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Breast

Use of Near-infrared Spectroscopy and Implantable Doppler for Postoperative Monitoring of Free Tissue Transfer for Breast Reconstruction: A Systematic Review and Meta-analysis

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Background: Failure to accurately assess the perfusion of free tissue transfer (FTT) in the early postoperative period may contribute to failure, which is a source of major patient morbidity and healthcare costs. This systematic review and meta-analysis aim to evaluate and appraise current evidence for the use of near-infrared spectroscopy (NIRS) and/or implantable Doppler (ID) devices compared with conventional clinical assessment (CCA) for postoperative monitoring of FTT in reconstructive breast surgery.

Methods: A systematic literature search was performed in accordance with the preferred reporting items for systematic reviews guidelines. Studies in human subjects published within the last decade relevant to the review question were identified. Meta-analysis using random-effects models of FTT failure rate and STARD scoring was then performed on the retrieved publications.

Results: Nineteen studies met the inclusions criteria. For NIRS and ID, the mean sensitivity for the detection of FTT failure is 99.36% and 100% respectively, with average specificity of 99.36% and 97.63%, respectively. From studies with sufficient reported data, meta-analysis results demonstrated that both NIRS [OR = 0.09 (0.02–0.36); $P < 0.001$] and ID [OR = 0.39 (0.27–0.95); $P = 0.04$] were associated with significant reduction of FTT failure rates compared with CCA.

Conclusions: The use of ID and NIRS provided equivalent outcomes in detecting FTT failure and were superior to CCA. The ability to acquire continuous objective physiological data regarding tissue perfusion is a perceived advantage of these techniques. Reduced clinical staff workload and minimized hospital costs are also perceived as positive consequences of their use. *(Plast Reconstr Surg Glob Open 2019;7:e2437; doi: 10.1097/GOX.0000000000002437; Published online 29 October 2019.)*

INTRODUCTION

Free tissue transfer (FTT) for breast reconstruction following mastectomy has become a standard procedure on account of its superior aesthetics and durability compared with implant reconstruction. Vascular microanastomosis is a critical step for tissue survival. Anastomosis failure causes a lack of oxygen and nutrients to be perfused within the FTT: thrombus or bleeding of either the recipient artery or donor vein may lead to ischemia and congestion, respectively, which may contribute to tissue necrosis. Studies have described that venous thrombosis is the most common microsurgical complication followed by arterial thrombosis and bleeding.[4] Most microsurgical complications have been reported to happen within the first 24–48 hours following surgery with higher rates within the first 4 hours.[5] Close monitoring is therefore necessary to detect signs of vascular complications to salvage the FTT and decrease the failure rate.[1–3] Although there is no standardization, conventional clinical assessments (CCA) usually consists of regular visual and kinetic

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evaluations of the FTT. As the final health status depends on the expertise of the clinical team, additional tools are often used. Hand-held acoustic Doppler sonography can also be used for assessment of the blood flow across pedicles. However, these assessments are discrete, prone to human error, and, cannot provide prompt, real time and systematic detection of possible microanastomotic complications. Due to the shortcomings of CCA, devices based on the biophysical and biochemical tissue properties have been developed for continuous monitoring of the FTT. Specifically, near-infrared spectroscopy (NIRS) and implantable ultrasound Doppler (ID) devices have been commonly used for continuous and objective assessment of the tissue health.[6–8]

In the context of growing interest in the use of NIRS and ID to aid early detection of FTT complication and to prevent adverse patient outcomes, it is pertinent that current evidence in regard to these technologies is reviewed. The purpose of this systematic review is to compare the clinical outcomes of NIRS and/or ID and CCA for FTT monitoring.

METHODS

Systematic Review

A systematic search of the literature (title and abstract of full papers and conference abstracts) was performed using the guidelines described by the preferred reporting items for systematic reviews (http://www.prisma-statement.org/) and meta-analysis statement to identify publications between 2008 and October 2018 regarding the use of (1) ID, (2) NIRS, and (3) combined NIRS and ID in the postoperative monitoring of FTT for immediate or delayed breast reconstruction following mastectomy.

