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Safety of Thrombolysis during Cardiopulmonary Resuscitation

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Abstract

The prognosis is generally poor for patients who experience a cardiac arrest. The most common causes of sudden cardiac arrest are massive pulmonary embolism (PE) and acute myocardial infarction (MI). While thrombolysis is a first-line treatment option in massive PE and acute MI, cardiopulmonary resuscitation (CPR) has been regarded as a relative contraindication for thrombolysis because of the anticipated bleeding risk caused by traumatic cardiocompressions. However, an increasing number of case reports and clinical studies on thrombolysis during and after CPR highlight an increased frequency of the return of spontaneous circulation and a better neurological outcome of surviving patients. These effects are mainly due to the thrombolysis of macroscopic blood clots and the amelioration of microcirculatory reperfusion.

This article reviews case reports and clinical studies of thrombolysis during and shortly after CPR in order to estimate the risk of severe bleeding events caused by CPR in association with thrombolysis compared with CPR without thrombolysis.

Although thrombolysis *per se* can cause severe and potentially fatal haemorrhage, there is no evidence that severe bleeding events occur more often when thrombolysis is combined with cardiocompressions. In addition, by far the majority of bleeding complications can be treated effectively. Thus, in many cases, the possible benefit of thrombolysis during CPR seems to outweigh the potential risks. However, there may be a publication bias in some case reports and studies towards reporting successful rather than unsuccessful CPRs. In addition, not enough controlled clinical trials have yet been conducted. Therefore, data from large randomised, multicentre studies are needed to definitely answer the question of the relationship between safety and efficacy of this promising treatment option.

We conclude that the currently available data do not indicate that thrombolysis contributes to a significant increase in bleeding complications when administered during CPR.

Cardiac arrest carries a poor prognosis. Whereas in-hospital cardiac arrest is associated with a survival rate of about 15%,[1,2] it has been estimated that only about 5% of patients who experience out-of-hospital cardiac arrest survive without severe neurological impairment.[3] Massive pulmonary embolism (PE) and acute myocardial infarction (MI) are the main causes of deterioration in more than 70% of patients requiring cardiopulmonary resuscitation (CPR).[4] Thrombolysis is an effective therapy

for patients with PE or MI.[5,6] However, it has not been regarded as a standard treatment for patients with cardiac arrest caused by acute PE or MI.

In the past few years, an increasing number of case reports and clinical studies of thrombolysis during and shortly before or after CPR have been published. Most of these studies not only showed a marked improvement of survival rates but also revealed good neurological outcome.[7,8] Thrombolytic drugs have not been widely used during resuscitation, since CPR has been regarded as a relative contraindication for thrombolysis because of an anticipated high risk of bleeding complications. However, this contraindication, which has repeatedly been underlined by various authors[5,9] and medical societies,[10,11] was never based on sufficient scientific evidence.[3,12] The recommendation of the American College of Cardiology and the American Heart Association, for example,[10] cites the Fibrinolytic Therapy Trialists' study[6] as the basis of evidence for this contraindication. However, this meta-analysis did not identify a subgroup of patients receiving CPR and lists only the overall incidence of bleeding. Other reviews just mention CPR as a contraindication for thrombolysis without providing evidence for this claim. Therefore, the bleeding risk of thrombolysis during CPR needs to be defined more precisely.

This article provides a comprehensive review of case reports and studies evaluating the risk of bleeding complications of thrombolytic therapy associated with CPR. It is based on a search of Medline, for which the following keywords were used: thrombolysis, cardiac arrest, bleeding complications, cardiopulmonary resuscitation and CPR. In addition, a manual search for references cited in relevant articles was conducted.

