

A Meta-Analysis Study on Internal Compression Therapy (ICT) in Deep Venous Insufficiency Therapy

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Abstract

Purpose: To evaluate the effectiveness and safety of the new internal compression therapy (ICT) system in deep vein insufficiency (DVI). Surgical treatments are impractical, and the success rate is lower in the treatment of deep vein insufficiency (DVI). We have developed a new technology called the ICT valve leak sealer reconstruction system (Invamed, Ankara/Turkey) for the treatment of primary DVI by applying internal compression.

Methods: Three research articles evaluated in this meta-analysis study, searched PubMed and Scholar Google using the words "internal compression therapy" and deep vein insufficiency therapy. Original full text articles on the ICT System for the treatment of DVI considered eligible studies published until July 2022.

Results: In the included studies, the procedure time was 11-23 minutes. At the end of one year or more of follow-up, the anatomical success rate was greater than 92%. The diameters of the veins decreased significantly. Venous Clinical Severity Score (VCSS) and Quality of Life (QoL) scores have improved at statistically significant rates.

Conclusion: ICT is a minimally invasive, fast, safe, and effective percutaneous method for the treatment of patients with DVI. The procedure applied in outpatient conditions and improves the patient's clinic in a short time.

Keywords: Internal Compression Therapy (ICT), Deep Vein Insufficiency (DVI), Cyanoacrylate

1. Introduction

Chronic venous insufficiency (CVI) is a major public health problem, as it affects approximately 30% of the general population and gradually deteriorates the patient's quality of life [1,2]. While it most commonly affects the superficial veins, it also affects the deep veins or perforating veins, and it may occur as combinations of these insufficiencies [3]. Venous insufficiency is seen primarily in the lower extremities, with the incidence of superficial and deep venous insufficiency (DVI) in the lower extremities being 90% and 30%, respectively [4].

In the treatment of CVI, the objective is to eliminate or at least reduce reflux in venous insufficiency, which results in health costs and loss of work force by causing infection, excessive swelling, soft tissue ulceration, and deep vein thrombosis (DVT) [5]. In the treatment of superficial venous insufficiency (SVI), there are different treatment options in addition to conservative and surgical treatments. Endovenous thermal ablations (EVTA) such as endovenous laser ablation (EVLA) and radiofrequency ablation (RFA), and more recently, nonthermal nontumescent (NTNT) applications such as catheter-guided cyanoacrylate ad-

hesive closure (CAC) systems and mechanochemical ablation techniques have achieved significant successes in the treatment of SVI [6-10].

However, none of the therapeutic modalities is satisfactory and there is still a large gap in the management of DVI [4]. Medical compression therapies remain the cornerstone of conservative management of DVI due to the less successful outcomes and the impracticality of the surgical treatments [11-17]. In fact, external compression of the leg prevents or reduces blood backflow by reducing the diameter of the vein lumen and improving venous calf pump function [11,18]. This reduction in reflux prevents the occurrence of DVT, post-thrombotic syndrome, and leg ulcers [19-21]. In this regard, different compression modalities continue to be tried as treatment options to improve the condition of patients with lower leg deep vein insufficiency [22,23].

In this context mentioned, we (Invamed RD Global, Ankara, Turkey) have developed a new technology called the ICT Valvular Leak Sealer Reconstruction System for the treatment of primary DVI by applying internal compression [5,24,25]. In this

system, a mixture of hyaluronic acid and hard n-butyl-2-cyanoacrylate (NBCA) gel is administered to the outer surface of the vein using the ICT device at the insufficient valve level between the deep vein and the muscle fascia. The mixture of hyaluronic acid and NBCA adheres around the valves and forms an exoskeleton with a nonabsorbable biopolymer around the vessel wall. Thus, this device allows the valves to approach each other by reducing the diameter of the vein and increasing their functions. This current meta-analysis study aimed to assess the efficacy and safety of ICT in the treatment of deep vein insufficiency of the lower extremities.

2. Methods

2.1. Study Design and Database Search

This meta-analysis study conducted in accordance with the guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [26]. We searched PubMed and Scholar Google using the words "internal compression therapy" and deep vein insufficiency therapy. Original full text articles on studies using the ICT valve leak sealer reconstruction system for the treatment of DVI considered eligible studies that published until July 2022 (Figure 1).

