

Timing of Thoracic Outlet Decompression after Thrombolysis for Primary Upper Extremity Deep Venous Thrombosis: A Systematic Review

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Background: The optimal timing of decompression surgery after thrombolysis in patients with primary upper extremity deep vein thrombosis (UEDVT) is still a matter of debate. This systematic review compares the safety and efficacy of early intervention versus postponed intervention in patients with primary UEDVT.

Methods: A structured PUBMED, EMBASE, and COCHRANE search was performed for studies reporting on the timing of surgical intervention for primary UEDVT. Studies reporting on timing of decompression surgery in combination with recurrent thrombosis, bleeding complications, and symptom-free survival were included. Two treatment groups were defined; group A received surgical decompression within two weeks after thrombolysis and group B after two weeks or more. All end points were assessed in accordance with the reported outcomes in the included articles. Mean percentages were calculated using descriptive statistics.

Results: Six articles (126 patients) were included: 87 patients in group A versus 39 in group B. In group A, bleeding complications occurred in 7% of patients versus 5% in group B. Two-third of the bleeding complications in group A occurred in patients receiving surgical decompression within 24 hr after thrombolysis while kept on intravenous heparin both preoperatively and postoperatively. Reported preoperative recurrent thrombosis was 7% in group A versus 11% in group B, another 13% had postoperative recurrent thrombosis versus 21% in group B. The effectiveness of both treatment strategies was comparable with a total of 89% of patients in group A with minimal or no symptoms at final follow-up compared with 90% in group B. The mean follow-up in group A was 35 months (1–168 months) and 28 months (1–168 months) in group B.

Conclusions: Based on the limited available data presented in this review, early decompression surgery within two weeks after catheter-directed thrombolysis seems as safe and effective as postponed surgical intervention in patients with primary UEDVT.

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INTRODUCTION

Primary upper extremity deep vein thrombosis (UEDVT) is an uncommon disease with an incidence of 1–2 per 100,000 people.¹ Primary UEDVT is usually caused by an impingement of the subclavian vein. Owing to repetitive compression of the vein in the thoracic outlet due to hypertrophic muscles, anatomic abnormalities of the first rib or clavicle or the presence of a cervical rib² results in fibrosis and thrombosis.

Patients with primary UEDVT are typically young, active, and otherwise healthy people with a mean age between 30 and 35 years.^{3,4} Adequate treatment is therefore of the utmost importance to ensure optimal functional outcome in this young population. According to current treatment guidelines on thrombosis and prevention, preferred therapy for primary upper extremity deep venous thrombosis is conservative with anticoagulation, whereas invasive therapies such as catheter-directed thrombolysis (CDT) and surgery are only recommended in selected patients.^{5–8} To date, no surgical society produced an official guideline on the treatment of UEDVT. The existing guidelines are based on the limited data available, and subsequently, the precise recommended treatment strategies vary between guidelines. This has led to two different treatment strategies being applied in daily practice, namely conservative versus invasive treatment. Moreover, the guidelines give no recommendations regarding the optimal timing of first rib resection after CDT. The invasive treatment consists of, at least, CDT followed by surgical decompression of the thoracic outlet. The goal of surgical decompression is to release the subclavian vein from its narrow passage through the thoracic outlet. This is achieved by dissecting the anterior scalene and subclavius muscle from the first rib and then removing the rib entirely. Based on surgeon's preference, the surgical approach can differ between the transaxillary, infraclavicular, supraclavicular, and the paraclavicular approach that combines the supraclavicular and infraclavicular approach. There is also great variety in supplementary treatments in addition to decompression surgery such as percutaneous transluminal angioplasty (PTA), patch angioplasty, venous stenting, and/or venous bypass surgery.⁹

When thrombolysis and surgery are considered, the optimal timing is still under debate.¹⁰ Some studies advocate early surgery to avoid recurrent thrombosis before thoracic outlet decompression can be performed. Other studies advocate a postponed surgical intervention to facilitate a remodeling and recovery of the injured vessel.¹¹ No randomized controlled trials comparing both strategies exist, and it is unknown which strategy is superior.