Inclusion and Exclusion Criteria

Only studies published in English before October 2018 containing original data where ID, NIRS, combined NIRS/ID, combined NIRS/CCA and combined ID/CCA were used to monitor FTT for breast reconstruction in humans were included. Review articles, oral or poster presentations, conference abstracts, letters, comments, any study describing the validation of animal or cadaveric simulation in surgical training, unpublished data, and any article using nonoriginal data (ie, previously published) were excluded.

Search

We conducted a systematic search strategy, which combined the following search terms and their variations with AND and OR operators using the OVID (EMBASE/Medline) database: "reconstruction," "autograft," "surgical flap," "implantable Doppler," "monitoring," "physical examination," "near-infrared spectroscopy," and "NIRS." An additional search concerning specific devices ("Cook-Swartz," "O2C," "Synovis") was performed. MeSH terms and truncation symbols were used where possible to widen the search.

Our systematic search strategy was applied the following online databases: Medline, Embase, PsycINFO, Global Health, HMIC, the Cochrane Libraries Database of Systematic Reviews, SCOPUS, NHS Evidence, the Transport Database. We used the OvidSP platform to search the Medline, EMBASE, PsychINFO, Global Health, and HMIC databases.

Selection Protocol and Data Extraction

Titles and abstracts of studies identified by the primary search were independently reviewed by M.B. and J.A. to identify potentially relevant articles. The full texts of potentially relevant articles were obtained to facilitate further review. In the cases were from the same patient population was presented in full or partially in separate publications either the most recent or relevant article was included. The reference lists of retrieved articles and relevant reviews were also hand-searched to identify other suitable publications. Any areas of disagreement between reviewers were resolved by P.B.

The articles satisfying the selection criteria were retrieved for independent data extraction by M.B. and J.A. Data include author, year of publication, country of design, patient number, characteristics of patient population, FTT overall survival rate, sensitivity, and, specificity of the monitoring method.

Statistical Analysis and Assessment of Quality Report

An additional meta-analysis is conducted using random effects, DerSimonian-Laird method (RevMan, Edition 5, Cochrane Library of Systematic Reviews) based on papers with adequate information to observe FTT failure results when respectively comparing ID and NIRS with CCA. Publication bias of included studies was assessed using funnel plots. The Egger test was used to assess funnel plot asymmetry. The I^2 value was used to assess heterogeneity between studies, to determine the degree of variation not attributable to chance alone. Low, moderate, and high degrees of heterogeneity were ascribed to I^2 values <25%, 25%–75%, and >75%, respectively. Statistical significance was assigned to P values <0.05. Methodological quality of the papers was independently assessed by M.B. and J.A. using the STARD checklist[28] against 34 criteria (**see appendices, Supplemental Digital Content 1,** which displays STARD checklists for ID retrieved publications, **http://links.lww.com/PRSGO/B226,** and **Supplemental Digital Content 2**, which displays STARD checklists for NIRS retrieved publications, **http://links.lww.com/PRSGO/B227**).

RESULTS

The initial search identified 129 citations, of which 98 were excluded upon title and abstract screen. Thirty-one citations underwent further review, upon which 21 citations were removed. The remaining 15 citations were retrieved. An additional 4 citations were identified through hand searching of bibliographies (Fig. 1). Data were extracted from the 19 retrospective and prospective studies (Tables 1 and 2).

