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Review

Emerging nonsurgical and surgical techniques to treat erectile dysfunction: A systematic review of treatment options and published outcomes

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Summary Erectile dysfunction (ED) is one of the most common causes of morbidity in male patients, with a prevalence of 50–60% in men aged 40–70 years. EDs may be caused by physical or psychological trauma, the former of which may be treatable through surgical intervention. Physical trauma may be further categorized as vasculogenic, neurogenic, or idiopathic in nature. Although many patients do not respond well to nonsurgical treatment options, few opt for surgical intervention. This is likely due to the difficulty of the procedures, as well as relatively low historical success rates. As such, a systematic review of the literature was performed to identify novel surgical interventions for ED.

A total of 19 manuscripts were included in this review, representing data of three minimally invasive approaches to ED treatment and seven novel surgical techniques. The data revealed compelling evidence in support of microsurgical treatments for ED – namely, microvascular arterial bypass penile revascularization surgery (MABS) and cavernous nerve graft reconstruction. Nerve grafts varied, with the use of end-to-side ilioinguinal, genitofemoral, and sural grafts, all demonstrating high rates of success. Furthermore, minimally invasive botulinum toxin (BoNT-A) treatment and adipose-derived stem cell (ADSC) therapy have shown extreme promise in rat models; with BoNT-A treatment entering phase II human clinical trials this year.

Many of the surgical methods investigated in this review are microsurgical interventions that demonstrate high rates of success in patients with neurogenic or vasculogenic

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ED. As such, microsurgeons are uniquely trained and positioned to be of value to ED treatment.

Contents

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve and maintain a penile erection for the purposes of sexual intercourse.[1,2] EDs can be caused by physical or psychological trauma, the former of which may be treatable through surgical intervention. The etiology of physiological ED may include poor sensation from neuropathy or trauma, poor perfusion from vascular diseases, or problems with venous outflow, but they are all categorized as vascular, neurogenic, endocrine, or idiopathic in nature.[2,3] Several diseases may contribute to physiological ED, including heart disease, hyperlipidemia, hypertension, diabetes, obesity, tobacco use, alcohol use, Peyronie's disease, and treatments for prostate cancer and other surgeries or injuries that affect the pelvic region or spinal cord.[4-6] Many pharmacological agents exist to improve ED, with the mechanism underlying phosphodiesterase inhibitor treatments well understood as a function of the action on cavernosal smooth muscle cells. Many novel surgical and microsurgical interventions have also demonstrated promise in augmenting erectile response in the treatment of both vascular and neurogenic ED.[7-10]

The Massachusetts Male Aging Study, a random sample observational survey of men aged 40–70 years, found that 52% of these men reported ED. There have also been an increasing number of radical prostatectomies performed for patients with prostate cancer, with many patients suffering from postoperative ED despite nerve-sparing surgery.[11] Although ED has an enormous impact on the United States (US) male population, very few elects for surgical intervention.[12] Furthermore, the correct surgical interventions are difficult to identify even when the cause of the patient's ED is known.[12,13]

With the advent of robot-assisted nerve-sparing radical prostatectomy, it was thought that the prevalence of ED would decrease. However, several studies have now shown that there are no significant differences in functional outcomes between robot-assisted surgery and conventional surgical methods such as laparoscopy or open surgery.[14] Regardless of the surgical technique used, prostatectomy results in the disruption of normal pelvic anatomy and disrupts both nerve and vascular supply to the penis.[15] As such, ED remains a significant problem among men above the age of 40 years, as well as those men surgically treated for prostate cancer.[14,15]

In addition to its prevalence among the US population, ED significantly limits the quality of life of a still growing number of men.[16] Given the increase in conditions predisposing to ED – such as prostate cancer, coronary artery disease, and diabetes – as well as a quickly aging male population, addressing ED with both medical and surgical therapy is necessary.[16] In light of the discovery of novel molecular mechanisms that impact ED, as well as innovations in the field of surgery, many new and exciting treatment options have been introduced in the past decade. This study aims to review evidence for emerging surgical and nonsurgical interventions for ED and establish recommendations for their use.

