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Does the uterine cervix become abnormally reinnervated after subtotal hysterectomy and what is the association with future trachelectomy?

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Abstract

Objective—To compare nerve fiber density in the cervixes removed by trachelectomy from women with pelvic pain with those cervixes removed for non-pain indications.

Methods—This is a retrospective cohort study from 2 university hospitals (Canadian Task Force classification II-2). Subjects who underwent trachelectomy during a 10-year time frame were identified. Two tissue sections were obtained from each preserved cervix specimen and stained for S100 antibody. The numbers of S100 immunoreactive peripheral nerve fibers were assessed in 6 high-powered fields (HPF) per tissue section (12 total HPF per patient). Information collected included patient characteristics and surgical findings. We excluded any patients with dysplasia/cancer and those without an available adequate specimen.

Results—We evaluated the cervix specimens from 35 patients who underwent trachelectomy for pain (n=25; group 1) and non-pain (n=10; group 2) indications, in addition to control cervixes (n=15; group 3) from benign hysterectomies performed for non-pain indications. There were increased numbers of nerve fibers in trachelectomy patients with pain vs. those without pain (group 1 vs. group 2, p=0.02). There were also increased numbers of nerve fibers in both trachelectomy groups compared to control (group 1 vs group 3, p<0.01; group 2 vs group 3,

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p=0.04) Adjusted average cervical nerve counts/HPF were 17.8 (95% CI 13.2, 22.3) for pain-indicated trachelectomies, 11.5 (95% CI 4.8, 18.2) for non-pain, and 6.3 (95% CI 0.8, 11.8) for controls. Regardless of trachelectomy indication, adjusted average nerve counts/HPF were 17.7 (95% CI 13.4, 22.0) for patients with endometriosis and 14.6 (95% CI 12.2, 17.1) for patients without endometriosis.

Conclusion—Nerve fibers in the cervical stump after supracervical hysterectomy are significantly increased in women undergoing trachelectomy for pain indications, compared to those who underwent trachelectomy for non-pain indications and controls. Though not statistically significant, endometriosis may be an independent risk factor for increased nerve fibers. These histopathologic observations may support the idea that the cervix should be removed in women undergoing hysterectomy for chronic pelvic pain or endometriosis.

Introduction

The prevalence of chronic pelvic pain is reported to be 3.8%, has multiple etiologies, and can be treated with a variety of surgical and medical therapies (1,2). The most common treatment for chronic pelvic pain in a woman who has completed childbearing is hysterectomy, either with or without removal of the tubes and ovaries (3). However, between 5 and 32% of women report pain lasting up to a year after hysterectomy, with the most common risk factors being a history of preoperative pain and increased acute postoperative pain (4,5). Others report that leaving the cervix behind during subtotal (supracervical) hysterectomy in patients who preoperatively have a diagnosis of pelvic pain or endometriosis increases the risk of persistent post-operative pain (6,7). In one study, women with self-reported endometriosis were much more likely than women who did not report endometriosis to have persistent pain after laparoscopic supracervical hysterectomy (OR 4.88, 95% CI 2.10-11.34) (7).

While the exact mechanism by which endometriosis causes pain is unknown, potential elements include inflammatory factors produced by the implants themselves which irritate the surrounding peritoneum, cause adhesions, and initiate denervation and re-innervation of adjacent structures (8). While events occurring in endometriosis implants may be important, other studies describe contributions from the uterus itself (9). Atwal, et al, examined nerve patterns in hysterectomy specimens from women with and without pain, further dividing them by those with an intraoperative diagnosis of endometriosis (9). Uteri from women with chronic pain, with or without endometriosis, as compared with pain-free controls, had an increased number of nerve fiber bundles in the lower uterine segments. Their findings suggest that in some cases, pain relief after hysterectomy may occur in part due to the severing of nerves supplying the organ. At this point, it is unknown whether these nerve fibers are the cause of pain or are the body's response to other nociceptive stimuli. In their article, they comment the cervix of their specimens "showed some features of reinnervation" but did not go further.

If re-innervation does occur in the cervix, subtotal hysterectomy would be an ideal set-up for this phenomenon. Such ingrowth of nerves might provide partial explanation for new and/or worse post-operative pain following supracervical hysterectomy among those patients with

pre-operative chronic pelvic pain and/or endometriosis. In this retrospective cohort study, our goal was to estimate any difference in the numbers of nerve fibers in the cervixes of those who had a trachelectomy for pain indications as compared to those who had a trachelectomy for non-pain indications. In addition, a sub-group analysis was performed to compare the nerve counts from patients with and without an operative diagnosis of endometriosis.

Materials and Methods

Patients from Vanderbilt University Medical Center and the University of North Carolina Medical Center who had a trachelectomy (by any route) between January 2001 and September 2010 were reviewed for inclusion. The patients were identified via ICD-9 codes (49329, 57530, 57531, 57540, 57545, 57550, 57556, 57555) after ethics approval was obtained from both medical centers' Institutional Review Boards. Any patient who underwent subtotal or supracervical hysterectomy and then subsequently had a trachelectomy was eligible. Patients whose indication for trachelectomy was dysplasia or malignancy were excluded. There were 41 eligible patients and 6 were excluded (for inadequate available histology) for an overall sample size of 35. Fifteen control samples (group 3) were obtained from patients who had undergone hysterectomy for benign non-uterine pathology such as uterine prolapse or adnexal disease. These were chosen at random, by the pathology departments at the University of North Carolina and Vanderbilt University, using surgical procedure codes, within the same time period. The final analysis included these 50 patients.