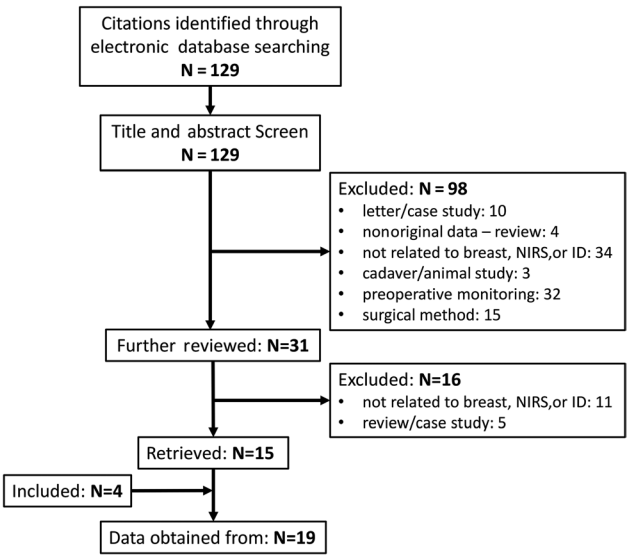

Fig. 1. PRISMA diagram of the search of the last 10 years of original publications on clinical studies on the investigation of implantable Doppler, NIRS, combined NIRS/implantable Doppler, combined NIRS/conventional clinical assessment, and combined implantable Doppler/conventional clinical assessment for the postoperative monitoring of FTT for immediate or delayed breast reconstructive surgery following mastectomy. PRISMA indicates preferred reporting items for systematic reviews.

STARD Methodological Quality Report

Assessment of reporting standards against the 34 criteria of the STARD checklist shows a mean of 17.1 (median: 18, range: 9–21) for ID and a mean of 19.2 (median: 17, range: 14–24) for NIRS. Tables 1 and 2 give the STARD score for each retrieved study.

Implantable Doppler

Of the studies identified, 8 used ID to monitor FTT. The extracted data from these studies are presented in Table 1.

Meta-analysis: FTT Failure Results

Comparisons between ID and clinical monitoring outcomes were made in 4 studies.[13,15,27,29] Meta-analysis of outcomes presented within these studies identified that ID monitoring was associated with reduced odds of FTT failure [OR = 0.39 (0.27–0.95); $P = 0.04$) (Fig. 2).

ID versus Clinical Monitoring

Schmulder et al,[29] Rozen et al,[13] and Whitaker et al[27] investigated the impact of using the Cook-Swartz ID (Cook Medical; Cook Ireland Ltd., Limerick, Ireland) compared with that of CCA (Table 1). Schmulder et al[29] and Rozen et al[13] found that using ID significantly improved the success rate of FTT surgery for breast reconstruction. However, Whitaker et al[27] found similar success rate for both CCA and ID. In addition, although Rozen et al[13] found that there are no statistical differences in the false-positive and re-exploration rates, Whitaker et al[27] did in favor of ID. This difference might be due to the difference between the number of cases monitored with CCA and that with

Table 1. A Summary of Studies Using ID for Postoperative Monitoring of FTT for Immediate or Delayed Breast Reconstruction following Mastectomy

Authors	Year	Country	Study Design	No. Patients	No. FTT	No. Re-explanations	Overall Survival (%)	Measured Sensitivity (%)	Measured Specificity (%)	*P* Value at 5%*	Device and Placement	STARD Score	References
Smit et al	2008	Sweden	RCS	103	121	14	98	100	99	—	Cook-Swartz Vein	18/34	10
Rozen et al	2010	Sweden	RCS	121	121	11	96.3	100	99	$P < 0.01$	Cook-Swartz Vein	18/34	13
Whitaker et al	2010	Denmark	RCS	103	121	11	97.5	100	99	$P = 0.93$	Cook-Swartz Vein	20/34	27
Schmulder et al	2011	Germany	RCS	37	37	6	97.3	—	—	$P = 0.049$	Cook-Swartz Vein	16/34	29
Levine et al	2013	United States	RCS	84	134	4	97.8	—	—	—	Cook-Swartz Artery/Vein	9/34	30
Um et al	2014	United States	RCS	76	109	11	98	100	99	—	Cook-Swartz Vein	21/34	18
Um et al	2014	United States	RCS	74	111	5	99	100	98	—	Synovis flow coupler vein	21/34	18
Kempton et al	2014	United States	RCS	50	85	6	95.3	100	94	—	Synovis flow coupler vein	19/34	15
Chang et al	2015	United States	RCS	53	—	—	—	100	88	—	Cook-Swartz Artery/Vein	16/34	31