Materials and methods

A systematic review of the literature was performed to identify novel and emerging interventions for ED and to investigate the details of each surgical procedure, as well as to identify clinical considerations for the support of in vivo study results.

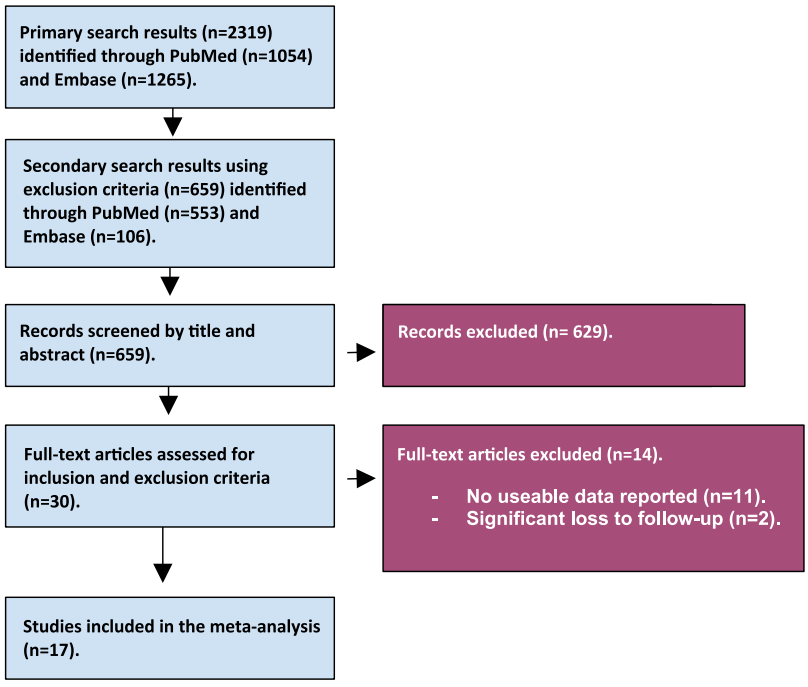

Figure 1 Flowchart depicting the stepwise approach for the identification of studies for surgical and nonsurgical interventions in the treatment of erectile dysfunction.

Table 1 Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Title and abstract assessment	Management of erectile dysfunction as the primary theme	Case report abstract only
	Diversified sample population.	Review article, Letter, Comments
	Surgical or therapeutic outcomes reported	Study before 1998 *(Last 20 Years)*
	Large enough sample population ($n > 5$)	Full text not available
Full-text assessment	Patient outcomes as the research theme	Does not report success rate or rate of complications
	Description of surgical technique performed with detailed outcomes	Does not report data used to calculate success rate or did not define "success"
	Data reported in a concise and extractable format	
	Adverse outcomes were reported	Data were not clearly labeled or organized
	Follow-up > 2 years	

A review of the literature was performed by authors OS and DG using the PubMed and EMBASE databases from July 2003 to January 2018. PubMed was searched with the following search terms: (((((("Neurosurgical Procedures"[Mesh]) AND "Erectile Dysfunction"[Mesh])) OR (("Vascular Surgical Procedures"[Mesh]) AND "Erectile Dysfunction"[Mesh])) OR (("Therapeutics"[Mesh]) AND "Erectile Dysfunction"[Mesh] AND "Last 5 Years"[PDat])). In EMBASE, the following search terms were used: (Erectile Dysfunction) and (Surgical Intervention) AND LIMIT-TO (YEARNAV, "2018, 2017, 2016, 2015, 2014″). The EMBASE search was limited to studies published in the last five years. Both searches were limited to manuscripts written in English. Primary search was limited to studies that included original data analysis, evaluated surgical treatment of ED in humans, mice, or rats, and reported the efficacy of the intervention. Systematic article selection and inclusion and exclusion criteria are detailed in Figure 1 and Table 1. The evaluation period of 15 years was chosen to provide a focused and concise update to more recent advances in microsurgery. Many of the techniques discussed in this review have been more extensively investigated in the past 10–15 years, and as such, the studies evaluated herein provide high-quality evidence for or against their efficacy.

