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Heterogeneity in Standard Operating Procedures for Catheter Directed Thrombolysis for Peripheral Arterial Occlusions in The Netherlands: A Nationwide Overview

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WHAT THIS PAPER ADDS

The practice of using catheter directed thrombolysis as a treatment for acute arterial occlusion of the lower extremities varies enormously between medical centres. There is a large variability in almost every clinical, logistical, and technical parameter. Guideline adherence is low and therefore their current value for clinical practice is questionable. This study shows that efforts should be made to prepare a more uniform strategy on an (inter)national level. The present data create the baseline data set for further prospective research initiatives to build a validated, commonly accepted treatment strategy. In general, initiatives to improve guideline adherence in catheter directed thrombolysis are strongly desired and the study provides direction on how to achieve them.

Objective: Catheter directed thrombolysis (CDT) for acute arterial occlusions of the lower extremities is associated with a risk of major bleeding complications. Strict monitoring of vital functions is advised for timely adjustment or discontinuation of thrombolytic treatment. Nevertheless, current evidence on the optimal application of CDT and use of monitoring during CDT is limited. In this study the different standard operating procedures (SOPs) for CDT in Dutch hospitals were compared against a national guideline in a nationwide analysis.

Methods: SOPs, landmark studies, and national and international guidelines for CDT for acute lower extremity arterial occlusions were compared. The protocols of 34 Dutch medical centres where CDT is performed were assessed. Parameters included contraindications to CDT, co-administration of heparin, thrombolytic agent administration, angiographic control, and patient monitoring.

Results: Thirty-four SOPs were included, covering 94% of medical centres performing CDT in the Netherlands. None of the SOPs had identical contraindications and a strong divergence in relative and absolute grading was found. Heparin and urokinase dosages differed by a factor of five. In 18% of the SOPs heparin co-administration was not mentioned. Angiographic control varied between once every 6 h to once every 24 h. In 76% of the SOPs plasma fibrinogen levels were used for CDT dose adjustments. However, plasma fibrinogen level threshold values for treatment adjustments varied between 2.0 g/L and 0.5 g/L.

Conclusion: The SOPs for CDT for acute arterial occlusions of the lower extremities differ greatly on five major operating aspects among medical centres in the Netherlands. None of the SOPs exactly conforms to current national or international guidelines. This study provides direction on how to increase homogeneity in guideline recommendations and to improve guideline adherence in CDT.

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INTRODUCTION

Catheter directed thrombolysis (CDT) to treat acute lower extremity arterial occlusions has been shown to be an effective endovascular alternative to surgical thrombectomy.[1] However, the high reported rate of major bleeding complications, as defined by the International Society on Thrombosis and Haemostasis[2] in patients undergoing CDT, remains a serious concern.[3,4] Although some risk factors for the occurrence of major bleeding have been identified, current guidelines lack specific guidance and are contradictory on the relative and absolute contraindications such as hypertension or pregnancy.[5—8] Also, clear protocols for patient monitoring during CDT are lacking. Mainly,

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plasma fibrinogen level (PFL) monitoring has been suggested as a predictor of major bleeding during CDT. However, PFL as the primary predictor of major bleeding remains unproven.[9] Furthermore, the optimal dose of the thrombolytic agent and co-administered heparin is largely undefined, and its impact on major bleeding complications as yet unknown. To study the outcome of CDT therapy and to analyse objectively the usefulness of specific operating procedure parameters, large prospective multicentre studies are needed. These prospective studies can only be performed when participating centres apply a standardised, consensus based CDT protocol. As such, it is crucial to overview current detailed practice patterns. In order to review adherence to guidelines and identify variations in treatment and patient monitoring, the currently applied CDT protocols of Dutch medical centres were reviewed.

METHODS

Between 2017 and 2018 departments of vascular surgery and/or interventional radiology of all Dutch medical centres that provide CDT for peripheral arterial occlusions were contacted. Their treatment protocol was requested and standard operating procedures (SOPs) were reviewed. National and international guidelines, and two landmark studies on CDT for peripheral arterial occlusions were reviewed.[6–8] End points were defined including absolute or relative contraindications; heparin usage; urokinase bolus administration dose, infusion speed, duration of administration; PFL monitoring; angiographic control frequency; and laboratory monitoring frequency. Protocols where urokinase was not the thrombolytic agent of choice were excluded.