The risks of thrombolytic therapy have been classified into five major categories: intracranial haemorrhage, systemic haemorrhage, immunological complications, hypotension and reperfusion injuries.[13] Immunological reactions have been described mainly with the use of streptokinase and anistreplase, the active components of which are produced by group C β-haemolytic streptococci. The readministration of streptokinase from 4 days after the first dose has not been recommended due to the high levels of antistreptokinase antibodies potentially causing allergic reactions or neutralisation of the second dose of streptokinase.[14] Even staphylokinase, a third-generation thrombolytic drug with the highest fibrin-selectivity of all thrombolytics, has an antigenicity that may limit its clinical use.[15] Acute allergic reactions associated with streptokinase and anistreplase have rarely been reported, whereas delayed immune complex reactions are more common, but usually less serious.[13] However, other currently available thrombolytic drugs are less antigenic and thus cause significantly fewer anaphylactic reactions, as has been shown for alteplase (recombinant tissue plasminogen activator; rt-PA).[16] Arterial hypotension is a common adverse effect of thrombolysis, which may occur with the use of any thrombolytic drug.[13] In most cases, however, hypotension can be treated effectively by administration of intravenous fluid or vasopressors. In the setting of resuscitation, neither allergic reactions nor hypotension are major problems, since the standard therapy for cardiac arrest includes the administration of vasopressors. Therefore, hypotension and severe anaphylactic reaction can be treated immediately and effectively. A reperfusion injury can be caused by toxic metabolites released from dying tissue and by clogging of the microcirculatory vessels by white blood cells.[13]

Therefore, bleeding complications are of paramount significance for the safety of thrombolysis during CPR. Most of the thrombolytics used in the case reports and studies presented in this review were classified as first- and second-generation thrombolytics. No substantial difference in overall bleeding risk has been revealed between these drugs, although some of them (streptokinase, urokinase) are less fibrin-specific than others (e.g. alteplase).[13] Data on some of the newer, fibrin-specific third-generation thrombolytics such as lanoteplase suggest a higher, but others (e.g. tenecteplase) a nonsignificantly lower incidence of bleeding complications.[15]

1. Classification of Bleeding Complications

To evaluate bleeding complications after thrombolysis and CPR, it is important to know about the incidence of bleeding events after thrombolysis without CPR and after CPR without thrombolysis.

Thrombolysis clearly increases the risk of bleeding. In nonsurgical patients undergoing thrombolysis for the treatment of acute MI, the incidence of non-intracranial major bleeds, defined as bleedings that required transfusion or were life-threatening, was 1.1% during the first 35 days after thrombolysis in a meta-analysis of nine large randomised trials; the risk for major bleeds without thrombolysis was 0.4%.[6] In addition, intracranial bleeding is a severe and potentially fatal complication of systemic thrombolysis. The same meta-analysis revealed an incidence of 0.8% for strokes most probably caused by intracranial haemorrhage during the first 35 days after thrombolysis, whereas controls had a risk of only 0.1%. The frequency of intracranial haemorrhage up to 14 days after PE thrombolysis in a retrospective analysis including 312 patients was 1.9%.[17] About one-third of intracranial haemorrhages may be fatal,[17] whereas non-intracranial bleedings can often be treated effectively by blood transfusion or surgical intervention.[18,19] If we assume no crossover effect between patients with intracranial and non-intracranial haemorrhages, the risk for major bleeding events in patients with acute MI or PE receiving thrombolytic therapy without CPR can be calculated to be between 1.9% and 3.0%, as compared with 0.5% in patients not receiving any thrombolytic drugs.

Concurrent treatment with heparin or aspirin (acetylsalicylic acid) may contribute to the incidence of haemorrhagic events during or after thrombolysis. To date, however, there is no study comparing the incidence caused by thrombolytics during CPR dependent on the use of heparin or aspirin. In fact, in many studies on thrombolysis the use of heparin and aspirin was not standardised.[6]