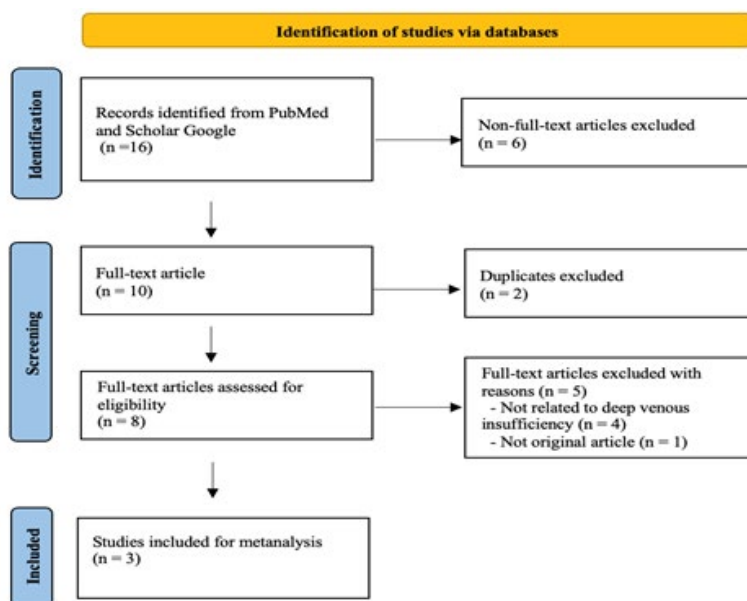


Figure 1: The PRISMA Diagram Regarding to Study Design and Database Searching

2.2. Data Assessment

Two independent commentators (N.A., E.A.) evaluated the data. In case of any disagreement, it was resolved by negotiating with the article's author (R.D).

2.3. Data Analysis

The mean difference (MD) used as the effect size of the venous clinical severity scores (VCSS) and the mean values of the measurement of the vein diameter before and after the procedure, both indicators of treatment success. The meta-analysis of these difference values, fixed effects, random effects subtitled weight coefficients, mean difference, and 95% confidence interval (CI) values were presented in Tables and Figures. To determine whether the studies included in the meta-analysis have publication bias, primarily the funnel plot used and then the Begg and Mazumdar rank correlation statistics were calculated. A for-

est chart with 95% CI used to graphically display the estimated weight results from the studies.

The Chi-square heterogeneity test with (k-1) degrees of freedom, known as the Cochran Q statistic, used to evaluate heterogeneity. Heterogeneity indicated by I². According to the heterogeneity status, the significance evaluated with the fixed effect and random effect model. If the I² value is less than 25%, it is determined as low heterogeneity, 26-75% moderate and over 75% high heterogeneity. The MedCalc statistical package program (MedCalc Software, Ostend, Belgium) used to evaluate the data.

3. Results

Table 1 shows the distribution of sex and mean age of the patients according to the studies included in the evaluation.

Study Name	Gender (male–female) n (%)	Age Mean ± Standard Deviation
Yavuz et al. [24]	172 (60.2%)–114 (39.8%)	55±13.2
Eroglu et al. [3]	12(40 %)-18(60 %)	40.9 ± 7.6
Tural et al. [11]	4(36.4 %)-7(63.6 %)	54.3±13.7

Table 1: Distribution of the Mean Age and Gender of the Patients Included in the Studies

The representations of funnel plots presented in Table-2 and Figures 2A and B, respectively. As seen in Table 2 in the publication

bias analysis, it was supported that there was no publication bias since the p values were greater than 0.05.

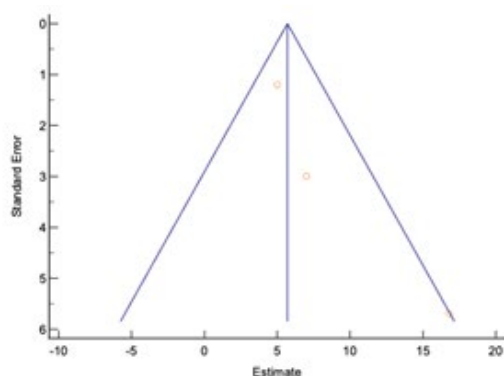
Parameters	Kendall's Tau	p value	Interpretation
VCSS	1.01	0.12	There is no significant bias ($p>0,05$)
Vein Diameter	0.33	0.61	There is no significant bias ($p>0,05$)

*Begg's test

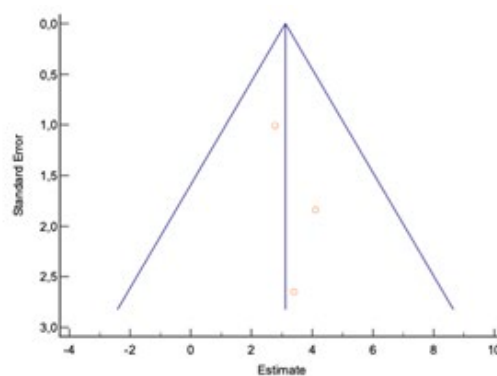
Table 2: Data Analysis of Publication Bias

When the funnel plot graphs in Figures 2A and B examined, it seen that the majority of the article study included in the research is symmetrically distributed. As we see in Table 3, VCSS shows a moderate heterogeneous distribution, and a random ef-

fects model recommended for its evaluation. On the other hand, vein diameters show a homogeneous distribution, and a fixed-effects model recommended for them.



