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Clinical outcomes of drug-coated balloon angioplasty for venous in-stent restenosis: A prospective clinical study

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Abstract: **Background**: In-stent restenosis (ISR) is still a significant barrier in achieving long-term benefits from venous stent placement for patients suffering from iliofemoral deep vein thrombosis (IFDVT). An innovative way for local drug delivery is with drug-coated balloon angioplasty (DCBs). **Objective**: The goal of this research was to compare the therapeutic effectiveness, clinical outcomes, and improved quality of life of drug-coated balloon angioplasty versus standard balloon angioplasty in patients with recurrent venous in-stent restenosis (RSI). **Methods**: A polycentric clinical study was conducted on 44 patients suffering RSI after venous stent placement. Patients were non-randomly assigned either to DCB (Group A, N=22) or standard balloon angioplasty (Group B, N=22). Restenosis was measured using duplex ultrasound with luminal narrowing criteria, and clinical outcomes, including pain intensity and quality of life associated with health and mobility, were assessed using the EQ-5D mobility domain and VAS. **Results**: During the 24-month study, the rate of restenosis in Group A was slightly lower than in Group B (9.2% vs 24.2%; $p < 0.05$). Patients treated with DCBs had notably better VAS scores (3.45 vs. 5.68; $p < 0.01$), pain scores and mobility. The DCB group had a mobility score of 80% compared to 20% in the standard balloon angioplasty group. **Conclusion**: Localized delivery of antiproliferative medications, such as paclitaxel, can be achieved with DCB therapy, thereby limiting systemic exposure, enhancing venous patency, and improving functional outcomes. Drug-coated stents based on sirolimus can be helpful for patients, underscoring the pharmacological relevance and future scope of this study.

Keywords: Drug therapy; Drug-coated balloon angioplasty (DCB); Drug delivery system; In-stent restenosis (ISR); Iliofemoral deep vein thrombosis (IFDVT)

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INTRODUCTION

Iliofemoral deep vein thrombosis (IFDVT) is a severe form of venous thromboembolism that occurs when blood clots form in the iliac and common femoral veins, causing compression on the drainage pathways of the affected veins and resulting in severe impairment of the affected venous outflow (Kahn *et al*., 2009). The IFDVT is estimated to represent approximately 25% of all lower extremity deep vein thrombosis cases worldwide, according to epidemiology; thus, IFDVT's clinical and therapeutic implications are paramount to the healthcare and pharmaceutical industries (Liu *et al*., 2015). Approximately 1 in 1,000 people develop an IFDVT event annually; therefore, the acute nature and long-term sequelae make this condition a priority in pharmacology and health systems. Despite many advances in the use of anticoagulants, the lifetime likelihood of developing an IFDVT is considered clinically significant. Despite the advancement in anticoagulation, IFDVT remains associated with relatively long-term morbidity. The effectiveness of drug-coated balloons in the treatment of venous stent reocclusion, particularly following IFDVT, is supported only minimally and inconsistently, and few studies exist to support their influence on clinical and quality-of-life outcomes after treatment of venous diseases. This informati on indicates a need for dedicated clinical studies assessing the therapeutic effectiveness of drug-coated balloons (DCBs) in treating venous stent reocclusion (Yasunaga *et al*., 2024).

The foundation of treating IFDVT with drugs is the use of systemic anticoagulants: low-molecular-weight heparin, vitamin K antagonists (VKAs), and a range of direct oral anticoagulants (DOACs), such as rivaroxaban and apixaban (Cushman *et al*., 2004). These classes of medications exert their effects by targeting critical components of the coagulation cascade, thereby preventing thrombus formation and further embolization (Saleem *et al*., 2023). Although anticoagulant treatment is very effective in reducing the risk of death from thromboembolic disease and the occurrence of acute thromboembolic complications, it is less effective in promoting thrombus resolution and restoring venous patency in large proximal veins. Consequently, anticoagulation alone is often insufficient to prevent chronic venous obstruction and subsequent functional impairment (Comerota *et al*., 2007).

Clinically, IFDVT is associated with significant morbidity, which includes: significant pain, high limb swelling (edema), reduced ability to move around and an overall decline in health-related quality of life (Delis *et al*., 2004). Compared with distal IFDVT, involvement of the iliac

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vein and femoral vein creates a much greater hemodynamic compromise due to the difference in the amount of blood returned to the heart from the feet versus from the thigh and pelvis (iliac vein). The increased hemodynamic compromise also stimulates a large amount of inflammation and results in chronic venous hypertension. Significantly, pharmacologic anticoagulants will not sufficiently alleviate the inflammatory and proliferative processes that follow thrombus organization after it has formed. Therefore, up to 50% of patients will have developed some form of chronic venous sequelae to their IFDVT after being treated with anticoagulants alone. Chronic sequelae may include post-thrombotic syndrome (PTS) characterized by venous claudication, skin changes, refractory edema, and in the most severe cases, ulceration of the limb or limb amputation (Wanha *et al*., 2024).