In addition, CPR itself is associated with a complication rate of 20–40%.[20,21] On autopsy of non-surviving patients after CPR, different haemorrhagic complications were found. In a prospective study in 705 patients the incidence of haemorrhages of the heart and the great vessels was found to be 10.6%,[22] which is comparable to the results of a retrospective study with 130 patients showing an incidence of 8% for cardiac haemorrhages.[20] Traumatic abdominal bleedings occurred in 24 of 705 patients who had received CPR after cardiac arrest (3.4%), while the incidence of haemothorax and lung contusions in this group was 1.6%.[22] In a retrospective study of 70 patients after CPR, mediastinal bleeding was found in three (4%).[21] By adding up these incidences, a complication rate of up to 15.6% can be estimated for haemorrhagic complications during and after CPR without thrombolytic therapy. Moreover, it has even been postulated that subarachnoid haemorrhage may be a complication of CPR, since cardiac massage can elevate intracranial and central venous pressure, which could cause intracranial microlesions.[23] However, this theory has not been generally accepted.

Besides thrombolysis itself and CPR itself, recent surgery can cause bleeding complications in patients who receive CPR and thrombolysis shortly after surgery. These patients carry an increased risk for bleeding as a result of the recent operation. Thus, in many case reports of thrombolysis during CPR after PE in postoperative patients, bleeding from surgical sites is reported.[18] In addition, bleeding at intravascular line sites[24] or spontaneous retroperitoneal haematoma[25] after thrombolysis and CPR were reported. This bleeding may be severe and may require blood transfusion or re-operation.

Taken together, these findings indicate that thrombolytic therapy is associated with a risk of about 1.9–3.0% for spontaneous bleeding that may be aggravated after recent surgery. Moreover, CPR itself without thrombolysis increases the risk of bleeding complications due to CPR-induced lesions by up to 15.6%. The major question is whether CPR-induced lesions occur more frequently or are more severe as a result of additional thrombolytic therapy.

2. Thrombolysis before and after Cardiopulmonary Resuscitation

Thrombolytic therapy is regarded as first-line treatment for acute MI[26,27] and PE.[5] Since about 10–20% of patients experiencing an acute MI also require CPR,[28,29] experience has been gained with the use of thrombolytic drugs shortly before or after resuscitation. These case reports and studies provide an estimation of the safety of thrombolysis when there is a close relationship in time between thrombolysis and CPR.

Except for one case of acute PE,[30] acute MI was the reason for resuscitation in all of the case reports listed in table I. There are two case reports of fatal haemorrhagic complications associated with CPR.[31,32] Haugeberg et al.[31] reported in 1989 a case of successful CPR followed by thrombolysis after acute MI. Symptoms of massive haemothorax caused by fractured ribs and sternum developed 12 hours after admission of the patient. No rupture of internal organs was found. Ten years later, Pezzi et al.[32] published a report of a fatal liver rupture after CPR and thrombolysis in a patient with acute MI. In contrast to reports in which the same complications were successfully treated by blood transfusion[33] or by surgery,[34,35] this patient experienced an irreversible haemorrhagic shock. Other CPR-related bleeding complications reported after thrombolysis, such as thoracic ecchymosis[24] or Mallory-Weiss tear,[33] were treated conservatively.

Several retrospective studies also focused on the bleeding risk of patients treated by thrombolytics either before or after resuscitation (table II). In none of these studies were haemorrhages reported that were directly related to CPR. Tenaglia et al.[36] retrospectively studied a subgroup of 59 out of 708 patients involved in the first three Thrombolysis and Angioplasty in Myocardial Infarction trials. Two of these 59 patients had thrombolysis before and 50 patients after CPR; in seven cases thrombolysis was performed during ongoing resuscitation (see table II). No patient required transfusion of red blood cells for any bleeding complication. The evidence of this study, however, may be limited, since the duration of resuscitation was between 1 and 5 (median 1) minutes, and chest compressions were performed only in about every second patient, whereas the other patients received defibrillation only. Scholz et al.[37] reported eight cases of bleeding in 37 patients with acute MI treated with intravenous or intracoronary thrombolytics before or after CPR, but none was directly related to cardiocompressions. In a subgroup analysis of the Spanish multicentre registry on thrombolysis after CPR, ARIAM (Análysis del Restraso en el Infarto Agudo de Miocardio [analysis of delay in acute MI]), two haemorrhagic strokes and two haematomas that required transfusion occurred in 303 patients with MI and CPR before hospital admission; 67 of these had received thrombolysis after CPR. However, these bleeding events were not CPR related; nor were they fatal.[38] In a retrospective study of 68 patients resuscitated out of hospital after cardiac arrest caused by acute MI, Voipio et al.[39] performed thrombolytic therapy after return of spontaneous circulation. Of these, 36

