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Length of stay and major adverse cardiac events

Comparison between percutaneous coronary intervention and thrombolytic therapy in patients with ST-elevation myocardial infarction

Implications for cost effectiveness

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2019, 36(4):494–502

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OBJECTIVE **To compare length of stay (LOS) and major adverse cardiac events (MACE) between thrombolytic therapy and percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction.** METHOD **A retrospective study was conducted at Aisyiyah Hospital from January 2014 to December 2017. Data on the revascularization method and outcome related to LOS and MACE were extracted from the medical records. Multiple logistic regression was used to assess the relationship between revascularization method and LOS, and MACE. In addition, a meta-analysis was conducted to summarize relevant findings from other regions.** RESULTS **A total of 294 patients with ST-elevation myocardial infarction (STEMI) between January 2014 and December 2017 were enrolled in this study. Of these, 186 patients were treated with thrombolytic therapy and 108 patients were treated with PCI. The findings showed that thrombolytic therapy was associated with increased risk of longer LOS, cardiogenic shock, and death compared with PCI. In addition, the meta-analysis showed that thrombolytic therapy was related with increased risk of prolonged LOS and reinfarction.** CONCLUSIONS **The higher LOS and MACE observed in the thrombolytic group means that thrombolytic therapy is associated with greater morbidity and incurs higher costs than PCI for treating patients with STEMI.**

Η διάρκεια της νοσηλείας και τα μείζονα ανεπιθύμητα καρδιακά συμβάματα μεταξύ της διαδερμικής στεφανιαίας παρέμβασης και της θρομβόλυσης σε ασθενείς με ισχαιμία μυοκαρδίου και ανάσπαση του ST: επιπτώσεις στη σχέση κόστους/αποτελεσματικότητας

Περίληψη στο τέλος του άρθρου

Key words

Cost efficiency
Myocardial infarction
Percutaneous coronary intervention
Thrombolytic therapy

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Thrombolytic therapy has been widely used for management of ST-elevation myocardial infarction (STEMI),[1] but because of several conditions, such as in-hospital delay[2] and fibrinolytic checklist,[3] thrombolytic therapy may not be applied for all STEMI patients. Since 1979, percutaneous coronary intervention (PCI) has been applied for STEMI management,[4] and has been proven to have an excellent long-term prognosis.[5,6] Since then, PCI has been widely used for treating patients with STEMI. Some reports[7,8] have shown that PCI is more effective than thrombolytic therapy in restoring thrombolysis in myocardial infarction (TIMI) flow, and better than coronary artery bypass grafting (CABG).[9] Although some studies have reported the benefits of PCI, others[10–20] reporting the comparison between PCI and thrombolytic therapy by evaluating major adverse cardiac events (MACE) including cardiac death, cardiogenic shock,

and reinfarction[21] showed conflicting results. Moreover, MACE is thought to have a role in cost effectiveness, and until now, the difference in cost effectiveness between PCI and thrombolytics is still open to controversy. These issues are directly related to the health insurance and sometimes may affect the treatment options.

Recently, health insurance has been widely used to coverage health costs. Under these conditions, health insurance may also have a role in determining the treatment options for the patients. In Indonesia, there is an assumption (health insurance-related assumption) that, evaluated by the costs, thrombolytic therapy is more efficient than PCI for treating patients with STEMI. For this reason, in some hospitals, PCI is limited. The total cost expenditure, however, for the disease is determined not only by the cost of primary therapy, but also the cost of treating future complications.[22] In this context, length of stay (LOS) and MACE should be considered. Our present study aimed, therefore, to investigate the comparison of LOS and MACE between PCI and thrombolytic therapy in the treatment of patients with STEMI. In addition, because studies concerning such comparisons were still underreported, we also performed a meta-analysis to combine and compare findings from other regions.