A. Funnel plots for VCSS



B. Funnel plots for vein diameter

Figure 2: Funnel Plots Representation of Publication Bias for VCSS and Vein Diameters

	p value	I^2 (%)	Interpretation
VCSS	0.12	43	It shows a moderate heterogeneous distribution, and a random effects model is recommended.
Vein Diameter	0.82	0	It shows homogeneous distribution, and a fixed effect model is recommended.

I^2 value: <25% low heterogeneity; 26-75% moderate heterogeneity; >75% high heterogeneity

Table 3: Analysis of Heterogeneity

According to the results of the 3 studies included in the study, according to the random effects model, the mean difference of the VCSS values in the pre- and post-procedure periods was 7.3,

while these differences ranged from 2.54 to 12.07 (Table-4, Figure 3A). Because of this evaluation, it was evidence-based that there was a difference in mean VCSS values ($p<0.01$).

Study	Sample size	MD (95% CI)	z	P	Weight (%)	
					Fixed	Random
Yavuz et al. [24]	286	16.8(5.64-27.96)	5.218	<0.001	3.68	14.09
Eroglu et al. [3]	30	5(2.65-7.35)			83.01	53.94
Tural et al. [11]	11	7(1.13-12.87)			13.31	31.97
Total (fixed effects)	327	5.7(3.56-7.84)	5.218	<0.001	100	100
Total (random effects)	327	7.3(2.54-12.07)	3.003	0.003	100	100

MD: mean difference

Table 4: Meta-Analysis of the Mean Difference in VCSS between the Pre-And-Post-Procedure Periods

According to the results of the 3 studies included in the study, according to the fixed effects model, the mean difference of the diameter values of the vein in the pre and post procedure periods was 3.12, while these differences ranged from 1.47 to

4.76 (Table 5, Figure 3B). Because of this evaluation, it was evidence-based that there was a difference in the mean vein diameter values ($p<0.01$).

Study	Sample size	MD (95% CI)	z	P	Weight (%)	
					Fixed	Random
Yavuz et al. [24]	286	3.4(1.78-8.56)			10.05	10.05
Eroglu et al. [3]	30	2.78(0.81-4.76)			69.17	69.17
Tural et al. [11]	11	4.1(0.49-7.71)			20.78	20.78
Total (fixed effects)	327	3.12(1.47-4.76)	3.716	<0.001	100	100
Total (random effects)	327	3.12(1.47-4.76)	3.716	<0.001	100	100

Table 5: Meta-Analysis of the Mean Difference in Vein Diameters between the Pre-And-Post-Procedure Periods

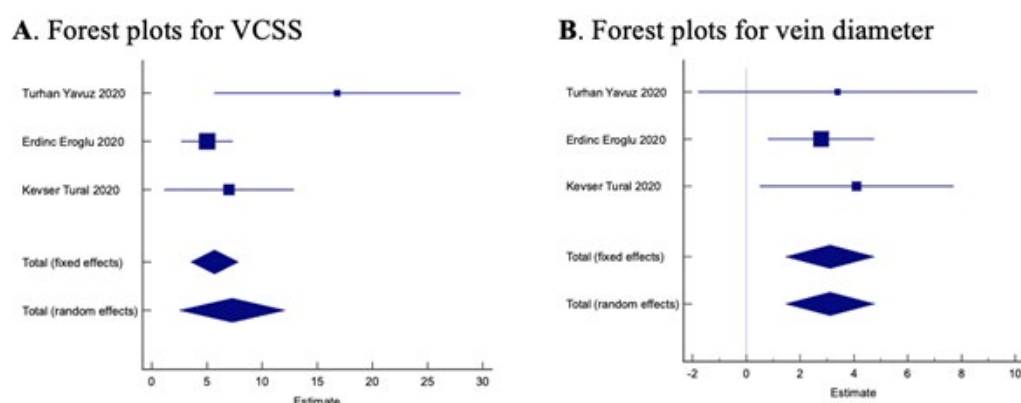


Figure 3: Forest Plot for VCSS and Vein Diameters

4. Discussion

DVI, a deficiency in the transfer of blood in the deep venous system of the lower extremities to the caval system, may occur as a complication of proximal vascular obstruction or may be present in the primary form due to valve failure or congenital valve malformation [3]. Despite the various techniques applied, mainly surgical, the huge gap in DVI treatment remains a major challenge. Generally, medical compression therapies have an important role for its management [11,17].