Table I. Thrombolysis before and after cardiopulmonary resuscitation (CPR): case reports

Reference	No. of patients	Thrombolytic agent	CPR-related bleeding complications	No. of survivors
Flügel et al.[30]	1	Streptokinase		1
Haugeberg et al.[31]	1	Streptokinase	Massive haemothorax	0
Merriman and Kalbfleisch[24]	1	Streptokinase	Chest wall bruise	1
Adams et al.[34]	2	Streptokinase/ urokinase	2 liver lacerations	2
Druwé et al.[35]	1	Anistreplase	Liver rupture	1
Cafri et al.[33]	3	Streptokinase	Liver laceration, haemothorax, Mallory-Weiss tear	3
Pezzi et al.[32]	1	Alteplase	Liver laceration	0
Total	**10**		**9 (90.0%)**	**8 (80.0%)**

Table II. Thrombolysis before or after cardiopulmonary resuscitation (CPR): retrospective studies

Reference	No. of patients	Thrombolytic agent	CPR-related bleeding complications	No. of survivors
Jäger et al.[42]	11	Streptokinase/urokinase		11
Scholz et al.[43]	7	Streptokinase/urokinase/ alteplase		3
Cross et al.[44]	24	NR		6
Scholz et al.[37]	37	Streptokinase/urokinase/ alteplase		18
van Campen et al.[45]	33	NR		20
Ruiz-Bailén et al.[38]	67	Streptokinase/alteplase	(2 haematomas)[a]	55
Voipio et al.[39]	68	Streptokinase/reteplase/ alteplase		36
Kürkciyan et al.[41]	132	Alteplase	Liver/spleen rupture; myocardial bleeding	83
Total	**379**		**4 (1.1%)**	**323 (61.2%)**
Tenaglia et al.[36][b]	52	Urokinase/alteplase		52/59

a Sites of haematomas were not specified; thus, relation to CPR is unclear.

b In this study, 50 patients had thrombolysis after, 2 before and 7 during CPR (see also table V); the outcomes of the subgroups are, however, not specified. Therefore, these patients could not be included in the accumulated results in this table.

NR = not reported.

patients were discharged from the hospital, 21 without any severe neurological disability. In one case, fatal intracranial haemorrhage occurred, and there was one patient with generalised bleeding, haematomas and bleeding from puncture sites. In addition, two gastrointestinal bleedings (not clearly specified) and one case of epistaxis were described. However, none of these bleeding complications could be clearly attributed to CPR, and no patient required a blood transfusion.[39] Recently, Schreiber et al.[40] showed a trend towards good neurological outcome in 42 patients treated with thrombolytics after cardiac arrest caused by acute MI. Bleeding complications were seen in five patients but, again, none was clearly related to cardiocompressions. These 42 patients were part of a larger retrospective study of 132 patients receiving thrombolysis for treatment of acute MI after out-of-hospital CPR. Major haemorrhage occurred in 13 patients (10%), but was clearly related to CPR in only two patients. Interestingly, in the control group (133 patients without thrombolytic treatment after acute MI and CPR), seven major bleeding complications occurred of which six were probably related to CPR (haemothorax, liver rupture).[41]

Reviewing the literature about bleeding caused by thrombolysis before and after CPR, it is remarkable that nine severe haemorrhages attributable to cardiocompressions are reported in seven case reports with a total of ten patients (table I), whereas retrospective studies including 379 patients described only two CPR-related bleedings and two haematomas, which are not clearly specified (table II). This means that case reports suggest an incidence of 90% for severe bleeding events, whereas retrospective studies reveal a bleeding risk of only 1.1%. This difference may be due in part to a publication bias towards emphasising adverse effects of thrombolysis in the case reports. In general, severe bleeding associated with CPR before or after thrombolysis does not seem to occur very frequently.

