

# Meta-analysis of venous anastomosis techniques in free flap reconstruction

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## Previous dissemination

This work has been presented at scientific meetings: ESPRAS Congress, Limassol, 2018 (oral presentation) and BAPRAS Winter scientific meeting, London 2018 (oral presentation). The Systematic Review was performed according to a pre-developed protocol which underwent peer-review and was published open-access in Systematic Reviews. (DOI: 10.1186/s13643-018-0871-x) A review record was registered and is maintained on the PROSPERO database (CRD42018110111).



## SUMMARY

**Background:** Coupler devices and hand-sewn anastomosis techniques are both routinely employed for venous anastomosis in microsurgical free flap transfer. However, uncertainty remains about whether those two techniques are different in terms of risk of venous thrombosis. The aim of this review was to evaluate the quality of the evidence and quantify the difference in venous thrombosis rates in both techniques.

**Method:** A PRISMA compliant systematic review and meta-analysis was performed according to a previously published protocol. MEDLINE and Embase databases were searched from inception to 1<sup>st</sup> October 2018. Clinical studies using coupler devices for venous anastomoses in free tissue transfer were included. The primary outcome was postoperative venous thrombosis risk. Surgical anastomosis time was a secondary outcome. The risk of bias was assessed with the ROBINS-I or NIH tool and recommendations were made using the GRADE criteria.

**Results:** A total of 10 851 patients across 32 observational retrospective studies were included, with data available for 12 769 free flaps in breast, head and neck, limb and other reconstructions. Direct comparison meta-analysis of 7 studies showed a reduced post-operative thrombosis risk for venous coupler, although this was an imprecise estimate (RR 0.68 [95% CI 0.39-1.19]). Risk of bias was consistently high across all studies.

**Conclusion:** Venous couplers may reduce risk of venous thrombosis but further randomised trial data is needed to improve the accuracy of this estimate. Further research should also assess size-mismatch between donor and recipient vessel and the influence of coupler size on outcomes.

*(PROSPERO registration ID: CRD42018110111)*

## KEYWORDS

Free Tissue Flaps; Microsurgery; Anastomosis, Surgical; Systematic Review

## INTRODUCTION

Microvascular free tissue transfer is a key principle of reconstructive surgery and enables surgeons to replace like-with-like tissue from a variety of anatomical donor sites. The key component of the procedure is the microvascular anastomosis, which is performed between the flap vessels and the recipient vessels. The first microvascular anastomosis was described in 1960 and was performed by approximating the vessel ends with microsutures by hand-held microsurgical instruments.<sup>1</sup> Hand-sewn anastomoses are routinely performed in modern microsurgical practice. The first metal coupling device for vessel anastomosis was described in 1962 and became commercially available in the 1980s.<sup>2, 3</sup> They were developed primarily for use in microsurgical venous anastomosis to simplify the technically demanding and ostensibly time-consuming process of performing a hand-sewn anastomosis.<sup>4</sup> Modern coupler devices use polyethylene rings with interlocking steel pins to securely attach blood vessels end-to-end or end-to-side.<sup>5</sup> Their use has gained popularity over the last decades, which has been reflected in the published literature.<sup>6-9</sup> Thrombosis of the flap vein can be an immediate complication following reconstructive microsurgery. If it occurs it is often identified through clinical examination in the immediate or acute post-operative period. It almost always requires a return to theatre for revision of the venous anastomosis and is considered a serious complication that can ultimately lead to failure of the flap.

Various advantages of venous coupler devices over hand-sewn anastomosis have been asserted in the literature, including reduced operative time, improved intimal alignment and reduced foreign material within the vessel lumen.<sup>5</sup> There is, however, significant uncertainty regarding the comparative efficacy of coupler versus hand-sewn techniques, with substantial variability in practice. The literature generally consists of level 4 studies with relatively high patient numbers, as well as three systematic reviews evaluating the use of venous couplers versus hand-sewn anastomosis.<sup>4, 10, 11</sup> The existing systematic reviews have essential methodological flaws and/or did not perform a meta-analysis. For example, a previous meta-analysis had no study protocol, risk of bias assessment or grading of the evidence, along with other methodological flaws.<sup>11</sup> Our objective was to perform a rigorous systematic review comprising a comprehensive search strategy, a full appraisal of the quality of the evidence using established criteria and to answer the following question: for patients

undergoing free flap reconstruction, what is the efficacy and safety of venous coupler devices compared to hand sewn anastomoses in terms of venous thrombosis?

