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Review

A Systematic Review and Meta-analysis of Randomised Controlled Trials Comparing Endovenous Ablation and Surgical Intervention in Patients with Varicose Vein CME

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WHAT THIS PAPER ADDS

- A systematic review and meta-analysis of randomised controlled trials was conducted, which aim to compare clinical outcomes between concurrent minimally invasive procedures and surgery for treating varicose veins. All relevant randomised controlled trials published up to August 2011 were included. Treatment comparisons were endovenous laser ablation, radiofrequency ablation, ultrasound-guided foam sclerotherapy and surgery. Clinical relevant outcomes, that is, primary failure, clinical recurrence, post-operative complications, pain and return to normal activities were covered. Evidence and recommendation suggested from our study were provided.

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ABSTRACT

Objectives and design: A systematic review and meta-analysis was conducted to compare clinical outcomes between endovenous laser ablation (EVLA), radiofrequency ablation (RFA), ultrasound-guided foam sclerotherapy (UGFS) and surgery.
Methods: We searched MEDLINE and Scopus from 2000 to August 2011 to identify randomised controlled trials (RCTs) comparing EVLA, RFA, UGFS, and surgery or combinations of these for treatment of varicoses. Differences in clinical outcomes were expressed as pooled risk ratio and unstandardised mean difference for dichotomous and continuous outcomes, respectively. Methodological quality was assessed using Cochrane tools.
Results: Twenty-eight RCTs were included. The primary failure and clinical recurrences were not significantly different between EVLA and RFA versus surgery with the pooled RR of 1.5 (95%CI:0.7, 3.0) and 1.3 (95%CI:0.7, 2.4) respectively for primary failure, and, 0.6 (95%CI:0.3, 1.1) and 0.9 (95%CI:0.6, 1.4) respectively for clinical recurrences. The endovenous techniques had advantages over surgery in lowering wound infections (RR = 0.3 (95%CI:0.1, 0.8) for EVLA), haematoma (RR = 0.5 (95%CI:0.3, 0.8) and 0.4 (95%CI:0.1, 0.8) for EVLA and RFA), and return to normal activities or work (mean differences = −4.9 days (95%CI: −7.1,−2.7) for RFA).
Conclusions: The primary failure and recurrence in EVLA and RFA were non-significantly different compared with surgery. However, they had lower haematoma, less wound infection, less pain and quicker return to normal activities.

Minimally invasive endovenous procedures (MIEPs) have been recently introduced for treating varicose veins to reduce post-operative complications, speed recovery and improve quality of life (QOL) compared to standard surgery.[1–3] These methods have been

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enthusiastically adopted (i.e., ultrasound-guided foam sclerotherapy (UGFS), radiofrequency ablation (RFA), and endovenous laser ablation (EVLA)), with less surgery and doubling of endovenous procedures during 2007–2008 in the UK.[4]

Although previous systematic reviews[1–3,5,6] favoured MIEPs, that is, similar efficacies but less complications, and shorter time to work, these results may bias since pooling effects were mainly based on observation studies or mixed with randomised controlled trials (RCTs). Some RCTs have been later published.[7–17] We therefore conducted a systematic review and meta-analysis solely of RCTs comparing all relevant outcomes including efficacies (i.e., primary failure and clinical recurrence), postoperative complications (i.e., wound infection, paresthesia, superficial thrombophlebitis, haematoma and ecchymosis), postoperative pain, time return to normal activities or work and QOL between these MIEPs and surgery and between MIEPs themselves.

Methods

Search strategy

We searched in MEDLINE and Scopus from 2000 to 20 August 2011. Search terms were ('varicose veins'[Mesh], 'saphenous vein'[Mesh], varicose and saphenous), (radiofrequency, RFA, VNUS, 'endovenous laser', EVLT, EVLA, sclerotherapy[Mesh], 'foam sclerotherapy', microfoam, stripping and sapheno-femoral ligation) and (obliteration, occlusion, recurrence, recurrent, recanalisation, neovascularisation, reflux, pain, 'return to normal activities', 'return to work', haematoma, paresthesia, 'nerve injury', 'wound infection', deep vein thrombosis (DVT) and thromboembolism). Reference lists of previous meta-analyses and all eligible papers were also explored.

Study selection

Identified studies were selected by two independent authors (B.S. and P.N.). Disagreements in selection were reviewed and adjudicated by a third party (A.T). For multiple publications, the relevant data were combined as one publication for analysis.

The inclusion criteria for eligible studies were as follows: RCTs, compared outcomes between any of MIEPs and surgery or between MIEPs in patients with great saphenous vein reflux, reported at least one outcome of interest. Studies were excluded if they were not English or had insufficient data.

Data extraction

B.S. and P.N. extracted data using a standardised extraction form. Disagreements were resolved by consensus and checked by A.T. Corresponding authors were contacted twice for missing information. The mean and SD were estimated from median and range for analysis.[18]

Risk of bias assessment

This was done by the same authors (B.S. and P.N.) using the Cochrane tool.[19] These considered six domains as follows: was allocation sequence adequately generated?, was allocation adequately concealed?, was knowledge of the allocated interventions adequately blinded?, were incomplete outcomes adequately addressed?, were reports free from selection?, and was there other source of bias (e.g., imbalance of patient characteristic between groups, protocol violation and the method dealing with data (intention to treat or per-protocol analysis))? Disagreements were resolved by A.T.

Outcomes

The primary outcome was failure to completely abolish reflux in the axial vein. Since MIEPs and surgery use different mechanisms to abolish refluxes, each had different failure definitions. Primary failure was recanalisation diagnosed by duplex scan for MIEPs: incomplete stripping, incomplete removal of an intended vein or recanalisation for surgery. Numbers of primary failure at the end of study were used for analysis. Failure to cannulate or pass a guide wire was considered as technical failure, and not analysed.