MATERIAL AND METHOD

Study design and patients

A retrospective study was conducted in the Aisyiyah Hospital, Malang, Indonesia. The target population was all patients with STEMI who were treated with either PCI or thrombolytic therapy in the Aisyiyah Hospital from January 2014 to December 2017. We used the total sampling method. The patient inclusion criteria were (a) suffered from STEMI, (b) aged over 18 years, and (c) treated with PCI or thrombolytic therapy. Patients with one of the clinical conditions: (a) renal dysfunction (creatinine ≥1.5 mg/dL), (b) hepatic disorder, (c) concomitant inflammatory disease, (d) neoplastic disease, (e) systemic disorder, (f) acute or chronic infectious disease, and (g) hematological disorder were excluded. Data on gender, age, diagnosis, infarct location, arrhythmia, hypertension, diabetes mellitus (DM), heart failure, cardiogenic shock, reinfarction, and mortality and LOS were extracted from the medical records. Our study was approved by an Internal Review Board (no 23/KM/RSIA/XII/2015).

Statistical analysis

The comparison of LOS and MACE (heart failure, cardiogenic shock, reinfarction, and death) between PCI and thrombolytic therapy was analyzed using multiple logistic regression with the enter method. All significance tests were two tailed and p-value of less than <0.05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS), v. 17.0 software (SPSS Inc, Chicago, IL) was used to analyze the data.

Meta-analysis

A meta-analysis was performed to assess the association between STEMI management and outcome (LOS and MACE). The meta-analysis approach was adapted from our previous studies.[23–28] The inclusion criteria for meta-analysis were: (a) retrospective studies; (b) prospective studies; (c) cross-sectional studies; (d) randomized-controlled trials (RCTs); (e) controlled before-and-after studies; (f) cross-over studies; (g) investigating the association between STEMI management and outcomes related to LOS and MACE; and (h) providing sufficient data for calculating ods ratio (OR) 95% confidence interval (CI). Briefly, articles related to the comparison of outcomes (LOS and MACE) between PCI and thrombolytic for treating STEMI were searched on PubMed and Embase up to September 20th, 2017. For the search strategy, we used the combination of the following key-words: (ST elevation myocardial infarction or STEMI) and (reperfusion or percutaneous coronary intervention or PCI or thrombolytic or fibrinolytic) and (outcomes or length of stay or LOS or major adverse cardiac events or MACE). The publication languages were limited to English. For each study, information related to: (a) first author name; (b) publication year; (c) country of origin; (d) sample sizes of PCI and thrombolytic group, and (e) mean±SD or frequencies and percents of each variable in PCI and thrombolytic group were extracted. The association between STEMI management and their outcomes (LOS and MACE) was estimated by calculating pooled OR and 95% CI. The significance of pooled ORs was determined by Z-tests ($p<0.05$ was considered statistically significant). A Q-test was performed to evaluate whether heterogeneity existed. A random effects model was used to calculate the OR 95% CI if heterogeneity existed ($p<0.10$) otherwise a fixed effects model was used. Egger's test was used to assess publication bias ($p<0.05$ was considered statistically significant). Comprehensive Meta-analysis (CMA) (CMA, New Jersey, USA), v. 2.0 software was used to analyze the data.

RESULTS

Characteristics of patients

A total of 108 patients with STEMI treated with PCI and 186 patients with STEMI treated by thrombolytic therapy were analyzed. The mean age of the PCI group was 55.3 (±9.3) years, and of the thrombolytic group 59.0 (±10.9) years (tab. 1). Other demographic and clinical characteristics of the patients such as gender, infarct location, hypertension, DM and arrhythmia are presented in table 1.

Table 1. Basic clinical characteristics and outcomes of patients with ST-elevation myocardial infarction (MI) treated by thrombolytic therapy or percutaneous coronary intervention (PCI).