## **METHODS**

This review was performed using methodology based on the Cochrane Handbook for Systematic Review of Interventions and was reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist.<sup>12, 13</sup> A comprehensive search strategy was developed to capture all relevant articles relating to the review question: to compare predefined outcomes of venous coupler anastomoses and hand-sewn anastomoses in accordance with the Meta-analysis of Observational Studies (MOOSE) guidance.<sup>14</sup> Prior to performing the review, a detailed study protocol was developed, peer-reviewed and published open access to maximise transparency.<sup>15</sup> Furthermore, a record is maintained in the PROSPERO database (CRD42018110111).<sup>16</sup>

### **Search strategy**

MEDLINE and Embase databases were searched from database inception to 1<sup>st</sup> October 2018. Both MeSH terms and free-text search strategies were applied using defined keywords by two authors (TR and AG) and was checked by the senior author (JW, trained in search methods).<sup>16,17</sup> The full search strategy is available on the PROSPERO record.<sup>17</sup> Studies in any language from any country of origin were eligible for inclusion. Two authors (TR and AG) independently searched ClinicalTrials.gov to ensure that no relevant ongoing study was omitted. The search results were merged and de-duplicated prior to screening. Titles and abstracts were then screened in duplicate (AG and TR) to eliminate irrelevant studies. Full texts were retrieved for the remaining studies to establish eligibility for inclusion. We performed additional screening of the bibliographies of included studies. Disagreements between the screening authors (AG and TR) were moderated and resolved by a third author (JW). Included studies were managed on a bespoke, pre-defined Excel sheet (Microsoft, Redmond, WA, United States). Citations were managed in EndNote (Clarivate Analytics, Boston, MA, United States).

### **Study selection criteria**

Study selection criteria were determined during the protocol stage according to the Population, Intervention, Comparison, Outcome (PICO) model for clinical questions.<sup>15</sup> Experimental studies

(randomised controlled trials (RCTs) and quasi-RCTs) and observational studies (cohort, case-control, and case series) using anastomotic couplers for venous anastomoses in free tissue transfer reconstruction were eligible for inclusion. Cohort studies were defined as studies of participants with the same exposure, allowing quantification of a difference of defined outcome measures between groups. Case series of individuals receiving all the same intervention without a control group make 'within group' risk calculation unfeasible.<sup>17</sup> Case reports, letters, opinion pieces and literature reviews as well as in-vitro, animal and cadaveric studies were excluded. Studies reporting on the outcome of both arterial and venous anastomoses were only included if the data for venous anastomoses could clearly be distinguished from arterial anastomoses. Of those studies, only the outcome measures of venous anastomoses were included. Studies comparing coupled with hand-sewn venous anastomoses were only included if sufficient data was provided to ascertain the defined outcome parameters of venous coupled and hand-sewn anastomoses separately. **Studies assessing only venous coupler anastomoses in free flap reconstruction were included whereas studies assessing only hand-sewn venous anastomosis in free flap reconstruction were excluded.** No limitation was made based on patient inclusion criteria or study size.

## **Data collection**

Data was extracted, verified and documented independently by two authors (TR and AG) on a predefined electronic form. The following data was collected for comparison:

1. Baseline study data (author, year of publication, journal, country)
2. Patient demographics (number of patients, gender, age)
3. Study design (study type, number of free flaps, number of venous anastomoses, anastomosis technique, coupler size, site of reconstruction)
4. Intra- and postoperative outcome measures (venous thrombosis risk, flap failure, time to complete a venous anastomosis and other complications)

Demographics were extracted for the entire study population, even if alternative anastomosis techniques were used. The authors evaluated each study to ensure there were no **major** differences in demographics between groups. The preferred unit of analysis was venous anastomosis. Where it was not possible to extract data for the primary outcome, study authors were contacted to provide further data via email. In case of no response after 2 weeks, a second email was sent at that point. No

response 2 weeks following the reminder email led to exclusion of the study, which was recorded in the PRISMA flow chart.