Results

A total of 19 articles are included in this review, representing data of seven different surgical techniques for the management of both vasculogenic and neurogenic ED. These manuscripts also provide data of three novel minimally invasive techniques for the management of neurogenic, vasogenic, or idiopathic ED.

Minimally invasive interventions

Botulinum toxin treatment

Veno-occlusive dysfunction can occur secondary to the failure of smooth muscle relaxation, and this is the proposed mechanism by which both venous ligation therapy and treatment with phosphodiesterase type 5 inhibitors (PDE5i) may fail to improve erectile function.[17] Therapy that targets cavernosal smooth muscle relaxation may be able to vastly improve the outcomes of PDE5i treatment. Two animal studies found that the use of botulinum neurotoxin A (BoNT-A) successfully led to the relaxation of cavernosal smooth muscles by inhibiting the release of neurotransmitters from adrenergic neurons.[17] This was followed by two randomized controlled trial (RCT) human studies conducted in Egypt. The first study was a phase I pilot RCT that involved 24 men with vasculogenic ED not responding to PDE5i therapy. The intervention group received treatment with a single dose of Botox 50 U. Of the 12 patients in the treatment group, 54% (7/12) could engage in penetrative sex with the help of sildenafil, with 43% (3/7) of them able to complete intercourse.[17] The second study is a phase II RCT that is still ongoing, with a larger patient population (160) and an intervention of Botox 100 U. Although phase I RCT results show promise, experimental treatment with BoNT-A should only be considered as a last resort for patients not responding to either surgical or pharmacological treatment for ED. Furthermore, results from the larger power phase II RCT currently being conducted (2018) are still necessary to confirm the results of the phase I RCT presented by Ghanem et al.[17]

Adipose-derived stem cell (ADSC) therapy

Adipose-derived stem cells (ADSCs) are currently the only cell type that can be isolated and transplanted on the same day. Furthermore, many devices for the quick and automated isolation of ADSCs are easily accessible and commercially available.[18] With recent success in rat models, the literature has demonstrated that with transplantation, ADSCs can exert a paracrine effect on the surrounding penile tissues after transplantation and differentiate into smooth muscle cells, endothelial cells, and neurons as necessary – vastly improving erectile function.[19]

In 2017, a meta-analysis of 20 studies with a total of 248 rats was performed by Hou et al. The pooled analysis shows that ADSC intervention significantly increased the ratio of intracavernous pressure to mean arterial pressure compared to control groups.[20] These data demonstrate that ADSC therapy can regenerate cavernous artery, vein, and nerve structures in rats and is thus able to restore erectile function under both neurogenic and vasculogenic conditions. Human trials are still necessary to confirm these results and to determine the efficacy of ADSC use in humans suffering from ED; however, these initial results are extremely promising.

Extracorporeal shockwave therapy

Extracorporeal shockwave therapy is a noninvasive technique used in the treatment of ED that uses high-amplitude acoustic waves to deliver a mechanical force to the directed penile smooth muscle tissue.[21] The exact mechanism of action is currently unknown, but the current literature suggests that shockwaves may trigger the expression of growth factors and nitric oxide synthesis, subsequently leading to angiogenesis and regeneration of nerve fibers.[22] Frey et al. included 18 patients in the study, with a total of seven patients (39%) improving their erectile function from baseline measurements after one round of treatment. However, these improvements were only maintained in four (22%) patients after a second round of treatment.[21] Even more so, the improvements did not allow for unassisted erections sufficient for intercourse in any of the patients in this study.[22]

These results demonstrate that extracorporeal shockwave therapy may potentially play a limited role in the improvement of erectile function, but further studies are justified in exploring this treatment regimen. In conclusion, extracorporeal shockwave therapy does not seem to have a role as a standalone therapeutic option for ED but may improve outcomes following surgical intervention, and future randomized controlled trials should focus on investigating this relationship.