Next to the safety and efficacy of a treatment, the cost and total duration of a therapy are important secondary factors to take into consideration. We believe that the early intervention has an advantage over delayed decompression when it comes to these secondary factors. Early intervention can reduce the

anticoagulation bridging period by weeks or even months. This will in turn reduce treatment costs and expedite patients' return to work.

The aim of this review is to evaluate the safety and efficacy of early surgical decompression after CDT compared with delayed surgical intervention. We hypothesized that early (<2 weeks) decompression is as safe as delayed decompression surgery regarding recurrent thrombosis and bleeding complications while achieving similar treatment results in terms of symptom-free survival.

MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.

Search Strategy

A search was performed of the MEDLINE, EMBASE, and COCHRANE databases in January 2019 and updated in August 2019. The following main keywords and their synonyms were used: "Thoracic Outlet Syndrome," "Upper extremity deep vein thrombosis," "Surgical decompression," and "Thrombolytic therapy." No filters or limitations were used in the search regarding the year of publication, language, or species. Cross-referencing for relevant articles was performed on all papers included for full-text review and excluded systematic reviews. A full version of the PubMed search is added in [Appendix 1](#).

Eligibility Criteria

Two independent reviewers (L.S. and R.d.K.) screened all titles and abstracts and reviewed the full-text articles for the following inclusion and exclusion criteria: original studies that reported on patients with primary UEDVT treated with thrombolysis followed by surgical decompression and specified the timing of surgical decompression were included in this study. Furthermore, randomized controlled trials and cross-sectional and longitudinal studies in peer reviewed journals were eligible for inclusion. Case reports, reviews, and conference abstracts were excluded. Only English and Dutch articles with full-text availability found during title and abstract screening were included for full-text review. Discrepancies between reviewers were discussed with a third reviewer (B.J.P.).

Primary Outcome

We used a total of four primary outcome measures; three were used to define the safety of the respective treatment strategies and one to define the effectiveness of each treatment. Our primary safety outcomes were bleeding complications, preoperative recurrent thrombosis and postoperative recurrent thrombosis. Bleeding complications were defined as any reported bleeding complication that occurred intraoperatively or postoperatively. As the included articles did not report bleeding complications using a standardized bleeding assessment, these were defined as reported in the included articles. Therefore, no formal bleeding complication assessment was possible. Preoperative recurrent thrombosis was defined as any reported recurrent thrombosis after successful CDT but before surgical decompression was performed. Patients with reported unsuccessful thrombolysis were excluded for this specific outcome. Postoperative recurrent thrombosis was defined as any reported postoperative recurrent UEDVT at the side of the decompressed limb measured from the first day postoperatively onward. A new deep vein thrombosis in other limbs or pulmonary embolisms without recurrent thrombosis of the originally occluded vessel were excluded for this outcome measure. Our primary efficacy outcome was the percentage of reported patients with minimal or no symptoms at the last follow-up. As no formal outcome measure was standardized in any of the included studies, we used the reported nonstandardized outcome measures.

Methodological Quality Assessment

The Strengthening the Reporting of Observational Studies in Epidemiology statement checklist was used to assess the methodological quality of all included studies.^{12,13} All articles were scored independently by two reviewers (L.S., R.d.K.). Discrepancies between reviewers were discussed before a final score was calculated for each manuscript. We classified a total score below 13 (<60% of total score) as poor quality, between 13 and 17 (between 60 and 80%) as moderate and above 17 (>80%) as good quality.

Statistical Analysis

Originally, we intended to calculate pooled proportions by means of log transformations. However, due to small sample sizes and limited number of events, no reliable pooled proportions could be calculated. Instead, mean percentages were

calculated using descriptive statistics. IBM SPSS statistics version 25.0.0.2 was used for statistical calculations.