3. Thrombolysis during Cardiopulmonary Resuscitation

3.1 Case Reports and Case Series

Since the first descriptions of thrombolysis during CPR in a patient with an acute PE in 1974,[46] many case reports, particularly from Germany, have followed (table III). With the exception of one pa-

tient[47] in whom an acute MI was the cause for cardiac arrest, all of the patients had an acute PE with subsequent cardiac arrest. Only two of 33 patients died, and 23 patients survived without severe neurological impairment. No survival data are available for the other eight patients. Since most of these patients had surgery shortly before PE with cardiac arrest, bleeding from surgical and intravascular line sites was reported frequently,[25,46,48-56] but never caused death. In contrast, CPR-related bleeding complications were seen in only four patients[57-60] and were never fatal.

An overview of case series on thrombolysis during resuscitation shows a similar picture (table IV). In ten case series including 54 patients, acute PE was the cause of cardiac arrest in 42 patients, whereas 12 patients[79-82] had an acute MI. Three of these 54 patients experienced a bleeding complication directly related to CPR. Horstkotte et al.[83] published a case series with 17 patients who were resus-

Table III. Thrombolysis during cardiopulmonary resuscitation (CPR): case reports

Reference	Thrombolytic agent	CPR-related bleeding complications	Survival
Renkes-Hegendörfer and Herrmann[46]	Streptokinase		Yes
Borst and Wolf[61]	Streptokinase	Massive haemothorax	Yes
Jester and Langheinrich[57]	Streptokinase		NR
Köstering et al.[58]	Streptokinase	Liver laceration	NR
Unseld et al.[48]	Streptokinase		Yes
Wester et al.[49]	Urokinase		Yes
Schäffer[62]	Streptokinase		NR
Langdon et al.[63]	Alteplase		Yes
Atzinger et al.[64]	Streptokinase		Yes
Hopf et al.[65]	Alteplase		Yes
Trenkwalder et al.[66]	Urokinase		Yes
Böttiger et al.[60]	Urokinase	Liver contusion	Yes
Harke[67]	Streptokinase		NR
Klinge et al.[59]	Streptokinase	Liver contusion	NR
Siebenlist and Gattenlöhner[68]	Alteplase		No
Böttiger et al.[69]	Urokinase		Yes
Fred and Yang[70]	Alteplase		No
Müller and Axthelm[71]	Alteplase		Yes
Pharo et al.[25]	Alteplase		Yes
Onoyama et al.[72]	Alteplase		NR
Oneglia and Rusconi[73]	Alteplase		NR
Schlüter et al.[51]	Alteplase		Yes
Soltesz et al.[74]	Urokinase		Yes
Kuisma et al.[75]	Reteplase		Yes
Schulte-Sinkus and Standl[76]	Alteplase		Yes
Cyrkowicz et al.[52]	Alteplase		Yes
Kehoe and DaCruz[77]	Alteplase		NR
Meier[53]	Alteplase		Yes
Wittmann and Dietz[54]	Alteplase		Yes
Duchateau et al.[78]	Alteplase		Yes
Grabner et al.[55]	Alteplase		Yes
Lapostolle et al.[47]	Alteplase		Yes
Nordmeyer[56]	Alteplase		Yes
Total (no. of reports = 33)		**4 (12.1%)**	**23/25 (92.0%; 8 NR)**

NR = not reported.