The limitations in this area indicate a significant need for medication-based treatment options to improve re-opening of veins after a blockage and to prevent re-blockage after mechanical opening has occurred (Piovella *et al*., 2002). To this end, an endovascular approach and localized delivery of medication via drug-coated devices. Balloon angioplasty provides instant decongestion of the veins. Still, one of the complications that frequently occurs during the operation is restenosis, the re-narrowing of the vessel by the excessive proliferation of tissues (intimal hyperplasia) occasioned by injury to the vessel wall during angioplasty. It is one of the main factors limiting the effectiveness of balloon angioplasty and venous stenting techniques.

Restenosis remains the primary driver of intensive biomedical research aimed at understanding biological processes and developing preventive measures (Zhang *et al*., 2023). After balloon angioplasty and stenting, the restenosis rate is different in the various vascular territories, ranging between 10 and 20 percent, which is of significant clinical importance because of repeated interventions and the increased health care costs, pain and heightened risk of complications as well as in some cases severe cardiovascular events (Zhang *et al*., 2023; Ravani *et al*., 2016).

The use of DCB has become another alternative treatment method to reduce the burden of restenosis and to deal with the shortcomings of traditional balloon angioplasty (Gray *et al*., 2010). Angioplasty balloons coated with an antiproliferative drug, paclitaxel, that inhibit cell growth in blood vessels are known as drug-coated balloons. Paclitaxel prevents the growth of smooth muscle cells by preserving microtubule integrity and inhibiting cell division, thereby minimizing intimal hyperplasia and vascular remodeling. While drug-coated balloons have been demonstrated to reduce restenosis rates in arterial locations such as the coronary and peripheral arteries, there are substantial differences in the structures, flow dynamics, and biological responses to injury between veins and arteries. Thus, one must exercise caution when extrapolating from arterial data to venous disease processes (Navarese *et al*., 1997). The proposed research will examine the outcomes users report from using drug-coated balloon angioplasty against those who use standard balloon angioplasty methods for treatment of recurrent venous in-stent restenosis after having developed IFDVTs.

MATERIALS AND METHODS

Research design

The proposed study is a prospective, non-randomized clinical trial to determine the effectiveness of DCB therapy in patients with IFDVT for preventing recurrent restenosis. In-stent restenosis is characterized by≥50% narrowing of the lumen in an area covered by an implanted stent, as measured by duplex ultrasound using peak venous velocity ratios, plus grayscale (gray) imaging or sonography of the vascular lumen. Paclitaxel-coated balloon angioplasty was conducted utilizing commercially available paclitaxel-coated (2-3.5 μg/mm²) drug-coated balloons based on the appropriate diameter and length of the vessel reference size. The inflation of the balloon was carried out at an approximate pressure of 8-12 atm over a period of 60-120 seconds, with one or two inflations applied to the lesion area following the guidelines. Non-coated balloon angioplasty used the same inflation pressures and duration but did not include the drug or coating. The primary goal was to determine the effectiveness of DCB angioplasty versus conventional balloon angioplasty in terms of venous restenosis, mobility, quality of life (QoL), and other significant outcomes over a long period of time. The research was held between March 2022 and July 2024.

Participants of the study

Patients who had already received venous stent placement for IFDVT were enrolled in the study. A convenience sample was utilized due to limited availability of patients with repeated venous in-stent restenosis.

Inclusion criteria for patients

All participants were selected based on a confirmed ISR diagnosis, with imaging, and considered appropriate candidates for DCB angioplasty or standard balloon angioplasty. There were 44 participants in total, with 22 in each treatment group (Group A: DCB; Group B: balloon angioplasty). Individuals aged 50 or older are eligible to participate if they demonstrate symptoms of venous-in-stent restenosis (presenting with at least 50% stenosis) that occur more than six months post-placement of the first stent. The minimum age of 50 years was chosen based on previous studies of other types of interventions for venous disease, as well as the fact that older individuals are more likely to develop both recurrent venous disease and restenosis than younger individuals.

Exclusion criteria for patients

Patients who have suffered from any trauma in the head region or have exhibited an acute stroke are excluded. The exclusion criteria were severe comorbidity that would affect follow-up or survival (e.g., advanced cancer, severe heart failure), active infection or other contraindications to paclitaxel, pregnancy or lactation, and patients who could not or would not comply with the study protocol or follow-up requirements. Long-term analysis of patients who were lost to follow-up was excluded from utilization, and missing data were not imputed.