Secondary outcomes were clinical recurrences assessed by physical examination (e.g., visible or palpable varicose), venous clinical severity scores (VCSSs), postoperative complications (i.e., wound infection, paresthesia, superficial thrombophlebitis, haematoma or ecchymosis), postoperative pain, time return to normal activities or work and QOL measured by Aberdeen varicose vein severity score (AVVSS). The secondary outcomes were measured at the end of study except complications and pain. Since complications were reported at different follow-up times, the maximum numbers were analysed. If a study reported both time return to normal activities and time to work, the former was used. First recorded and highest pain scores by visual analogue scale (VAS) were used to pool. Only thigh haematomas were pooled.

Statistical analysis

Data were pooled if there were at least three studies for each comparison. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated and pooled. If there was a zero cell, a continuity correction was used. The RRs were pooled using the DerSimonian and Laird if heterogeneity was present, otherwise the inverse variance was applied. For continuous data, mean differences (MDs) along were estimated and pooled using an unstandardised method.

Q test and the degree of heterogeneity (I^2) were used to assess heterogeneity. If either $I^2 \geq 25\%$ or the Q test was significant, the random-effect model was used. Heterogeneity source was explored by fitting covariables (i.e., mean age, follow-up time and wavelength) in a meta-regression. If the co-variable could reduce the I^2, a subgroup or sensitivity analysis of that factor was performed.

Publication bias was assessed by Egger test and funnel plot.[20] The possible cause of asymmetry (e.g., heterogeneity or reporting bias) was explored using a contour-enhanced funnel.[20,21] The meta-trim and fill was applied to impute missing studies. Analyses were performed using STATA version 12.0. A p-value <0.05 was considered statistically significant, except for the heterogeneity test, where a 0.10 was used.

Results

Seventy-seven and 66 RCTs from MEDLINE and Scopus were identified (see Fig. 1). After removing duplicates, 91 studies were screened out, leaving 28 studies for data extraction. Among them, 11 RCTs[7–10,22–28] compared EVLA with surgery, 8 RCTs[11,12,29–34] compared RFA with surgery, 4 RCTs[13,14,35,36] compared UGFS with surgery and 5 RCTs[15–17,37,38] compared RFA with EVLA with one multiple comparison study.[38]

General characteristics of the eligible studies are presented in Table 1. Sample sizes ranged from 16 to 500 patients involving 28–580 limbs. The mean age ranged from 33 to 55 years, and duration of follow-up was 1 week–5 years. Most included patients were within CEAP C2 category. The risk of bias assessment is presented, the highest quality was other source of bias from applying intention to treat analysis (83%), follows with allocation concealment and selective outcome report (78%) whereas the lowest was blinding (43%) (see Table 2).

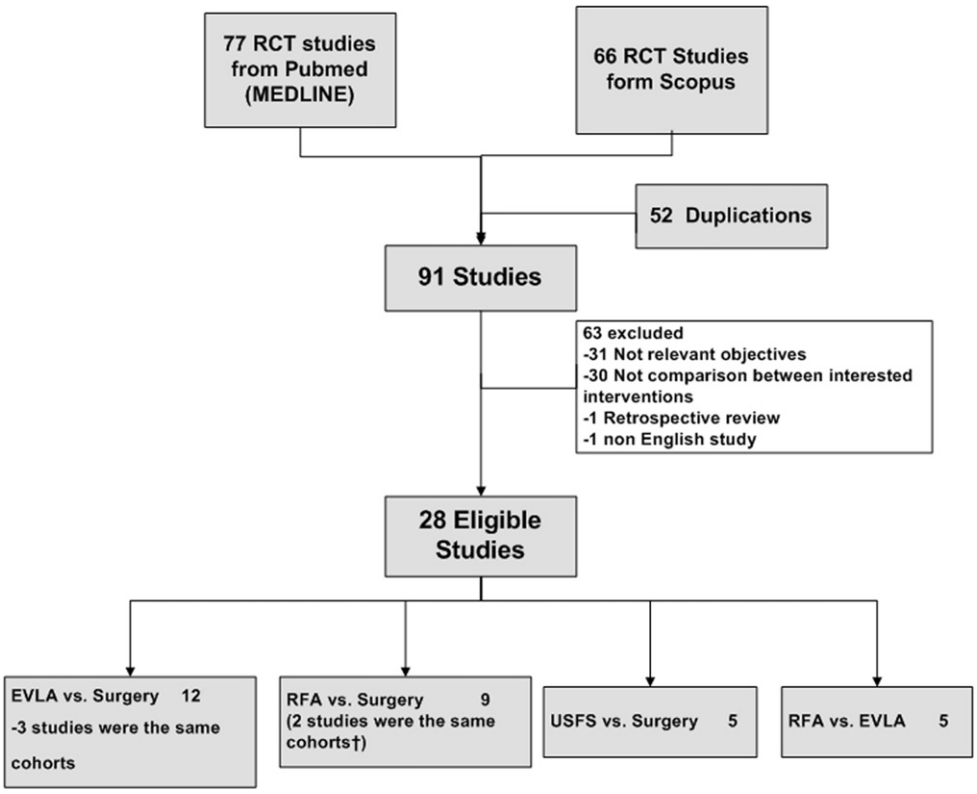

Figure 1. Studies selection flow.

Primary failure

EVLA versus surgery

Nine studies[8–10,22–24,26,28,38] compared primary failure between EVLA and surgery with 712 and 675 limbs, respectively. The heterogeneity was moderate (Q = 11.60, d.f. = 8, p = 0.170, I^2 = 31.1%) with the pooled RR of 1.5 (95%CI:0.7, 3.0) (see Fig. 2A), suggesting that EVLA had 1.5 times higher risk of primary failure than surgery but this was non-significant.

Fitting age, follow-up time, pull-back type and wavelength in the meta-regression suggest that only wavelength might be a source of heterogeneity. Pooling studies using wavelengths of 810[23–26,28] and 980 nm[8–10,38] yielded homogenous results (I^2 = 26.5% and 0%, respectively) with the pooled RR of 0.95 (95% CI:0.39, 2.32) and 2.36 (95% CI:0.96, 5.76), respectively. A subgroup analysis within studies <1- and ≥1-year follow-up resulted in the pooled RR of 3.5 (95% CI:0.7, 17.1) and 1.3 (95% CI:0.5, 3.0), respectively. A sensitivity analysis excluding three studies with different techniques (cryostripping[25] and EVLA with high ligation[24,28]) yielded the pooled RR of 1.3 (95% CI:0.5, 3.0) with I^2 of 44.6%.

