Resuscitation (2006) **70**, 31—36

ELSEVIER

RESUSCITATION

www.elsevier.com/locate/resuscitation

CLINICAL PAPER

A meta-analysis of cardiopulmonary resuscitation with and without the administration of thrombolytic agents☆

Xin Li[a], Qing-ling Fu[b], Xiao-li Jing[a], Yu-jie Li[a], Hong Zhan[a], Zhong-fu Ma[a], Xiao-xing Liao[a,*]

[a] *Department of Emergency, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong 510080, PR China*
[b] *Department of Anatomy, The University of Hong Kong, 21 Sassoon Road, Hong Kong, PR China*

Received 18 March 2005; received in revised form 21 November 2005; accepted 26 November 2005

KEYWORDS
Cardiopulmonary resuscitation (CPR);
Drug therapy;
Thrombolysis

Summary
Objective: To pool data on the role of thrombolytic agents in cardiopulmonary resuscitation (CPR) and evaluate the efficacy and safety of thrombolysis.
Materials and methods: The clinical studies in MEDLINE database from 1966 to August 2004 that studied the efficacy and safety in CPR with and without treatment with thrombolytic agents were assessed by a meta-analysis performed to evaluate the effect of the treatment.
Results: A total of eight papers evaluating the effect of thrombolysis in CPR were identified. This meta-analysis showed that thrombolytic agents significantly improved the rate of return of spontaneous circulation, 24 h survival rate, survival to discharge and long-term neurological function in patients treated with CPR ($p < 0.01$). However, the patients receiving thrombolysis had a risk of severe bleeding ($p < 0.01$).
Conclusion: Thrombolytic agents during CPR can improve the survival rate to discharge and neurological function.

Introduction

Cardiopulmonary resuscitation (CPR) is essential for the treatment of cardiac arrest and protection of cerebral function. However, the efficacy of this treatment is still unsatisfactory even after 40 years. The most common causes of cardiac arrest are acute myocardial infarction (AMI) and massive pulmonary embolism (PE). Moreover, CPR also results

☆ A Spanish translated version of the summary of this article appears as Appendix in the online version at doi:10.1016/j.resuscitation.2005.11.016.

* Corresponding author. Tel.: +86 20 87755766 8511; fax: +86 20 87755766 8773.
E-mail address: qlfu@hkusua.hku.hk (X.-x. Liao).

0300-9572/$ — see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.resuscitation.2005.11.016

in microthrombosis. From this we know that it is feasible to perform thrombolysis during CPR. However, the therapy has been in question because of the anticipated severe bleeding risk. Some research groups have studied the efficacy of thrombolysis during CPR. However, there is some inconsistency in the results, which affects evaluation of the efficacy of thrombolytic therapy. Meta-analysis is a method of synthesise a group of data composed of small samples received from different research and to analyse data from each quantitatively to increase the validity of the final conclusion. In order to evaluate the effect of thrombolytic therapy on cardiac arrest patients who had been given CPR, we did a meta-analysis.

Materials and methods

Materials

Research papers were searched from the MEDLINE database from 1966 to August 2004.

Literature research method

Keywords used in the search were [(cardiac arrest) or (cardiopulmonary resuscitation) or (cardiopulmonary-cerebral resuscitation)] and [thrombolysis or (thrombolytic agent) or urokinase or streptokinase or (tissue-type plasminogen activator) or t-PA]. The search was limited by the search words of ''>19 years'', ''Publication Date since 1966/01/01 till 2004/08/01'', ''English'', ''Human'' and ''MEDLINE''. We excluded those research papers with the following keywords: ''case reports'', ''letter'', ''review'', ''practice guideline'', ''review literature'', ''review of reported cases'', ''review, academic'', ''review, multicase'', ''review, tutorial'', ''scientific integrity review'', ''congresses'', ''interview'', ''overall'', ''comment'', ''news'', ''newspaper article'' and ''address''. Some papers not included in the MEDLINE database were also used in this analysis.