Study procedure

This study was conducted at two tertiary care centres primarily focused on vascular diseases. The participants were selected after signing informed consent, based on the predetermined protocol for DCB angioplasty or conventional balloon angioplasty. The way patients were assigned to treatment types depended on how the institution used to treat those patients, so one site used DCB angioplasty, while the other performed conventional balloon angioplasty. Standardized procedures and follow-up schedules were used at both sites to reduce centre-related variability. The hospital site was included as a factor in the results to account for any differences between sites. Each participant underwent baseline tests, including duplex ultrasound to assess stenosis severity, leg edema, pain intensity, and mobility limitations. The two treatment groups (Group A - DCB and Group B - balloon angioplasty) were assessed in accordance with the clinical protocols of their institutions. Participants were observed for immediate post-procedure complications, and evaluations were conducted at 12 and 24 months. The follow-ups included clinical and imaging analysis to determine re-narrowing, quality of life (QoL), and functional outcomes. Harvesting of participants who failed to report to follow-ups was assigned to trained field staff, who made phone calls and visited participants' homes to determine the standards of healing.

Data collection

The data were gathered through clinical examination, which included the use of questionnaires and imaging tests performed at baseline, midline, and endline after the procedure. The type of clinical information gathered included assessment of leg edema, the pain experienced during ambulation and self-care activities, as well as the patient's medical history of hypertension, diabetes, and heart disease. Baseline measurement of pre-procedure stenosis, post-procedure stenosis, and anticoagulation monitoring were performed. Functional impairment was assessed with the help of standardized tools and the quality of life of the patient was measured with the help of the EQ-5D. The iliofemoral vein stenosis residues and the degree of re-narrowing were determined by duplex ultrasound. These variables were used to assess the effect of the intervention on daily activities, health status, and adverse life events among the patients.

Primary and secondary outcomes

In this study, the primary and secondary outcomes of DCB angioplasty compared with conventional balloon angioplasty were assessed in patients with ISR after IFDVT. The primary outcome measure was the frequency of venous in-stent restenosis (in-stent occlusion) at 12 months post-treatment and 24 months.

The secondary outcomes will be pain intensity (VAS), health-related quality of life (EQ-5D), functional mobility, self-care ability, and complications associated with the venous stenting procedure. Each dimension was assessed in terms of the degree of issues reported during baseline and follow-up periods, on a scale of 1 (no problems) to 3 (severe problems) (Oppe *et al*., 2007). The research determined the safety of DCB angioplasty compared to traditional balloon angioplasty using the major adverse event as the primary outcome. Lastly, structured questionnaires examining the state of anxiety and depression and general satisfaction with the treatment were utilized to determine the psychological effects.

Data analysis

The descriptive and inferential statistics were used in the analysis. The mean, standard deviations and t-tests studied age and stenosis percentage, which were continuous variables, between the two groups. Patient-reported EQ-5D domain scores and VAS scores were used to measure mobility and functional results; gait and performance-based measures were not employed. The chi-square tests evaluated categorical variables in terms of prevalence of leg swelling, pain and mobility limitation across groups. The statistical significance level was set at p-value less than 0.05. Baseline group differences were measured and subsequently adjusted using multivariate regression analysis as needed. All the analyses have been done using the statistical programme SPSS version 26.0.

Ethical consideration

The research was formulated within the ethical principles that were set forth in the Declaration of Helsinki. The study was approved by the Institutional Review Boards of both centres involved in the study (Approval No. 14.11.2023-779320). Trial registration has been done accordingly. Each of the participants was informed about the objectives, risks and benefits of the study and he/she agreed to take part in it. Written informed consent was obtained from all participants before enrollment. The subjects were informed that they had the right to pull out of the research any time without any negative repercussions. The data on the participants were kept confidential and in a private manner, with all data anonymized before analysis.

Table 1: Demographic and health characteristics of participants at baseline

Demographic and health characteristics	Outcomes	Groups			
		Group A		Group B	
		Frequency	%	Frequency	%
Gender	Male	13	54.2%	11	45.8%
	Female	9	45.0%	11	55.0%
Hypertension	Yes	13	43.3%	17	56.7%
	No	9	64.3%	5	35.7%
Diabetes	Yes	14	46.7%	16	53.3%
	No	8	57.1%	6	42.9%
Heart disease	Yes	22	50.0%	22	50.0%
	No	0	0.0%	0	0.0%
Smoking	Yes	6	37.5%	10	62.5%
	No	16	57.1%	12	42.9%
Anticoagulant drugs	Yes	19	54.3%	16	45.7%
	No	3	33.3%	6	66.7%
Leg swelling post treatment at baseline	None	0	0.0%	0	0.0%
	Mild	6	60.0%	4	40.0%
	Moderate	13	61.9%	8	38.1%
	Severe	3	23.1%	10	76.9%
Pain severity at after procedure at baseline	None	0	0.0%	0	0.0%
	Mild	0	0.0%	5	100.0%
	Moderate	11	52.4%	10	47.6%
	Severe	11	61.1%	7	38.9%

