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Domburg, J. A.; van de Vondervoort, D.; Tielliu, I. F. J.; Smit, M.

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ORIGINAL ARTICLE

Intra-arterial thrombolysis: Is ICU admission necessary?

J.A. Domburg[1], D. van de Vondervoort[1], I.F.J. Tielliu[2], M. Smit[3]

Departments of [1]Anesthesiology, [2]Vascular Surgery, and [3]Critical Care, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Correspondence
M. Smit - m.smit@umcg.nl

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Abstract

Background: Intra-arterial thrombolysis is an effective and safe method for treating acute limb ischaemia. However, during thrombolysis, patients are at risk of life-threatening haemorrhagic complications. In the literature there is no consensus on how patients should be monitored during treatment. Patients in our hospital are admitted to an intensive care unit (ICU) during treatment even though ICU beds are scarce and ICU admission is a stressful event. This raises the question: is ICU admission necessary to prevent major bleeding complications?

Methods: A retrospective study was conducted where all patients having received intra-arterial thrombolysis between January 2015 and February 2017 were included. Patients' files were reviewed for adverse events, laboratory results, information about transfusion of blood products and additional interventions.

Results: In total 52 procedures were analysed. No major complications and no haemodynamic instability occurred; 11 minor complications occurred in nine individual patients (18.8%). No transfusions of fresh frozen plasma or packed red blood cells were given during thrombolysis. In three patients packed red blood cells were given within one week of thrombolysis. No other additional treatment was necessary.

Conclusions: Treatment outside of the ICU during peripheral intra-arterial thrombolysis should be considered a safe option on the condition that continuous patient monitoring for local and systemic complications is carried out. A protocol for escalation of treatment in case a complication occurs is mandatory.

Introduction

Arterial thrombosis leading to acute and subacute (<14 days) lower limb ischaemia can be treated with intra-arterial thrombolysis.[1-4] In comparison with surgical treatment, intra-arterial thrombolysis is less invasive. Intra-arterial thrombolysis has proven to be an effective and safe method.[3] Nonetheless, patients receiving intra-arterial thrombolysis are at risk of potentially life-threatening haemorrhagic complications such as retroperitoneal or intracranial bleeding. The incidence of major bleeding complications ranges between 2.9% and 13.5%.[2]

All thrombolytic agents in current clinical usage are plasminogen activators which cause depletion of fibrinogen. The Surgery vs Thrombolysis for Ischemia of the lower extremity (STILE) trial, a multicentre, prospective randomised trial that compared surgical revascularisation with catheter-directed thrombolysis with either urokinase of recombinant tissue plasminogen activator (rt-PA) for non-embolic leg ischaemia was published in 1994 and included 393 patients. Failure of catheter placement occurred in 28% of the patients randomised to thrombolysis. One of the conclusions of this trial was that in the thrombolysis group, fibrinogen depletion predicted haemorrhagic complications.[4] Although this trial was one of the largest and earliest trials on intra-arterial thrombolysis, it was terminated at the first interim analysis and therefore the secondary analyses should be interpreted with caution. In a retrospective series of 69 tissue plasminogen activator infusions, 10 infusions resulted in major bleeding. Infusions in which fibrinogen levels decreased below 1.5 g/l were associated with a significantly higher rate of major bleeding.[5] However, Lee et al. found that a fibrinogen level below 1.5 g/l during thrombolysis was not associated with an increased risk of bleeding in a retrospective study of 42 patients. They did find a relation between both a higher dose of thrombolytic agent and a longer duration of thrombolysis and risk of bleeding.[6] A randomised blinded animal model study even showed that excessive bleeding did not occur until fibrinogen and factor VIII had decreased to 20% of their initial level.[7]

Because of the absence of reliable laboratory tests that can adequately predict the risk of bleeding, the available literature

advises to monitor patients for bleeding complications during thrombolysis: 'The patient should be kept under continuous surveillance to detect any eventual signs of haemorrhage, and frequent haematocrit/haemoglobin counts should be compared with baseline values'.[2] However, there is no consensus in the literature on how monitoring should be carried out and at what interval haemoglobin and fibrinogen levels should be determined.[3,8,9]

Procedural care has never been studied nor has it been the subject of discussion. As a result, the practice and protocols differ in different hospitals. The safest option, therefore, seems to be to admit all patients to the ICU with very frequent laboratory testing of fibrinogen and haemoglobin and continuous monitoring of vital parameters and clinical signs of bleeding. However, this is a costly procedure, not only in terms of money but also in terms of scarce healthcare resources such as ICU capacity, personnel workload, staffing. Besides these high costs, ICU admission is a stressful experience for most patients.[10,11]

