Pharmacomechanical Thrombectomy Versus Catheter-Directed Thrombolysis for Iliofemoral Deep Vein Thrombosis: A Meta-Analysis of Clinical Trials

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Abstract

Early catheter-directed thrombolysis (CDT) for deep vein thrombosis (DVT) can reduce postthrombotic morbidity. Pharmacomechanical thrombolysis (PMT) is a new therapy that can be selected for the treatment of iliofemoral deep vein thrombosis (IFDVT). We performed a meta-analysis of clinical trials comparing PMT versus CDT for treatment of acute IFDVT. Literature on this topic published between January I, 1990, and June I, 2018, was identified using PubMed, Embase, Cochrane Library, and Web of Science. Six trials were included in the meta-analysis. Compared to CDT, PMT significantly reduced the Villalta score (P = .007; $I^2 = 0\%$), thrombus score (P = .01; $I^2 = 0\%$), the duration in the hospital (P = .03; $I^2 = 64\%$), and thrombolysis time (P < .00001, $I^2 = 0\%$). There was no significant difference in valvular incompetence events (P = .01; $I^2 = 0\%$), minor bleeding events (P = .59; $I^2 = 0\%$), stent events (P = .09; $I^2 = 24\%$), and clot reduction grade I events group into PMT plus CDT versus CDT group and significant differences were found (P = .03, $I^2 = 0\%$) as well as for PMT alone versus CDT group (P = .88, $I^2 = 37\%$). This metaanalysis shows that PMT reduces the severity of postthrombotic syndrome (PTS), thrombus score, duration in hospital, and thrombolysis time compared to CDT. More specifically, PMT plus CDT reduces clot reduction grade I events of reduction grade I events. No significant difference in valvular incompetence events, stent events, and minor bleeding events were found when PMT was compared to CDT.

Keywords

pharmacomechanical thrombectomy, catheter-directed thrombolysis, iliofemoral deep vein thrombosis

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Introduction

Iliofemoral deep venous thrombosis (IFDVT) is strongly related to severe postthrombotic morbidity, embodied by a reduction in the quality of life.¹ It can impact the daily routine and lead to consequential complications, such as varicosity, limitation in activity, postthrombotic syndrome (PTS), and even pulmonary embolism (PE).² Treatment options for IFDVT have developed with the increasing utilization of catheter-directed thrombolysis (CDT) and pharmacomechanical thrombolysis (PMT).^{3,4} Catheter-directed thrombolysis is a therapy that the guidewire passed through the thrombus lesion under the assistance of a supporting catheter, followed by a multiple-sidehole infusion catheter. The catheter was placed within the thrombosed vessel and secured in place. The urokinase solution was infused continuously at a dose of 600 to 1200 U/kg/h over 48 to 72 hours. Catheter-directed thrombolysis has been performed for several years in patients with IFDVT, with

positive outcomes. However, the dose of lytic agent needed for therapy is high, and thrombolysis time is long.⁵ From emerging technology, PMT is a method of the AngioJet device (Possis Medical, Inc, Minneapolis, Minnesota) for rheolytic thrombectomy. The Angiojet device was inserted to the thrombus lesion and the operation continued with a solution of urokinase. The design of AngioJet device is such that it allows for thrombus fragmentation

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Figure 1. Flow diagram of literature review.

and rapid evacuation through the effluent lumen. This sequence may be repeated in the event that significant residual thrombus remains on subsequent venograms. Pharmacomechanical thrombolysis has been developed with catheter infusion approaches for thrombolysis treatment with considerable success and enthusiasm. Although some studies have demonstrated that PMT is safe and effective with decreased treatment time, hospital stay, and dosage of lytic agent compared to CDT, PMT and CDT have similar venous outcomes in patients with acute IFDVT.⁶⁻⁸ We performed a meta-analysis of 9 studies comparing PMT with CDT for the treatment of IFDVT in an attempt to solve the discrepancy between study outcomes and provide evidence to clinicians.