*P value obtained with a t test at 5% comparing the significant difference in the monitoring outcomes with the use of ID and conventional clinical monitoring methods.
RCS, retrospective case series.

Table 2. A Summary of Studies Using NIRS Devices for Postoperative Monitoring of FTT for Immediate or Delayed Breast Reconstruction following Mastectomy

Authors	Year	Country	Study Design	No. Patients	No. FTT	No. Re-explorations	Overall Survival (%)	Measured Sensitivity (%)	Measured Specificity (%)	*P* Value at 5%*	NIRS Device	STARD Score	References
Repez et al	2008	Slovenia	PCS	48	50	13	94	100	100	—	InSpectra Model 325	20/34	32
Keller	2009	United States	RCS	145	208	8	100	100	100	—	ViOptix	14/34	33
Lin et al	2010	United States	RCS	164	234	16	93.8	100	100	$P = 0.015$	ViOptix	17/34	26
Pelletier et al	2011	United States	PCS	25	25	4	96	100	100	—	ViOptix in ICU	19/34	34
Pelletier et al	2011	United States	PCS	25	25	3	100	100	100	—	ViOptix in the ward	19/34	34
Whitaker et al	2012	United Kingdom	PCS	10	10	4	99	100	100	—	InSpectra Model 650	17/34	35
Rothenberger et al	2013	Germany	PCS	34	34	5	97	100	97	—	O2C Machine	17/34	36
Koolen et al	2015	United States	RCS	451	670	29	96.6	96.5	99.8	$P = 0.464$	ViOptix	24/34	37
Vranken et al	2017	The Netherlands	PCS	29	29	2	96.5	100	96.4	—	Invos 5000C Oximeter	16/34	38
Ricci et al	2017	United States	RCS	595	900	32	99.7	96.5	99.8	—	ViOptix	19/34	39
Fox et al	2013	United States	PCS	27	32	1	100	100	100	—	Spectros T-Stat	14/34	40
Mericli et al	2017	United States	PCS	68	81	3	100	100	100	—	Spectros T-Stat	16/34	54

*P value obtained with a t test at 5% comparing the significant difference in the monitoring outcomes with the use of NIRS devices and conventional clinical monitoring methods.
PCS, prospective case series; RCS, retrospective case series.

the ID. In Rozen et al[13] study, about 3.5 times more FTT cases were monitored with CCA alone while about 2 and 1.1 times more in Whitaker et al[27] and Schmulder et al[29] studies, respectively. Additional differences can originate from CCA results which remain subjective and require expertise.

Sensitivity and Specificity of ID Probes

Focusing on the sensitivity and specificity of the use of Cook-Swartz ID, Chang et al[31] found that they are both high despite 40.4% of negative findings on re-exploration. When looking at all types of surgery, Chang et al[31] advocate that positioning the ID on the artery is recommended as sensitivity and specificity are greater than when placed on the vein (respectively, $N_{patient} = 267$ at 94.2% sensitivity and $N_{patient} = 101$ at 74.0% sensitivity). They also found no statistical difference in the results when an ID is placed only on the artery compared with the results when placing 2 ID probes on each the vein and artery ($N_{patient} = 71$).