RESULTS

Given the limited sample size, absolute numbers are provided alongside percentages to improve data interpretation accuracy. Groups A and B showed significant differences in baseline demographic and health characteristics. Males showed a higher proportion (13/22, 54.2) in Group A and lower proportion (11/22, 45.8) in Group B and the reverse was true in the case of hypertensive patients (17/22, 56.7 in Group B compared to 13/22, 43.3 in Group A) and in the case of those without hypertension (9/22, 64.3 in Group A compared to 5/22, 35.7 in Group B). Group B (16/22, 53.3%) had a significantly higher prevalence of diabetes than Group A (14/22, 46.7%). There was a variation in smoking behaviors whereby a larger proportion of the non-smokers fell within Group A (16/22, 57.1) than in Group B (12/22, 42.9). Group B showed significantly more severe leg swelling after treatment (10/22 patients) than Group A (3/22 patients). Severe baseline pain was observed in 11/18 patients in Group A, compared with 7/18 in Group B (Table 1).

Table 2 outlines the health outcomes 6 months after the procedure in Group A (DCB) and Group B (balloon angioplasty). Group A had better outcomes across different areas. It is important to note that Group A had considerably lower levels of leg edema, with most participants having mild swelling, whereas Group B showed severe swelling in all participants. Group A had lower pain intensity, with 9/22 (69.2%) reporting mild to moderate pain, while Group B had 100% severe pain. Participants in Group A were more mobile, as 13/22 (76.5%) could walk 301-400 meters, whereas participants in Group B could walk only 100-200 meters. Group B had very high levels of fatigue, with 13/22 (86.7%) reporting severe fatigue.

Additionally, Group A showed better self-care outcomes, and fewer participants had serious problems (7/22). On the contrary, (13/22) 65.0% of participants in Group B reported having a severe problem with self-care. Group A had much lower anxiety and depression levels, with 100 percent claiming not to have anxiety or depression, unlike Group B where (13/22) 56.5 percent had severe anxiety or depression. In summary, the treatment with DCB in Group A provided better physical outcomes, reduced discomfort, and improved psychological outcomes compared to balloon angioplasty in Group B.

At the 12-month follow-up, Group A (DCB) results were much better than those of Group B (balloon angioplasty). Their findings showed that 16/22 (72.7%) had no leg swelling, compared with 6/22 (27.3%) in Group B.

Group A had a lower number of people reporting no pain and (13/22) 92.9% of them reported no pain as opposed to (1/22) 7.1 in Group B. Compared to Group B, Group A had better mobility and (20/22) 80 percent of participants accepted that they were not challenged in any way. In contrast, Group B was challenged in (5/22) 20 percent of self-care, and (18/22) 94.7 percent of participants reported being challenged in regular activities.

Table 2: Post treatment outcome of group A (DCB) and group B (Balloon Angioplasty) at midline (12 months)

Post treatment physical outcomes	Result	Groups			
		Group A		Group B	
		Count	Row N %	Count	Row N %
Leg swelling At 12 month	None	0	0.0%	0	0.0%
	Mild	13	92.9%	1	7.1%
	Moderate	9	42.9%	12	57.1%
	Severe	0	0.0%	9	100.0%
Pain severity At 12 month	None	0	0.0%	0	0.0%
	Mild	9	69.2%	4	30.8%
	Moderate	13	52.0%	12	48.0%
	Severe	0	0.0%	6	100.0%
Redness At 12 month	Yes	19	63.3%	11	36.7%
	No	3	21.4%	11	78.6%
Walk distance At 12 month	100-200m	0	0.0%	9	100.0%
	201-300m	2	18.2%	9	81.8%
	301-400m	13	76.5%	4	23.5%
	401-500m	7	100.0%	0	0.0%
Fatigue in walking	None	0	0.0%	0	0.0%
	Mild	9	100.0%	0	0.0%
	Moderate	11	55.0%	9	45.0%
	Severe	2	13.3%	13	86.7%
Mobility	No Problems	0	0.0%	0	0.0%
	Some Problems	17	89.5%	2	10.5%
	Extreme Problems	5	20.0%	20	80.0%
Self-Care	No Problems	0	0.0%	0	0.0%
	Some Problems	15	62.5%	9	37.5%
	Extreme Problems	7	35.0%	13	65.0%
Usual activities	No Problems	0	0.0%	0	0.0%
	Some Problems	10	55.6%	8	44.4%
	Extreme Problems	12	46.2%	14	53.8%
Pain/Discomfort	No pain or discomfort	0	0.0%	0	0.0%
	Moderate pain or discomfort	21	91.3%	2	8.7%
	Extreme pain or discomfort	1	4.8%	20	95.2%
Anxiety/Depression	Not Anxious or depressed	6	100.0%	0	0.0%
	Moderately anxious or depressed	6	40.0%	9	60.0%
	Extremely anxious or depressed	10	43.5%	13	56.5%

Group A had a higher capacity to report pain and discomfort, with 11/22 (61.5%) reporting no discomfort or pain, compared to Group B, which reported severe pain or discomfort 100%. Furthermore, the anxiety and depression were significantly higher in Group A than in Group B with (15/22) 88.2 per cent of Group A reporting no symptoms and 100% of Group B showing severe anxiety or depression leading to a reduced quality of life among Group B (Table 3). Percentages reaching 100% shows the use of categorical scales in which all patients in a particular group had same response category at that respective time point. Group A had better performance in walking distance, with 401-500 meters or more, and Group B was limited to shorter distances. Group A reported more favorable experiences despite fatigue, and all participants reported fatigue as mild or none. In contrast, most Group B participants (95% of the total) reported severe fatigue. DCB treatment in Group A showed better physical and psychological results than balloon angioplasty in Group B.