Surgical interventions

Venous ligation therapy

Historically, it was thought that cavernous vein (CV) occlusion was a result of excessive drainage from veins, with therapies aimed at reducing venous flow.[13] However, it is now the consensus that occlusive dysfunction is a result of vascular endothelial and smooth muscle damage.[13] A technique aimed at targeting dysfunctional venous endothelium is treatment by dorsal vein ligation. Hassan et al. demonstrated a success rate of 31% (10/32 patients), as defined by full rigid erection without adjuvant therapy.[23] The study also demonstrated that, and additional 28% (9/32 patients) showed drastic improvement but necessitated additional therapy (PDE5i) to achieve full erection.[23] Although early results were promising, a follow-up study by Afsar et al. also concluded that treatment by dorsal vein ligation did not fare well in the long-term group, with many patients relapsing after only 4 months postoperatively.[24]

These results were further corroborated by Rahman et al., ultimately declaring that penile venous surgery did not have a lasting effect.[25] This was hypothesized to be a result of venous leakage because of greater systemic disease or, rather more simply, the result of penile smooth muscle atrophy, both of which would prevent venous ligation therapy from successfully restoring erectile function. Therefore, venous ligation therapy does not appear to be a viable option for the long-term surgical management of vasculogenic ED.

Penile venous stripping surgery

With the recent advents in the study of penile venous anatomy, penile venous stripping surgery has now become a realistic option for the treatment of patients with cavernosal veno-occlusive dysfunction.

A circumcision is first performed to identify the deep dorsal vein (DDV), which is subsequently freed from the retrocoronal sulcus. The vein is then stripped distally to the level of the glans penis, and a pull-through maneuver is performed to minimize tissue damage. A pubic incision is then performed to pass the DDV and the CV trunk underneath. The DDV and CV systems are then ligated until the infrapubic angle is reached. Engorged circumflex veins and paraarterial veins are also ligated.[26]

With a reported follow-up period of 5.1–8.2 years, Hsu et al. demonstrated an improvement rate of 90.4% (151/167) in their patients, with a low rate of complications compared to that reported in the literature.[27] However, with very few other published studies demonstrating the efficacy of penile venous stripping surgery, there is still a need for further assessment. Even so, penile venous stripping surgery may be a viable option in patients with vasogenic ED.

Endovascular arterial revascularization

Endovascular therapy for the obstruction of the common iliac and hypogastric arteries has conventionally been performed for years and is well documented in the literature.[3] Furthermore, recent advents in medical technology have led to the downsizing of catheters and have greatly facilitated endovascular revascularization of even smaller penile arteries.[28] A recent study by Rogers et al. showed that 60% of patients undergoing stent placement showed functional improvement after endovascular revascularization.[28] The restenosis rate was reported to be approximately 34%. Wang et al. also demonstrated, with a group of 20 patients, that angioplasty down to the level of the penile arteries is safe and feasible, with 60% (12/20 patients) showing clinical improvement.[29] These studies validate the use of endovascular arterial revascularization as a viable and feasible option for the treatment of vasculogenic ED.

Emerging microsurgical techniques

Recent advances in microsurgical techniques have led to several new options for the surgical management of ED. These techniques are still in their infancy but may offer durable and potent restoration of functional erection. The benefit of microsurgical approaches is in the ability to treat neurologic and vasculogenic causes separately or in conjunction through direct revascularization with alternate inflow as well as through sensory reinnervation or transfer.

