NERVE GRAFTING AT THE TIME OF RADICAL PROSTATECTOMY: SHOULD WE BE DOING IT?

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Background: With increasing numbers of younger men being diagnosed with prostate cancer and subsequently undergoing radical prostatectomy, there is an increasing focus on quality of life postoperatively, especially potency. In patients with locally advanced disease, it has been suggested that use of nerve grafts at the time of radical prostatectomy may improve potency. The technique was first described in 1999 and several papers have been published about its utility. However, there is still controversy over its use because of the lack of any large, blinded trials, the anatomy of the cavernous nerves and the necessity of excising the neurovascular bundles (especially bilaterally). In addition, the results achieved with nerve grafting, a procedure not without significant morbidity and mortality, do not exceed those produced by surgeons carrying out nerve-sparing procedures.

Results: In the published work reviewed, erections sufficient to produce vaginal penetration following unilateral nerve grafting (with contralateral nerve sparing) were evident in 41.7–63.6% of patients. This is similar to the rates of 23–64% with unilateral nerve sparing alone. The rates of erectile function sufficient to produce vaginal penetration following bilateral nerve grafting were 34–72%, whereas it is widely accepted that very few men without nerve grafting would have any degree of potency.

Conclusions: Currently, there does not appear to be a widespread role for nerve grafting at the time of radical prostatectomy.

Key words: erectile function, nerve grafting, prostatectomy.

INTRODUCTION

Since the advent of PSA testing in the early 1990s, the average age of men diagnosed with prostate cancer has fallen and simultaneously, the number of men aged <55 years undergoing radical prostatectomy has increased. In young, potent men with localized prostate cancer, the quality of life, postoperatively, will be almost as important as cure of the disease. One of the chief constituents of quality-of-life post-radical prostatectomy is erectile function. As such, various centres have suggested a variety of operative techniques to maximize the rates of potency postoperatively. These include the anatomical nerve-sparing prostatectomy, carried out by either an open, laparoscopic or a robotic approach. All these techniques are based on the premise that erectile function, post-radical prostatectomy, is related to the preservation of the cavernous nerves that run in the neurovascular bundles (NVB). As a corollary, preservation of both NVB produces the greatest postoperative potency rates and wide excision of both NVB essentially condemns the man to impotence.

In 1999, Kim et al. described the use of the sural nerve as an interposition graft for the cavernous nerves following wide excision of the NVB. This has been followed by several other centres publishing their experiences of nerve grafting at the time of radical prostatectomy. Concurrently, there is a contrary view that this technique will probably be neither anatomically nor clinically feasible. This paper aims to review the published work thus far on nerve grafting at the time of radical prostatectomy, and in the absence of a randomized control study in the area, offer some conclusions.

METHODS

The PubMed database was searched from 1950 to April 2007 for English language articles using the terms: ‘sural nerve’, ‘nerve grafting’, ‘radical prostatectomy’ and ‘erectile dysfunction’. In all, six studies were retrieved that directly dealt with erectile function following interposition nerve grafting at the time of radical prostatectomy (Table 1). In addition, recent papers reporting erectile function following nerve-sparing retropubic, laparoscopic and robotic prostatectomies were reviewed to gauge these results against the results reported with nerve grafting so as to form conclusions on the efficacy of nerve grafting.

RESULTS

In large, contemporary series from centres of excellence, preservation of both NVB at the time of open prostatectomy produces potency rates of 40–76%, whereas unilateral nerve sparing produces rates of 23–64%. Initial work on nerve grafting for the cavernous nerves was carried out by Quinlan in 1991. This produced promising results in a rat model; however, it has since been elucidated that the rat model is quite dissimilar to humans. A fundamental difference is
that the rat’s cavernous nerve is a relatively large and distinct structure, whereas in humans, extensive anatomical studies have shown that the cavernous nerve is, in fact, a tiny plexus of nerves intermingling with vessels. In addition, the nerves in this NVB innervate not only the corpora cavernosa, but also the rectum, prostate, and levator ani.1,2,25

The first researchers to carry out nerve grafting at the time of radical prostatectomy were Kim et al. In 2001, the group published an article describing their method for nerve grafting.11 It involved use of the sural nerve and emphasized the importance of loupe magnification, a tension-free anastomosis, precise identification of both ends of the NVB and use of a graft 10–20% longer than the defect to be grafted. In this study, they had a 12-man treatment group, all of whom had bilateral NVB resections. The mean follow up was 21 months, and over this time, seven men (58.3%) had erections sufficient for sexual intercourse (either with or without sildenafil). Of the matched controls (also 12 men having bilateral NVB resection) none had erections sufficient for sexual intercourse.