No	Characteristics	PCI (n=108)	Thrombolytic (n=186)
1	Age	55.3±9.3	59.0±10.9
2	Male	84 (77.8)	139 (74.5)
4	Anterior MI	59 (54.5)	98 (52.7)
5	Inferior MI	44 (40.9)	78 (41.9)
6	Hypertension	33 (30.6)	60 (32.3)
7	Diabetes mellitus	15 (13.6)	28 (14.9)
8	Arrhytmia	15 (13.6)	28 (14.9)
Outcomes			
1	Length of stay	3.1±1.9	6.0±2.5
2	Heart failure	54 (50.0)	96 (51.6)
3	Cardiogenic shock	39 (36.4)	24 (13.0)
4	Reinfarction	5 (4.5)	5 (2.5)
5	Death	5 (4.5)	18 (9.9)

Note: Data are presented as mean±SD or frequencies (percentages)

The comparison of outcomes between PCI and thrombolytic groups

The outcomes in the PCI and thrombolytic therapy groups are presented in table 1 and the associations are summarized in table 2. We found that LOS in the PCI group was shorter than in the thrombolytic group. The frequency of cardiogenic shock and the mortality rate were less in the PCI group than in thrombolytic group (tables 1, 2). Other complications, such as heart failure and reinfarction showed no significant difference between the PCI and thrombolytic groups.

Meta-analysis

We found several studies comparing the outcome between PCI and thrombolytic therapy for treating STEMI. Of 16 studies, five studies were excluded after review because the data were not sufficient for calculation of OR (95% CI). A flowchart of the literature search for studies to be included in the meta-analysis is depicted in figure 1.

We found seven papers, including our own results,[11,13,15,16,18,19] that evaluated the comparison of LOS between PCI and thrombolytic groups. The results of the meta-analysis indicated that LOS in the PCI group was shorter than in the thrombolytic therapy group (OR 95% CI: 3.33 [1.94–5.72], p<0.0001) (tab. 3). For heart failure, six studies including our own[15,20,21,24,25] were identified, and showed that the rate heart failure between subjects in the PCI and thrombolytic groups was not significantly different (OR 95% CI: 1.07 [0.64–1.77], p=0.7990) (tab. 3). Six studies including our own results,[10,13–15,19] evaluating the comparison of cardiogenic shock between PCI and thrombolytic groups were identified. Cardiogenic shock was not significantly different in the PCI and thrombolytic groups (OR 95% CI: 0.79 [0.63–1.01], p=0.0620) (tab. 3). For reinfarction, we identified 8 studies including our own.[10–13,15,16,18] We found that reinfarction was more frequent in the thrombolytic than in PCI group (OR 95% CI: 2.10 [1.58–2.81], p<0.0001). Eleven studies including our own[10–13,15–20] compared the mortality between the PCI and thrombolytic groups, showing no significant difference in mortality between the two groups (OR 95% CI: 1.43 [0.98–2.08], p=0.0620).

Table 2. Summary of odds ratio (OR) and 95% confidence interval (CI) regarding outcomes between thrombolytic therapy and percutaneous coronary intervention (PCI) (thrombolytic vs PCI).

No	Parameters	OR	95% CI	p
1	Length of stay	2.46	1.74–3.49	<0.0001
2	Heart failure	0.55	0.17–1.73	0.3030
3	Cardiogenic shock	0.15	0.04–0.57	0.0060
4	Reinfarction	1.55	0.06–42.05	0.7950
5	Death	29.98	2.29–92.49	0.0100

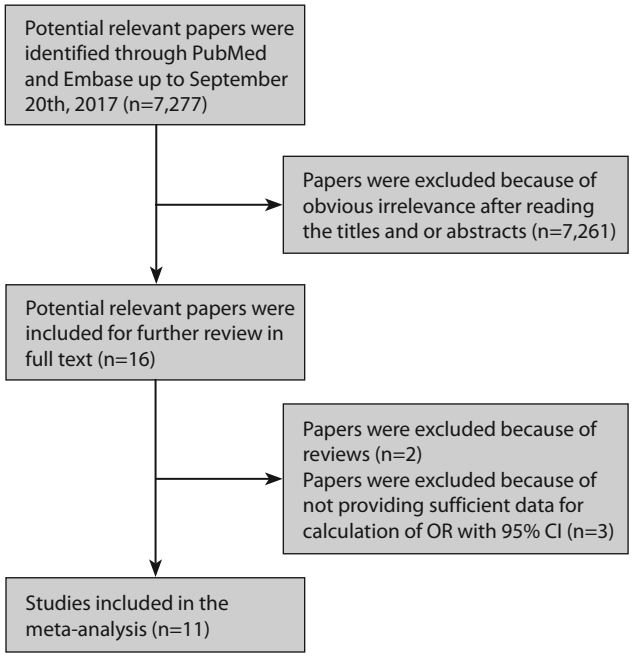

Figure 1. Flowchart of search for studies to be included in the meta-analysis.