RFA versus surgery

Seven studies[11,12,29–32,38] compared primary failure between RFA and surgery (n = 381 vs 378 limbs) with low heterogeneity (Q = 7.46, d.f. = 6, p = 0.281, I^2 = 19.5%) with a pooled RR of 1.3 (95% CI:0.7, 2.4) (see Fig. 2B). ClosureVNUS was applied to all except one study[38] which used ClosureFAST catheter. Excluding this study did not change much results (pooled RR = 1.19, 95% CI:0.57, 2.47).

A sensitivity analysis by excluding the cryostripping study[29] yielded the pooled RR of 1.2 (95% CI:0.5, 2.8). The pooled RRs were 0.9 (95% CI:0.3, 2.8) and 2.0 (95% CI:0.8, 5.1) for studies with <1- and ≥1-year follow-up.

UGFS versus surgery

Five studies[13,14,35,36,38] compared primary failure between UGFS and surgery with 406 and 350 limbs, respectively. The pooled RR was 2.4 (95%CI:1.6, 3.6) with low heterogeneity (Q = 5.17, d.f. = 4, p = 0.270, I^2 = 22.7%) (see Fig. 2C), suggesting that UGFS was about twofold higher risk of failure. Subgroup analysis by follow-up time <1 and ≥1 year yielded the pooled RRs of 1.3 (95% CI:0.6, 2.9) and 3.1 (95% CI:1.8, 5.3), respectively.

RFA versus EVLA

Four studies[15,17,37,38] compared primary failure between RFA and EVLA (n = 304 vs 296 limbs) with moderate heterogeneity (Q = 4.39, d.f. = 3, p = 0.222, I^2 = 31.7%) with the pooled RR of 1.5 (95% CI:0.7, 3.4) (see Fig. 2D). Pooling studies with[17,38] and without[15,37] applying ClosureFast yielded the pooled RR of 0.84 (95% CI:0.30, 2.34) and 2.36 (95% CI:0.55, 10.15), respectively.

Publication bias was assessed and suggested that there was no evidence of publication bias for all comparisons of primary failure except for EVLA versus surgery (see Fig. 3A–D), in which the Egger test and the contour-enhanced funnel plot suggested asymmetry (see Fig. 3A). All except one study fell in the non-significant area, suggesting that the cause of asymmetry may be heterogeneity rather than publication bias. Meta-trim and fill indicated four missing studies, and pooling these with existing nine studies resulted in pooled RR of 1.0 (95% CI:0.4, 2.1).

Clinical recurrence

EVLA versus surgery

Four studies[8,10,23,38] comparing clinical recurrences between EVLA and surgery were pooled (n = 395 and 397 limbs) with moderate heterogeneity (Q = 6.63, d.f. = 3, p = 0.085, I^2 = 54.8%) (see Fig. 4A). The pooled RR was 0.6 (95% CI:0.3, 1.1), indicating

Table 1
General characteristics of eligible studies.

Source (year of publication)	Duration of follow-up	Intervention	No. of limbs	Mean age	Severity	Anaesthesia	Compression technique	TA	CP
EVLA vs surgery									
Demeideros[28] (2005)	13 days	EVLA 810 nm plus high ligation	20	46	C2-3(55%), C4-6(45%)	RA	Compression wrap 2 days	No	Yes
		Conventional	20	46	C2-3(80%), C4-620%)	RA	Compression wrap 2 days	No	Yes
Darwood[26] (2008)	12 months	EVLA 810 nm(step.)	47	40	C2-3(87%),	LA	CS 1 week	Yes	No
		EVLA 810 nm(cont.)	29	46	C4-5(11%)	LA	CS 1 week	Yes	No
		Inversion	32	44	C2-3(91%), C4-5(3%)	GA	CS 2 weeks	No	Yes
Disselhoff[25] (2008)	60 months	EVLA 810 nm	60	49	C2-3(94%), C4-5(3%) C2(100%)	GA, LA	CS 1 week	Yes(LA),	No
		Cryostripping	60	49	C2(100%)	GA, LA	CS 1 week	TS(GA)	No
Kalteis[24] (2008)	4 months	EVLA 810 nm plus high ligation	47	42	C2-3(93%),	GA, RA	CS 2 weeks	– No	Yes
		Conventional	48	42	C4(7%) C2-3(96%),	GA, RA	CS 2 weeks	No	Yes
Christenson[9] (2010)	24 months	EVLA 980 nm	100	45	C4(4%) C2-3(92%),	GA, RA	CS 3 weeks	Yes	Yes
		Conventional	100	46	C4-6(8%) C2-3(77%),	GA, RA	CS 3 weeks	No	Yes
Pronk[8] (2010)	12 months	EVLA 980 nm	62	49	C4-6(23%) C2-3(94%),	LA	Panelast® 1 week	Yes	No
		Inversion	68	50	C4-5(6%) C2-3(91%),	LA	Panelast® 1 week	Yes	No
Rasmussen[10,27] (2007, 2010)	24 months	EVLA 980 nm	69	53	C4-5(8%) C2-3(85%),	LA	CS 2 weeks	Yes	Yes
		Invagination	68	54	C4(15%) C2-3(94%),	LA	CS 2 weeks	Yes	Yes
Carradice[7] (2011)	12 months	EVLA 810 nm	139	49	C4(5%) C2(69%),	LA	CS 6 weeks	Yes	Yes
		Inversion	137	49	C3(31%) C2(70%), C3(30%)	GA	CS 6 weeks	No	Yes
RFA vs surgery									
Lurie[32,33] (2003, 2005)	24 months	RFA (Closure)	45	49	C2-3(90%),	GA,RA,LA	–	TA(some)	Yes
		Invagination	36	47	C4(9%) C2-3(89%), C4(11%)	GA,RA,LA	–	TA(some)	Yes
Rautio,[34] Perala[31] (2002, 2005)	36 months	RFA (Closure)	15	33	–	GA	CS 7 days	TS	Yes
		Conventional	13	38		GA	CS 7 days	No	Yes
Hinchliffe[30] (2006)	6 weeks	RFA (VNUS)	16	55	C2-3(94%),	GA, RA	CS 2 weeks	TS	Yes
		Inversion	16	55	C4(6%) C2-3(94%), C4(6%)	GA, RA	CS 2 weeks	No	Yes
Stoetter[29] (2006)	12 months	RFA (Closure)	20	–	–	GA	CS 6 weeks	TS	–
		Invagination	20			–	CS 6 weeks	–	–
		Cryostripping	20			–	CS 6 weeks	–	–
Subramonia[12] (2010)	1 week	RFA (ClosurePLUS)	47	44	C2-3(98%),	GA	CS 2 weeks	Yes	Yes
		Invagination	41	41	C4(2%) C2-3(98%), C6(2%)	GA	CS 2 weeks	–	Yes
Elkaffas[11] (2011)	23 months	RFA (Closure)	90	33	C2-3(87%),	LA	–	Yes	Yes
		Conventional	90	35	C4-5(13%) C2-3(87%), C4-5(13%)	GA	–	–	Yes
UGFS vs surgery									
Bountouroglou[36] (2006)	3 months	UGFS	30	45	–	LA	CS 2 weeks	–	No
		Inversion	28	46		GA	CS 3 weeks	–	Yes
Wright[35] (2006)	12 months	Varisolve	178	50	C2-3(89%),	LA	CS	–	No
		High ligation(92%), stripping(88%), avulsion phlebectomy(53%)	94	49	C4(11%) C2-3(89%), C4(11%)	GA,RA,LA	–	–	Yes
Abela[14] (2008)	2 weeks	Catheter directed UGFS	30	45	C2-3 (100%)	GA	CS 15 days	Yes	Yes
		Conventional, Invagiantion	60	45	C2-3 (100%)	GA	CS 15 days	Yes	Yes
Figueiredo[13] (2009)	6 months	UGFS,repeat up to 3 times q 30 days	27	53	–	LA	CS 3 months	No	No
		Conventional	29	49		RA	CS 3 months	Not stated	Yes
RFA vs EVLA									
Almeida[17] (2009)	1 month	RFA (ClosureFAST)	46	52	C2 (94%)	LA	CS 2 weeks	Yes	No
		EVLA 980 nm	41	52	C2 (88%)	LA	CS 2 weeks	Yes	No
Gale[15] (2010)	12 months	RFA (ClosurePLUS)	70	49	–	LA	CS 2 weeks	Yes	Yes
		EVLA 810 nm	72	51		LA	CS 2 weeks	Yes	Yes