Methods

Literature Search

Literature, published between January 1, 1990, and June 1, 2018, was searched using PubMed, Embase, Cochrane

Library, and Web of Science. The search terms included the following: CDT or PMT or pharmacomechanical thrombectomy or mechanical thrombectomy or iliofemoral/lower extremity or deep vein thrombosis, and/or comparative studies or randomized controlled trials or cohort studies or retrospective or prospective studies. Inclusion criteria were studies comparing PMT plus CDT or PMT (experimental group) with CDT (control group) and presence of intact clinical data. No language restrictions were enforced. Ten studies were found (Figure 1).

Two investigators independently extracted data utilizing a data abstraction tool: number of patients in experimental group and control group, study quality, time of follow-up, primary and secondary outcomes. Primary outcomes were the Villalta score (a measure that could be used to diagnose and classify the severity of PTS). Postthrombotic syndrome was classified as mild if the Villalta score is 5 to 9, moderate if the Villalta score is 10 to 14, and severe if the Villalta score is ≥ 15); clot

	Table	١.	Baseline	Characteristics	of	Included	Clinical	Trials
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Study	Group	Sample	Follow-Up	Mean Age, Years	Female Sex	Region	Outcomes	Study Quality Score
Kuo et al ⁷	CDT	31	24 months	64.5	14	Taiwan, China	Villalta score, thrombus score,	Retrospective
	PMT	30		67	12		Clot reduction grade I, valvular incompetence, bleeding, stent events, duration of hospital stay	NOS:8
Vogel et al ¹⁰	CDT	20	44 months	NA	NA	United States	Valvular incompetence events	Retrospective
-	PMT	49		NA	NA			NOS:8
Huang et al ¹¹	CDT	18	12 months	64	6	Taiwan, China	Villalta score, thrombus score	Retrospective
	PMT	16		62	7		Clot reduction grade l, valvular incompetence, bleeding, stent events	NOS:8
Lin et al ⁸	CDT	46	38 months	NA	NA	United States	Clot reduction grade I, bleeding events	Retrospective
	PMT	52		NA	NA		Duration of hospital stay	NOS:7
Trabal et al ⁶	CDT	21	28 months	52	7	United States	Thrombus score, thrombolysis time, clot reduction grade I events	Retrospective NOS:9
	$PMT \pm CDT$	22		44	15		Bleeding, stent events	
Kim et al ⁵	CDT	26	32 months	43	17	United States	Thrombus score, clot reduction grade I events	Retrospective
	PMT + CDT	19		53	12		Bleeding, stent events	NOS:7

Abbreviations: CDT, catheter-directed thrombolysis; NA, not available; NOS, Newcastle-Ottawa Scale; PMT, pharmacomechanical thrombolysis.

Table 2. Primary and	Secondary	Outcomes	in Clinical	Trials
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Study	Group	Villalta Score	Thrombus Score	Valvular Incompetence Events	Clot Reduction Grade I Events	Duration of Hospital Stay, Days	Thrombolysis Time, Hours	Minor Bleeding Events	Stent Events
Kuo	CDT	3.13 ± 3.0	1.1 ± 1.8	12	6	10.9 <u>+</u> 1.5	NA	NA	2
et al ⁷	PMT	1.87 <u>+</u> 2.7	0.83 ± 1.4	9	3	9.9 <u>+</u> 5.0	NA	NA	7
Vogel	CDT	NA	NA	13	NA	NA	NA	NA	NA
et al ¹⁰	PMT	NA	NA	25	NA	NA	NA	NA	NA
Huang	CDT	5.06 ± 4.07	2.22 <u>+</u> 3.49	NA	2	NA	NA	I	6
et al 11	PMT	2.06 ± 2.95	0.56 <u>+</u> 0.93	NA	0	NA	NA	0	10
Lin et al ⁸	CDT	NA	NA	NA	6	8.4 <u>+</u> 2.3	NA	2	NA
	PMT	NA	NA	NA	11	4.6 <u>+</u> 1.3	NA	3	NA
Trabal	CDT	NA	5.74 ± 4.4	NA	8	NA	55.4 \pm 21.3	5	12
et al ⁶	$PMT \pm CDT$	NA	3.0 ± 3.7	NA	2	NA	23.4 \pm 21.5	4	14
Kim	CDT	NA	NA	NA	2	NA	56.5 ± 27.4	I	6
et al ⁵	PMT + CDT	NA	NA	NA	0	NA	30.3 <u>+</u> 17.8	0	3

Abbreviations: CDT, catheter-directed thrombolysis, NA, not available; PMT, pharmacomechanical thrombolysis.

reduction grade I events, thrombus score, valvular incompetence events, and secondary outcomes included thrombolysis time, stent events, duration in hospital, and bleeding events. masking of participants, intention-to-treat analysis, incomplete or unclear data, and time to follow-up) was also assessed. Study quality was assessed by the Newcastle-Ottawa Scale (NOS).⁹ Disagreements between reviewers were resolved by consensus.