RESULTS

Study Selection

The search and additional cross-referencing yielded a total of 336 unique articles (Fig. 1). 261 articles were excluded based on title and abstract or were case reports and reviews. Of the 69 articles left, 12 conference abstracts were excluded. In addition, 3 articles were excluded because of language criteria and another 2 due to nonavailable full text. The remaining 52 full-text articles were assessed, leading to the exclusion of a further 46 articles. Most exclusions were due to an unclear description of the timing between thrombolysis and surgical decompression or a lack of distinction between treatment strategies when reporting outcomes. A total of six articles, published between 1997 and 2013, were eventually included.^{14–19} Table I displays an overview of the six included articles.

Methodological Quality Assessment

Table II shows an overview of the quality assessment for all articles. Two articles were classified as poor quality, three as moderate, and one as good quality. Especially, the results and discussion sections in the included articles were frequently of poor quality.

Study Sample

Six studies including data from 126 patients were included into this review. Based on the included articles, the patients could be divided into two treatment groups. Group A consisted of 87 patients who received early decompression surgery within 2 weeks of CDT. Group B consisted of 39 patients who received late decompression surgery after waiting at least two weeks after thrombolytic therapy. All patients received thrombolysis and thoracic outlet decompression, whereas some patients received some form of additional treatment such as PTA, patch angioplasty, venous stenting, or bypass surgery. Postoperative anticoagulation strategies ranged from no postoperative anticoagulation therapy to 18 months of anticoagulation. Total follow-up time differed strongly between studies and ranged from 2 days to 14 years. The mean follow-up in group A was 35 months (1–168 months) and 28 months (1–168 months) in group B. Because some primary outcomes were

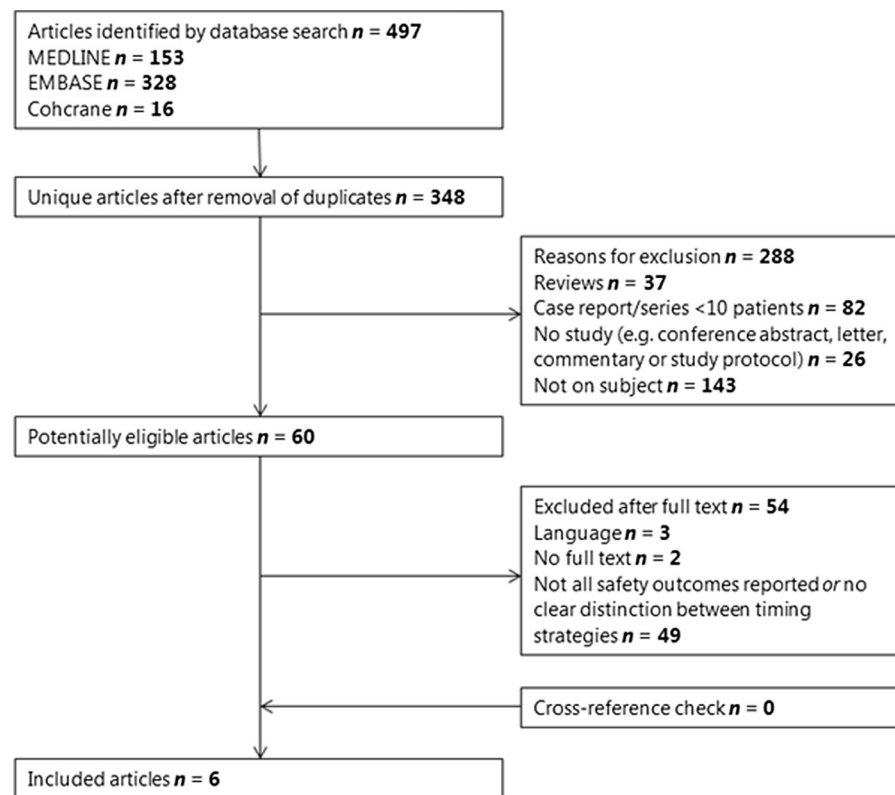


Fig. 1. Flowchart inclusion process.

not applicable on all patients, these percentages were calculated over a subset of patients.

Bleeding Complications

There were no bleeding complications related to thrombolytic therapy in both groups. There were a total of 6 (8%) patients with bleeding complications in group A compared with 2 (5%) patients in group B.