### **Outcome measures**

The primary outcome was postoperative venous thrombosis risk. No distinction was made between thromboses occurring intra-operatively or post-operatively. Reporting of results only included venous anastomoses which were assessed for the primary outcome. Venous anastomoses that were clearly excluded prior to assessment in the original studies were also excluded from our results data extraction. Secondary outcomes were the time to complete the venous anastomosis, flap failure, iatrogenic venous injury, kinking of veins, anastomotic leakage and economic outcomes.

### **Quality assessment**

A risk of bias assessment was performed **in duplicate (AG and TR)** using the ROBINS-I tool for studies describing direct comparisons, therefore included in the meta-analysis (Table 1).<sup>18</sup> The risk of bias for case series and cohort studies without direct comparison of the primary outcome were assessed with the National Institutes of Health (NIH) study quality assessment tool (Table 2).<sup>19</sup>

### **Data analysis and synthesis**

Descriptive analysis was performed for patient demographics. The risk of microvascular venous thrombosis was calculated for each group (venous coupler versus handsewn anastomosis) for comparison of results across the included studies. The primary outcome, venous thrombosis, was calculated and displayed as a risk (%). If two or more studies reported the same outcome, then the risk estimates from each study were pooled for comparative analysis. Only risk estimates for direct comparison studies were pooled, i.e. one study population containing patients with both hand-sewn and venous coupler anastomoses and estimable risks for each group. A direct comparison meta-analysis was performed, using RevMan5 to calculate the relative risk ratios with 95% confidence intervals using the Cochran-Mantel-Haenszel test.<sup>20</sup> A random-effects model was used due to the anticipated study heterogeneity, and subgroup analyses were undertaken for site of reconstruction, as described in the review protocol. Statistical heterogeneity was quantified for all direct comparisons using the I-squared statistic, and significance was set at the 5% level. The meta-analysis results are

displayed as forest plots.<sup>21</sup> Sub-group analyses were planned for reconstructive subsites as described in the review protocol.<sup>16</sup>

## RESULTS

The search strategy identified 895 individual studies, for which the titles and abstracts were screened against the predefined inclusion criteria. At this stage, 839 papers were excluded and 56 studies were read in full and assessed for eligibility. Of these, 24 studies were excluded due to the following reasons: only arterial coupling (n = 3), review (n = 1), not distinguished between hand-sewn (HS) and venous coupled (VC) anastomoses (n = 9), only flap failure as outcome measure (n = 4), no clear outcome measures (n = 3), not only free flap reconstruction (n = 3) or case report (n = 1) (Figure 1, Supplementary Table 1). A total of 32 studies were deemed eligible and underwent full data extraction. Seven of those included study reports contained direct comparisons and sufficient data for extraction and meta-analysis (Figures 2 and 3a-c). Three authors were contacted by email and provided requested missing data to allow inclusion.<sup>22-24</sup>

### Characteristics of Included Studies

Ten included studies were retrospective cohort and twenty-two were retrospective case series. The studies were conducted in the United States of America<sup>5, 6, 8, 23, 25-39</sup>, China<sup>40-42</sup>, Germany<sup>24, 43, 44</sup>, United Kingdom<sup>22, 45</sup>, France<sup>46, 47</sup>, Sweden<sup>48</sup>, Japan<sup>49</sup> and Taiwan<sup>9</sup>. A total of 10 851 patients with a mean age of 35-65 years received 12 769 free flaps (1.18 free flaps per patient) in reconstructive free tissue transfer procedures. Of these, 6 644 (52%) free flaps were used for breast reconstruction, 5 126 (40.1%) for head and neck reconstruction, 986 (7.8%) for lower limb reconstruction and 13 free flaps (0.1%) for other indications. A total of 13 317 venous anastomoses were performed (1.04 venous anastomoses per free flap). Where reported, anastomoses were either performed end-to-end (89%) or end-to-side (11%). The reported coupler sizes ranged from 1 to 4mm (Table 1 and 2).