Inclusion criteria

Elligible patients had a cardiac arrest and had been treated with CPR. The diagnosis of cardiac arrest and CPR was based on the International 2000 guidelines. The process of diagnosis and management was registered according to the Utstein model. The method was a randomized comparative study or a non-randomized comparative study done at the same time. Some historical cases were used as controls in some papers. Patients in the treatment groups were those surviving from cardiac arrest and with treatment by thrombolytic agents during CPR. The types and doses of agents were not restricted. Patients in the control groups were those who underwent cardiac arrest and were treated by CPR without thrombolysis. The efficacy and complications were compared between treatment and control groups. The incidence of return of spontaneous circulation (ROSC), 24 h survival rate, the rate of survival to discharge, the incidence of severe and minor bleeding and assessment of major organ function were recorded.

Statistical analysis

Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated for the articles included. Pooled estimates of the odds ratio and 95% CI were obtained by the fixed-effects model of Peto and testing for homogeneity was done by the Breslow—Day test, with Review Manager 4.2 software. Publication bias was assessed by calculating fail-safe number (Nfs)[1] according to the formula $\text{Nfs}.05 = (\sum u/1.645)2 - N$. A fail-safe number indicates the number of non-significant, unpublished studies that would need to be added to a meta-analysis to reduce the overall statistically significant results to non-significance. If the number is large relative to the number of observed studies, one can feel fairly confident in the summary conclusions.

Results

Eligibility of literature

The search retrieved 121 papers, and 9 of them[2—10] were cohort studies on cardiopulmonary resuscitation and thrombolysis in the same period. One paper[11] was retrieved from MEDLINE after searching the relevant references. However, the authors did not present details of the groups of patients, the types and dose of thrombolytic agents and the criteria for severe bleeding. This paper was finally excluded in this meta-analysis. Another paper[8] was also excluded because it lacked research indices. Only eight cohort studies were included in this meta-analysis to analyse the effect of thrombolytic agents in CPR. Participants and the selected study design characteristics of the eight cohort studies included in the meta-analysis are detailed in Table 1. Seven are retrospective stud-

Table 1 Characteristics of studies included in the meta-analysis

Authors	Type of study	Whether was CPR performed by guide	Data expression	Observational end-point	The dosage of thrombolytic agent	Anticoagulant	Underlying diseases
Janata et al.[2]	Retrospective cohort	Yes	Utstein Style	ROSC, 24 h survival, discharge, severe bleeding	rt-PA, 100 mg	Heparin	Acute myocardial infarction (AMI)
Kurkciyan et al.[3]	Retrospective cohort	Yes	Utstein Style	Long-term neurological function, severe bleeding	t-PA, 100 mg	Aspirin, heparin	AMI
Schreiber et al.[4]	Retrospective cohort	Yes	Utstein Style	Long-term neurological function	t-PA, 100 mg	Aspirin, heparin	AMI
Lederer et al.[5]	Retrospective cohort	Yes	Utstein Style	ROSC, 24 h survival, discharge, severe bleeding	t-PA, 100 mg	Heparin	Non-traumatic aetiology
Ruiz-Bailen et al.[6]	Retrospective cohort	Yes	Utstein Style	Severe bleeding	t-PA, 100 mg	Heparin	AMI
Bottiger et al.[7]	Prospective cohort	Yes	Utstein Style	ROSC, 24 h survival, discharge, severe bleeding	t-PA, 100 mg	Heparin	Cardiological diseases
Kurkciyan et al.[9]	Retrospective cohort	Yes	Utstein Style	ROSC, discharge, severe bleeding	t-PA, 100 mg	Heparin	Pulmonary embolism (PE)
van Campen et al.[10]	Retrospective cohort	Yes		Severe bleeding	t-PA, 100 mg	Aspirin, heparin	PE

ies and the one is a prospective cohort control study.