Table 3. Summary of meta-analysis regarding comparison of outcomes between thrombolytic therapy and percutaneous coronary intervention (PCI) (thrombolytic vs PCI).

Outcomes	Number of studies	Model	PCI		Thrombolytic		OR	95% CI	*p*H	*p*E	p
			n	Values	n	Values					
Length of stay	7	Random	8,131	9.4±2.6	17,219	11.3±3.4	3.33	1.94–5.72	<0.0001	0.6780	<0.0001
Heart failure	6	Random	1,687	117 (6.9)	1,827	190 (10.4)	1.07	0.64–1.77	0.0590	0.4240	0.7990
Cardiogenic shock	6	Fixed	1,960	189 (9.6)	2,049	183 (8.9)	0.79	0.63–1.01	0.1240	0.2770	0.0620
Reinfarction	8	Random	12,427	286 (2.3)	21,528	984 (4.6)	2.10	1.58–2.81	0.0270	0.2620	<0.0001
Death	11	Random	12,627	581 (4.6)	21,729	1884 (8.7)	1.43	0.98–2.08	<0.0001	0.4520	0.0620

Note: Data are presented as mean±SD or frequencies (percentages)

OR: Ods ratio, CI: Confidence interval, *p*H: *p* heterogeneity, *p*E: *p* Egger

As evidence of heterogeneity was found for LOS (p<0.0001; I2=95.41), heart failure (p=0.0590; I2=52.98), reinfarction (p=0.0270; I2=55.70), and mortality (p<0.0001; I2=82.45), data were analyzed using the random effect model. Heterogeneity was not found for cardiogenic shock (p=0.1240; I2=42.11) and therefore, we analyzed the data using the fixed effect model. No publication bias could be detected (p<0.05).

DISCUSSION

LOS is often regarded as an indicator of efficiency and has been found to be closely correlated with medical costs[29] and quality assessment.[30] Data from our hospital showed that the thrombolytic therapy group showed a two-fold longer LOS compared with the PCI group (tab. 2). Our results thus suggest that PCI was better than thrombolytic therapy as assessed from LOS. However, our hospital is type C and therefore, such data had a tendency to be considered as low level of evidence. Because of this, we collected seven other studies evaluating the comparison between PCI and thrombolytic therapy correlated with LOS. Of these, six studies showed that PCI was significantly associated with lower LOS; other showed no significant association. We combined our data with other data from all over the world using meta-analysis and found that the PCI group had lower LOS than the thrombolytic therapy group. Our results were consistent with several reports which revealed that PCI was significantly associated with reduced LOS, and most of the reports defined less than two days or 48 hours as an ideal LOS after PCI.[30–32] However, the revascularization method by either PCI or thrombolytic is not the only factor influencing LOS. Many factors must be considered, including age, payment classification, source of referral, specialty of doctor, and ethnic group.[33]

Prolonged LOS has been widely known to be correlated with total costs. Some studies found that longer LOS had a dominant impact on the total costs,[34–36] while others showed otherwise.[37,38] There is a tendency for the total cost of prolonged LOS to be commonly incurred in the cases treated in the intensive care unit (ICU),[39,40] as in STEMI. In the evaluation of the cost effectiveness, therefore although the treatment cost for PCI is relatively higher than that for thrombolytic therapy, the longer LOS after thrombolytic therapy should be taken into account.