RESULTS

After contacting 51 Dutch medical centres, eight (16%) academic hospitals and 26 (51%) peripheral hospitals across the country provided their SOPs. A total of 10 (20%) hospitals were merged or collaborated with others and therefore used the same SOP. These were included once. Three (6%) centres did not respond, despite numerous attempts, and four (8%) centres did not carry out CDT treatment. In total 34 (67%) SOPs were eligible for analysis.

Contraindications

In total, 29 different absolute and relative contraindications were described. A list of contraindications and their specifications are given in Table 1. None of the 34 SOPs was matched for definition of type or grade of contraindications. In two SOPs there was no distinction between relative or absolute contraindications. An overview of distinction for the four most frequent contraindications is shown in Table 2. A comparison of the contraindications mentioned in the SOPs with guidelines or the two landmark studies is given in Table 3.

Heparin administration

A heparin bolus via the catheter sheath was administered in 13 SOPs, at a dose of 2500 IU/hour ($n = 4$), 3000 IU/hour ($n = 1$), or 5000 IU/hour ($n = 9$). In two SOPs a therapeutic dose of 5700 IU low molecular weight heparin was administered subcutaneously twice daily. Continuous intravenous heparin was administered during CDT in 26 SOPs, at a dose ranging from 200 IU/hour to 1000 IU/hour. An overview of heparin administration is shown in Table 4.

Urokinase administration

An overview of urokinase administration and maximum administration duration is given in Table 5. Bolus administration dose differed from 100,000 IU to 500,000 IU. Seven different continuous urokinase administration dosages were identified. Although information from six SOPs is lacking, nearly all administered a bolus of urokinase into the clot.

Control angiography

The number of angiograms during CDT differed from once daily to four times daily (Table 6).

CDT dose adjustment

In most (76%) SOPs the urokinase dose was adjusted based on laboratory findings during CDT. In most SOPs CDT was adjusted or terminated based on PFLs. Frequency of blood sample collection differed from once to 12 times daily. An overview of the selected threshold values for CDT dose adjustment and frequency of blood sample collection is shown in Tables 7 and 8. In two SOPs dose adjustment was based on clinical parameters and in six SOPs was not reported at all.

DISCUSSION

In this study, an overview of SOPs for CDT for acute peripheral arterial occlusions in the Netherlands is provided. Broad variance in CDT treatment with regard to contraindications, heparin administration, urokinase administration, angiographic control, and patient monitoring is demonstrated. Application of CDT is not without risk. Two decades ago CDT treatment was associated with a major bleeding complication rate of 11%.[10] Unfortunately, at present, major complication rates of 13% are still reported.[3,4]

Presumably, contraindications in SOP protocols were derived from the STILE and TOPAS (Thrombolysis or Peripheral Arterial Surgery) trials.[10,11] However, the contraindications stated in these two landmark studies differ (Table 3). International guidelines giving contraindications for CDT are limited.[6,7] In the Dutch medical guideline ("College ter Beoordeling van Geneesmiddelen" [CBG]) for the use of urokinase (Medacinase), contraindications are well reported. However, none of the 34 Dutch SOPs was compliant with this guideline.[5] The supporting evidence for the contraindications mentioned in these trials or guidelines remains unclear. Also, the variation in classification of contraindications amongst SOPs being either "relative" or

Table 1. List of contraindications

Contraindication	Standard operating procedures (*n*)	Contraindication	Standard operating procedures (*n*)
Recent stroke	29	Endocarditis	13
<2 months	9	Recent high energy trauma	13
<3 months	13	<10 days	2
<12 months	2	<4 weeks	5
Not specified	5	<6 weeks	1
Hypertension	29	<8 weeks	5
>170 mmHg	1	Cardiac thrombus	12
>180 mmHg	12	Sepsis	12
>185 mmHg	1	Irreversible lower extremity ischaemia	11
>200 mmHg	9	Inflammation of the gastrointestinal tract	10
Not specified	6	Age	10
Recent gastrointestinal bleeding	23	>75 years	7
<10 days	10	>80 years	1
<14 days	1	>85 years	2
<1 month	4	Menstruation	9
<3 months	2	Oesophageal varices	8
<6 months	1	Recent cardiopulmonary resuscitation < 10 days	8
Not specified	5	Neurological surgery or head trauma	8
Recent surgery	23	<3 weeks	1
<3 days	1	<8 weeks	2
<10 days	17	<12 weeks	5
<14 days	1	Nephrolithiasis	6
<2 months	1	Recent biopsy	6
Not specified	3	<10 days	3
Pregnancy	22	<28 days	3
<18 weeks	7	Recent delivery of a child	6
>18 weeks	1	Spinal anaesthesia	5
Not specified	14	International normalised ratio	4
Active bleeding site	20	>1.5	3
Eye surgery or diabetic haemorrhagic retinopathy	20	>2.5	1
Coagulopathies	16	Agitation (probability of accidental sheath removal)	3
Intracerebral malignancy	16	Anticoagulation	2
Severe renal and hepatic impairment	14	Life expectancy < 1 year	1