### Venous thrombosis risk

All studies, including 8 626 coupled venous anastomoses, reported postoperative venous thrombosis rates between 0% and 13.7% (Supplementary Table 2). Seven studies reported direct comparison of venous thrombosis rates for venous coupler (n = 4 565) versus hand-sewn (n = 4 582) anastomosis, totalling 9 147 venous anastomoses.<sup>6, 22, 28, 29, 36, 39, 48</sup> The risk estimates from these seven studies



were pooled in a direct comparison meta-analysis, which identified an imprecise estimate of a lower risk of venous thrombosis for the venous coupler group (RR 0.68 [95% CI 0.39-1.19]) (Figure 2). Subgroup analysis was performed for three different reconstruction sites: breast, head & neck and lower limb. Data for two studies reporting venous thrombosis rates in all three subsites was divided and included in all three subgroup analyses.<sup>28, 29</sup> Again there was an imprecise estimate indicating a lower risk of venous thrombosis in breast reconstruction (RR 0.58, 95%CI [0.29, 1.15], Figure 3a). This observation was not seen in head and neck reconstruction (RR 1.26, 95%CI [0.73, 2.19], Figure 3b) or for lower limb reconstruction (RR1.37, 95%CI [0.63, 2.99], Figure 3c).

### **Secondary outcome measures**

Sixteen studies calculated the average time of performing a venous coupled anastomosis ranging between 3 and 15 minutes (Supplementary Table 3).<sup>5, 9, 22, 25-27, 30, 32, 33, 38, 40, 42, 46-49</sup> Two of these 16 studies with a total of 1 505 venous anastomoses, directly compared the anastomosis time of venous couplers with those of hand-sewn. Hand-sewn anastomoses took significantly longer compared to venous coupled in those two studies: 20.75 vs. 9.3 mins ( $p = 0.001$ ) and 24.7 minutes vs. 9 minutes ( $p = 0.0001$ ).<sup>22, 48</sup> Variability in outcome reporting impeded further analysis of secondary outcome, such as flap failure. Further adverse events such as iatrogenic venous injury and leakage were also insufficiently reported and were therefore not able to draw conclusions. One study calculated economic outcomes of venous coupled anastomoses suggesting that the cost of using one venous coupler was equivalent to the savings made through reduced operating time.<sup>22</sup>

### **RISK OF BIAS**

The risk of bias of the included studies was evaluated using the ROBINS-I and the NIH tool. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to make recommendations based on the risk of bias and the quality of the evidence.<sup>50</sup> All seven studies included in the meta-analysis were at serious risk of overall bias according to the ROBINS-I assessment tool. The key issue in these seven studies is the risk of confounding between the two groups. The majority of studies included in the meta-analysis were at serious risk of bias due to confounding, deviations from intended interventions and missing data. Also, most studies lacked appropriate classification of interventions and consistent methods of outcome assessment (Table 1). The remaining cohort and case series studies not included in the quantitative synthesis were at high

risk of bias with poorly stated objectives and poorly described statistical methods across those studies (Table 2).

### **Quality of evidence and strength of recommendations**

The overall quality of the research supporting venous anastomosis technique was very low, based on a serious risk of overall bias according to the ROBINS-I assessment tool and the NIH Tool for Cohort studies and Case Series Appraisal. Due to the high risk of bias, predominantly due to confounding within the non-randomised included studies, it is not possible to make robust recommendations according to the GRADE criteria (Supplementary Table 4). However, relative to the research in this specific area, an observational data analysis exceeding 12 000 free flaps may be considered high quality. Therefore, at present the results of this systematic review and meta-analysis could be used to make recommendations, on the understanding that our estimates of venous thrombosis risk are imprecise and should be interpreted with caution due to the high risk of bias. Further primary research would improve the imprecision of the estimates observed in this meta-analysis, particularly if participants are randomised prospectively to either intervention, negating the effects of bias and confounding.