Data Extraction and Quality Assessment

Details of the publication, inclusion and exclusion criteria, demographics of the study participants, interventions, and outcomes (primary and secondary outcomes) were collected and reviewed. Risk of bias in the studies (eg, including

Statistical Analysis

Statistical analysis was performed using Review Manager (Cochrane Collaboration software, version 5.3). Random

	1	РМТ			CDT			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weigh	t IV, Random, 95% Cl	IV, Random, 95% Cl
Huang 2015	2.06	2.95	16	5.06	4.07	18	34.29	-0.82 [-1.52, -0.11]	±
Kuo 2016	1.87	2.7	30	3.13	3	31	65.89	6 -0.44 [-0.94, 0.07]	.
Total (95% CI)			46			49	100.09	-0.57 [-0.98, -0.15]	
Heterogeneity: Tau ² =	0.00; Cł	ni² = 0.	74, df=	= 1 (P =	0.39);	$ ^2 = 0\%$,		-100 -50 0 50 100
Test for overall effect:	Z = 2.69	(P = 0	.007)						Favours PMT Favours CDT
		10					0.007	72 000	
Meta-analysis of vil	lata so	ore (9	25% C	1, -0.9	8,-0.	15; P :	=0.007	;1=0%)	
	1	РМТ			CDT			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weigh	t IV, Random, 95% Cl	IV, Random, 95% CI
Huang 2015	0.56	0.93	16	2.22	3.49	18	24.19	-0.62 [-1.31, 0.07]	+
Kuo 2016	0.83	1.4	30	1.1	1.8	31	45.59	-0.16 [-0.67, 0.34]	•
Trabal 2008	3	3.7	22	5.74	4.4	21	30.49	-0.66 [-1.28, -0.05]	•
 Accord BRANE-CONSIGN - BRANERSSON - STOCKSTONES - 181 									
Total (95% CI)			68			70	100.09	· -0.43 [-0.76, -0.09]	
Heterogeneity: Tau ² =	0.00; Cł	ni² = 1.	90, df=	= 2 (P =	0.39);	I ² = 0%			100 50 0 50 100
Test for overall effect:	Z = 2.46	(P = 0	.01)						Eavours PMT Eavours CDT
									Favours Finit Favours CD1
Meta-analysis of the	ombus	scor	e (959	%CL -	0.76	-0.09	P = 0	$01: I^2 = 0\%$	
			. (,	••,				
		PMT		CD	Т			Odds Ratio	Odds Ratio
Study or Subgroup	Eve	nts 1	Fotal	Events	Tot	al W	eight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
David 2012		25	49	13	2	0 5	2.3%	0.56 (0.19, 1.65)	
Kun 2016		9	30	12	3	1 4	7 7 %	0.68 (0.23, 1.97)	
100 2010			~~					0.00 (0.20, 1.01)	
Total (95% CI)			79		5	1 10	0.0%	0.62 [0.29, 1.31]	•
Total events		34		25					
Heterogeneity: Chi ²	= 0.06	df = 1	(P = 1)	1811	= 0%			F	
Test for overall effer	+ 7 = 1	25 (P	- 0.2	1)	- • /•			0.	01 0.1 1 10 100
restion overall eller	A. 2 - 1	.20 (1	- 0.2	.,					Favours PMT Favours CDT
Meta-analysis of Va	lvular	incon	npeter	ice eve	ents (95% (CI, 0.2	9- 1.31; P =0.21; I ² =	0%)

Figure 2. Meta-analysis of primary outcomes of clinical trials (Villata score P = .007, $I^2 = 0\%$, thrombus score P = .01, $I^2 = 0\%$, valvular incompetence events P = .21, $I^2 = 0\%$).