One study, in contrary to the rest of the studies in group A, performed decompression surgery directly after thrombolysis or at least within a maximum of 24 hr after CDT. Moreover, patients remained under intravenous heparin infusion both preoperatively and postoperatively.¹⁸ This study reported bleeding complications in 4 of 23 (17%) patients and was responsible for two-thirds of all bleeding complications in group A. For the remaining 2 patients, the preoperative anticoagulation regimen consisted of intravenous heparin until 60 min preoperatively. Postoperative anticoagulation therapy was unclear for these two patients. In total, three patients in group A suffered a hemothorax, of whom, one received surgical decortication.¹⁸ The remaining three patients in group A had wound hematomas,

two of which required surgical drainage, the third was treated conservatively.

In group B, one patient, who received low molecular weight heparin up until surgery and warfarin postoperatively, developed a wound hematoma that required surgical reintervention.¹⁹ The second patient had a hemothorax, with no reported treatment consequences.¹⁵ Anticoagulation treatment was unclear for this patient.

Preoperative and Postoperative Recurrent Thrombosis

Fourteen patients, twelve in group A and two in group B, had unsuccessful CDT and were therefore excluded for analysis for preoperative rethrombosis. There were 5 (7%) patients with preoperative recurrent thrombosis in group A¹⁵ versus 4 (11%) in group B.^{15,17} Postoperative recurrent thrombosis occurred in 11 patients (13%) in group A^{14–16,18} compared with 8 patients (21%) in group B.^{15,16} In total, there were 16 events of recurrent thrombosis (18%) in group A versus 12 events (31%) in group B. Fourteen patients in group A received postoperative stenting because of residual stenosis after surgery and PTA.¹⁸

Table I. List of studies reporting on safety outcomes and timing

Study	N	Design	Quality	Mean age in years (range)	Additional treatment	Bridging	Postoperative anticoagulation	Preop DVT	Postop DVT	Bleeding	Symptom-free survival (%)
TOD <2 weeks											
Lee	11	RC	13/21	30 (15–54)	- 5 Preop PTA - 7 Venolysis - 3 Patch angioplasties - 2 Venous bypasses	Intravenous heparin	3–6 months Coumadin	1	2	0	10 (90.9%)
Taylor	41	RC	16/22	NR	None	Heparin until 60 min preop	Aspirin or 3 months of warfarin	5/29 ^a	2	2	36 (87.8%)
Angle	9	RC	17,5/21	27 (17–37)	- 9 Venolysis - 3 postop PTA	NR	Intravenous heparin 4–6 hr after surgery. Followed by Coumadin for 3 months. (INR 2,5–3,0)	0	2	0	8 (88.9%)
Kreienberg	23	RC	13/21	30 (18–58)	- 23 PTA - 14 Stents	Intravenous heparin	Intravenous heparin, followed by Warfarin 6–18 months (INR 2.0–2.5)	0	5 ^b	4	20 (87.0%)
Feugier	3	RC	12/21	31 (18–42)	None	LMWH	Coumadin for unspecified duration	0	0	0	3 (100%)
TOD >2 weeks											
Taylor	15	RC	16/22	NR		Unclear	Aspirin or 3 months of warfarin	3/13 ^a	7	1	11 (73.3%)
Angle	9	RC	17,5/21	36 (26–46)	- 9 Venolysis - 2 Postop PTA	Warfarin for 3 months	Heparin 4–6 hr after surgery. Coumadin for 3 months. INR 2,5–3,0	0	1	0	9 (100%)
Adelman	11	RC	11,5/21	NR	- 11 CDT - 10 TOD ^c	Warfarin INR 2.0–2.1	No postop anticoagulants	1/11	0/10	0/10	11 (100%)
Feugier	4	RC	12/21	24 (18–32)	- 2 Venous bypasses	LMWH	Coumadin for unspecified duration	0	0	1	4 (100%)

DVT, deep vein thrombosis; LMWH, low molecular weight heparin; Na, not applicable; NR, not reported; PTA, percutaneous transluminal angioplasty; RC, retrospective cohort; TOD, thoracic outlet decompression.