Group A: The results of renarrowing did not show any meaningful difference between the 12-month and 24-month outcomes ($M = -0.9817$, $SD = 3.1701$, $t(21) = -1.452$, $p = .161$), which indicated that there was no significant difference in renarrowing between 12 and 24 months.

The VAS score, which assesses pain intensity, decreased significantly from the 12th month ($M = 5.55$, $SD = 0.800$) to the 24th month ($M = 3.45$, $SD = 0.963$). The average of the difference was e2.091e ($SD = 0.811$, $t\ 21 = 12.090$, $p < .001$). This shows that the level of pain in Group A declines significantly over time. The Total Midline - Total end line score revealed a significant decrease ($M = 5.045$, $SD = 1.397$, $t(21) = 16.946$, $p < .001$), indicating a significant improvement in the overall outcome for Group A participants.

Table 3: Post treatment outcome of group A (DCB) and group B (Balloon Angioplasty) at end line (24 months)

Post treatment outcomes	Result	Groups			
		Group A		Group B	
		Count	Row N %	Count	Row N %
Leg swelling post-treatment at baseline	None	0	0.0%	0	0.0%
	Mild	6	60.0%	4	40.0%
	Moderate	13	61.9%	8	38.1%
	Severe	3	23.1%	10	76.9%
Leg swelling at the 24th month	None	16	72.7%	6	27.3%
	Mild	6	46.2%	7	53.8%
	Moderate	0	0.0%	7	100.0%
	Severe	0	0.0%	0	0.0%
Pain severity at the 24th month	None	13	92.9%	1	7.1%
	Mild	9	56.3%	7	43.8%
	Moderate	0	0.0%	12	100.0%
	Severe	0	0.0%	0	0.0%
Redness at the 24th month	Yes	2	11.1%	16	88.9%
	No	20	83.3%	4	16.7%
Mobility	No problems	20	80.0%	5	20.0%
	Some problems	2	11.8%	15	88.2%
	Extreme problems	0	0.0%	0	0.0%
Self-care	No problems	18	100.0%	0	0.0%
	Some problems	4	16.7%	20	83.3%
	Extreme problems	0	0.0%	0	0.0%
Usual activities	No problems	21	91.3%	2	8.7%
	Some problems	1	5.3%	18	94.7%
	Extreme problems	0	0.0%	0	0.0%
Pain/discomfort	No pain or discomfort	8	61.5%	5	38.5%
	Moderate pain or discomfort	14	66.7%	7	33.3%
	Extreme pain or discomfort	0	0.0%	8	100.0%
Anxiety/ depression	Not anxious or depressed	15	88.2%	2	11.8%
	Moderately anxious or depressed	7	38.9%	11	61.1%
	Extremely anxious or depressed	0	0.0%	7	100.0%
Walk distance at 24th months (m)	100-200m	0	0.0%	4	100.0%
	201-300m	0	0.0%	13	100.0%
	301-400m	3	50.0%	3	50.0%
	401-500m	14	100.0%	0	0.0%
	>500m	5	71.4%	2	28.6%
Fatigue at 24th month	None	7	100.0%	0	0.0%
	Mild	6	100.0%	0	0.0%
	Moderate	8	88.9%	1	11.1%
	Severe	1	5.0%	19	95.0%

Renarrowing has increased from a mean of 13.1±5.2% at 12 months to 24.2±12.5% at 24 months in Group B (p=0.002) (Table 4). The average difference was estimated at -11.115 (SD = 14.2246); t = -3.494, p = .002. The VAS score showed a significant but more modest improvement than in Group A, as it changed from the 12th month (M = 6.82, SD = 1.435) to the 24th month (M = 5.68, SD = 1.887). This gave a mean difference of e1.136e (SD = 2.077, t(21) = 2.566, p =.018). This means there was a reduction in pain, but compared with Group A, the effect was not as substantial. The Total Midline - Total end-line score also showed a significant improvement (M = 3.450, SD = 1.605, t(19) = 9.612, p =.001), indicating improved performance; however, it was not as significant as that of Group A. Overall, both groups showed pain relief and improvements in outcomes, but Group A showed stronger progress, especially in pain relief. Group B showed an increase in deterioration and re-narrowing, indicating a high risk of recurrence. The results show differences in recovery patterns, and Group A is expected to achieve the best long-term results. The Quality of Life (QoL) scores at 12 and 24 months were compared and showed that Group A (DCB) was superior to Group B (balloon angioplasty), demonstrating the advantage of DCB treatment (Table 5). Group A (DCB) showed improvements in mobility, self-care, routine activities, pain/discomfort, and anxiety/depression with significant but high levels of symptom alleviation at the 12-month mark.