effects models were used for some primary outcomes (Villalta score and thrombus score [0-open vein free of thrombus; 1-partially occluded vein with a flow Doppler signal; 2-completely occluded vein with no flow signal]), and some secondary outcomes (thrombolysis time and duration in hospital) and utilized fixed-effects models for outcomes related to clot reduction grade I events (the clot reduction grade I events represented the patients with acute IFDVT after thrombolytic therapy used venography showing achievement of clot lysis of <50%. The clot reduction grade III events implied the patients with acute IFDVT after thrombolytic therapy used venography showing achievement of clot lysis of 90%-100%), stent events, valvular incompetence, and bleeding events. Statistical heterogeneity was assessed by I^2 . The level of heterogeneity was defined as low ($I^2 = 0\%$ -49%), moderate ($I^2 = 50\%$ -74%), and high $(I^2 \ge 75\%)$ heterogeneity. Primary and secondary outcomes were analyzed using odds ratios or standardized mean difference, with a 2-sided significance level of 5%.

Results

Study Characteristics and Quality

The initial search strategy identified 20 full-text articles, and 14 citations were screened. Six trials^{5-8,10,11} satisfied the appropriate criteria for inclusion in the meta-analysis (Figure 1). Six comparative studies included experimental groups that received PMT therapy for acute IFDVT and control groups that received CDT therapy for acute IFDVT. The qualities of trials were assessed by NOS score. Table 1 shows the baseline characteristics for each study.

Primary Outcomes

Primary and secondary outcomes are shown in Table 2. Three studies^{6,7,11} included the results of thrombus score, 5 studies^{5-8,11} included the results of clot reduction grade I events, 2 studies^{7,10} included the results of valvular incompetence events, and 2 studies^{7,11} included the results of Villalta

	PM	Г	CD1			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
2.15.1 PMT alone Su	bgroup						
Huang 2015	0	16	2	18	10.4%	0.20 [0.01, 4.49]	· · · · · · · · · · · · · · · · · · ·
Kuo 2016	3	30	6	31	24.0%	0.46 [0.10, 2.05]	
Lin 2006	11	52	6	46	22.7%	1.79 [0.60, 5.30]	
Subtotal (95% CI)		98		95	57.0%	0.94 [0.43, 2.08]	•
Total events	14		14				
Heterogeneity: Chi ² =	3.17, df =	2 (P =	0.21); I2 =	= 37%			
Test for overall effect:	Z=0.15	(P = 0.8	(8)				
2.15.2 PMT+CDT Sub	group						
Kim 2006	0	19	2	26	9.4%	0.25 [0.01, 5.54]	
Trabal 2008	2	22	8	21	33.6%	0.16 [0.03, 0.89]	
Subtotal (95% CI)		41		47	43.0%	0.18 [0.04, 0.81]	
Total events	2		10				
Heterogeneity: Chi ² =	0.06, df =	1 (P=	0.81); I ² =	= 0%			
Test for overall effect:	Z= 2.23	(P = 0.0)	(3)				
Total (95% CI)		139		142	100.0%	0.62 [0.32, 1.20]	
Total events	16		24				
Heterogeneity: Chi ² =	7.03, df =	4 (P=	0.13); I ² =	= 43%			
Test for overall effect:	Z=1.42	P = 0.1	6)				0.01 0.1 1 10 100
Test for subaroup dif	ferences:	Chi ² = 3	3.62. df =	1 (P=	0.06). I ² =	72.4%	PMT CDT
Meta-analysis of clot	reductio	n grad	le I even	its (95	% CI, 0.	32-1.20; P =0.13;	I ² =43%); Meta-analysis of subgroup
PMT alone group (9:	5% CI, 0	.43-2.0	08; P =0	.88; I ²	=37%); 1	Meta-analysis of su	ubgroup PMT+CDT group (95% CI,
$0.04-0.81 \cdot P = 0.03 \cdot T^{-1}$	$^{2}=0\%$						
0.0170.01,1 -0.05,1	070).						