In 2006, Sim et al. published their results for 41 men who had unilateral sural nerve grafts using the same technique described by Kim et al.12 At 24 months, 63.2% had rigid erections sufficient for intercourse with or without use of sildenafil. This was similar to the institution’s database of radical prostatectomies with unilateral NVB excision where 26.5% of men had erections sufficient for intercourse at 2 years.

Also in 2006, Nelson et al. studied the efficacy of genitofemoral nerve grafts at the time of radical prostatectomy in 27 patients.14 The rationale for the use of the genitofemoral nerve was that it obviated the need for a separate incision to harvest the nerve graft (as is necessary for the sural nerve). At a mean follow up of 14 months, 63.6% of the 22 men who had unilateral nerve grafts had erections sufficient for sexual intercourse. This included those men requiring medication (either sildenafil or alprostadil).

In line with increasing utilization of laparoscopy for radical prostatectomy, in 2005, Porpiglia et al. reviewed 15 men with laparoscopically carried out unilateral sural nerve grafting.15 Follow up was complete for 12 men and the mean follow-up period was 18 months. A percentage of 41.7% of men had erections sufficient for vaginal penetration with or without sildenafil. In the control group of 10 men, 30% had erections sufficient for vaginal penetration.

The most recent paper in the MEDLINE database was by Secin et al. in 2003.13 That study, an 18-man cohort with bilateral nerve grafts, had 13 (72%) who could achieve intercourse at a mean of 15 months. This group used Cavermap (Blue Torch Medical Technologies, Ashland, MA, USA) to facilitate the nerve grafting.

Although all these papers have shown some degree of efficacy for nerve grafting at the time of radical prostatectomy, a paper by Walsh in 200117 challenged both the necessity and the efficacy of nerve grafting. In his study group of 12 men (6 treatment and 6 control) he found no difference between the erectile function in the two groups at 5 years. It was these results that have challenged the efficacy of nerve grafting at radical prostatectomy.

**DISCUSSION**

The technique of using autologous nerve grafts in humans at the time of radical prostatectomy was first described by Kim et al. in 1999.9,10 However, there is controversy regarding its necessity and efficacy based on three issues: lack of a large randomized controlled trial; the anatomy of the cavernous nerves in humans; and the necessity of wide excision of the NVB at the time of radical prostatectomy.

As shown by Table 1, the size of the largest treatment group in any study published on nerve grafting is 44 patients. As such there has been no large randomized control multicentre study adequately powered to effectively show the efficacy of nerve grafting. The difficulty in achieving this is how to blind the study if the sural nerve is to be used, as all members of the treatment group will have an incision site at their ankle that members of the control group will not have. In addition, the subjectiveness of an end-point such as ‘erectile function sufficient to produce sexual intercourse’ makes cross correlation of results at different centres difficult. Although several centres have attempted to compensate for this by using measurements such as nocturnal tumescence with Rigiscan (Timm Medical Technologies Inc, Eden Prairie, MN, USA) the final analyses have centred around the percentage of patients reporting erections sufficient for penetrative intercourse.