"absolute" was remarkable. The consideration to either initiate CDT treatment or select a different treatment for peripheral arterial occlusions may have a profound effect on patient outcome. Identifying accurate contraindications for CDT is crucial to avoid exposing patients at unnecessary risk or to wrongly withhold optimal treatment.

Table 2. Contraindications

Contraindication	Relative	Absolute	Not reported
Recent stroke	3 (9)	24 (73)	5 (15)
Hypertension	17 (51)	9 (27)	7 (21)
Recent surgery	14 (42)	11 (33)	8 (24)
Recent gastrointestinal bleeding	4 (12)	17 (51)	12 (36)

Note. Data are *n* (%).

Most SOPs co-administered heparin during CDT. Although not mentioned in the SOPs, this, presumably, aims to avoid clotting in the introducer tip (sheath). However, the TOPAS trial showed that continuous heparin administration was an independent risk factor for major bleeding and therefore concomitant heparin was no longer administered during that trial.[10] The added value of therapeutic co-administration of heparin for clot lysis during CDT has been questioned.[12–14] Moreover, therapeutic heparin usage and its prolongation of the partial thromboplastin time is associated with an increased incidence of bleeding complications.[14]

The urokinase bolus dose varied significantly between 100,000 IU and 500,000 IU. In the STILE trial a bolus of 250,000 IU was administered and in the TOPAS trial no bolus was used.[10] Bleeding complications have been

Table 3. Definitions of contraindications

	TOPAS[10]	STILE[11]	College ter Beoordeling van Geneesmiddelen[8]	Mode standard operating procedures[a]
Hypertension	Yes, ≥ 180 mmHg	Yes, ≥ 180 mmHg	Yes, ≥ 200 mmHg	Yes, ≥ 180 mmHg
Stroke	Yes, within 6 mo	Yes, any CVA/TIA	Yes, any CVA/TIA	Yes, within 3 mo
Gastrointestinal bleeding	Yes, within 14 d	Yes, within 10 d	Yes, duration undefined	Yes, within 10 d
Recent surgery	No	Yes, within 10 d; 21 d for vascular surgery	Yes, until wound healing	Yes, within 10 d

Note. [a] Most frequently appeared contraindication in all standard operating procedures.
TOPAS = thrombolysis or peripheral arterial surgery; CVA = cerebrovascular accident; TIA = transient ischaemic attack; STILE = a trial for surgery versus thrombolysis for ischemia of the lower extremity. College ter Beoordeling van Geneesmiddelen - Medical Evaluation Board.

Table 4. Heparin administration

	Centres (*n*)
Continuous heparin administration	
<500 IU/h	8
500 IU/h	5
>500 IU/h	8
≥1000 IU/h	4
None	2
Not available	4
Heparin bolus	
2500 IU	4
5000 IU	9
None	17
Not available	1

Table 5. Urokinase administration

Urokinase bolus	Centres (*n*)
100,000 IU	14
250,000 IU	9
500,000 IU	5
Not available	6
Continuous urokinase administration	
50,000 IU/h	2
60,000 IU/h	1
90,000 IU/h	1
100,000 IU/h	18
Graded infusion regimen (250,000–60,000 IU/h)	5
Radiologist preference (50,000–250,000 IU/h)	2
Not available	5
Maximum duration	
24–48 h	9
48–72 h	11
Not available	14

Table 6. Angiographic control

Angiography frequency	Number of standard operating procedures
Once a day	7
Twice a day	6
Three times a day	2
Four times a day	7
Radiologist preference	4
Not available	8