Figure 3. Meta-analysis of primary outcomes of clot reduction grade l events on primary outcomes with subgroup analysis. (total P = .16, $l^2 = 43\%$), PMT alone versus CDT group (P = .88, $l^2 = 37\%$), and PMT + CDT versus CDT group (P = .03, $l^2 = 0\%$). CDT indicates catheter-directed thrombolysis; M-H, Mantel-Haenszel (a stratification analysis method); PMT, pharmacomechanical thrombolysis.

score. Meta-analysis indicated that PMT reduced the Villalta score (P = .007; $I^2 = 0\%$) and thrombus score (P = .01; $I^2 =$ 0%) compared to CDT and did not result in a significant difference in clot reduction grade I events (P = .16; $I^2 = 43\%$) and valvular incompetence events (P = .21; $I^2 = 0\%$) compared to CDT. There were 2 types of PMT therapy including PMT plus CDT therapy and PMT alone therapy. When the clot reduction grade I events group was divided into PMT plus CDT versus CDT group, and PMT alone versus CDT group, subgroup analysis demonstrated that PMT plus CDT reduced clot reduction grade I events (P = .03, $I^2 = 0\%$) compared to CDT. Pharmacomechanical thrombolysis alone did not result in a significant difference in clot reduction grade I events (P = .88, $I^2 = 37\%$). This meta-analysis showed that PMT plus CDT is more effective in the treatment of IFDVT than CDT alone. Results of the meta-analysis of the primary outcomes are shown in Figures 2 and 3.

Secondary Outcomes

Two articles^{5,6} had data on thrombolysis time (in hours), 4 articles^{5,6,8,11} included data on minor bleeding events,

4 studies^{5-7,11} included the results of stent events, and 2 articles^{7,8} had data on duration in hospital. There was a statistically significant decrease in duration in the hospital (P = .03; $I^2 = 64\%$) and thrombolysis time (P < .00001, $I^2 = 0\%$) for PMT compared to CDT. There was no significant difference in stent events (P = .09; $I^2 = 24\%$) and minor bleeding events (P = .59; $I^2 = 0\%$) between the treatments. The results of the metaanalysis of secondary outcomes are shown in Figure 4.

Discussion

Postthrombotic syndrome is the result of venous outflow obstruction, venous reflux, and calf muscle pump dysfunction after severe DVT.¹² Postthrombotic syndrome is also associated with severe clinical symptoms, such as chronic lower limbs pain, intractable edema, varicose veins, skin alterations, and venous ulcer.¹³ Iliofemoral deep venous thrombosis is a strong risk factor for developing PTS, resulting in a reduction in the quality of life. Treatment with thrombolysis is aimed to lower PTS morbidity.^{14,15} The rationale to use thrombolytic treatment is based on the efficacy to remove an early thrombus and improve vein patency, prevent valvular incompetence, and potentially