^aPercentages were calculated over the amount of patients with successful thrombolysis.

^bAll recurrent thrombosis occurred in stented patients.

^cOne patient had preoperative recurrent thrombosis and refused further surgical decompression. Safety and efficacy outcomes are presented as reported number of events; symptom-free survival was defined as the percentage of patients with minimal to no symptoms at the last follow-up.

Table II. STROBE checklist

Authors	Lee	Adelman	Taylor	Feugier	Kreienberg	Angle
Title and Abstract	1/2	1/2	1/2	1/2	1/2	1/2
Introduction						
Background	1	1	1	1	1	1
Objectives	1	1	1	1	1	1
Methods						
Study design	1	1	1	1	1	1
Setting	1	1	1	1	1	1
Participants	1	1	1	1	1	1
Variables	0	0	1/2	1/2	1/2	1
Data source	1/2	1/2	1	1	1	1
Bias	0	0	0	0	0	1/2
Study size	1	1	1	1	1	1
Quantitative variables	Na	Na	1	Na	Na	Na
Statistical methods	0	0	1/2	0	0	1/2
Results						
Participants	1/2	1/2	1	1	1	1
Descriptive data	0	0	0	1/2	1/2	1
Outcome data	1	1	1	1	1	1
Main results	0	0	0	0	0	1/2
Other analysis	0	0	1	0	0	0
Discussion						
Key results	1	1/2	1	0	1	1
Limitations	1/2	0	1/2	0	0	1/2
Interpretation	1	1/2	1	1/2	1/2	1
Generalizability	1	1	0	0	0	1
Other information						
Funding	1	1	1	1	1	1
Total score	13/21	11,5/21	16/22	12/21	13/21	17,5/21

A total score below 13 was considered poor, between 13 and 17 moderate, and above 17 good.

Na, not applicable; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Five of these stents (36%) occluded, which accounted for almost half (46%) of the recurrent postoperative thrombosis in group A.

The timing of recurrent postoperative thrombosis was unclear for most patients. In group A, two stents occluded after 2 and 3 days, another two after 1 year, and a fifth stent occlusion occurred after 3 years. Another two patients in group A suffered rethrombosis after 5 days and 4 weeks postoperatively.¹⁴ In the remaining four patients, the timing of postoperative rethrombosis was not reported.^{15,16} The time of postoperative recurrent thrombosis was not mentioned for any of the eight patients in group B.^{15,16} Because the timing of rethrombosis was so poorly described, we were not able to define what percentage of rethrombosis occurred under anticoagulant therapy.

Efficacy

The effectiveness of both treatment strategies was comparable with a total of 77 (89%) patients in

group A with minimal or no symptoms at final follow-up compared with 34 (90%) in group B. The mean follow-up in group A was 35 months (1–168 months) and 28 months (1–168 months) in group B.

DISCUSSION

Results

In patients with primary UEDVT, we found no numerical significant difference between the safety and efficacy of early or late decompression after CDT.

We found that two-thirds of bleeding complications in group A occurred in patients who received surgical decompression within 24 hr after CDT and who remained on intravenous heparin both preoperatively and postoperatively. The other two patients received intravenous heparin up until 60 min preoperatively. In group B, we found no

bleeding complications in combination with intravenous heparin therapy.

Also worth mentioning is that almost half of all recurrent thrombosis in group A occurred in one study¹⁸ among 14 patients who received postoperative stenting. We strongly believe that stents placed in the dynamic thoracic outlet are prone to recurrent thrombosis and stent fracturing, even when the thoracic outlet is adequately decompressed. In our institute, stent placement was performed in a select population of eight patients, either before or after thoracic outlet decompression. Results were disappointing, with stent fractures in two patients and recurrent thrombosis in another five patients. Several case series on stenting in the thoracic outlet report diverse results on recurrent thrombosis after stenting (with or without decompression surgery), ranging from 0 to 100% of stented patients.^{20–22}

Limitations

This review has several limitations. Data analysis was hampered by the limited number of studies, the low-to-moderate quality of these studies, the small amount of patients in both groups, and the low number of events. Hence, pooled proportions could not be calculated and we had to rely on basic descriptive statistics to compare both strategies. The nonstandardization of reported bleeding complications and efficacy outcomes, the heterogeneity in additional treatments, and the limited information on recurrent thrombosis in relation to postoperative anticoagulation strategies are further major factors that influenced our analysis.