Table 4: Paired sample tests of renarrowing, vas score, midline and end line in group A (DCB) and group B (Balloon Angioplasty).

Paired samples statistics

Groups			Mean	N	Std. deviation	Std. error mean
Group A	Pair 1	Renarrowing At 12 months	8.19405	22	4.227284	.901260
		Renarrowing At 24 months	9.17571	22	4.621428	.985292
	Pair 2	VAS score At 12th Month (Rate the pain from 1 To 10)	5.55	22	.800	.171
		VAS score At 24th month (Rate the pain from 1 To 10)	3.45	22	.963	.205
	Pair 3	Total midline	11.32	22	1.171	.250
		Total endline	6.27	22	.703	.150
Group B	Pair 1	Renarrowing At 12 months	13.06500	20	5.211755	1.165384
		Renarrowing At 24 months	24.18000	20	12.466190	2.787525
	Pair 2	VAS score At 12th month (Rate the pain from 1 To 10)	6.82	22	1.435	.306
		VAS score At 24th month (Rate the pain from 1 To 10)	5.68	22	1.887	.402
	Pair 3	Total midline	13.50	20	1.051	.235
		Total end line	10.05	20	1.234	.276

Paired sample T- test

Groups			Paired differences					t	df	Sig. (2-tailed)
			Mean	Std. deviation	Std. Error mean	95% confidence interval of the difference				
						Lower	Lower			
Group A	Pair 1	Renarrowing at 12 months - Renarrowing at 24 months	-0.981664	3.170124	0.675873	-2.387218	0.423891	-1.452	21	0.161
	Pair 2	VAS score at 12th month (Rate the pain from 1 to 10) - VAS score at 24th month (Rate the pain from 1 to 10)	2.091	0.811	0.173	1.731	2.451	12.090	21	0.000
	Pair 3	Total midline - Total endline	5.045	1.397	0.298	4.426	5.665	16.946	21	0.000
Group B	Pair 1	Renarrowing at 12 months - Renarrowing at 24 months	-11.115000	14.224637	3.180725	-17.772335	-4.457665	-3.494	19	0.002
	Pair 2	VAS score at 12th month (Rate the pain from 1 to 10) - VAS score at 24th month (Rate the pain from 1 To 10)	1.136	2.077	0.443	0.215	2.057	2.566	21	0.018
	Pair 3	Total midline - Total end line	3.450	1.605	0.359	2.699	4.201	9.612	19	0.000

To test the temporal changes, a paired samples t-test was conducted separately on Group A and Group B.

Table 5: Comparing the midline and end-line quality-of-life scores of group A (DCB) with group B (Balloon Angioplasty)

	Group A (12 months)	Group B (12 months)	Group A (24 months)	Group B (24 months)
Mobility	2.23	2.91	1.09	1.59
Self-care	2.32	2.59	1.18	1.82
Usual activities	2.55	2.64	1.05	1.73
Pain/Discomfort	2.05	2.91	1.64	1.95
Anxiety/Depression	2.18	2.59	1.32	2.05
QoL	11.32	13.64	6.27	9.14
VAS score	5.55	6.82	3.45	5.68

Group B (balloon angioplasty) continued to face significant problems, especially in terms of mobility and pain control. The Total QoL level in Group A was lower, indicating fewer problems, whereas Group B had a higher score, indicating more health-related issues. In addition, the VAS scores in Group A were lower, indicating lower pain levels. These results support the claim that DCB angioplasty has a significant positive effect on physical and psychological outcomes, whereas balloon angioplasty has better long-term results.

Correlation analysis was conducted as an exploratory method due to the limited sample size, and it was intended to identify respective associations rather than infer causal relationships. The Pearson correlation analysis was used to test the relationships among variables such as age, gender, hypertension, diabetes, smoking, infection, functional impairment, hospitalization, and mortality. The analysis has identified several significant findings. Infection was found to have a moderate positive relationship with functional impairment ($r = 0.438$, $p = 0.003$), which indicated that people with infections are more likely to experience functional impairment. Also, it was found that hospitalization and functional impairment have a significant positive correlation ($r = 0.478$, $p = 0.001$), which implies that the functionally impaired people are more likely to be hospitalized (Table 6).

Overall mortality rates for both groups were very low for the follow-up period. The mortality rate for Group A was 9.1% (2/22 patients in Group A died), while that of Group B (conventional balloon angioplasty) was significantly higher at 18.2% (4/22 patients in Group B died). In both groups, the majority of deaths resulted from severe infections, which supports previous evidence that there is a positive correlation between severe infections and high rates of mortality ($r = 0.570$, $p < 0.001$).