Cardiogenic shock, defined as state of end-organ hypoperfusion due to cardiac failure,[41] is the leading cause of death in patients hospitalized for STEMI.[42] Overall, cardiogenic shock occurs in 3% to 20% of patients with myocardial infarction (MI) treated either by PCI or thrombolytic therapy,[43] although thrombolytic therapy has been considered to reduce cardiogenic shock in STEMI patients.[44] In our study, however, the incidence of cardiogenic shock was significantly greater in the thrombolytic therapy than in the PCI group. This finding was supported by Hasdai and colleagues[45] who reported that cardiogenic shock was a common complication of STEMI after thrombolytic therapy, with an incidence of 5% to 8%, lower than in our data and meta-analysis. The management of cardiogenic shock has been widely established including strict monitoring in the ICU and the use of intra-aortic balloon pump (IABP).[46] It has been reported that the management of cardiogenic shock is very expensive;[47–49] thus, because thrombolytic therapy is associated with increased risk of cardiogenic shock, its cost effectiveness needs to be reconsidered. The meta-analysis from six studies, including a total of 1,960 patients treated by PCI and 2,049 patients on thrombolytic therapy showed no significant difference in the incidence of cardiogenic shock between PCI and thrombolytic groups. Concerning heart failure, the results from both our hospital data and the meta-analysis showed no significant association between heart failure and revascularization method.