	DMT		CDT			Odde Patio	Odds Patio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Huang 2015	10	16	6	18	17.1%	3.33 [0.81, 13.64]	
Kim 2006	3	19	6	26	34.5%	0.63 [0.13, 2.90]	
Kuo 2016	7	30	2	31	12.2%	4.41 [0.84, 23.30]	
Trabal 2008	14	22	12	21	36.1%	1.31 [0.39, 4.47]	-
Total (95% CI)		87		96	100.0%	1.80 [0.91, 3.56]	◆
Total events	34		26				
Heterogeneity: Chi ²	= 3.93, df =	3 (P = 1	0.27); I ² =	: 24%			0.01 0.1 1 10 100
lest for overall effec	t Z = 1.69 (i	² = 0.0	9)				Favours PMT Favours CDT
Meta-analysis of ste	nt events (95% C	I, 0.91-	3.56;	P =0.09;	I ² =24%)	
	PMT		CDT			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% CI	M-H, Fixed, 95% CI
Huang 2015	0	16	1	18	15.6%	0.35/0.01/9.311	
Kim 2006	ő	10	1	26	14.1%	0.44 (0.02 11 20)	
Lin 2006	3	52	2	46	22.7%	1 35 10 22 9 441	
Trobal 2000	3	32	2 5	40	47.6%	0.71 (0.16.0.10)	
Trabal 2008	4	22	5	21	47.5%	0.71 [0.16, 3.12]	_
Total (95% CI)		109		111	100.0%	0.76 [0.28, 2.07]	-
Total events	7		9				
Heterogeneity: Chi ²	= 0.70, df =	3 (P = 1	0.87); I ² =	:0%			
Test for overall effec	t Z = 0.53 (f	P = 0.5	9)				0.01 0.1 1 10 100
			-,				Favours PMT Favours CDT
			(0.50			n o co n ² oou	
Meta-analysis of mi	nor bleedin	ig even	nts (95%	6 CI, 0	.28- 2.07	; P =0.59; I [*] =0%)	
	DUT			DT			Maan Difference
Study or Subgroup	PMT Moon SD	Total	C	DT	tal Moia	Mean Difference	Mean Difference
Study or Subgroup	PMT Mean SD	Total	CI Mean	DT SD To	tal Weig	Mean Difference	Mean Difference CI IV, Random, 95% CI
Study or Subgroup Kuo 2016	PMT Mean SD 9.9 5	Total 30	CI Mean 10.9	DT <u>SD To</u> 7.5	tal Weig 31 34.1	Mean Difference ht IV. Random, 95% -1.00 (-4.19, 2.1	Mean Difference CI IV, Random, 95% CI 9]
Study or Subgroup Kuo 2016 Lin 2006	PMT Mean SD 9.9 5 4.6 1.3	Total 30 52	Cl <u>Mean</u> 10.9 8.4	DT <u>SD To</u> 7.5 2.3	o <u>tal Weiq</u> 31 34.1 46 65.9	Mean Difference ht IV. Random, 95% 6 -1.00 (-4.19, 2.1 % -3.80 (-4.55, -3.0	Mean Difference CI IV, Random, 95% CI 9] 5]
Study or Subgroup Kuo 2016 Lin 2006 Total (95% CI)	PMT <u>Mean SD</u> 9.9 5 4.6 1.3	<u>Total</u> 30 52 82	Cl <u>Mean</u> 10.9 8.4	DT <u>SD To</u> 7.5 2.3	<u>otal Weiq</u> 31 34.1 46 65.9 77 100.0	Mean Difference ht IV. Random, 95% (% -1.00 (-4.19, 2.1 % -3.80 (-4.55, -3.0 % -2.85 (-5.45, -0.2)	Mean Difference CI IV, Random, 95% CI 9] 5]
Study or Subgroup Kuo 2016 Lin 2006 Total (95% CI) Heterogeneity: Tau ² =	PMT <u>Mean SD</u> 9.9 5 4.6 1.3	Total 30 52 82 2.80 d	Cl <u>Mean</u> 10.9 8.4	DT <u>SD To</u> 7.5 2.3	<u>otal Weiq</u> 31 34.1 46 65.9 77 100.0 ² = 64%	Mean Difference ht IV, Random, 95% (% -1.00 [-4.19, 2.1 % -3.80 [-4.55, -3.0 % -2.85 [-5.45, -0.2)	Mean Difference CI IV. Random, 95% CI 9] 5] 5]