The protocol in our hospital states that patients receive a bolus of 100,000 IU urokinase, followed by 100,000 IU urokinase per hour (intermediate dose thrombolysis).[9] Furthermore they receive nadroparin 5700 IU subcutaneously twice daily. The aim is to end thrombolysis within 48 hours. During thrombolysis, patients are admitted to an ICU for continuous monitoring of vital parameters and two hourly determination of haemoglobin and fibrinogen levels. If the fibrinogen level decreases below 1.5 g/l, the urokinase infusion rate is halved. If fibrinogen decreases below 1 g/l, urokinase infusion is temporarily stopped until fibrinogen levels have been sufficiently restored. This intensive monitoring protocol allows for early detection and treatment of a major bleeding complication. However, the question remains whether frequent laboratory testing is necessary to prevent major bleeding complications and whether admission to an ICU is indicated. The aims of the current study were to investigate the incidence of major bleeding complications in patients undergoing intra-arterial thrombolysis in our hospital and to investigate the incidence of significant decrease in fibrinogen and haemoglobin.

Materials and Methods

A retrospective study was conducted. All patients who received intra-arterial thrombolysis between January 2015 and February 2017 were included. There were no exclusion criteria. All discharge letters, medical files and laboratory results were reviewed for major or minor haemorrhage, decreases in fibrinogen level below 1.0 g/l and significant decreases in haemoglobin and other major or minor complications.

In addition, information about haemodynamic instability, additional interventions and transfusion of blood products was reviewed. In May 2016 a new electronic patient data management system was implemented which made it possible to retrieve the settings of the urokinase infusion pump.

The Medical Ethics Review Board of our institution declared that all requirements for patient anonymity were fulfilled and that this study is in agreement with regulations for publication of patient data (METC M19.228983).

Definitions

Major haemorrhage was defined as blood loss that led to additional therapy, extended hospitalisation, surgery, or blood transfusion during thrombolysis. Intracranial haemorrhage was also considered a major haemorrhage. Minor haemorrhage was defined as blood loss that did not require additional therapy during thrombolysis, besides cessation of the urokinase infusion. A significant decrease in haemoglobin was defined as a decrease of >2.0 mmol from baseline. Major complications were defined as any undesired event that required therapy, prolonged hospitalisation (>48 h) or any complication that resulted in death, and minor complications were defined as any undesired event that did not require therapy.

Statistics

Statistical analysis was performed using IBM SPSS Statistics 22. Means and standard deviations were calculated for continuous variables. The sample size was too small for meaningful further analysis.

Table 1. Demographic and treatment characteristics

Total number of procedures	52
Total number of patients	41
Male (%)	26 (63)
Female (%)	15 (37)
Mean age in years (SD)	65.1 (15.1)
Mean duration of urokinase infusion in hours (SD)	23.5 (11.6)
Mean number of laboratory tests (SD) per procedure	10.7 (5.1)
Mean length of stay in ICU in days per procedure (SD)	1.3 (0.53)

Results

In the current retrospective study of 52 procedures during a two-year period, no major complications or haemodynamic instability occurred during peripheral intra-arterial thrombolysis, although the fibrinogen level decreased below 1.0 g/l in 11 procedures (21.2%).

In total 52 procedures were performed in 41 patients, 15 women and 26 men with a mean age of 65.1 years (SD 15.1). Of these patients, 35 received intra-arterial thrombolysis once, three patients received intra-arterial thrombolysis twice, one patient received intra-arterial thrombolysis four times and one patient received intra-arterial thrombolysis six times. The mean duration of infusion of thrombolytic agent was 23.5 hours (SD 11.6), mean number of blood samples analysed was 10.7 (SD 5.1) per procedure. *Table 1* summarises the demographic data and treatment characteristics. The mean sampling interval for

fibrinogen and haemoglobin determination was two hours and twelve minutes. In total 554 blood samples were analysed. All patients combined stayed over 67 days in the ICU.

Table 2 shows the complications that occurred in this patient group. No major complications occurred and none of the patients developed haemodynamic instability. In eight out of the 11 cases with a fibrinogen <1.0 g/l, the infusion of a thrombolytic agent was stopped. It is unclear why the infusion of the thrombolytic agent was continued in the other three cases. One patient had a significant decrease in haemoglobin due to a groin haematoma that developed during a repeat angiography. Five other patients had a spontaneous groin haematoma. Two of these patients (33%) had a fibrinogen < 1.0 g/l. *Table 3* shows the relationship between groin haematoma and fibrinogen level. No fresh frozen plasma or packed red blood cell transfusion was given, nor did any patient require fibrinogen or prothrombin complex during thrombolysis. However, three patients received packed red blood cells in the first week after thrombolysis. The miscellaneous minor complications comprised fever, haematuria or dislocation of the intra-arterial thrombolysis catheter. No additional treatment was given due to complications *(table 3)*. In the six patients who received thrombolysis multiple times, one groin haematoma occurred without a decrease in fibrinogen level and two patients had a decrease in fibrinogen level without complications.