ID Probe Placement

Unlike Chang et al,[31] Swartz et al[41,42] have demonstrated that when placed on the artery, while arterial occlusion is immediately detected, detection of venous occlusion is delayed for up to 6 hours due to persistent arterial pulse. Likewise, when placed on the vein, venous occlusion is immediately detected and arterial occlusion is detected after 6 minutes in average. The difference in the practical use of the probe might come from the characteristics of the FTT, such as the size of the pedicle, the patient's vascular pattern, or the type and weight of the FTT.

Near-infrared Spectroscopy

Of the studies identified, 11 used NIRS devices to monitor FTT. The extracted data from these studies are in Table 2.

Meta-analysis: FTT Failure Results

Comparisons between NIRS and CCA were made in only 2 studies,[26,37] with NIRS monitoring being greatly associated with reduced odds of FTT failure [OR = 0.09 (0.02–0.36); $P < 0.001$] (Fig. 3).

NIRS versus Conventional Monitoring

Lin et al[26] and Koolen et al[37] compared the outcomes of CCA with these of the T.Ox. (ViOptix Inc.). For Lin et al,[26] the difference in the outcomes between the 2 methods is statistically significant, while it is not for Koolen et al.[37] Similar studies were conducted by Fox et al[40] with the T-Stat device (Spectros Corp., Portola Valley, Calif.), by Whitaker et al[35] and by Repez et al[32] with the InSpectra device (Novatech Resources Pte Ltd.), and Rothenberger et al[36] using the O2C machine (LEA Medizintechnik GmbH). In general, results show an increase in the FTT salvage rate and an early detection of complications, even before clinical evidence. Differences in the results might come from subjectivity in CCA results as it requires expertise.

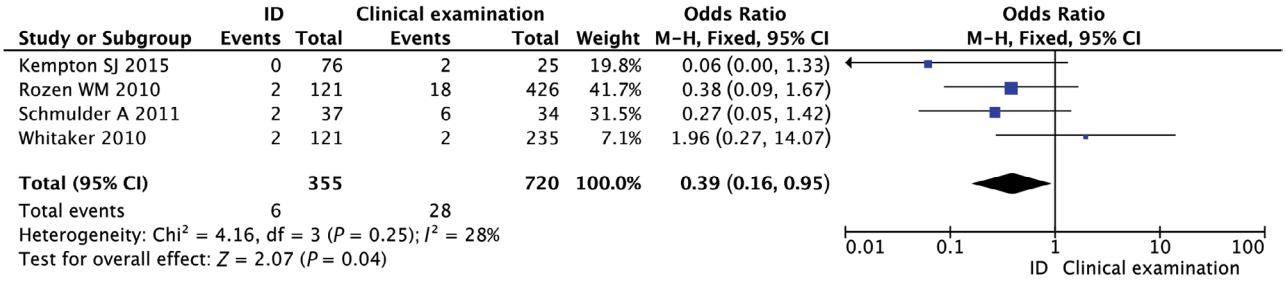

Fig. 2. A forest plot of the odds ratios (ID monitoring vs clinical monitoring).

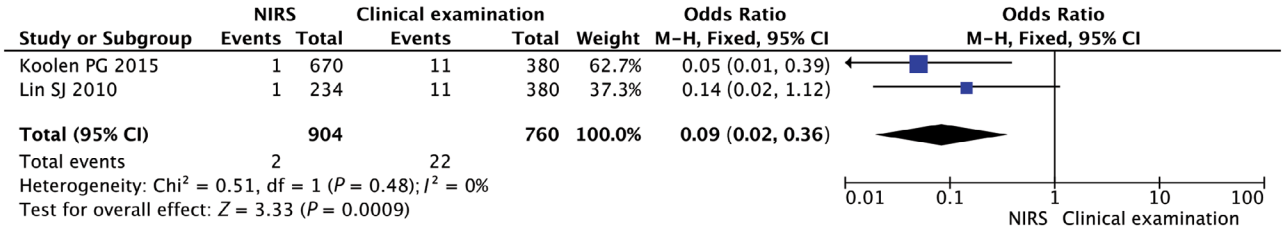

Fig. 3. A forest plot of the odds ratios (NIRS monitoring vs clinical monitoring).