Study or Subgroup Kuo 2016 Lin 2006 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect	PMT <u>Mean SD</u> 9.9 5 4.6 1.3 2.52; Chi ² = 7 = 2.15 (P =	Total 30 52 82 2.80, d	Cl <u>Mean</u> 10.9 8.4 f = 1 (P =	DT <u>SD To</u> 7.5 2.3 0.09); 1	<u>otal Weiq</u> 31 34.1 46 65.9 77 100.0 ² =64%	Mean Difference ht IV, Random, 95% (% -1.00 [-4.19, 2.1 % -3.80 [-4.55, -3.0 % -2.85 [-5.45, -0.2)	Mean Difference CI IV, Random, 95% CI 9] 5] 5] -100 -50 0 50 100
<u>Study or Subgroup</u> Kuo 2016 Lin 2006 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect:	PMT <u>Mean SD</u> 9.9 5 4.6 1.3 2.52; Chi ² = Z = 2.15 (P =	Total 30 52 82 2.80, d : 0.03)	Cl <u>Mean</u> 10.9 8.4 f = 1 (P =	DT <u>SD To</u> 7.5 2.3 0.09); I	otal Weiq 31 34.1 46 65.9 77 100.0 *= 64%	Mean Difference ht IV, Random, 95% (% -1.00 (-4.19, 2.1 % -3.80 (-4.55, -3.0 % -2.85 (-5.45, -0.2)	Mean Difference CI IV, Random, 95% CI 9] 5] 5] -100 -50 0 50 100 Favours PMT Favours CDT
Study or Subgroup Kuo 2016 Lin 2006 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect:	PMT 9.9 5 4.6 1.3 2.52; Chi ² = Z = 2.15 (P =	<u>Total</u> 30 52 82 2.80, d : 0.03)	Cl <u>Mean</u> 10.9 8.4 f = 1 (P =	DT <u>SD To</u> 7.5 2.3 0.09);1	otal Weiq 31 34.1 46 65.9 77 100.0 *= 64%	Mean Difference ht IV. Random, 95% (~ -1.00 (-4.19, 2.1 % -3.80 (-4.55, -3.0 % -2.85 (-5.45, -0.2)	Mean Difference CI IV, Random, 95% CI 9] 5] 5] -100 -50 0 50 100 Favours PMT Favours CDT
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<u>Study or Subgroup</u> Kuo 2016 Lin 2006 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Meta-analysis of dua <u>Study or Subgroup</u> Kim 2006 Trabal 2008	PMT <u>Mean SD</u> 9.9 5 4.6 1.3 2.52; Chi ² = Z = 2.15 (P = ration of ho <u>PMT</u> <u>Mean SD</u> 30.3 17.8 23.4 21.5	<u>Total</u> 30 52 82 2.80, d 0.03) ospital <u>Total</u> 19 22	Cl <u>Mean</u> 10.9 8.4 f = 1 (P = stay (95 Cl <u>Mean</u> 56.5 2 55.4 2	DT <u>SD</u> To 7.5 2.3 0.09);1 5% CI, 5% CI, DT <u>SD</u> To 27.4 21.3	otal Weiq 31 34.1' 46 65.9' 77 100.0 *= 64% , -5.45,-0 otal Weiq 26 53.4 21 46.6	Mean Difference ht IV, Random, 95% (% -1.00 [-4.19, 2.1 % -3.80 [-4.55, -3.0 % -2.85 [-5.45, -0.2 .25; P =0.03; I ² =64 Std. Mean Different ht IV, Random, 95% % -1.08 [-1.71, -0. % -1.47 [-2.15, -0.	Mean Difference CI IV, Random, 95% CI 9] 5] -100 -50 0 50 100 Favours PMT Favours CDT %) Ce Std. Mean Difference 6CI IV, Random, 95% CI 44] 79]
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Figure 4. Meta-analysis of secondary outcomes of clinical trials (stent events P = .09, $l^2 = 24\%$; minor bleeding events P = .59, $l^2 = 0\%$, duration of hospital stay P = .03, $l^2 = 64\%$, and thrombolysis time P < .00001, $l^2 = 0\%$).