Table IV. Thrombolysis during cardiopulmonary resuscitation (CPR): case series

Reference	No. of patients	Thrombolytic agent	CPR-related bleeding complications	No. of survivors
Horstkotte et al.[83]	17	Urokinase	2 cases of haemothorax, lung contusion	12
Siebenlist and Gattenlöhner[84]	2	Alteplase		2
Hopf et al.[85]	7	Alteplase		6
Josephs et al.[79]	2	APSAC/streptokinase		2
Sigmund et al.[86]	2	Streptokinase/alteplase		2
Westhoff-Bleck et al.[80]	10	Alteplase		4
Scheeren et al.[87]	3	Alteplase		2
Tiffany et al.[81]	3	Alteplase		3
Ruiz-Bailén et al.[88]	6	Alteplase		4
Zahorec[82]	2	Streptokinase		2
Total	**54**		**3 (5.6%)**	**39 (72.2%)**

APSAC = anisoylated plasminogen streptokinase activator complex.

citated after acute PE. They found three thoracic bleeding events that were most likely caused by cardiocompression.[83] In their case series of five patients with acute MI and five patients with acute PE who were given thrombolytic drugs during resuscitation, Westhoff-Bleck et al. found intracranial haemorrhage in two of the ten patients (one of each group).[80] In another case series with six patients with acute PE, two significant bleeding events from puncture sites and the gastrointestinal tract were observed.[79] However, as outlined above, intracranial haemorrhage and bleeding from puncture or surgical sites or gastrointestinal bleeding can occur as a complication of thrombolysis *per se* and are not specific side effects of cardiocompression during thrombolysis.

To summarise, although case reports and case series do not yield robust data about the incidence of bleeding complications directly related to CPR, the reports published over a period of 29 years do not suggest a very high incidence of severe bleeding events when thrombolysis is performed during CPR. In fact, there were only seven CPR-related bleeding complications in 85 patients. Furthermore, it is remarkable that at least 60 of these 85 patients survived without severe neurological impairment. However, the results of the case reports of thrombolysis during CPR may reflect a considerable publication bias.[89] On the other hand, thrombolysis was never used at the beginning of resuscitation, but always as an *ultima ratio* (i.e. a 'therapy of last resort') therapy in situations after prolonged, unsuccessful CPR when discontinuing the therapy would have been the only other alternative.[90]

3.2 Clinical Studies

3.2.1 In-Hospital Thrombolysis during Cardiopulmonary Resuscitation

In addition to the case reports and case series described above, there is some evidence about the safety and efficacy of thrombolytic therapy from several clinical studies (table V and table VI). Most of them refer to thrombolysis that was performed after the patient had been admitted to hospital (table V).

The first prospective study on thrombolysis during CPR in patients with acute PE was published in 1984.[91] In that study, 20 patients with cardiac arrest after PE underwent pulmonary angiography and local thrombolysis via a pulmonary catheter during CPR. No massive bleedings were seen, with drops in haemoglobin levels not exceeding 10%. In 11 patients, a return of spontaneous circulation could be achieved. Another prospective study focused on *ultima ratio* thrombolysis after cardiac arrest in 28 patients with acute MI.[92] Resuscitation was primarily successful in nine patients, and there were three long-term survivors. Four of nine primarily stabilised patients showed bleeding complications,

Table V. Thrombolysis during cardiopulmonary resuscitation (CPR): in-hospital clinical studies

Reference	No. of patients	Underlying disease	Study type	Thrombolytic agent	CPR-related bleeding complications	No. of survivors
Köhle et al.[91]	20	PE	Pros	Streptokinase		11
Scholz et al.[43]	9	PE	Retro	Streptokinase/urokinase/ alteplase	Pectoral/sternal haemorrhage, liver laceration	5
Gramann et al.[92]	28	MI	Pros	Streptokinase/ alteplase	Pericardial/sternal haemorrhage (4)	3
Scholz et al.[37]	6	MI	Retro	Streptokinase/urokinase/ alteplase		3
Kürkciyan et al.[19]	21	PE	Retro	Alteplase	2 liver ruptures, mediastinal bleeding	2
Total	**84**				**9 (10.7%)**	**24 (28.6%)**
Tenaglia et al.[36]a	7	MI	Retro	Urokinase/ alteplase		52/59

a In this study, 50 patients had thrombolysis after, 2 before and 7 during CPR (see also table II); the outcomes of the subgroups are, however, not specified. Therefore, these patients could not be included in accumulated results in this table.

