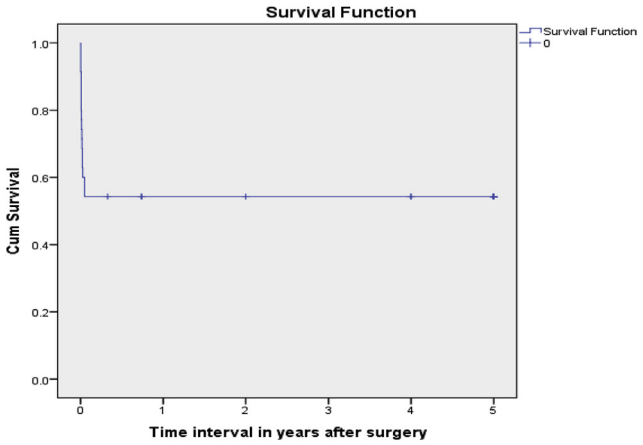

Fig. 1. Kaplan–Meier survival curve.

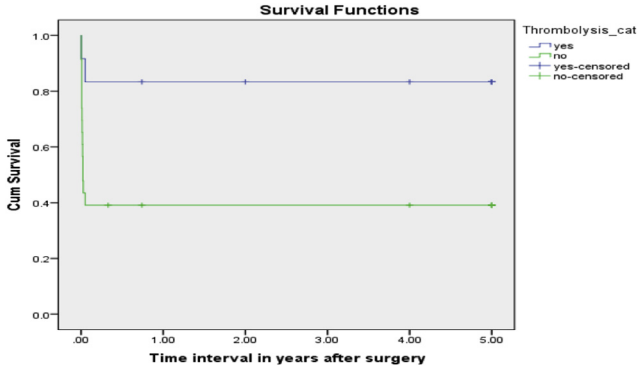

Fig. 2. Kaplan–Meier survival curve showing improved survival in patients who received early thrombolysis before surgical repair as compared to those who did not.

pathways, early preoperative thrombolysis may provide survival benefit. To the best of our knowledge, this is the first study that shows that preoperative early thrombolysis may be associated with decreased odds of operative mortality in PMI-VSR repair cohort. The GUSTO (Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries) investigators' analysis of mortality within one day of thrombolytic therapy, however, shows that deaths within four hours of treatment were not influenced by establishment of arterial patency by thrombolysis and the patients who died already had larger infarcts and severe myocardial dysfunction.[8,9] The SHOCK (Should we emergently revascularise occluded coronaries for cardiogenic shock) trial ($n = 24$) in contrast investigated that the median time from AMI to VSR in 13 subjects given thrombolytic therapy was 18 h as compared to the median time of 6 h among the 11 patients who were not thrombolyzed, although the difference was not statistically significant.[10] Srinivas et al[11] ($n = 30$) concluded that there was no significant difference in mortality between patients receiving thrombolysis and those who were not, although thrombolysis led to earlier development of VSR. The results of the study by Rhydwen et al[12] ($n = 29$) are in sharp contrast to those of our study where prior thrombolysis within the surgical group led to a survival rate of 25% in the thrombolysis group as compared to 69% without thrombolysis, but the study was not designed to address the mortality data.

We observed a high operative mortality rate of 46% which is consistent with the 47% mortality rates described in GUSTO trial[8] and other reports,[3] representing the highest risk of all cardiac procedures.[13] One-year mortality in our study was 49% as against the operative mortality of 46%, suggesting that the long-term prognosis of the patients, who survive a month beyond the surgery, is good. Consistent to our study, Arnaoutakis et al[13] (Society of thoracic surgeons (STS) Database, $n = 2876$) showed mortality rates of 54% if early VSR repair was conducted as compared to 18% if conducted beyond a week. This is possibly because of infarct evolution and formation of myocardial fibrous tissue which may help in anchoring the prosthetic patch better than the necrotic myocardium, when repair is delayed. However, early surgery may be the only option in patients with hemodynamic compromise and may thus represent survival bias.

Similar to our study, cardiogenic shock at presentation has been identified as the single most important predictor of mortality in many other articles,[2,3,14] most probably because of extensive infarct area when ventricular septal rupture develops. Posterior VSRs, despite being associated with poorer outcomes due to right ventricular dysfunction,[4] complex ruptures,[15] difficult surgical exposure, and challenging repair[16] due to close proximity of posterior descending artery and posteromedial papillary muscle, did not result in decreased mortality in the present study. Concomitant CABG did not offer any survival benefit in this study as in other articles.[13]

4.1. Limitations of the present study

The present study is limited by its nonrandomized retrospective design, which permits confounding. The low sample size in our study is due to low incidence of PMI-VSR. The study population extends over a six-year period, with different management and

operative strategies making comparative analysis difficult. Lack of mortality data of patients with PMI-VSR who died before getting operated is another lacuna of this study. Time from thrombolysis to development of VSR was not noted because many subjects were referred form primary care centers. Considering high operative mortality, a randomized controlled trial seems difficult for PMI-VSR. A prospective multicenter study is needed to verify the results of the current research.

5. Conclusion

Preoperative early thrombolysis is associated with survival, and cardiogenic shock at presentation is associated with increased odds of operative mortality after surgical repair of PMI-VSR.

Key questions

- What is already known about this subject?
  - ✓ Post–myocardial infarction ventricular septal rupture (PMI-VSR) has a mortality rate approaching 100% with medical management and close to 50% with surgical repair.
- What does this study add?
  - ✓ This is the first study which shows that preoperative early thrombolysis (<12 h after acute myocardial infarction) is associated with decreased odds of operative mortality in PMI-VSR repair cohort.
- How might this impact clinical practice?
  - ✓ In a resource-constrained country such as India, where facilities for percutaneous or surgical coronary revascularization may not be universally available, preoperative early thrombolysis may provide survival benefit in PMI-VSR repair cohort when surgical repair is contemplated.

Author contributions

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version submitted.

Conflicts of interest

All authors have none to declare.

Author disclosures

None.

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