(*continued on next page*)

Table 1 (*continued*)

Source (year of publication)	Duration of follow-up	Intervention	No. of limbs	Mean age	Severity	Anaesthesia	Compression technique	TA	CP
Goode[37] (2010)	9 months	RFA (RFiTT)	40	46	–	GA	CS 2 weeks	TS(some)	Yes
		EVLA 810 nm	39	48		GA	CS 2 weeks	TS	Yes
Shepherd[16] (2010)	6 weeks	RFA (ClosureFAST)	66	49	C2 (35%),	GA	CS 1 week	Yes	Yes
		EVLA 980 nm	61	48	C3-6 (65%) C2 (41%), C3-6 (58%)	GA	CS 1 week	Yes	Yes
Multiple comparisons									
Rasmussen[38] (2011)	12 months	EVLA 980, 1470 nm	125	52	C2-3 (95%), C4-6 (5%)	LA	Short CS 20 mmHg 2 weeks	Yes	Yes
		RFA (ClosureFAST)	125	51	C2-3 (92%), C4-6 (8%)	LA	Short CS 20 mmHg 2 weeks	Yes	Yes
		UGFS, retreatment allowed in 1 month	124	51	C2-3 (96%), C4-6 (4%)	LA	Groin 30 mmHg CS 2 weeks	No	Yes
		Pin stripping	124	50	C2-3 (97%), C4-6 (3%)	LA	Short CS 20 mmHg 2 weeks	Yes	Yes

Step., stepwise mode; cont., continuous mode; TA, Tumescent anaesthesia; TS, Tumescent saline; LA, Local anaesthesia; GA, General anaesthesia; RA, Regional anaesthesia; CP, Concomitant phlebectomy; CS, compression stocking.

that EVLA had 40% less chance of clinical recurrence, but this was non-statistically significant. Source of heterogeneity (i.e., age and follow-up time) could not be identified. A sensitivity analysis was performed by excluding one study[8] that did not undertake concomitant phlebectomies yielded very similar results.

RFA versus surgery

The RRs of clinical recurrence between RFA versus surgery were homogeneous ($Q = 2.97$, d.f. $= 3$, $p = 0.396$, $I^2 = 0\%$) among four studies[11,31–33,38] with a pooled RR of 0.9 (95% CI:0.6, 1.4) (see Fig. 4B).

Venous clinical severity score

Five studies[9,23,25–27] compared VCSS between EVLA and surgery with no heterogeneity (Supplementary Fig. 1). The pooled MD was −0.01 (95% CI:−0.07, 0.06).

Postoperative complications

Wound infection

Eight[7–9,24–27,38] and five studies[11,12,30,33,38] reported wound infections between EVLA and RFA versus surgery, respectively. The corresponding pooled RRs were 0.3 (95% CI:0.1, 0.8) and 0.3 (95% CI:0.1, 1.4), with no heterogeneity (Table 3). Comparing overall EVLA and RFA with surgery based on 12 studies yielded a pooled RR of 0.3 (95%CI:0.1, 0.7) (Supplementary Fig. 2), that is, wound infection was significantly reduced by 70% in the endovenous techniques compared with surgery. The estimated number needed to treat (NNT) was 80 subjects to prevent one wound infection.

Paresthesia

Nine studies[7–9,24–28,38] reported paresthesia between EVLA and surgery. The RRs were homogeneous with the pooled RR of 0.8 (95% CI:0.6, 1.1), suggesting no difference of paresthesia between groups

Table 2
Risk of bias assessment of eligible studies.