Microvascular arterial bypass penile revascularization surgery (MABS)

The aim of this microvascular surgical technique is to bypass the obstructed (distal) cavernosal arteries to deliver increased systolic perfusion and blood flow from a donor artery (the inferior epigastric artery [IEA]) directly to the recipient dorsal artery of the penis.[3] The surgery has three parts: dorsal artery dissection, IEA harvesting, and microvascular anastomosis of the donor and recipient arteries.[30]

Dicks et al. demonstrated an overall postoperative success rate of approximately 60%, with many patients followed up for greater than 10 years.[30] Munarriz et al. also reported a high success rate of MABS, with 36–80% successful outcomes following IEA to dorsal vein anastomosis and 91% successful outcomes following IEA to dorsal artery anastomosis.[31] These patients were able to achieve erectile function without the need for PDE5i supplementation. Both studies concluded that MABS is currently the only existing effective treatment option for restoring complete erectile function for those suffering from vasculogenic ED without the postoperative use of mechanical devices, pharmacological agents, or placement of a penile prosthesis.

Vardi et al. conducted a long-term study to corroborate these results and demonstrated a long-term success rate of 48% (25/52 patients) after undergoing MABS for vasculogenic ED.[32] The study found that the type of procedure performed (IEA to dorsal artery vs. IEA to dorsal vein) did not have any statistically significant effect on the success of MABS.[32] Overall, it can be concluded that these studies demonstrate with compelling evidence that MABS is an extremely effective long-term surgical intervention for the treatment of vasculogenic ED.

Cavernous nerve graft reconstruction

Cavernous nerve graft reconstruction has always posed a tremendous challenge to the surgeon because of the narrow space by which the surgery must be performed. Suturing of the grafted nerve must be performed at the most posterior end of the pelvic cavity, which greatly limits the scope of the surgery and relies heavily on the skill of the surgeon.[33] The size of the cavity limits the suturing of the nerve to only three to four sutures at most, and the cavity often easily fills with blood. This makes the field increasingly difficult to view under a microscope. Under these conditions, the graft is at risk for failure because of inadequate perfusion or delayed scar and stricture.[33] Even so, these barriers may be overcome with the involvement of an experienced microsurgeon.

To prevent graft failure, Fujioka et al. used a sural nerve graft supplemented by the novel autologous veinguide technique.[33] This study showed that after grafting, 88% (7/8) of patients were able to perform intercourse, although four required the assistance of pharmaceutical agents.[33] This method shows promise in the surgical management of neurogenic ED and should be further investigated.

Trindade et al. described another novel reinnervation technique using four sural nerve grafts and end-to-side neurorrhaphy to bilaterally connect the femoral nerve to both the cavernous corpus and the dorsal penile nerves.[34] In this study, the use of two nerve grafts to the bilateral corpora cavernosa aimed to provide the largest number of axons to the smooth muscle fibers of the penis.[34] A total of 60% (6/10) of the patients enrolled were able to achieve full penetration after reinnervation surgery.[34]

The efficiency of concomitant sural graft during radical prostatectomy has also been investigated in several studies by Sim et al. and Hanson et al.[35,36] Sim et al. demonstrated a success rate of 63% (24/38), defined as the ability to achieve erections sufficient for intercourse with or without the use of PDE5i. This was significantly greater than those who did not undergo concomitant nerve graft, of which only 27% (13/49) could achieve erection after surgery.[35] Similarly, Hanson et al. demonstrated a success rate of 72% (21/29), defined as the ability to achieve penetration following surgery.[36] These results suggest that the involvement of a microsurgeon at the time of nerve-sparing radical prostatectomy may greatly reduce the prevalence of postoperative ED.

Although sural grafts have shown relative success, ilioinguinal to dorsal penile neurorrhaphy was also demonstrated as an alternative option in Jacobs et al.[37] In this study, two patients with spina bifida-induced neuropathic ED were surgically treated with dorsal penile reinnervation through the

Table 2 Summary of microsurgical techniques currently available for the treatment of neurogenic erectile dysfunction.