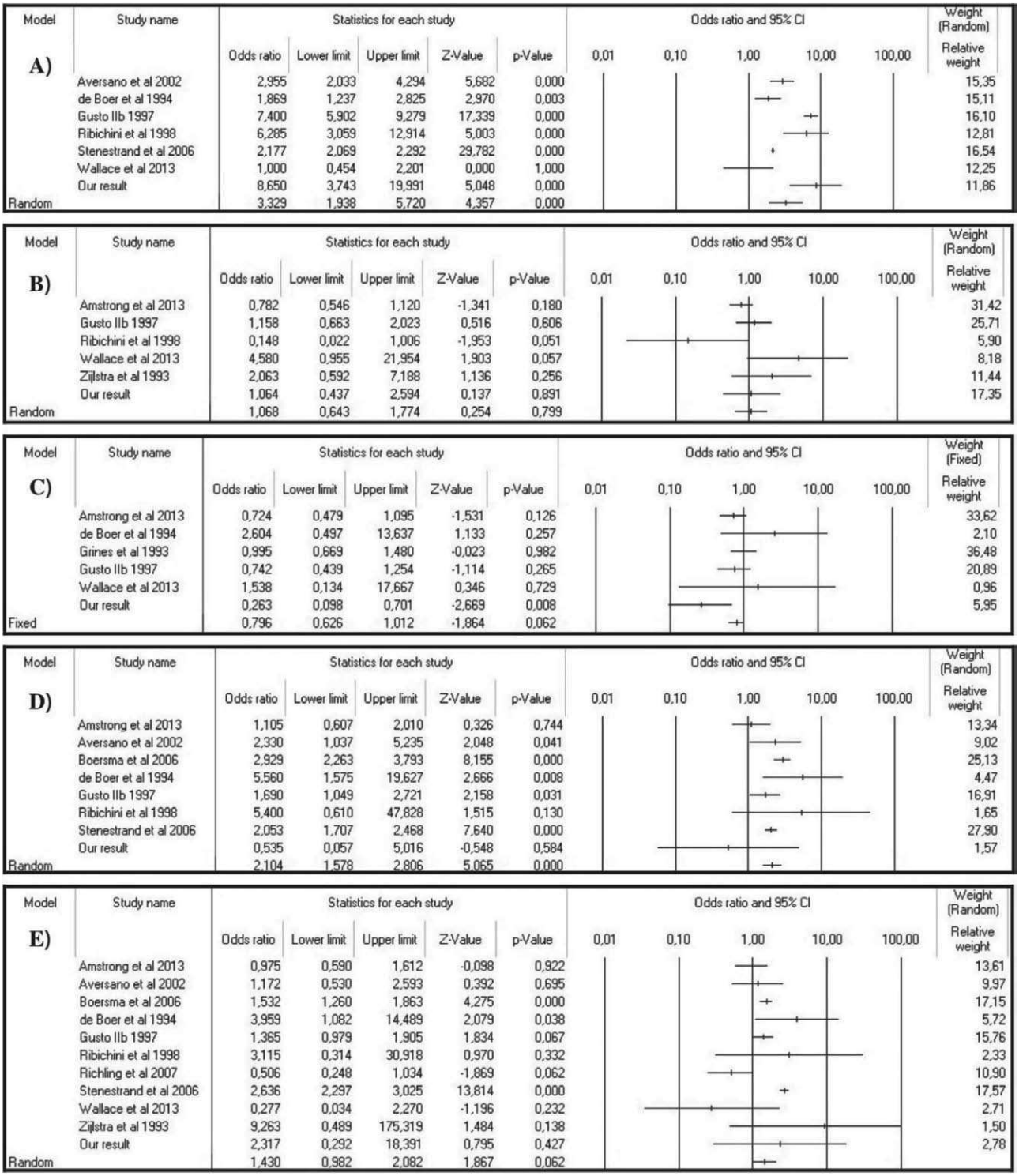

Figure 2. Forest plot regarding the association between revascularization method and their outcomes. (A) Length of stay; (B) Heart failure; (C) Cardiogenic shock; (D) Reinfarction; (E) Death.

Reinfarction is defined as reocclusion of the infarct artery occurring within 28 days of an incident, or recurrent MI, and should be considered when ST-elevation of >0.1 mV reoccurs or a new pathognomonic Q wave appears, on at least at two contiguous leads, particularly when associated with ischemic symptoms for 20 minutes or longer.[50] One study reported that reinfarction was more common after PCI,[51] while another study showed the reverse.[52] After

thrombolytic therapy, the incidence of reinfarction was reported in 5% to 30% of patients, but clinical reinfarction was documented in only 4% of patients.[53] The data from our hospital revealed that the incidence of reinfarction was 4.5% after PCI and 2.5% after thrombolytic therapy, but this difference was not significant. Combining our results with data from other studies using meta-analysis, we found that reinfarction was more common after thrombolytic therapy (4.6%) than after PCI (2.3%). In the STEMI guidelines, the suggested management for reinfarction after thrombolytic therapy is PCI.[54] Therefore, evaluated from the cost effectiveness viewpoint, because reinfarction was observed more frequently in thrombolytic therapy, the use of thrombolytic therapy over PCI to treat patients with STEMI needs to be reconsidered.

Although our meta-analysis data showed no significant correlation between revascularization method and mortality, the findings from our hospital data revealed that thrombolytic therapy was associated with increased risk of death compared with PCI. It is recognized that mortality in STEMI is dominantly caused by cardiogenic shock and or reinfarction, as confirmed by studies that reported the high mortality rate of cardiogenic shock[44,55] or reinfarction[53,56] in the setting of STEMI. Our study showed that, compared with PCI, thrombolytic therapy had an increased risk of cardiogenic shock and reinfarction. Moreover, PCI has been shown to decrease the mortality rate in STEMI patients.[43] This may explain the higher mortality rate after thrombolytic therapy versus PCI in our series. The revascularization method is not the only factor influencing the mortality in patients with STEMI, and other factors, including such as age, DM, and previous MI need to be addressed to prevent or decrease STEMI mortality.[57]

In our study thrombolytic therapy was associated with increased LOS, cardiogenic shock, and death, and the meta-analysis showed that thrombolytic therapy was correlated with longer LOS and reinfarction. It is well known that increasing the odds of having these various conditions (prolonged LOS, reinfarction, cardiogenic shock, and death) is correlated with the higher cost of hospital care. Therefore, although it may appear that the cost of thrombolytic therapy is lower, the costs incurred in treating these complications after thrombolytic therapy are high. Based on our results, there is a tendency for the treatment of patients with STEMI, evaluated from the cost possibility, thrombolytic therapy may, in the long run, require higher additional costs than PCI. For the organization of cardiology services in preparing the guidelines for treatment of STEMI, we highly recommend considering the cost factor. Thus, various issues related to costs and health insurance may be minimized.

This study has several strengths. Firstly, the findings of reduced LOS, reinfarction, and mortality were robust across the PCI group. Second, the data from our hospital, supported by meta-analysis of 11 studies, strengthened the level of evidence. However, this study has also several important limitations. Firstly, this study was a retrospective. To reach a better level of evidence, further studies with a randomized controlled trial (RCT) design are required. Second, because this was a restrospective study, we only retrieved data from medical records. We could not evaluate the covariates which may have a role but were not in the medical record. Third, because of the regulations in our hospital, we could not compare the total cost specifically. Fourth, in the meta-analysis, most of the collected studies also were retrospective. Further studies including only RCT are required to derive conclusions with a higher level of evidence.