An overall examination showed a strong relationship between mortality and infection ($r = 0.570$, $p < 0.001$), functional impairment ($r = 0.890$, $p < 0.001$), and hospitalization ($r = 0.602$, $p < 0.001$). This shows that patients who suffer infections, those with functional impairment, or those being hospitalized are at a high risk of death. Smoking was also weakly correlated with hospitalization, with $r = 0.283$ ($p = 0.063$), and therefore was not statistically significant at the 0.05 level.

Finally, hypertension and diabetes did not show any meaningful correlation to hospitalization, nor did age and gender. This observation suggests that the isolated effects of these factors are unlikely to be good predictors of outcomes in this dataset. The results highlight the significant influence of infection, functional impairment, and hospitalization on high mortality rates. Functional impairment considerably affected hospitalization rates and, and there were no significant relationships between age, gender, hypertension, diabetes, and smoking with mortality.

DISCUSSION

This research indicates that using DCB during angioplasty for patients with Iliofemoral venous ISR may lead to enhanced mid- to long-term venous patency and improved functional outcomes. Patients receiving DCB treatment exhibit lower rates of re-narrowing and have demonstrated trend improvements in symptoms, such as decreased pain, increased mobility, and better quality-of-life scores (Begum *et al*., 2019). Thus, it appears that local delivery of antiproliferative drugs may provide improved performance of venous stent technology. Nevertheless, caution is warranted regarding the extent and durability of this benefit, given limitations in the study design.

The rationale for the benefit of DCB therapy is based on biology. Neointimal hyperplasia is a major factor in the development of ISR (Lei *et al*., 2024). Antiproliferative agents, such as paclitaxel, may reduce smooth muscle cell proliferation and suppress inflammatory responses after endovascular injury (Nakamura *et al*., 2024). This mechanism has been well studied in the context of treating arterial ISR, but there is still less certainty about its application to venous ISR. Understanding the differences between arterial and venous vessels in terms of biology and flow dynamics will require further investigation before conclusions can be drawn about the transferability of findings from arterial studies to venous ISR (Xue *et al*., 2018). In the DCB group, rates of restenosis remained relatively consistent at follow-up intervals.

Table 6: Exploratory correlation between baseline characteristics and adverse events.

		Age	Gender	Hypertension	Diabetes	Smoking	Infection	Functional impairment	Hospitalization	Mortality
Age	Pearson Correlation	--								
Gender	Pearson Correlation	-0.062	--							
	Sig. (2-tailed)	0.689								
Hypertension	Pearson Correlation	0.088	-0.036	--						
	Sig. (2-tailed)	0.570	0.818							
Diabetes	Pearson Correlation	0.100	-0.134	-0.048	--					
	Sig. (2-tailed)	0.520	0.387	0.759						
Smoking	Pearson Correlation	-0.002	0.026	0.009	0.212	--				
	Sig. (2-tailed)	0.990	0.868	0.953	0.167					
Infection	Pearson Correlation	-0.183	0.043	0.057	-0.027	0.110	--			
	Sig. (2-tailed)	0.233	0.783	0.713	0.864	0.475				
Functional impairment	Pearson Correlation	0.134	0.173	0.204	0.097	0.085	.438**	--		
	Sig. (2-tailed)	0.386	0.263	0.184	0.531	0.585	0.003			
Hospitalization	Pearson Correlation	0.026	0.014	-0.023	0.146	0.283	.365*	.478**	--	
	Sig. (2-tailed)	0.867	0.926	0.882	0.344	0.063	0.015	0.001		
Mortality	Pearson Correlation	0.038	0.199	0.149	0.149	0.062	.570**	.890**	.602**	--
	Sig. (2-tailed)	0.807	0.195	0.334	0.334	0.690	0.000	0.000	0.000	
	N	44	44	44	44	44	44	44	44	44

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

In contrast, the conventional balloon angioplasty group experienced a significantly greater rate of re-narrowing than the DCB group. This indicates that drug-based local therapy may provide a lasting reduction in the occurrence of restenosis (Abdul *et al*., 2020; Huang *et al*., 2025). However, results also indicate that some patients treated with DCBs experience recurrent stenosis.

Restenosis rates were relatively balanced at 12 and 24 months of follow-up in the DCB group, indicating that paclitaxel-coated balloons continue to reduce venous wall hyperplasia and endothelial cell growth (Bhandari *et al*., 2025). However, the expected high prevalence of restenosis in the balloon angioplasty group was observed, highlighting the inefficacy of traditional ballooning in preventing recurrent occlusions. These findings are in line with other studies, such as one evaluating the use of drug-coated balloons in arterial restenosis, which found that paclitaxel coating reduces the number of repeat procedures in a significant way (Navarese *et al*., 2013; Xue *et al*., 2020). It has been observed that stenosis treated with balloon angioplasty is prone to restenosis (Abdul *et al*., 2020).