Comparing the outcome with and without the treatment of thrombolytic agents during CPR

1. We compared the rate of ROSC between thrombolytic and control groups. The rate of ROSC was compared between two groups in four articles.[2,5,7,9,11] Thrombolytic therapy was performed during or within 15 min after CPR. The eligible criteria for thrombolytic therapy were that patients were between 19 and 75 years of age and without trauma or indications of internal or external bleeding. One hundred milligrams of recombinant tissue-type plasminogen activator (rt-PA) was administered during thrombolytic therapy. All patients undergoing thrombolysis received heparin as well. Among the four articles, one[2] concluded that thrombolysis did not increase the rate of ROSC. However, the other papers[5,7,9] showed contrary results. This meta-analysis indicates that thrombolytic therapy can significantly improve the rate of ROSC ($p < 0.01$) (Table 2). The calculation for the fail-safe number is 25.93. It suggests that there should be 26 articles with a negative conclusion to reverse the conclusion. The conclusion from this meta-analysis is convincing, with little risk that it is caused by publication bias.
2. We compared the 24 h survival rate between the thrombolytic and control groups. Survival rate for more than 24 h was compared between the two groups in three articles.[2,5,7] Only one article[7] revealed that thrombolytic agents did not improve 24 h survival rate. The other two articles[2,5] drew quite different conclusions. Our meta-analysis showed that thrombolytic therapy significantly improved the 24 h survival rate ($p < 0.01$) (Table 3). Sensitivity analysis reveals that ten negative studies would have to have been missed to reverse the statistical significance (Nfs = 3.69).
3. We compared the survival to discharge between thrombolytic and control groups. Four articles[2,5,7,9] did this comparison. Three revealed that thrombolysis did not improve the rate of survival to discharge. However, the number of cases in those three articles was small.[2,7,9] The remaining article[5] produced a different result. Meta-analysis indicates that thrombolytic therapy can significantly improve the rate of survival to discharge ($p < 0.01$) (Table 4). The Nfs is 1.41 and shows the con-

Table 2 Meta-analysis of the rate of ROSC between thrombolytic and control group

Authors	Thrombolytic group		Non-thrombolytic group		OR	95% CI
	No.	No. of ROSC	No.	No. of ROSC		
Janata et al.[2]	36	24	30	13	2.62	0.96, 7.12
Lederer et al.[5]	108	76	216	110	2.29	1.40, 3.74
Bottiger et al.[7]	40	27	50	22	2.64	1.11, 6.28
Kurkciyan et al.[9]	21	17	21	9	5.67	1.41, 22.76
Total	205	144	317	154	2.57	1.76, 3.74

The homogeneity test of the literatures: $q = 1.46$, $p > 0.10$ means that homogeneity is good; OR combined hypothesis testing, $Z = 4.89$, $p < 0.01$; Nfs = 25.93.

Table 3 Meta-analysis of the 24 h survival rate between thrombolytic and control group

Authors	Thrombolytic group		Non-thrombolytic group		OR	95% CI
	No.	No. of survival of 24 h	No.	No. of survival of 24 h		
Janata et al.[2]	36	19	30	7	3.67	1.26, 10.70
Lederer et al.[5]	108	52	216	71	1.90	1.18, 3.04
Bottiger et al.[7]	40	14	50	11	1.91	0.75, 4.85
Total	184	85	296	89	2.08	1.40, 3.08

The homogeneity test of the literatures: $q = 1.27$, $p > 0.10$, means that homogeneity is good; OR combined hypothesis testing, $Z = 3.69$, $p < 0.01$; Nfs = 9.65.

clusion could be influenced by publication bias.

4. We compared long-term neurological function between the thrombolytic and control groups. Only two articles[3,4] included the on Cerebral Performance Categories (CPC) scale. Good outcome was recorded for patients who could perform their normal activities independently (CPC 1or 2), and bad, poor or unfavorable outcome was predicted for patients who are dependant on others, vegetative or dead (CPC 3, 4 or 5). The authors measured the CPC several times between ROSC and 6 months after discharge. The best CPC score was recorded and analysed. Both articles revealed that long-term neurological function in the thrombolytic group was much better than in the control group. Our meta-analysis showed that thrombolytic therapy can significantly improve long-term neurological function ($p < 0.01$) (Table 5).