In this context, the ICT (Figure 4) method, the application procedure of which is detailed in the included studies, has some ad-

vantages over the traditional surgical treatment of DVI. Conventional surgical treatments carry certain risks, such as deep vein thrombosis (DVT), surgical infection, postoperative hospitalization necessity and cosmetic concerns [13-15]. However, ICT is easy to apply and can be applied in outpatient settings. Patients who underwent ICT can usually return home on the same day. In most cases, no antibiotic or anticoagulant treatment [11]. Furthermore, conventional surgical treatments for DVI are carried out primarily to provide ulcer regression in patients with the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) score 5-6. Although ICT can be applied to patients with CEAP score 3-4, which allows earlier intervention [14,24].



Figure 4: Internal Compression Treatment (ICT) Valvular Leak Sealer Reconstruction Device and Delivery System

The effectiveness of the method used in the treatment of DVI is evaluated according to several criteria such as changes between CEAP, VCSS and QoL of patients, reflux times and vein diameters before and after the procedure [6,7,14,17,27]. All patients had preoperative CEAP scores above C3 in the three studies included in the current study. At one year or more of follow-up, the overall success rate of the ICT method applied to 317 patients with DVI was greater than 92%. No significant reported procedure-related morbidity or mortality was observed. The processing time has been reported to be as short as 11-23 minutes. Eroglu et al. also reported that quality of life (QoL) scores improved statistically in the post-procedure period. All three studies reported that reflux improved and valvular coaptation resulted in success following the procedure by duplex ultrasound scanning (DUS).

Although retrospective design of the current studies included in the investigation, the bias analysis supported that there was no publication bias for any of the articles, since the p-values were greater than 0.05 (Table 2). Studies are mostly symmetrically distributed in funnel plot graphs, which is related to bias evaluation for scientific research (Figure 2). When evaluating the heterogeneity test that informs the proportion of variance in the observed effect, VCSS shows a moderate heterogeneous distribution, while vein diameters show a homogeneous distribution (Table 3).

The mean difference between the VCSS values before and after the procedure was observed to be 7.3 and was evidence-based with $p < 0.01$ (Table-4, Figure-3A). The mean difference for vein diameters was 3.12 and was evidence-based with $p < 0.01$ (Table-5, Figure-3B). These observations strongly encourage the application of ICT in DVI treatments. In this system, the hyaluronic acid in the mixture strengthens the connective tissue around the vessel, while the cyanoacrylate solidifies with polymerization and acts as an exoskeleton [28]. This system helps to restore the venous valve function by reducing the lumen diameter of the vein, which allows the valvular re-coaptation. In some

experimental studies, the compression effect of ICT application on the vessel has been reported to continue and cyanoacrylate is as durable as sutures [24]. Despite the durability of cyanoacrylate, no serious adverse effects of ICT application were reported during short- or mid-term follow-up, as well as the experimental studies [3,5,11,24,28]. To date, toxicological, carcinogenic, and mutagenic effects against hyaluronic acid and cyanoacrylate have also not been reported in vascular use [24]. The findings indicate that ICT is effective, safe, and even user-friendly.

Unlike other investigators used for DVI, Bolat et al evaluated the efficacy of the ICT method in patients with chronic superficial venous insufficiency [5]. They reported that reflux time and VCSS improved significantly. Great saphenous veins have even been reported to be effectively and safely treated with micro-foam sclerotherapy without postoperative symptoms when the lumen of the vessel is reduced by perivenous injection of hyaluronan gel injection [29].

In an experimental porcine model, Yasim et al, observed increases both perivascular collagen I subtype by immunohistochemical staining and connective tissue growth factor (CTGF) mRNA expressions by genetic analysis [28].

4.1. Limitation of the Study

Although the preliminary results of the ICT technique show that it is successful, it has some limitations. Since it is a new method, there are only a few studies on the results of this treatment method. Another limitation is the lack of long-term studies for the same reason.

5. Concluding Remark

The ICT shows promise for the treatment of patients with deep vein insufficiency. It is a minimally invasive, fast, safe, and effective percutaneous method. This procedure can be performed in outpatient clinics due to its ease of application and early recovery time. It improves the patient's clinic in a short time, not only in patients with deep venous insufficiency, but also in pa-

tients with superficial venous insufficiency.

Ethics Approval Statement

This manuscript, which is a review article, does not include studies with human or animal participants. Institutional review board approval was therefore not required.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Competing Interest

RD is president of Invamed RD Global Company.

Author's Contributions

The concept, design and writing of the research was done by Rasit Dinc. Rasit Dinc read and approved final version of the article.

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