The difference in the anatomy of the rat and the human with regards to the cavernous nerves gives rise to another criticism levelled at nerve grafting. The preliminary work on sural nerve grafting by Quinlan was in a rat model.24 In the rat, with its relatively large and distinct cavernous nerve, grafting of any defect seemed feasible. However, separate anatomical studies by Walsh and Costello25 have shown the complexity of the cavernous nerves in humans. The cavernous nerves run as multiple small branches in a NVB (with branches of the inferior vesical artery and vein). At the prostatic base, the neural constituents of the bundle may be as much as 3 cm apart (in anteroposterior measurement). They then run outside the prostatic capsule and condense at the mid-prostatic level; however, they then diverge
again as they approach the level of the prostatic apex—where the
distal end of the nerve graft would be placed. To further confound
graft placement, the nerves in the NVB innervate not only the
corpora cavernosa, but also the prostate, rectum and levator ani.
And, in general, whereas, the nerves to the corpora are located
anteriorly at the level of the apex, identifying them at the level of
the prostatic base is very difficult as there is no definite functional
organization at this level. Therefore, the anatomy of the cavern-
ous nerves makes grafting a difficult prospect, as there is no
distinct nerve to the corpora, and identification of the correct
nerves, especially if a high proximal resection has to be carried
out (for instance in a patient with seminal vesicle involvement), is
difficult.

There is no universal agreement as to when to widely excise the
NVB at radical prostatectomy. In most of the studies on nerve
grafting, there was generally a decision made at the time of op-
eration; however, preoperative planning to excise one or both
bundles was often made based on Ohori’s nomogram for predicting
extracapsular extension. Walsh has challenged the necessity for
NVB excision in many patients. Although it is generally accepted
that patients with organ-confined disease can have both NVB
preserved, Walsh has stated that many patients with extracapsular
extension may also have their NVB preserved based on the hist-
topathological characteristics of prostate cancer. When prostate
cancer breaches the capsule, it travels less than 2 mm laterally in
75% of patients before extending cephalad toward the seminal
vesicles. As the average distance of the NVB from the prostate
is 4.9 mm, it is still often feasible to preserve the NVB even in the
presence of extracapsular extension.4,17,27 The cues used by Walsh
at the time of surgery to suggest that the NVB does need to be
excised are induration of the lateral pelvic fascia; adherence of the
NVB to the prostate; and inadequate tissue covering the postero-
lateral aspect of the prostate once it has been removed.

Using these cues, Walsh had a positive margin rate of 5%. He
carried out bilateral nerve sparing in 86.6% of patients, unilateral
nerve sparing in 13% and excised both NVB in only 0.4%. Given
his indications for excision of the NVB, it would be very rare that
a patient requiring bilateral wide excision of the NVB would be
a candidate for surgery, as he would most probably have dissemi-
inated disease by this stage. In addition, high pathological stage
was shown to be an independent predictor of poor recovery of
sexual function on multivariate analysis.4 Similar rates of NVB
excision were produced by Lepor and Kaci.28 He carried out
bilateral nerve sparing in 81%, unilateral nerve sparing in
16.6% and excised both NVB in 2.4%. These datasets show that
bilateral nerve grafts should be extremely rare events.

One caveat to these results is that they represent highly selected
patient populations and surgeons doing larger numbers of radical
prostatectomies rather than the experience of most urologists in
Australia and New Zealand. Although these results can be
achieved in specific settings, in most institutions, the standard
practice is still to excise the NVB on the side of a positive prostate
biopsy.29-31 Even in the presence of wide local excision, positive
surgical margins in unscreened populations are found in 16–30%
of patients.29,30,32

A factor to be considered when deciding the role of nerve
grafting, more so when using the sural nerve, is the associated
morbidity of the procedure. As stated by Kim et al. the possible
risks include: haematoma, infection, pain, sensory loss on the
lateral aspect of the foot, neuroma formation, reflex sympathetic
dystrophy, infection and increased blood loss and operating
time.11 However, whereas most men in each series developed
a sensory deficit of 6 cm × 3 cm on the lateral aspect of the sole of
the foot that was evident even at 12 months, this was not
considered bothersome. The only other reported complication
was one instance of wound infection. In addition, no series
reported increased transfusion requirements in the patients under-
going nerve grafting.11-16 This suggests that concerns regarding
morbidity of nerve grafting alone should not preclude its use.

In the current published work, erections sufficient to produce
vaginal penetration following unilateral nerve grafting (with con-
trolateral nerve sparing) were evident in 41.7–63.6% of patients.
This is similar to the rates of 23–64% with unilateral nerve spar-
ing alone.11-16 Based on these figures there is not a great differ-
ce in erectile function rates, although any true conclusions are
severely hampered by the lack of a large-scale study with regard
to unilateral nerve grafting. It does seem that with optimal surgi-
cal technique, unilateral nerve sparing provides similar return of
erectile function without nerve grafting on the contralateral side.