Sensitivity and Specificity of NIRS: Clinical Use

Keller[33] and Mericli et al[54] compared NIRS monitoring to CCA for early detection of FTT complications. Results show higher sensitivity and specificity with a detection of complications before clinical evidence using the NIRS device.

Ricci et al[39] investigated the potential use of NIRS device as a mean to reduce intensive monitoring and lower consequent care costs. As high sensitivity and specificity were found using the T.Ox device, they advocate that the use of a NIRS device for postoperative monitoring can reduce the time patients spend in an intensive monitoring setting while saving hospital cost for similar outcomes compared with CCA. Similarly, Pelletier et al[34] found concurring results and suggest that a NIRS device can completely replace specialized clinical staff for postoperative monitoring.

NIRS Placement

Vranken et al[38] investigated the use of NIRS devices as a reliable mean for postoperative FTT monitoring and can provide early detection of a complication. Using the Invos 5000C (MedTronic Ltd.), which is primary designed for cerebral/somatic use, results were conclusive and the authors advocate that the comparison of the StO_2 measurements pattern from "healthy" FTT with the measurements of the FTT under monitoring can help in the identification of complications at an early stage. However, the pattern was not fully determined and merely described as increasing or decreasing slopes. The authors also compared the measurements of the monitored FTT with another sensor placed on the native breast tissue which acts as a personalized reference value. They advocate that their comparison provides a deeper insight on the absolute value of the variation of StO_2 within the FTT.

DISCUSSION

The main limitation of the ID lies in its positioning. Improper positioning can result in (1) false-positive alerts, especially if the probe has moved, which may induce negative re-explorations; (2) hematoma following anastomosis rupture, sometimes due to inadvertent pulling or removal of the wire; (3) blood vessel thrombosis, if the probe is too tightly secured onto the blood vessel. With experience, the number of complications due to the use of the ID generally reduces. Also, by combining the ID outcomes with CCA and other monitoring methods, false-positive alarms can be backed up to avoid negative re-explorations.[44]

NIRS devices have limitations that are intrinsic to (1) the device's hardware, (2) the device's algorithm for the analysis of the measurements, and (3) the patient's demographic details.[9,21] Components (light emitter and light detector) placement and light wavelengths induce hardware limitations which result in a specific range of penetration depth and a relative measurement of the concentration of blood compound or tissue components. Hardware limitations can be overcome with the design of a specific algorithm for the analysis of the measurements, for signal amplification and adjustment when investigating a given compound.[21] Ozturk et al[45] showed that surgical and clinical parameters, such as blood pressure, supplemental oxygen saturation, FTT type, perforator's size and number, patient's demographic details (such as skin tone and age), and the environment's characteristics into which measurements are taken (such as ambient light) can also affect the final outcome of the NIRS device.[9,21,25] Mostly due to these limitations, it is difficult to provide absolute StO_2 measurements or to rigorously compare StO_2 measurements between different NIRS devices.

To directly compare ID and NIRS devices, it is necessary to acknowledge their differences: (1) between what is measured, respectively blood flow perfusion, and, StO_2 and its related parameters; (2) between their positions, respectively, implanted at the entrance/exit of the FTT (onto the pedicles) and at an external localized area.[49] Although these differences are related because a change

in blood flow perfusion will affect the overall StO_2 independently to where the measurement is taken, they can affect the minimum time taken to detect a complication. To compensate for autonomic denervation, inflammatory reaction, and ischemia, which are normal reactions following FTT harvest, StO_2 consumption increases. This induces an increased blood flow perfusion and a decreased vascular resistance that dilates the microcirculation within the tissue, which facilitate the dissolution of possible microthrombosis and the repair of micronecrosis.[50–52] These physical responses can vary according to the vascular pattern, nicotine or alcohol abuse, demographics, and comorbidities of the patient.[45,49,51] Raittinen et al[52] argued that although the readings might vary across patients, the StO_2 trend remains the same. This trend has been described as a sharp increase followed by a decrease and ultimately a stabilization within the first 3 days following surgery.[52,53]