Also, the included studies were very heterogeneous with regard to additional treatments and anticoagulation strategies. Four of six studies used additional treatments besides CDT and decompression surgery, and the studies used different bridging and postoperative anticoagulation protocols.

Another factor that could influence our results is the time bias in all studies for the preoperative recurrent thrombosis outcome. The chances of recurrent thrombosis are unequivocally smaller in the early intervention group due to the shorter follow-up of 2 weeks compared with the delayed decompression group. Another time bias exists in the difference in mean follow-up. Although symptom-free survival was comparable in both groups, the mean follow-up in group B was 20% shorter than in group A (28 vs. 35 months), and the range was very wide in both groups (1–168 months). This shorter follow-up in group B might have distorted the postoperative recurrent thrombosis occurrences.

We had to exclude numerous studies for not distinctly reporting recurrent thrombosis or bleeding complications. It seems unlikely that no such events occurred in these studies. Publication bias might also be an issue here considering the fact that we found virtually no studies with unfavorable results regarding recurrent thrombosis and bleeding complications.

Finally, we chose an arbitrary cutoff value of 2 weeks to separate the early from the late intervention group based on the included studies and group sizes. A different cutoff value might have changed our results. Unfortunately, we were not able to investigate other timing cutoff values because of the small sample sizes.

Excluded Articles

One excluded article is worth mentioning, considering its large sample size. Unfortunately, this article did not distinctly report on our chosen safety outcomes and was therefore excluded from this review. The article described a series of 126 patients who received CDT followed by decompression surgery and patch angioplasty within two weeks.²³ The total follow-up ranged between 6 months and 25 years at which point one hundred percent of patients reported minimal to no symptoms. Based on these figures, CDT followed by decompression surgery within 2 weeks of symptom onset seems to be a particularly effective treatment for primary UEDVT.

Reporting Standards

A significant amount of articles were excluded because they did not clearly report on the required safety outcomes of recurrent thrombosis and bleeding complications or because the authors did not sufficiently specify on the timing of surgical intervention. Also, other important factors such as clear description of the preoperative and postoperative anticoagulation therapy were frequently lacking. This makes comparing studies and case series difficult. In their 2016 article, the society of vascular surgery suggested a reporting standard for all three forms of thoracic outlet syndrome.²⁴ We recognize that following these guidelines will greatly increase the comparability of future studies on this rare condition. We want to add that, despite these reporting standards, a clear scoring system for defining the severity of residual symptoms or post-thrombotic syndrome is still lacking. Therefore, the development of a post-thrombotic syndrome score for the upper extremity is highly warranted.

Advantages of Early Intervention

Besides safety and efficacy of a treatment, the cost and duration of treatment are also important factors to take into consideration. In this case, an early intervention could reduce anticoagulation bridging by weeks or even months compared with the prolonged staged approach. Based on the type of bridging, this reduction will not only reduce health care cost but will also directly benefit the patient; For example, by reducing the time spent in international normalized ratio checkups or by reducing the amount of uncomfortable shots with low molecular weight heparin. Furthermore, although there were no events of anticoagulation therapy–related bleeding complications in our review, a reduction in the duration of anticoagulation bridging should reduce the risk for anticoagulation therapy–related complications. Most patients, with a mean age between 30 and 35 years, will already have a low risk of bleeding, but this risk will be further reduced by shortening the time spent under therapeutic or prophylactic anticoagulation therapy.

CONCLUSION

Based on the limited available data presented in this review, early decompression surgery within two weeks after CDT seems as safe and effective as postponed surgical intervention in patients with primary UEDVT. Future studies comparing different timing strategies for surgical intervention are warranted to define the optimal timing for surgical intervention.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.avsg.2020.01.083>.

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