## DISCUSSION

This systematic review aimed to evaluate the quality of the evidence and quantify the differences in thrombosis rates of venous couplers versus hand-sewn anastomoses in microsurgical free flap reconstruction. Direct comparison meta-analysis of 9 147 microsurgical venous anastomoses indicates an imprecise estimate of a reduced risk of venous thrombosis when a venous coupler was used compared to a hand-sewn anastomosis technique. The observed relative risk reduction was approximately 32% for venous couplers compared to hand sewn anastomoses, ranging from a reduced risk of 61% to an increased risk of 19%. There was an absolute risk of thrombosis of 2% in the venous coupler group and 2.7% in the hand sewn anastomosis group. This equates to an estimated absolute risk reduction of 0.7%. These observations are supported by large scale observational data which were at high risk of bias, predominantly due to confounding. Venous thrombosis incidences in individual studies included in our meta-analysis were variable. Five studies had similar venous thrombosis rates in coupled and hand-sewn anastomoses. However, in the study by Hanson et al., venous couplers carried higher risk of developing thrombosis. In contrast, O'Connor et al. found the opposite and recommended the use of venous couplers due to its lower risk of thrombosis. One strength of this data synthesis exercise is generation of summary statistics, based on very large patient numbers, that can moderate findings from smaller, individual studies.

Venous couplers are commonly used devices for microsurgical reconstruction, especially in head and neck, breast and lower limb free flap reconstruction. Couplers aim to simplify the technically demanding process of micro-anastomotic sutures and to reduce the time to complete a venous anastomosis.<sup>5</sup> Further potential benefits such as a reduction in post-operative complications due to lower haemoglobin (Hb) levels<sup>51</sup>, less fatigue<sup>22</sup> and economic benefits<sup>52</sup> have been discussed in recent literature.<sup>52</sup> However, across-the-board use of coupler devices over hand-sewn anastomosis may result in a deskilling of surgical trainees, limiting their abilities to perform a hand-sewn anastomosis when necessary.<sup>5, 22</sup>

Other factors must be considered in the evaluation of microsurgical complications. Sullivan et al. reported the use of venous couplers to manage vessel size discrepancies of 2:1 to 3.5:1 with 100% flap survival, theorising that the coupler enabled secure intima-to-intima contact between both vessels

despite the size difference. They even concluded that venous couplers are the preferable tool when performing anastomoses for vessels with large size discrepancy. However, this was in a relatively small population (n=39) with a high risk of bias in the study. The coupler size itself has shown to affect the outcome after free tissue transfer. Hanson et al. recently reported venous thrombosis rates of 6.9% using 1.5 mm venous couplers. Venous anastomoses performed with couplers of larger diameter ( $\geq 2$  mm) resulted in lower venous thrombosis rates between 1.2% and 2.4% (p=0.04). When excluding those with 1.5 mm couplers, no difference in postoperative thrombosis rates between venous couplers and hand-sewn anastomoses was detected (p=0.53).<sup>29</sup> Kisser et al. reported similar findings in head and neck reconstruction. They showed that an increase in coupler size significantly reduced overall flap revision surgery by more than 40% for each additional millimetre.<sup>44</sup> Although both studies had large study populations (Kisser et al. n=437; Hanson et al. n=4 662), they still had methodological issues affecting the reliability of their results (Table 1). Although 27 of 32 included studies reported the size of coupler, only Hanson et al. and Kisser et al. compared different coupler sizes in terms of venous thrombosis rates. Their findings support the notion that the coupler size may play an important role in influencing the flap-related outcomes. Future studies should therefore consistently report coupler size where possible so that further analysis is feasible.

The two studies comparing the time to complete a venous anastomosis suggest that venous couplers can reduce the time to complete a venous anastomosis. However, the reported data was limited precluding definitive conclusions.<sup>22, 48</sup> The time required to complete a hand-sewn venous anastomosis was unusually high in both studies and does not comply with the authors' experience.