Author	Domains					Other sources of bias	Comments
	Sequence Generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome report		
EVLA vs surgery							
Carradice[7]	Unclear	Yes	Yes	Yes	Yes	Yes	Applied ITT
Rasmussen[10,27]	Unclear	Yes	No	Yes	Yes	Yes	Applied ITT
Pronk[8]	Yes	Yes	No	Yes	No	Yes	Applied ITT
Christenson[9]	Yes	Yes	No	No	Yes	No	Applied PP
Kalteis[24]	No	No	No	Yes	No	No	Applied PP
Disselhoff[22,25]	Unclear	Yes	Yes	Yes	Yes	Yes	Applied ITT
Darwood[26]	Unclear	Yes	Yes	No	Yes	Yes	Applied ITT
Demedeiros[28]	Yes	Yes	Yes	Yes	Yes	Yes	Applied ITT
RFA vs surgery							
Elkaffas[11]	Unclear	Yes	Yes	Yes	Yes	Yes	Applied ITT
Subramonia[12]	Yes	Yes	Yes	Yes	Yes	Yes	Applied ITT
Stoetter[29]	Unclear	Unclear	No	Yes	No	Yes	Applied ITT
Hinchliffe[30]	Unclear	Unclear	Yes	Yes	Yes	Yes	Applied ITT
Perala[31,34]	Unclear	Yes	No	No	Yes	Yes	Applied ITT
Lurie[32,33]	Unclear	Yes	No	No	Yes	Yes	Applied ITT
USFS vs surgery							
Figueiredo[13]	Unclear	Yes	No	Yes	Yes	Yes	Applied ITT
Abela[14]	Yes	Yes	No	Yes	Yes	Yes	Applied ITT
Wright[35]	Unclear	Yes	No	Yes	Yes	Yes	Applied ITT
Bountouroglou[36]	Unclear	Yes	No	No	Yes	Yes	Applied ITT
RFA vs EVLA							
Shepherd[16]	Unclear	Yes	Yes	Yes	Yes	No	Applied PP
Goode[37]	Yes	Unclear	Yes	No	No	No	Applied PP
Gale[15]	Unclear	No	No	No	No	Yes	Applied ITT
Almeida[17]	Yes	Yes	Yes	Yes	Yes	Yes	Applied ITT
Multiple comparisons							
Rasmussen[38]	Unclear	Yes	No	Yes	Yes	Yes	Applied ITT

Yes = Low risk of bias No = High risk of bias Unclear = uncertain risk of bias ITT, intention to treat analysis; PPA, per protocol analysis.

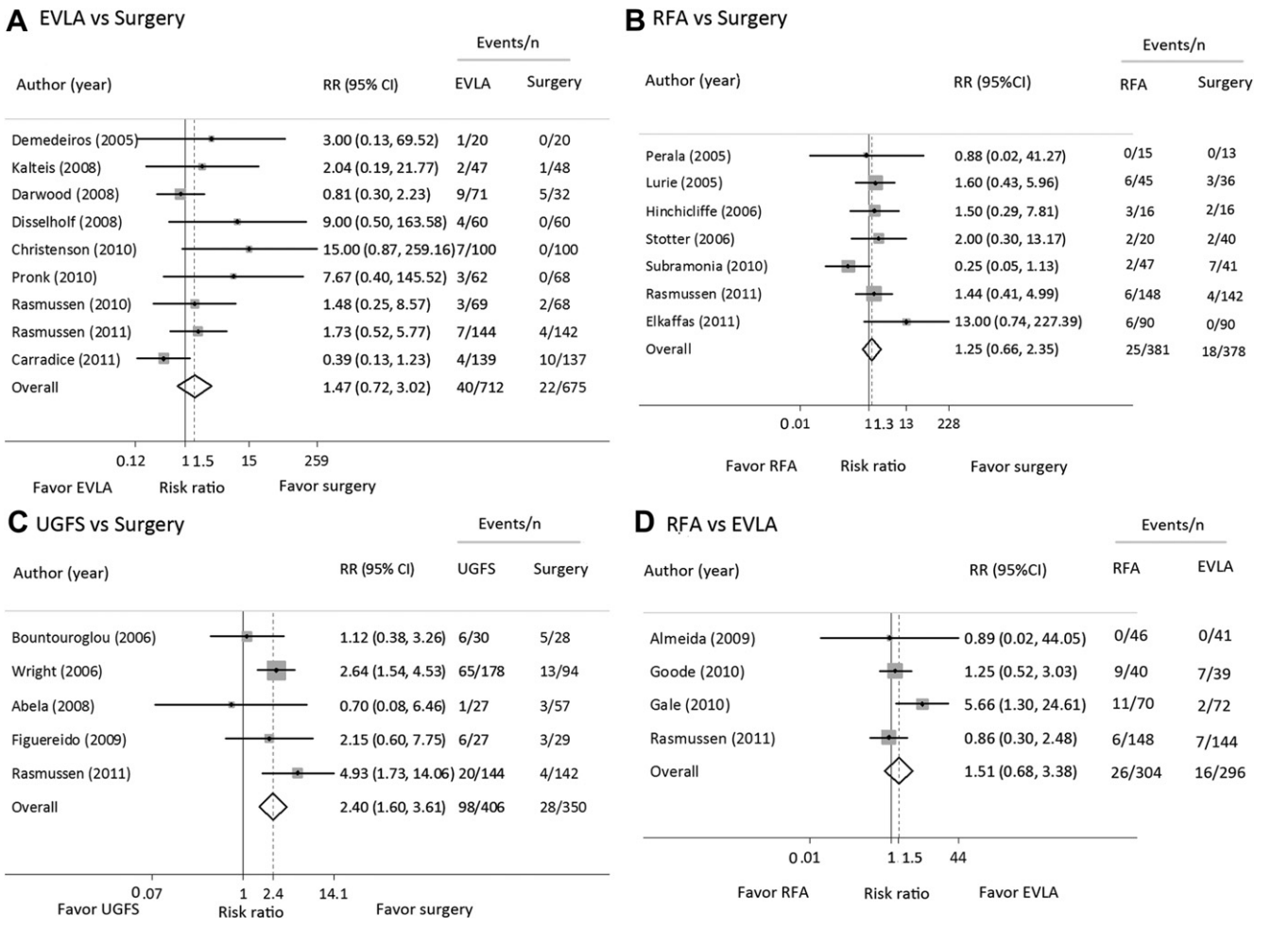

Figure 2. Forest plots of intervention effects on primary failure. The size of each square is proportional to percent weight that each study contributed in the pooled risk ratio. The pooled risk ratio is indicated by the diamond . CI, confidence interval ; RR , risk ratio.