Author, year[33-37]	Nerve graft	Technique	Study population	Study size	No. successful erection-penetration/total study pop.
Fujioka et al., 2007	Sural	End-to-side	Human	8	88%
Trindade et al., 2017	Sural	End-to-side	Human	10	60%
Sim et al., 2006	Sural	Concomitant, End-to-side	Human	87	63%
Hanson et al., 2008	Sural	Concomitant, End-to-side	Human	29	72%
Jacobs et al., 2013	Ilioinguinal	End-to-side	Human	2	100%
Viterbo et al., 2018	Genitofemoral	End-to-side	Human	N/A	N/A

ilioinguinal nerve. Eighteen months of postoperative assessment suggested successful reinnervation of the penis in both patients.

The techniques described above demonstrate a promising role for microsurgery in the treatment of patients experiencing neurogenic ED and are summarized in Table 2.[33-37] These methods should be further investigated with larger clinical trials to strongly recommend these techniques for future use. Furthermore, involvement of a microsurgeon may improve outcomes of these procedures as advances in surgical techniques in recent years have all been utilized in the toolbox of most microsurgeons for the improvement of outcomes for free functional muscle transfer, facial reanimation, and functional nerve transfers.[36,37]

Recent advances in reinnervation include nerve transfers from other dermatomal distributions to the dorsal penile nerve. Dr. Viterbo and colleagues recently presented genitofemoral to dorsal penile nerve transfers in addition to ilioninguinal grafts, with promising results and long-term functional sensory outcomes for the treatment of low spinal cord injuries and spina bifida patients.[34]

Conclusions

Review of the literature has revealed compelling evidence in support of various microsurgical procedures that exist to improve ED, but many lack a large enough study population to make material claims. Despite this limitation in power, the available evidence suggests some degree of efficacy for eight of the ten techniques presented in this review in improving erectile function, as defined by the ability to complete intercourse with or without the use of pharmaceutical agents.

Of the three minimally invasive interventions investigated, botulinum toxin treatment was the most promising future method as the last resort for patients presenting with idiopathic or nonoperable ED. This treatment modality has already completed stage 1 clinical trials and has begun its stage 2 clinical trials this year (2018), with an additional pilot study performed in Greece.

Of the eight surgical techniques investigated for both neurogenic and vascular ED, a majority of the studies investigated (7/8) proved the efficacy of these techniques. To date, cavernous nerve graft reconstruction has reported the highest rate of success in treating neurogenic ED. Furthermore, MABS has also reported the highest rate of success in treating vascular ED, but penile venous stripping surgery has shown extreme promise as well, limited only by the very few published studies verifying the efficacy of this technique.

Animal models were also reported in the treatment of ED in rats using ADSC therapy. These studies were included because of recent advents in medical technology that have allowed for same-day isolation and transplantation of stem cells using affordable and commercially available equipment – allowing stem cell therapies to become a much more realistic option in the near future. The results of the studies have shown that ADSC therapy was able to regenerate cavernous arteries, veins, and nerve structures in rats and is thus able to restore erectile function. With human trials soon to come, ADSC has an exciting future in the treatment of neurogenic, vascular, and idiopathic ED.

Importantly, the surgical options for ED may all benefit from the involvement of a microsurgeon. Microsurgeons are trained in small-vessel anastomosis, as well as nerve transfers and reconstructions. As such, they are uniquely trained and positioned to be of value to ED treatment. There is no doubt that the combination of urological and plastic and reconstructive surgical teams will prove to be a potent force in the management of penile trauma and replantation, as it already has in Fournier's reconstruction and transgender surgery.[38-40] This may represent yet another urological disease process that may benefit from an interdisciplinary approach.

Ultimately, the limitations of this review reflect those of the currently available literature in the surgical management of ED. Very few studies can enroll a large enough sample population to evaluate the efficacy of the surgical technique under investigation. Furthermore, it is necessary to perform direct comparisons of surgical options in the management of ED to provide a higher level of evidence to suggest the use of one technique compared to another. This study serves to organize the most up-to-date data in treating ED and to help guide future clinical decision making. Although many of the studies presented in this review show extreme promise, they all require further clinical evidence.

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