reduce the incidence of PTS.^{16,17} The most recent American College of Chest Physicians guidelines still suggest anticoagulation therapy alone over CDT in acute proximal DVT; however, CDT could be selected as therapy for selected patients with IFDVT who have symptoms for <14 days, good functional status, life expectancy of >1 year, and low risk of bleeding.^{18,19}

Some randomized controlled trials (RCTs)s demonstrated that CDT can improve patency of the iliofemoral vein or decrease severity of PTS compared to anticoagulation therapy alone.^{20,21} The Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis Trial (ATTRACT) study²² showed that pharmacomechanical CDT

(PCDT)-reduced symptoms of IFDVT and the severity of PTS; however, it may not prevent the incidence of PTS. The efficacy of CDT therapy is verified,²³ and PMT therapy also may be a safe and effective alternative treatment for IFDVT.

Our meta-analysis, based on 6 comparative studies.^{5-8,10,11} compared PMT to CDT for the treatment of acute IFDVT. Only 2 studies^{7,11} included the results of the Villalta score and 3 studies^{6,7,11} of the thrombus score. Two studies^{7,10} included the result of valvular incompetence events: the 24-month follow-up in the study by Kuo et al^7 and the 44-month follow-up in the study by Vogel et $al.^{10}$ The severity of PTS, using the Villalta score, was highly correlated with postoperative thrombus score and severity of venous obstruction and was moderately correlated with severity of valvular incompetence. The postoperative thrombus score also strongly correlated with severity of venous obstruction. Our meta-analysis indicated that PMT reduced the Villalta score (P = .007; $I^2 = 0\%$) and thrombus score (P = .01; $I^2 = 0\%$) compared to CDT. However, there was no significant difference between the PMT and CDT group for valvular incompetence events (P = .21; $I^2 =$ 0%). In the study by Kuo et al,⁷ all patients with PTS had venous obstruction, but only half of them had valvular incompetence. This shows 2 connotations: (1) valvular incompetence results from venous outflow obstruction. (2) Valvular incompetence is not the main cause of PTS. Our results showed that PMT reduced the severity of PTS compared to CDT.

Five studies included^{5-8,11} the results of clot reduction grade I events. Although our meta-analysis showed that clot reduction grade I events (P = .16; $I^2 = 43\%$) were not significantly different between the PMT and CDT group, other therapy methods may have affected this result of clot reduction grade I events. The clot reduction grade I events group were divided into PMT plus CDT versus CDT and PMT alone versus CDT. Subgroup analysis indicated that PMT plus CDT reduced clot reduction grade I events (P = .03, $I^2 = 0\%$) compared to CDT. Pharmacomechanical thrombolysis alone did not result in a significant difference for clot reduction grade I events (P =.88, $I^2 = 37\%$) compared to CDT. Definite thrombus removal at an early stage and the amount of residual thrombus are important prognostic factors for developing PTS. It is most likely that a thorough, early intervention to remove a thrombus, either by CDT or PMT, is beneficial to prevent PTS. After PMT procedure, CDT can be used to remove a residual thrombus to prevent PTS.

Four studies^{5,6,8,11} included the result of minor bleeding events. After a systematic review of relevant studies, the majority of studies reported no major bleeding complications and PE events. In our meta-analysis, minor bleeding was not significantly different (P = .59; $I^2 = 0\%$) between PMT and CDT. Data analysis also demonstrated that the heterogeneity of the results was low. With PMT or CDT therapy, most minor bleeding complications occurred in the puncture site. Four studies^{5-7,11} included the result of stent events. Meta-analysis showed that there was no significant difference in stent events (P = .09; $I^2 = 24\%$) between the PMT and the CDT group. In 4 studies, the type of patients who needed angioplasty and stenting was not mentioned. Moreover, in the PMT plus CDT group, stenting should be performed after PMT or CDT procedures, but this was not mentioned in the studies. Thrombolytic agent was continuously infused in the CDT group, and lower doses of thrombolytic agents were used in the PMT group, especially in the PMT plus CDT group. Two studies^{5,6} included the result of thrombolysis time (in hours). In our meta-analysis, thrombolysis time was significantly shorter in the PMT group (P < .00001, $I^2 = 0\%$) compared to CDT. The duration of hospital stay was significantly shorter in the PMT group (P = .03; $I^2 = 64\%$) compared to CDT. This may have been caused by the reduction in thrombolysis time in the PMT group. The shorter duration of hospital stay may decrease the economic burden of patients without health insurance.

Our meta-analysis had limitations. There were no RCTs in this meta-analysis, and the quality of studies was not high. Therefore, the data from the non-RCTs with lower quality may affect the results of the meta-analysis. Although the heterogeneity of most primary and secondary outcomes was not high, we did not carefully explore the sources of heterogeneity. Also, study quality, sample size of the studies, and followup time may be important factors influencing the results of the meta-analysis, and we did not eliminate other sources of heterogeneity, such as age, gender, race, dose of thrombolytics and different drugs for thrombolysis. High-quality RCTs are required to reduce heterogeneity and provide more reliable data.

Conclusion

This meta-analysis demonstrates that PMT results in a low severity of PTS compared to CDT therapy alone. Moreover, the average duration of hospital stay and thrombolysis time was shorter in the PMT group compared to the CDT group. However, the PMT group was not significantly different in valvular incompetence events, stent events, and minor bleeding events compared to the CDT group.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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