(see Table 3 and Supplementary Fig. 3A). The RRs of paresthesia between RFA and surgery were moderately heterogeneous across seven studies[11,12,29,30,33,34,38] (see Table 3 and Supplementary Fig. 3B). The pooled RR was 1.0 (95% CI:0.5, 1.7).

Superficial thrombophlebitis

Six studies[7,9,25–27,38] reported superficial thrombophlebitis between EVLA and surgery with homogeneity (see Table 3 and Supplementary Fig. 4A). The pooled RR was 1.0 (95% CI:0.5, 1.8). The Egger test suggested asymmetry of funnel, adding one missing study by meta-trim and fill in the pooling yielded an RR of 0.9 (95% CI:0.4, 1.8). To minimise confounding effects from tumescence anaesthesia (TA), subgroup analysis according to similarity of applying TA was performed. Two studies[27,38] applied TA to both groups, whereas four studies[9,23,25,26] applied TA to only EVLA group. This subgroup analysis yielded the pooled RRs of 1.0 (95% CI:0.5, 2.2) and 0.8 (95% CI:0.3, 2.5), respectively.

Superficial thrombophlebitis between RFA and surgery was pooled from six studies[11,12,30,33,34,38] with low heterogeneity. The risk of superficial thrombophlebitis was 2.3 (95% CI:1.1, 5.0) times significantly higher in RFA than surgery (see Table 3 and Supplementary Fig. 4B). None of studies had similarity in applying TA in both intervention groups.

Haematoma

Effects of EVLA versus surgery on haematoma were pooled in four homogeneous studies[7,9,24,27] (see Table 3). The pooled RR was 0.5 (95% CI:0.3, 0.8), that is, EVLA had 50% significant relative risk reduction of haematoma (see Supplementary Fig. 5A). The estimated NNT was 10. Among four studies, one study[27] applied TA in both EVLA and surgery, whereas another study[24] did not apply in both groups. Pooling these two studies yielded the pooled RR of 0.6 (95% CI:0.4, 0.9).

Effects of RFA versus surgery were highly heterogeneous across five studies[11,12,29,33,34] with the pooled RR of 0.4 (95% CI:0.1, 0.8), suggesting that the risk of haematoma was 60% significantly reduced in RFA relative to surgery. The estimated NNT was four. None of the studies were similar in applying TA.

Ecchymosis

Ecchymosis between EVLA and surgery was highly heterogeneous across six studies[7,9,25–28] with the pooled RR of 0.7 (95% CI:0.3, 1.6) (see Table 3, and Supplementary Fig. 6). Pooling 2 studies with similarity of applying TA (i.e., used[27] and unused[28] in both groups) yield the pooled RR of 0.4 (95% CI:0.2, 0.7).

Postoperative pain

As described in Table 4 and Supplementary Fig. 7, the first-recorded pain was significantly lower after EVLA and RFA than surgery with pooled MD of −0.6 (95% CI:−1.1, −0.2) and −1.6 (95% CI:−2.1, −1.1), respectively. The RFA caused significantly less pain than EVLA with pooled MD of −0.8 (95% CI:−1.5, −0.1).

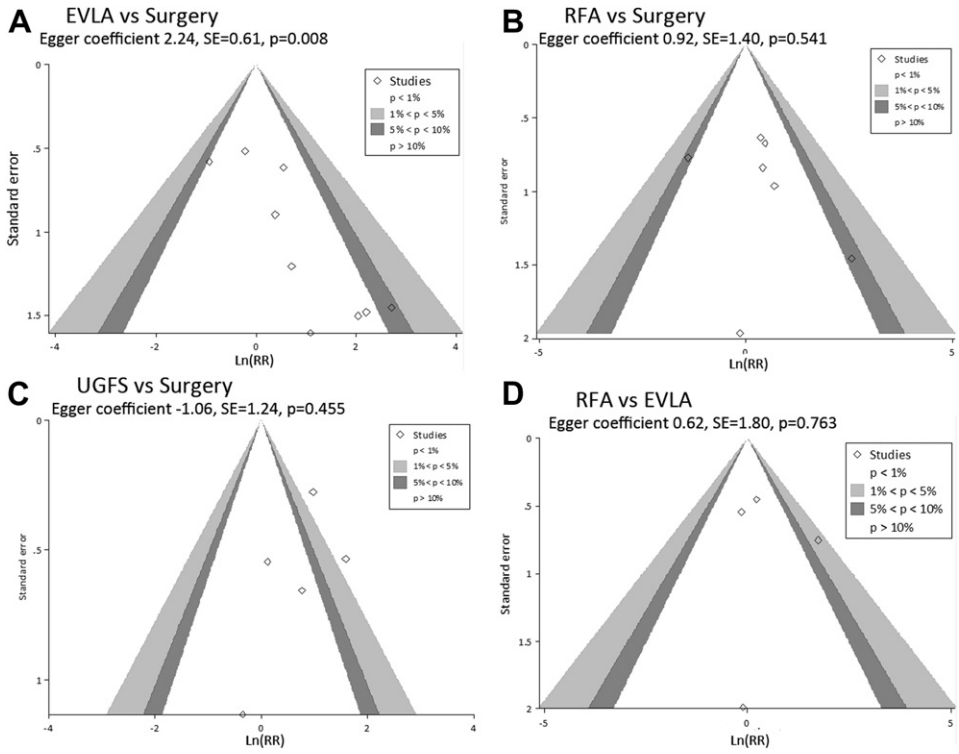

Figure 3. Contour enhanced funnel plots of primary failure between various types of interventions.