Comparing the degree of bleeding between the thrombolytic and control groups

The morbidity from severe bleeding was compared between the groups in seven articles.[2,3,5,6,7,9,10] Severe bleeding is defined as life-threatening bleeding and/or bleeding that requires transfusion, including: (1) bleeding into body cavities: haemopericardium, haemothorax and haemoperitoneum; (2) intraparenchymal haematoma following organ rupture or laceration; (3) intracranial haemorrhage; (4) any bleeding needing blood transfusion. None of seven articles showed that throm-

Table 4 Meta-analysis of rate of survival to discharge between thrombolysis and control group

Authors	Thrombolytic group		Non-thrombolytic group		OR	95% CI
	No.	No. of survival to discharge	No.	No. of survival to discharge		
Janata et al.[2]	36	7	30	2	3.38	0.65, 17.68
Lederer et al.[5]	108	27	216	33	1.85	1.04, 3.27
Bottiger et al.[7]	40	6	50	4	2.03	0.53, 7.75
Kurkciyan et al.[9]	21	2	21	1	2.11	0.18, 25.17
Total	205	42	317	40	2.0	1.23, 3.27

The homogeneity test of the literatures: $q = 0.46$, $p > 0.10$, means that homogeneity is good; OR combined hypothesis testing, $Z = 2.79$, $p < 0.01$; Nfs = 1.41.

Table 5 Meta-analysis of long-term neurological function between thrombolysis and control group

Authors	Thrombolytic group		Non-thrombolytic group		OR	95% CI
	No.	No. of CPC 1 or 2	No.	No. of CPC 1 or 2		
Kurkciyan et al.[3]	132	68	133	37	2.76	1.66, 4.59
Schreiber et al.[4]	42	29	115	57	2.27	1.07, 4.80
Total	175	97	249	94	2.59	1.70, 3.95

The homogeneity test of the literatures: $q = 0.18$, $p > 0.10$, means that homogeneity is good; OR combined hypothesis testing, $Z = 4.42$, $p < 0.01$.

Table 6 Meta-analysis of morbidity of severe bleeding between thrombolysis and control group

Authors	Thrombolytic group		Non-thrombolytic group		OR	95% CI
	No.	No. of severe bleeding	No.	No. of severe bleeding		
Janata et al.[2]	36	9	30	3	3.00	0.73, 12.30
Kurkciyan et al.[3]	132	13	133	7	1.97	0.76, 5.10
Lederer et al.[5]	45	6	46	7	0.86	0.26, 2.78
Ruiz-Bailen et al.[6]	67	3	236	2	5.48	0.90, 33.53
Bottiger et al.[7]	40	2	50	0	6.56	0.31, 140.60
Kurkciyan et al.[9]	21	3	21	0	8.14	0.39, 167.98
van Campen et al.[10]	33	1	36	0	3.37	0.13, 85.63
Total	374	37	552	19	2.20	1.25, 3.88

The homogeneity test of the literatures: $q = 4.95$, $p > 0.10$, means that homogeneity is good; OR combined hypothesis testing, $Z = 2.74$, $p < 0.01$; Nfs = 1.60.

bolytic therapy can increase morbidity due to severe bleeding. While our meta-analysis indicates that the morbidity of severe bleeding in thrombolytic group is significantly higher than control group ($p < 0.01$) (Table 6).The small fail-safe number (1.60) shows that the conclusions could be influenced by publication bias.

Discussion

Currently, the outcome of cardiopulmonary resuscitation (CPR) is still not satisfactory. The successful resuscitation rate in the hospital setting lies between 15% and 25% and then in out of hospital arena it is less than 5%. Some cases have an enormous neurological deficit. Approximately 81% of cardiac arrests are caused by coronary atherosclerotic heart disease. Immediate coronary artery angiography in those patients who have undergone successful CPR shows that 48% of them had acute coronary artery obstruction. Some studies showed that nearly 50% of cardiac arrests are accompanied by acute thrombosis and/or rupture of a plaque and 46% were accompanied by acute coronary artery disease.[12] Our meta-analysis indicates that thrombolytic therapy during CPR can improve ROSC significantly, mainly because thrombolysis can re-establish blood flow in the occluded coronary artery.

The treatment of cardiac arrest is immediate CPR. Research has shown that cardiac arrest and CPR can both lead to immediate activation of coagulant cascade, while intrinsic fibrinolysis is not activated to the same degree. The misbalance between coagulant and anticoagulant properties quickly shifts in favour of procoagulation, which then leads to wide spread microthrombosis. Microthrombi have been found in the microcirculation of patients after cardiac arrest. Autopsies of patients who have undergone CPR for 5—10 min have revealed wide spread microthrombosis. The Fischer research group has used thrombolytic agents and anticoagulants in the resuscitation of cat cardiac arrest model. They found that treatment with these agents could reduce thrombosis and promote bloods to flow to tissues and cells. Accordingly, acute cellular injury and necrosis was decreased.[13] Our study indicates that an increased survival rate at 24 h and to discharge and improved long-term neurological function result mainly from the amelioration of microcirculatory reperfusion which is able to alleviate injury in major organs and improve the prognosis.