Table 7. Plasma fibrinogen level

Plasma fibrinogen level (g/L)	Dose reduction or temporary cessation (centres, *n*)	Therapy cessation (centres, *n*)	No adjustments (centres, *n*)
2.0–1.5	1	0	27
1.5–1.0	4	0	24
1.0–0.5	9	14	5
<0.5	5	21	2
Not available	6		

Table 8. Laboratory monitoring frequency (per day)

Laboratory monitoring frequency (per day)	Centres (*n*)
1	4
3	3
4	13
6	2
8	2
12	2
Variable	2
None	1
Not available	5

correlated with the administration of a bolus thrombolytic agent.[15] The CBG guideline does not mention administration of a bolus. Although a graded infusion regimen for continuous urokinase administration is described in most trials,[10,11,16,17] and recommended by the CBG guideline,[5] only five SOPs were compliant.

Monitoring of PFLs has often been thought to provide added value in the prediction of adverse bleeding complications during CDT.[8] This assumption was based on the association between low PFLs and bleeding

complications.[10,11] However, the predictive value of PFL for bleeding complications remains unproven.[9] A broad variation between SOPs in terms of laboratory monitoring was found. While most adjusted CDT based on PFLs, there was strong inconsistency in the threshold value for CDT adjustment or cessation. Also, the frequency of laboratory monitoring differed greatly. Recommendations from national guidelines contradict this, recommending CDT adjustments when PFL is $<$ 1.5 g/L or 1.0 g/L.[5,8] International guidelines lack information on laboratory monitoring.[6,7] This study has a strong limitation. There is no self evidence that protocols are strictly followed by clinicians and treatment or patient monitoring could differ by clinical preference. During the writing of this manuscript, urokinase was temporarily unavailable in the Netherlands. Therefore, several centres used alteplase as a substitute thrombolytic agent. However, the same parameters with regard to contraindications, co-administration of heparin, angiographic control, and patient monitoring still apply. Furthermore, nearly all SOPs stated "major bleeding risk" as a potential treatment complication. However, they did not state criteria to define major bleeding.

It remains a challenge to point out which CDT treatment parameter has the strongest correlation with potential major bleeding complications. However, the accumulation of extensive differences in all parameters shows strong heterogeneity in CDT treatment amongst Dutch medical centres and, presumably, worldwide. Consequently, this lack of guideline adherence might account for the high rates of major bleeding. Although limited, the available evidence supporting the current CDT guidelines remains the gold standard and best practice. Therefore, it is undesirable to perform unproven alternative therapies or to diverge from these guidelines. At the same time, the data create more homogeneity in recommendations applied within several of the guidelines. As clinicians expect high rates of major bleeding, there is no incentive to distrust their SOPs. Also, it is probable that a lack of guideline awareness is accountable for SOP heterogeneity. In general, the results clearly demonstrate that even with medical treatments known for a high rate of major complications, guideline adherence is low. Therefore, more awareness of the presence of current guidelines should be generated. Initiatives to present guideline information or guideline updates on a repeated basis is strongly desirable. The inability of guidelines to provide necessary uniform recommendations to assist in CDT treatment decisions reflects the urgent demand for more prospective observational research in CDT treatment for acute peripheral arterial occlusions. Furthermore, CDT efficacy could be improved. If the same clinical results were to be achieved with lower thrombolytic dosage this could significantly reduce hospital costs. For the future, there is a clear need to make CDT safer, either based on patient selection or on the adjustment of specific SOP parameters. In order to be able to perform further large scale prospective studies, CDT SOPs need to be further harmonised. As available level I evidence on most of these SOP parameters is lacking, standardisation can only be based on consensus.

CONCLUSION

CDT for arterial thrombotic occlusion is applied in most Dutch vascular centres. In this study, considerable differences were found in CDT for acute peripheral arterial occlusions amongst Dutch medical centres. A lack of guideline adherence and contradictory guidelines may account for this heterogeneity, which might put patients at unnecessary major bleeding risk or, conversely withhold optimal treatment. There is an urgent need to generate (inter)national uniformity on CDT treatment protocols and patient monitoring to be able to optimise clinical outcomes and obtain high quality evidence. Above all, the data prompt action to define generally accepted homogeneous recommendations and increased guideline awareness and adherence.

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