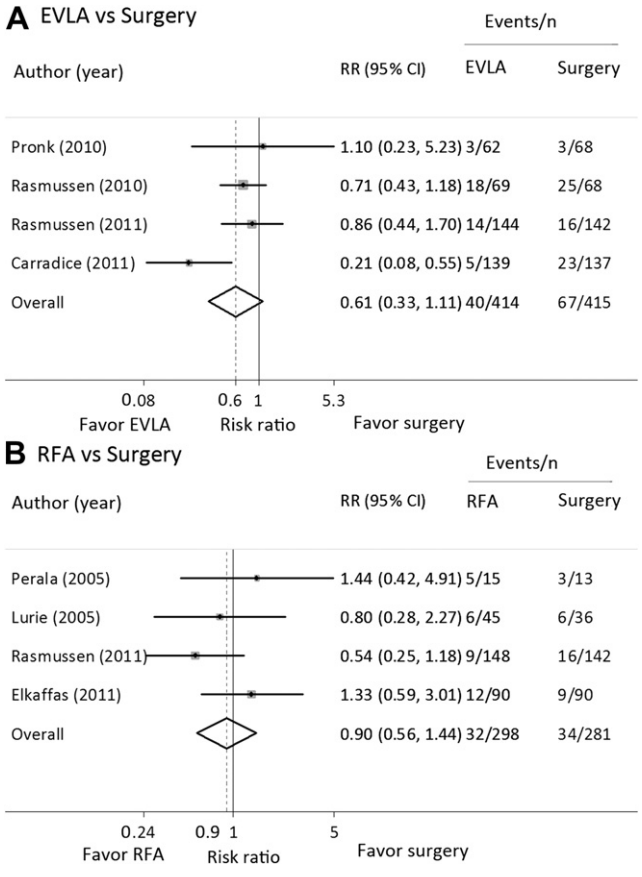

Figure 4. Forest plots of intervention effects on clinical recurrence. CI, confidence interval ; RR , risk ratio.

Maximum pain at days 1–7 was significantly less after EVLA and RFA than surgery with pooled MD of −0.6 (95% CI:−1.0, −0.1) and −1.6 (95% CI:−2.0, −1.1), respectively. The maximum pain after RFA was less than EVLA with an MD of −1.2 (95% CI:−1.6,−0.9).

Return to normal activities or work

Return to normal activities or work was significantly shorter for RFA but not for EVLA compared with surgery with pooled MD of −4.9 days (95% CI:−7.1, −2.7) and −2.7 (95% CI:−6.0, 0.6) days, respectively (see Table 4, Supplementary Fig. 8).

QOL

Six studies[7,9,10,25,26,38] compared QOL measured at 2–24 months between EVLA versus surgery (see Table 4 and Supplementary Fig. 9). The pooled MD was −0.2 (95%CI:−0.9, 0.6) with heterogeneity. Fitting mean age, disease severity (percent C2-3) and follow-up time in meta-regression did not suggest any source of heterogeneity (data were not shown).

Discussion

Our results suggest primary failure and recurrence rates after EVLA and RFA were not significantly different to surgery. However, EVLA and RFA had 70% lower rates of wound infection, with NNT of 80. Also, both EVLA and RFA reduced haematoma by approximately 50–60%, with NNT of 4–10. Furthermore, patients could return to normal activities or work 3–5 days earlier.

Primary failure of the ablated vein was a surrogate outcome of clinical recurrence.[39] Other causes may play a role on clinical recurrence including below knee GSV reflux,[40] reflux in tributaries,[41] neovascularisation,[42] saphenopopliteal reflux,[40] non-axial branches[23] and perforator insufficiency. Recurrence at a new

Table 3
Comparisons of postoperative complications between endovenous and surgical techniques.

Outcomes	Comparison arms	No. of studies	No. of patients	Heterogeneity			Egger test		Pooled RR (95%CI)
				Q	P	I^2(%)	Beta	P	
Wound infection	EVLA vs Surgery	8	1347	2.07	0.956	0	0.71	0.232	0.3 (0.1, 0.8)
	RFA vs Surgery	5	671	1.34	0.855	0	0.88	0.764	0.3 (0.1, 1.4)
Paresthesia	EVLA vs Surgery	9	1387	7.83	0.450	0	−0.60	0.274	0.8 (0.6, 1.1)
	RFA vs Surgery	7	759	8.71	0.190	31.2	0.33	0.836	1.0 (0.5, 1.7)
Superficial thrombophlebitis	EVLA vs Surgery	6	1121	4.81	0.440	0	2.94	0.006	1.0 (0.5, 1.8)
	RFA vs Surgery	6	699	5.45	0.364	8.2	0.41	0.718	2.3 (1.1, 5.0)
Haematoma	EVLA vs Surgery	4	708	3.3	0.344	9.9	−1.37	0.241	0.5 (0.3, 0.8)
	RFA vs Surgery	5	437	11.17	0.025	64.2	−1.56	0.163	0.4 (0.1, 0.8)
Ecchymosis	EVLA vs Surgery	6	876	18.35	0.003	72.8	−0.70	0.516	0.7 (0.3, 1.6)

CI, confidence interval; RR, relative risk (Incidence Gr.1/Incidence Gr.2).

site of reflux is a natural progression of the disease.[40] However, the incidence of reflux in tributaries and neovascularisation might differ between the procedures with and without sapheno-femoral ligation (i.e., more reflux in tributaries in the procedures without sapheno-femoral ligation, and more neovascularisation after sapheno-femoral ligation[22,43,44]) which may influence long-term effectiveness between endovenous techniques and surgery in addition to primary failure.