MI = myocardial infarction; **PE** = pulmonary embolism; **Pros** = prospective; **Retro** = retrospective.

mainly mediastinal haematomas. One of them experienced a fatal pericardial haemorrhage. In addition, two cases of gastrointestinal bleedings and one case of bleeding from a subclavian catheter puncture site that were treated conservatively were reported. In a retrospective study of nine patients with angiographically demonstrated PE receiving thrombolytic therapy during resuscitation, Scholz et al.[43] found two CPR-related bleeding complications that required blood transfusion or surgery. In two other patients, small lung contusions and minor pericardial bleeding were diagnosed by autopsy. There were no fatal bleeding complications. Two years later, the same group of authors published a retrospective analysis of 590 patients who had been treated with thrombolysis after hospital admission for acute MI. In 6 of these 590 patients, thrombolytics were given during ongoing resuscitation. No bleeding complications directly related to cardiocompressions were reported.[37] In a subgroup analysis of 708 patients involved in the first three Thrombolysis and Angioplasty in Myocardial Infarction trials, Tenaglia et al.[36] did not report any bleeding complications attributed to CPR in 59 patients, of whom 7 had been given thrombolytics during CPR (table V) and 52 after CPR (table II).[36] Finally, Kürkciyan et al.[19] studied 21 patients admitted to the emergency department with cardiac arrest after PE. Of these patients, 11 had thrombolysis during CPR, whereas 10 had thrombolysis shortly before or after CPR. Only two patients survived more than 24 hours after admission to hospital, and CPR-related bleeding

Table VI. Thrombolysis during cardiopulmonary resuscitation (CPR): out-of-hospital studies

Reference	No. of patients	Study type	Thrombolytic agent	CPR-related bleeding complications	No. of survivors
Klefisch et al.[93]	34	Pros	Streptokinase	Haemothorax	5
Böttiger et al.[7]	40	Pros, controlled	Alteplase		6
Lederer et al.[8]	108	Retro, matched-pairs controls	Alteplase	2 pericardial tamponades, 1 haemothorax	27
Abu-Laban et al.[94]	117	Pros, randomised, controlled	Alteplase	1 pulmonary haemorrhage, (1 'major' haemorrhage)a	1
Total	**299**			**6 (2.0%)**	**39 (13.0%)**

a Site of haemorrhage was not specified.

Pros = prospective; **Retro** = retrospective.

complications were seen in three patients, one of whom required emergency surgery for liver rupture.

In summary, the in-hospital clinical studies concerning thrombolysis during CPR revealed nine CPR-related bleeding complications in 84 patients (10.7%). Thus, compared with the incidence of bleeding complications during CPR without thrombolysis found by autopsy, which can be estimated to be up to 15.6%, in-hospital thrombolysis during CPR does not seem to significantly increase the risk of bleeding events.

3.2.2 Out-of-Hospital Thrombolysis during Cardiopulmonary Resuscitation

Data from out-of-hospital resuscitation are particularly relevant, since in Western developed countries, the incidence of resuscitation in patients with out-of-hospital cardiac arrest is estimated to be 40–90 per 100 000 people annually.[95] Because conventional CPR is unsuccessful in most of these cases,[20,21] a potential benefit in survival using thrombolysis during CPR should be most pronounced in this group.[96] Recently, a number of studies of pre-hospital thrombolytic therapy during resuscitation have been published that allow estimation of the risk of bleeding complications (table VI).