We were unable to report on differences in flap failure between hand-sewn and coupled anastomosis. Free flap failure is multifactorial and can be divided into pre-, intra- and postoperative factors.<sup>53</sup> Postoperative factors include but are not limited to venous and arterial thrombosis, and haematoma resulting from vessel leakage.<sup>54</sup> Once free flaps fail, additional factors such as postoperative care, free flap monitoring and the time of returning to theatre can influence the overall flap survival. The inclusion of flap failure as outcome measure and its statistical analysis therefore requires meticulous documentation of those factors. The fact that, most of the included studies lacked to explicitly report flap failure causes made any reliable data collection and analysis of this outcome impossible.

One included study reported on the economic outcomes of coupled venous anastomoses concluding that there is no financial benefit nor deficit using venous couplers in free flap reconstruction, not considering the initial coupler device investment costs.<sup>22</sup> An economic model by Head et al. that was not included in our data extraction and analysis compared the costs of a coupled venous anastomosis with a hand-sewn anastomosis. Economic benefit was calculated by the difference between the incremental disposable costs (coupler ring vs. used sutures) and potential cost savings resulting from shorter operating time when using the coupler. According to his model, costs of up to 235 USD can be saved per anastomosis by using the venous coupler. At least 13 coupled anastomoses were therefore required to pay back the initial costs of the reusable coupling device in the respective study (2 985 USD).<sup>52</sup>

### **Strengths and Limitations**

Previously published systematic reviews showed superior results for venous coupled anastomoses in terms of venous thrombosis rates.<sup>4, 10, 11</sup> However, all these reviews have significant methodological flaws. Only one review performed meta-analysis but was neither preceded by a study protocol nor included a comprehensive risk of bias assessment or grading of the evidence. Moreover, the unit of analysis for venous thrombosis in Liu et al. was defined as number of flaps, which can only be deemed acceptable where the number of venous anastomoses equals the number of flaps. No further information on this issue was provided in this publication and the results are at serious risk of bias.<sup>11</sup>

Our direct comparison meta-analysis comparing venous coupler with hand-sewn anastomoses indicates no difference in risk of venous thrombosis overall and in the subgroup analysis for reconstructive site. Our systematic review is based on robust methods with a study protocol registered on PROSPERO (CRD42018110111) and published open access.<sup>15</sup> Assessment of the risk of bias and quality of evidence appraisal additionally weighs the reliability of included studies and extracted data.

All included studies were observational studies and therefore are vulnerable to a variety of biases, especially confounding, according to the ROBINS-I and NIH assessment tool (Table 1 and 2).

Reporting of outcomes was inconsistent throughout the reviewed studies and most of them showed

methodological frailties. Moreover, clear exclusion and inclusion criteria for selection of included patients were missing in most included studies making selection bias likely. Different co-morbidities and individual risk-factors showed to have an effect on flap survival after microsurgical reconstructions.<sup>53, 54</sup> These include but are not limited to diabetes, vascular disease, previous or ongoing radiotherapy, pulmonary disease and smoking.<sup>54</sup> The inclusion of those factors might have affected type of intervention and outcome.

The definition of a venous thrombosis and the methods of the outcome assessment (such as clinical, radiographic or solely intraoperative assessment) varied among included studies. Low event rates of venous thrombosis shown in the reviewed retrospective studies require a large sample size in the setting of a prospective cohort study. This most likely makes such an attempt unfeasible and might be an explanation why such a prospective study has not been published to our knowledge.

## **CONCLUSION**

The use of venous couplers may marginally reduce the risk of venous thrombosis and also may have the potential to decrease overall operating time. Other potentially contributing factors to venous thrombosis, such as vessel size discrepancy should be further investigated. Further high-quality observational and experimental research may be indicated, focusing on comprehensive, standardised outcome measurement and lessons learned from previous studies. This would improve the accuracy and reliability of the observed risk reduction in venous thrombosis for venous coupler.

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## **CONFLICT OF INTEREST STATEMENT**

None

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