Pooling primary failure, reflux in tributaries and neovascularisation together as composite outcomes of clinical recurrence resulted in dilution of the RR of EVLA and RFA versus surgery to 1.1 (95% CI:0.6, 2.2; I^2 = 63.4%) and 1.1 (95% CI:0.6, 1.8; I^2 = 20.7%), respectively (see Supplementary Fig. 10). Subgroup analysis by follow-up and a sensitivity analysis excluding the cryostripping study[25] and EVLA with high ligation[24,28] did not change effects on efficacy. These results and similarity of clinical recurrences demonstrated similarity of effectiveness of RFA and EVLA to surgery. Although UGFS seems to be inferior to surgery, it is still applied in clinical practise because of its lower cost, safety and repeatability.[4]

For postoperative complications, RFA and EVLA had significantly lower wound infection and haematoma, but similar paresthesia and ecchymosis compared to surgery. By contrast, RFA had significantly more superficial thrombophlebitis than surgery. However, these complications might be confounded by TA. Although subgroup analyses by similar of TA in both interventions showed similar results to overall poolings, these were based on small numbers of studies. A sensitivity analysis excluding the study did not perform concomitant phlebectomy[26] left complication rates unchanged. Deep venous thrombosis was not pooled because it was rare and most studies reported no event.

Our review suggested that EVLA and RFA had significantly lower pain scores than surgery with MD of −0.6 and −1.7, respectively. These reached clinical significance (at least 0.9) for RFA but not for EVLA.[45,46] Return to work was significantly sooner with RFA than with surgery but not for EVLA. This might result from different ablative mechanisms which can cause vein wall perforation in EVLA (810 and 980 nm with bare tip),[47] but not for RFA.[48] This concern has led to evolution of a new 1470-nm EVLA with a radial fibre which claimed to cause less pain with similar short term efficacy.[49] QOL in EVLA and surgery groups were not significantly different. Although all included studies used the same scale (i.e., AVVSS), pooling was moderate heterogeneity (I^2 = 60.1%). None of the sources (e.g., mean age, disease severity and follow-up time) could explain heterogeneity.

Although the primary failures between EVLA and RFA versus surgery were similar to previous meta-analyses,[1,3,5,6] our evidence was based on pooling of solely RCTs. Our results were also similar to the most recent systematic review by the Cochrane[50] while preparing this article. However, more studies were pooled, including three large RCTs[11,23,38] and one study with long-term follow-up.[22] Consequently, our estimations of treatment effects were more precise. For instance, we included seven studies in pooling primary failure between EVLA versus surgery compared to four for the Cochrane. The corresponding pooled RRs were 1.5 (95% CI:0.7, 3.0) versus 3.30 (95% CI:0.8, 12.74). In addition, more objective pooling of treatments effects on complications, pain, return to normal activities and QOL were discussed in our review. Furthermore, we assessed effects of RFA versus EVLA and UGFS. Our results about the benefit of less pain and return to normal activities in EVLA and surgery were also consistent with, and more precise than the results from a recent large RCT.[38]

Table 4
Comparisons of postoperative pain, return to normal activities or work and quality of life between various endovenous and surgical techniques.

Comparison arms	Outcomes	No. of studies	Total number of patients	Heterogeneity			Egger test		WMD (95%CI)
				Q	P	I^2(%)	Beta	P	
EVLA vs Surgery	First reported pain	6	1010	7.33	0.198	31.7	1.90	0.599	−0.6 (−1.1, −0.2)
	Maximum pain	6	1010	7.59	0.180	34.1	1.84	0.610	−0.6 (−1.0, −0.1)
	NA or work	7	1227	164.3	0.000	96.4	−3.87	0.342	−2.7 (−6.0, 0.6)
	NA	6	1132	159.1	0.000	96.9	−6.17	0.208	−3.5 (−7.1, 0.0)
	AVVSS	6	1122	12.3	0.031	59.2	−0.21	0.862	−0.2 (−0.9, 0.6)
RFA vs Surgery	First reported pain	4	438	0.59	0.899	0	1.85	0.341	−1.6 (−2.1, −1.1)
	Maximum pain	4	438	0.98	0.805	0	3.43	0.124	−1.6 (−2.0, −1.1)
	NA or work	6	727	38.23	0.000	86.9	−1.71	0.516	−4.9 (−7.1, −2.7)
	NA	5	699	30.91	0.000	87.1	−0.74	0.825	−4.2 (−6.5, −2.0)
RFA vs EVLA	First reported pain	4	542	11.65	0.009	74.3	−3.36	0.512	−0.8 (−1.5, −0.1)
	Maximum pain	4	542	0.73	0.867	0	1.29	0.252	−1.2 (−1.6, −0.9)

AVVSS, Aberdeen varicose vein severity scores; CI, confidence interval; MD, weight mean difference (mean of group 1 − mean of group 2); NA, return to normal activities; work, return to work.

The strength of our study was included only in RCTs, the most powerful design for therapeutic study. We considered all relevant outcomes in all techniques currently used nowadays. Treatment effects were mild to moderate heterogeneities with no evidence of publication bias. Therefore, our results should help physicians decide on the most appropriate interventions for their individual patients. However, we had limitations. Some included studies were correlated data, that is, different interventions were applied to the same subjects. The units of analysis for these studies were number of limbs, but pooling based on summary data did not allow adjustment for this correlation. Duration of follow-up varied across studies with a median of 12 months (range 0.2–60 months). Using summary data did not allow us to explore short, intermediate and long-term primary failures and other clinical outcomes of these interventions. Only few studies[22,31] with long-term follow-up (36 months or longer) were available. The clinical recurrences of endovenous techniques seemed to be lower but not significant than surgery based on four studies. More studies with long-term follow-up are necessary to update. Only one study[23] reported cause of clinical recurrence and thus we could not explore whether truncal ablation or other causes play a role of clinical recurrence. Some clinical outcomes (i.e., clinical recurrence, pain score and QOL) were subjective and 56.5% of included studies were poor methodological qualities from which they did not perform blind assessments. An ascertainment bias of outcome measures might be present. Not all included studies had applied ITT analysis for dealing with data; bias from protocol violation (e.g., exclude cannulation failure, incomplete outcome or protocol violation) might be present.

Summary

In summary, UGFS seems inferior to surgery. Primary failure and recurrence rates with EVLA and RFA were not different compared with surgery, but had a lower rate of complications such as wound infection and haematoma, less pain and shorter return to work. Within the endovenous techniques, RFA seems to be slightly better tolerated than EVLA except that it shows a significantly higher rate of superficial thrombophlebitis.

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Conflicts of Interest

None.

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Appendix A. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.ejvs.2012.05.017.

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