The rates of erectile function sufficient to produce vaginal pen-
etration following bilateral nerve grafting were 34–72%, whereas
it is widely accepted that very few men without nerve grafting
would have any degree of potency. These results do look impres-
sive, especially the series by Chang et al.13 However, these results
must be interpreted with caution because of the small size of the
cohorts. Most importantly, bilateral nerve grafting should not be
carried out in men who could have a nerve-sparing procedure; this
is a view held by both those who support and challenge nerve
grafting.16,17

One concern raised by Walsh17 with regard to bilateral nerve
grafting is the likelihood that these patients will require adjuvant
radiation or hormonal therapy, which will further reduce the like-
lihood that they will regain erectile function. However, wide exci-
sion of the NVB, as would occur in a nerve grafting operation,
may lead to lower rates of positive surgical margins than if nerve
sparing was carried out. Several centres have shown that in
patients with extracapsular extension, nerve sparing leads to a
higher proportion of positive surgical margins than wide local
excision.29,33-35 Partin et al.36 reviewed patients with extracapsular
extension and compared those who underwent nerve sparing to
those who underwent wide excision and found that the rate of
positive surgical margins was significantly greater in the group
undergoing nerve sparing (55 vs 42%). Although this does indi-
cate that wide local excision is preferable for cancer control, it
does show that a significant number of patients with extracapsular
extension may require adjuvant therapy even in the presence of
wide local resection. Although no studies to date have considered
the effect of irradiation or androgen deprivation on erectile func-
tion following nerve grafting, it is probable that they would fur-
ther impair the return of erectile function, as acknowledged by
centres carrying out nerve grafting.14

Currently, unilateral nerve grafting has not been shown to be
better than unilateral nerve sparing in preserving erectile function
post-prostatectomy. The main reason for this would seem to be the
lack of a definite cavernous nerve. As such, techniques that would
aid the identification of the cavernous nerves may improve out-
comes with nerve grafting. One such technique may be the use of
Cavermap, a device that uses electrical stimulation of nerves to
provoke tumescence; the tumescence is then measured with a sen-
sor that can detect a 0.5% increase in penile girth. In a single-
blinded multicentre trial involving 61 patients with mean follow
up of 1 year, in the group in which the Cavermap was used at the
time of nerve-sparing prostatectomy 74% were potent as assessed
both subjectively (with a patient questionnaire) and objectively

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(with Rigiscan). This was compared to 51% in the control group who had a conventional nerve-sparing operation. It is noteworthy that the treatment group had their operation prolonged by a mean of 17 min and an increase in mean blood loss of 25%. Given these results, it may be possible to use the Cavermap to identify the proximal and distal ends of the cavernous nerve at the time of nerve grafting, which may improve the efficacy of the procedure. Indeed, Cavermap was used by Chang to produce his impressive results of 72% potency following bilateral nerve grafts. However, as mentioned by Klotz in his review of the Cavermap technology, there are concerns about the lack of specificity of the tunescence response and that, whereas nerve stimulation is an aid, it does not replace surgical judgement or experience.

Use of various chemotactic and neurotrophic factors in rats at the time of nerve grafting have been shown to improve results compared with grafting alone. These agents included nerve growth factor and acid fibroblast growth factor whereas Schwann cell-impregnated tubes produced better results than grafts alone. None of these factors has been used in human trials, and although their efficacy in animal models is promising, trials using them in humans are necessary.

CONCLUSION

The use of nerve grafts following excision of the NVB at radical prostatectomy has now been occurring for more than 9 years. However, there is still controversy over its use because of the lack of any large, blinded trials, the anatomy of the cavernous nerves and the necessity of excising the NVB (especially bilaterally). Although the success rates of bilateral nerve grafting are encouraging, those of unilateral nerve grafting are not significantly better than unilateral nerve sparing alone. At present, there is no widespread performance of nerve grafting in Australia and New Zealand and results to date indicate that complete nerve resection with subsequent nerve grafting is not a substitute for nerve sparing if this is possible.

REFERENCES

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