CONCLUSIONS

Most studies found the ID as an effective, efficient, and safe monitoring system that is a valuable adjunct to CCA. Specifically, Rozen et al,[13] Schmulder et al,[29] and Whitaker et al[28] have reported that the system can improve salvage rates. However, Smit et al[10] reported no such improvement in salvage rates, but encourage its use as it reduces the workload of the clinical staff and interruptions on the patients. Chang et al[31] suggest that CCA should remain the gold standard for postoperative FTT monitoring, especially when a cutaneous paddle on the FTT is available. Using a weighted average analysis, based on the total number of FTT cases, the overall re-exploration rate, survival rate, sensitivity, and specificity were calculated. Overall studies investigating the results of the Cook-Swartz placed at the venous pedicle,[10,13,18,27,29] with a total number of 509 FTT cases, results demonstrate a 10.41% re-exploration rate, 97.20% survival rate, 100% sensitivity, and 99.00% specificity. Similarly, with the Synovis Flow Coupler placed at the venous pedicle,[15,18] with a total number of 196 FTT cases, results show 5.63% re-exploration rate, 97.39% survival rate, 100% sensitivity, and 96.26% specificity.

Most studies reported that NIRS is a highly sensitive, specific, and reliable technique that can improve the FTT salvage rate. Most studies have a 0% false-positive rate.[26,27,32–34] Ricci et al[39] and Koolen et al[37] studies have a false-positive rate at 0.1% and 0.15%, respectively. In these studies, no particular definition of a false-positive result was given. Vranken et al[38] and Rothenberg et al[36] did not provide false-positive results; however, their high specificities suggest low false-positive rates. In addition, Pelletier et al[34] advocate that the use of NIRS devices can reduce the FTT monitoring cost structure. Although further research on the use of NIRS technique for buried FTT has been reported,[24,43] at the moment NIRS devices are conventionally used when a cutaneous paddle is available. A weighted average analysis based on the number of FTT cases was performed. Overall studies investigating the results of the ViOptix,[26,33,34,37,39] with a total number of 2,062 FTT cases, results show 4.41% re-exploration rate, 97.92% survival rate, 97.24% sensitivity, and 99.75% specificity.

Table 3. Costs of the NIRS and ID Devices Which Are Currently Available and Used in the Reviewed Studies

Company	Name	Controller Machine Price	Disposable Probe Price
Cook Medical	Cook-Swartz	2,494.00 GBP	380.00 GBP
Synovis Micro	Flow Coupler	2,305.00 GBP	714.00 GBP
ViOptix	T.Ox	25,000.00 USD	1,450.00 USD
Spectros	T-Stat	32,000.00 USD	629.00 USD

Specific studies investigating either implantable or NIRS methods, compared with or without CCA have been conducted. With the included studies, the weighted average results show that NIRS, using the T.Ox machine, gives better outcomes than when using the Cook-Swartz or Synovis ID, with, respectively, 4 and 10.5 times more FTT cases recruited. However, large studies aiming to compare NIRS and ID on the same patients under the same clinical conditions would need to be conducted for a more rigorous comparison. Table 3 shows the prices of the most common devices used in the presented clinical studies.

Many studies have demonstrated that both methods are useful and reliable as they reduce the staff burden and improve the overall FTT salvage rate. However, few studies have tried to decipher which method is the most appropriate taking into consideration the multiple variables across the range of microsurgical applications. In addition to high accuracy and robustness, wider and systematic use of such methods lies into their (1) ease of use, with a relatively short learning curve, (2) acceptance (based on the medical relevance, learning curve, and large studies outcomes), and (3) relative costs.

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