Table 2. Complications

	Number of procedures (%)	Number of patients with fibrinogen <1.0 g/l (%)
Total	52	11
Haemoglobin decreased[1] (SD)	1 (1.90)	0
Lowest Hb in mmol/l (SD)	7.3 (1.21)	7.5 (1.16)
RBC in first week after thrombolysis	3	2
Major complications	0	0
Minor complications	11 (21.2)	2 (18.2)
- Groin haematoma (SD)	6 (11.5)	2 (18.2)
- Miscellaneous (SD)	5 (9.6)	0
No complications (SD)	40 (76.9)	9 (81.8)

[1]>2.0 mmol from baseline; Hb = haemoglobin; RBC = packed red blood cell transfusion

Discussion

In the current study no major complications or haemodynamic instability occurred during peripheral intra-arterial thrombolysis, although 11 patients had a fibrinogen level <1.0 g/l (21.2%). There were six groin haematomas (minor complications) which occurred mostly in patients with a fibrinogen level >1.0 g/l. Although our study groups were too small to perform a reliable statistical analysis, these findings do not support the conclusions of earlier studies where a decrease of fibrinogen <1.5 g/l significantly increased bleeding complications.[4,5] Rather, our findings seem consistent with later trials which concluded that a fibrinogen level <1.5 g/l during thrombolysis was not associated with an increased bleeding risk.[6,9]

One could argue that the absence of major bleeding complications in our retrospective study might be the result of cessation of the urokinase infusion when the fibrinogen level decreased below 1.0 g/l. However, in the retrospective study by Skeik et al.[5] a significant increase of bleeding complications was reported when fibrinogen levels decreased below 1.5 g/l, whereas in our study the infusion was not paused until the fibrinogen level dropped below 1.0 g/l. Another explanation for this discrepancy might be that in both the STILE trial and the study by Skeik et al., patients received both urokinase or rt-PA as well as additional intravenous heparin continuously in therapeutic doses during thrombolysis after an initial bolus of 5000 IU.[4,5] In this way not only the fibrinogen storage is depleted by plasmin as a result of the urokinase, but the remaining fibrinogen is less readily converted into fibrin by thrombin due to the heparin infusion, which is a factor Xa and thrombin inhibitor. This could make patients with a low fibrinogen more susceptible to bleeding complications. The patients in our hospital received a therapeutic dose of nadroparin instead of heparin, which has a less profound effect on thrombin.

The mean sampling interval for fibrinogen and haemoglobin determination was two hours and twelve minutes, showing ICU personnel strictly followed the protocol. Another component of procedural care which makes ICU admission obligatory is continuous monitoring of vital parameters. Our data show that none of the patients receiving intra-arterial thrombolysis who had a haematoma or a decrease in fibrinogen level had haemodynamic instability needing vasopressor support or intravenous fluid resuscitation. Also, no transfusions of packed red blood cells or fresh frozen plasma were needed during thrombolysis.

There are some limitations to this study. First it is a retrospective analysis over a two-year period with a relatively small sample size. This could account for the fact that no major complications occurred.

Based on the absence of major complications and haemodynamic instability in this group of patient in combination with the latest literature which does not show a correlation between low fibrinogen and bleeding complications, it seems safe to manage these patients outside the ICU. Since these patients are still at risk of serious bleeding complications, they should be monitored in a ward equipped to recognise these complications and intervene immediately. Before any major change in patient management can occur, we advise to perform a risk analysis with input from all the disciplines involved. Furthermore, this should be thoroughly discussed with the nursing and medical staff of the ward involved and additional training is needed. Also, the protocol should be amended. Even though each of these steps may be time-consuming, in the interest of patient

safety they cannot be overlooked. In the near future, patients receiving intra-arterial thrombolysis in our hospital will be admitted to a surgical ward where intensive patient monitoring can be carried out 24 hours a day by trained personnel, with protocolised escalation of treatment should a complication occur. These procedural changes will be evaluated in a Plan-Do-Check-Act (PDCA) manner. The first evaluation is planned after three months and/or after the first three patients have been treated in this manner.

Table 3. Relationship between groin haematoma and fibrinogen level

	Number of procedures with fibrinogen ≥1.0 g/l (%)	Number of procedures with fibrinogen <1.0 g/l (%)	Total number of procedures
Groin haematoma absent	37 (89.2)	9 (77.8)	46
Groin haematoma present	4 (10.8)	2 (22.2)	6
Total	41	11	52

Conclusions

The results of this study have triggered a multidisciplinary discussion on the appropriate and judicious use of critical care facilities in our hospital. Treatment outside of the ICU during peripheral intra-arterial thrombolysis should be considered a safe option on condition that continuous patient monitoring for local and systemic complications is carried out. A protocol for escalation of treatment in case a complication occurs is mandatory.

Disclosures

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