The main goal of this study was to evaluate adverse events, especially the highest correlation between restenosis, functional impairment, and hospitalization. The results showed that there is a close relationship between severe restenosis and a higher level of hospitalization, high morbidity, and mortality risks in the long run. This supports the fact that in-stent restenosis can lead to recurrence of cardiovascular adverse events and in some instances, sudden cardiac death (Zhang *et al*., 2020). There is also evidence to support this, as recurrent venous obstruction is associated with post-thrombotic syndrome, chronic venous insufficiency, and venous ulceration, thus increasing the burden on healthcare, which explains the consistency of this result (Kirkilesis *et al*., 2020; Deng *et al*., 2020). Since DCB therapy has shown lower rates of restenosis, wider use of this therapy may reduce hospital admissions and improve patient outcomes with IFDVT (Haraguchi *et al*., 2024).

Reports of reduced pain and improved functional ability were also more common among patients in the DCB group than in the standard balloon angioplasty group. The improvement in venous patency may explain this difference; however, since the pain, mobility, and psychosocial outcomes were measured using patient-reported tools, these are subjective measures that might be affected by the patient's expectations, baseline health condition, and psychosocial environment. Therefore, it is reasonable to interpret these outcomes as high-level evidence supporting, rather than proving, that DCB technology provides a superior functional outcome compared to standard balloon angioplasty techniques (Murphy *et al*., 2022).

There was a difference in baseline characteristics between the two groups, including the proportion of males to females and the frequency of hypertension and diabetes, which are potential confounding factors. The groups also did not receive randomized treatment allocation, as patients were assigned to treatment based on the hospital where they presented. The use of this method of treatment allocation could potentially have introduced center-specific treatment effects that differ due to procedural techniques, post-intervention care, or selection biases. These reasons all contribute to the difficulties in making causal inferences from comparisons between the two groups.

There were no obvious safety issues associated with the use of DCBs in this clinical study, and the overall safety of DCBs appears acceptable, with the exception of an apparent lack of increased incidence of major adverse drug events as a result of DCB use. However, the small sample size and limited power in this study do not allow us to draw valid conclusions about infrequent, long-term safety outcomes associated with DCB use. There continues to be significant debate regarding paclitaxel-containing devices, and therefore, the ongoing need for further surveillance of DCBs and large, methodologically sound studies is essential (Liu *et al*., 2022).

Sirolimus-coated balloons might be viable alternatives, based on a different form of action to prevent cell proliferation, but were not studied as part of this trial. Thus, comments on current and future technologies using sirolimus should be considered speculative and applicable only to future research topics (Kleber *et al*., 2013). No adjustment for multiple comparisons was applied in the study, these findings should be interpreted with care. The current study confirms this claim by showing that DCB therapy is effective not only in preventing restenosis but also in reducing the risk of serious complications.

Limitations

Even though the results strongly support the use of DCB therapy as the best option to treat ISR in patients with IFDVT, some limitations should be considered. The study's sample size was limited to detect statistically significant differences, and the non-randomized group allocation will probably limit the generalizability of the results to other patient populations. In addition, although paclitaxel-coated balloons showed excellent performance, further studies should focus on other drug coatings, including sirolimus, which could be helpful in the treatment of arterial in-stent restenosis and venous use as well (Mori *et al*., 2021). The level of patient compliance with anticoagulant drugs after surgery is a significant variable that might have contributed to outcomes but has not been studied and should be considered in future studies (Pouncey *et al*., 2022).

CONCLUSION

The current study suggests that DCB treatment is notably more effective than standard balloon angioplasty for treating ISR in patients with IFDVT. The results of the present research support the proposed method of integrating DCB therapy into the usual clinical practice for ISR management of patients with IFDVT. DCB therapy is a positive method for the management of venous stenosis, reducing restenosis, alleviating pain, improving mobility, and improving patients' quality of life. Such findings require confirmation through a large, multicenter, randomized controlled trial, with the introduction of additional optimization methods to improve the long-term outcomes of patients with IFDVT. The increased morbidity of repeated venous blockage implies that the wide use of DCB therapy would transform the management of post-stenting care in the clinical and economic aspects of the world.

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Author's contributions
The author has been the key contributor to the creation of this research by way of the ideas and overall design. Orhan carried out both data collection and clinical assessment, and analyzed and interpreted the data. The first draft of the manuscript was also written by Orhan and included critical evaluations of the manuscript's significant intellectual and pharmaceutical content.

Data availability statement
All data generated or analysed during this study are included in this published article and its supplementary information files.

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Ethical approval
This study was approved by the Acıbadem University Istanbul Turkiye Ethical Approval Committe, (Approval No. 14.11.2023-779320). Written consent from participants were collected.

Conflicts of interest
The authors declare that they have no conflicts of interest related to this work.

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