It is feasible in theory to perform thrombolytic and anticoagulant therapy to achieve successful

CPR. However, CPR has been absolutely or relatively contraindicated in guidelines because of the anticipated risk of bleeding and increased mortality. This meta-analysis reveals that thrombolysis can increase morbidity due to hemorrhage but all patients were treatable. There was no evidence that a secondary bleed could result in death. There is also a theoretical bias towards more bleeding in the patients receiving thrombolysis because of their increased survival rate, so the estimated OR from Table 6 should be a slight overestimate, but the extent of this bias cannot be estimated reliably from the available data.

Conclusion

Many researchers consider that it is feasible to perform thrombolytic therapy during or after CPR. The possible advantage of thrombolytic therapy seems to outweigh the potential risks in CPR. Thus, the effect of thrombolysis in reducing morbidity and mortality should not be ignored. The studies of thrombolytic therapy during or after CPR are scattered and retrospective. Therefore, large randomised, prospective multicentre studies should be conducted to examine the indications and decrease the risk factors and increase the efficacy of this promising treatment.

Conflict of interest

There are no financial and personal relationships with other people or organizations that could influence our work inappropriately.

Acknowledgement

This work was supported by the Great Technology Fund of Guangzhou (2004Z3-E0381).

References

1. Rosenthal R. The file drawer problem and tolerance for null results. Psychol Bull 1979;86:638—41.
2. Janata K, Holzer M, Kurkciyan I, et al. Major bleeding complications in cardiopulmonary resuscitation: the place of thrombolytic therapy in cardiac arrest due to massive pulmonary embolism. Resuscitation 2003;57:49—55.
3. Kurkciyan I, Meron G, Sterz F, et al. Major bleeding complications after cardiopulmonary resuscitation: impact of thrombolytic treatment. J Intern Med 2003;253:128—35.
4. Schreiber W, Gabriel D, Sterz F, et al. Thrombolytic therapy after cardiac arrest and its effect on neurological outcome. Resuscitation 2002;52:63—9.
5. Lederer W, Lichtenberger C, Pechlaner C, et al. Recombinant tissue plasminogen activator during cardiopulmonary resuscitation in 108 patients with out-of-hospital cardiac arrest. Resuscitation 2001;5(0):71—6.
6. Ruiz-Bailen M, Aguayo de Hoyos E, Serrano-Corcoles MC, et al. Efficacy of thrombolysis in patients with acute myocardial infarction requiring cardiopulmonary resuscitation. Intensive Care Med 2001;27(6):1050—7.
7. Bottiger BW, Bode C, Kern S, et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. Lancet 2001;357:1583—5.
8. Bulut S, Aengevaeren WR, Luijten HJ, Verheugt FW. Successful out-of-hospital cardiopulmonary resuscitation: what is the optimal in-hospital treatment strategy? Resuscitation 2000;47:155—61.
9. Kurkciyan I, Meron G, Sterz F, et al. Pulmonary embolism as a cause of cardiac arrest: presentation and outcome. Arch Intern Med 2000;160:1529—35.
10. van Campen LC, van Leeuwen GR, Verheugt FW. Safety and efficacy of thrombolysis for acute myocardial infarction in patients with prolonged out-of-hospital cardiopulmonary resuscitation. Am J Cardiol 1994;73:953—5.
11. Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350(2):105—13.
12. Newman DH, Greenwald L, Calleway C. Cardiac arrest and the role of thrombolytic agents. Ann Emerg Med 2000;35(5):472—80.
13. Fischer M, Bottiger BW, Popov-Cenic S, Hossmann KA. Thrombolysis using plasminogen activator and heparin reduces cerebral no-reflow after resuscitation from cardiac arrest: an experimental study in the cat. Intensive Care Med 1996;22(11):1214—23.