Klefisch et al.[93] used thrombolysis as 'rescue thrombolysis' during CPR in 34 out-of-hospital patients with suspected acute MI or PE. This therapy was successful in 5 of 21 patients presenting with ventricular fibrillation refractory to conventional advanced cardiac life support, but not so in patients presenting with asystole or pulseless electrical activity of the heart. Three patients survived without neurological deficit. One patient showed a haemothorax after prolonged cardiocompression (75 minutes) which had to be drained 5 days after resuscitation.

A prospective study of 40 patients with out-of-hospital cardiac arrest after unsuccessful resuscitation lasting longer than 15 minutes was performed at our department.[7] Most of the patients (88.9%) presented either with asystole, ventricular fibrillation, or ventricular tachycardia, whereas other initial cardiac rhythms such as pulseless electrical activity of the heart were found in only 11.1% of patients. Six of 40 patients (15%) who received thrombolysis during CPR were discharged from the hospital alive, five of them without severe neurological impairment. In two patients treated with alteplase, internal bleeding from gastric ulcers developed 2 and 12 days after resuscitation, and transfusion of packed red blood cells was necessary. There were, however, no CPR-related bleeding complications.

A retrospective chart review of 108 out-of-hospital patients receiving alteplase during CPR revealed a total of six severe bleeding complications in a subgroup of 45 nonsurviving patients after autopsy (13.3%).[8] Three of these bleedings (6.7%) were directly related to CPR (table VI), two were caused by ruptured aortic aneurysms, and one intracerebral haemorrhage was noted. However, in the corresponding matched pairs autopsy control subgroup that had not had treatment with alteplase, the incidence of severe bleeding events was not significantly different (15.2%). Even in the control group there were three CPR-related bleedings (pericardial tamponades), two ruptured aortic aneurysms, and two intracranial haemorrhages.

Very recently, the first randomised, double-blind, placebo-controlled trial on out-of-hospital thrombolysis during cardiac arrest was published.[94] Most of the patients (48.7% in the alteplase group and 57.8% in the control group) presented with pulseless electrical activity of the heart. In contrast to the studies cited above, the authors did not find beneficial effects of thrombolysis on survival. However, the study was strongly criticised mainly because of the extremely poor prognosis of the control group (0% survivors), the selection of the study population and the late onset of thrombolytic therapy (median 36 minutes after collapse).[97] The sole surviving patient (1/233) in that study had been treated with alteplase and was found to have a not clearly specified pulmonary haemorrhage. In total, two major haemorrhages (the second was not specified) were reported in the alteplase-treated group, whereas in the control group there was no major haemorrhage.

In summary, out-of hospital studies suggest an incidence of 2.0% for severe CPR-related bleeding events (table VI). Compared with the incidence of

CPR-related bleeding complications in patients who did not receive thrombolytic therapy (i.e. up to 15.6% found by autopsy[17-19]), this suggests that out-of-hospital thrombolysis does not contribute to an increased number of bleedings caused by cardiocompression. When intracranial haemorrhage or a ruptured aortic aneurysm was associated with cardiac arrest, the outcome was often fatal independently of the use of thrombolysis.[98]

4. Conclusions

Although systemic thrombolysis clearly increases the risk of bleeding in general, there is no evidence that thrombolysis during CPR is associated with a significantly increased frequency of bleeding complications as compared with resuscitation without thrombolysis. Clinical studies addressing thrombolysis both during and soon before or after CPR do not suggest an additional bleeding risk when CPR is combined with thrombolysis. Therefore, thrombolysis should no longer be contraindicated during CPR, especially if an acute MI or a large PE is the possible cause of cardiac arrest. In view of the promising data currently available, we await the results of a large randomised, interdisciplinary multicentre trial currently under way in Europe,[99] which will further elucidate the safety and efficacy of thrombolytic therapy during resuscitation.

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