In conclusion, our hospital study indicates that compared with PCI, thrombolytic therapy is associated with increased risk of prolonged LOS, cardiogenic shock, and death. Our meta-analysis reveals evidence that thrombolytic therapy is associated with increased risk of longer LOS and reinfarction. Our results suggest that thrombolytic therapy, evaluated from LOS and MACE, may incur higher additional costs for treating patients with STEMI.

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ΠΕΡΙΛΗΨΗ

Η διάρκεια της νοσηλείας και τα μείζονα ανεπιθύμητα καρδιακά συμβάματα μεταξύ της διαδερμικής στεφανιαίας παρέμβασης και της θρομβόλυσης σε ασθενείς με ισχαιμία μυοκαρδίου και ανάσπαση του ST: επιπτώσεις στη σχέση κόστους/αποτελεσματικότητας

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ΣΚΟΠΟΣ Η σύγκριση της διάρκειας νοσηλείας (ΔΝ) και των μείζονων ανεπιθύμητων καρδιακών συμβαμάτων (ΜΑΚΣ) ανάμεσα στη θρομβολυτική θεραπεία (ΘΛΘ) και στη διαδερμική στεφανιαία παρέμβαση (ΔΣΠ). **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Μια αναδομική μελέτη διεξήχθη στο Νοσοκομείο Aisyiyah από τον Ιανουάριο του 2014 έως τον Δεκέμβριο του 2017. Τα δεδομένα από τη μέθοδο επαναγγείωσης και τα αποτελέσματα σχετικά με τη ΔΝ και τα ΜΑΚΣ αντλήθηκαν από τα ιατρικά αρχεία. Η μέθοδος που εφαρμόστηκε προκειμένου να εκτιμηθεί η συσχέτιση ανάμεσα στη μέθοδο επαναγγείωσης αφ' ενός με τη ΔΝ και αφ' ετέρου με τα ΜΑΚΣ ήταν η πολλαπλή λογιστική παλινδρόμηση (multiple logistic regression). Επί πλέον, διενεργήθηκε μετα-ανάλυση προκειμένου να πραγματοποιηθεί η σύνοψη των ευρημάτων από άλλες περιοχές. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Συνολικά, 294 συμβάματα με οξύ έμφραγμα του μυοκαρδίου και ανάσπαση του ST (ST-elevation myocardial infarction, STEMI) μεταξύ Ιανουαρίου του 2014 και Δεκεμβρίου του 2017 συμπεριλήφθηκαν στην παρούσα μελέτη. Μεταξύ αυτών, οι 186 ασθενείς αντιμετωπίστηκαν με ΘΛΘ και οι 108 με ΔΣΠ. Τα ευρήματα της μελέτης αυτής ανέδειξαν ότι η ΘΛΘ σχετίστηκε με υψηλότερο κίνδυνο για μεγαλύτερη ΔΝ, καρδιογενές shock και θνητότητα. Επί πλέον, η μετα-ανάλυση που ακολούθησε ανέδειξε ότι η ΘΛΘ συσχετίστηκε με αυξημένο κίνδυνο παρατεταμένης ΔΝ και υποτροπής του STEMI. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η μεγαλύτερη ΔΝ και τα συχνότερα ΜΑΚΣ που παρατηρήθηκαν στην ομάδα των ασθενών με θρομβόλυση υποδεικνύουν ότι για τη ΘΛΘ πιθανόν να απαιτείται μεγαλύτερο κόστος απ' ό,τι με τη ΔΣΠ όσον αφορά στην αντιμετώπιση των ασθενών με STEMI.

Λέξεις ευρετηρίου: Αποτελεσματικότητα κόστους, Διαδερμική στεφανιαία παρέμβαση, Έμφραγμα μυοκαρδίου, Θρομβόλυση

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