Tissue preparation

For each cervix studied, sections were taken from each of two well preserved paraffin blocks. Unstained sections, 3-5 micrometer thick, were cut from each block, rehydrated, and immunostained for S100 (an antibody stain that is specific for cells of the peripheral nervous system) on a Leica Bond Max. The stain and staining methods are based on the referenced article by Atwal, et al (9). Endogenous peroxidase was neutralized with 0.03% hydrogen peroxide followed by a casein-based protein block (Dako, Carpinteria, CA) to block nonspecific staining. The sections were incubated with rabbit anti-human S100 Z0311 (Dako, Carpinteria, CA) diluted 1:900 for 30 minutes. The Leica Bond Polymer Refine Detection system was used to detect the antibody. Slides were lightly counterstained with Mayer's hematoxylin.

Tissue analysis

The numbers of S100 immunoreactive peripheral nerve fibers were assessed in all tissue sections using a BX41 microscope (Olympus Corp, Center Valley, PA). A total of 6 microscopic fields were evaluated in each section (3 fields in the inner [mucosal] and 3 fields in the outer half of the section), separated from each other by at least 5 mm to reduce sampling error. Each field was evaluated using a 10× microscopic objective (field diameter 2.2 mm). Three features were evaluated in each field: 1) the total number of well defined nerve fibers (Figure 1A and 1B); 2) the number of microneuromas (Figure 1C and 1D); and 3) the number of vascular profiles with a perivascular nerve proliferation (Figure 1E and

1F). Microneuromas consist of a central nerve trunk, with smaller nerve fibers apparently radiating outwards from it into the surrounding stroma (Figure 1C). We also included in our definition disorganized clusters of nerve fibers (Figure 1D). A vascular profile with a perivascular nerve proliferation is defined as a large artery that was at least half surrounded by peripheral nerve fibers. These nerve fibers took the form of either small, very loosely packed nerves in the peri-adventitial tissues (Figure 1E), or dense perivascular nerve proliferations that usually overlaid, at least in part, the adventitia of the vessel and extended into surrounding stroma (Figure 1F). Small individual nerves that were interspersed between stromal cells were not counted, as these were innumerable and were essentially ubiquitous. For each specimen, the total count of nerve fibers was the sum of these three significant features. All signs of innervation (microneuromas, nerve fibers, and perivascular nerve bundles) were counted and combined. We did not look at one type as being more significant than the others. The numbers of S100 immunoreactive peripheral nerve fibers were assessed in 6 high-powered fields (HPF) per tissue section (12 total HPF per patient).

The same pathologist reviewed all slides and submitted nerve counts. This person was blinded to the indication for the trachelectomy.

Statistical analysis

Patient data were abstracted, including: age at time of surgery, indication for trachelectomy, route of trachelectomy, route of previous hysterectomy, history of morcellation, tobacco use, body mass index, operative findings at time of trachelectomy, cervix pathology, history of hormone replacement therapy, presence of ovaries in situ, gravidity/parity, previous pap smear pathology, and previous cervical procedure(s). Patients who underwent trachelectomy for any pain indication (cyclic pain, noncyclic pain, and dyspareunia) were included in the “pain indication” group (group 1). Patients who underwent trachelectomy for any other indication (typically bleeding or prolapse) were included in the “non-pain indication” group (group 2).

The sample size estimation was based on a power calculation showing that 9 subjects were needed in each group for a power of 80%, detecting a difference of 8 nerve fibers/HPF with $\alpha=0.05$. A difference of 8 nerve fibers/HPF (standard deviation=6) was determined to be clinically significant based on the previous work by Atwal, et al. (9).

Stata v.11 statistical software (College Station, TX) was used for all analyses. The primary outcome for this study was the average nerve count (total count divided by number of slides) in the trachelectomy specimen, which had a non-parametric distribution. Thus, results will be reported as medians, as opposed to means; and bivariate analyses were conducted with Wilcoxon Rank-sum and Kruskal-Wallis tests. Fisher’s Exact was used in analyses where the categories had smaller numbers. Confounders were defined as variables that are related to the exposure (pre-trachelectomy pain) and a risk factor for the outcome (nerve counts). These were identified during the initial bivariate analysis and included in the multivariate analysis. A final multivariate analysis (ANCOVA) with linear regression was conducted to look for an association between nerve counts and indication for trachelectomy (pain vs. non-pain vs. control).

A secondary analysis was performed (without control specimens) to look at the association between a diagnosis of endometriosis (made by inspection +/- pathology at the time of trachelectomy) and the average cervix nerve counts. ANCOVA was also utilized for this analysis, adjusting for significant co-variates (smoker status, BMI, age at surgery, and prior morcellation).

Results

Patient demographics (Table 1) were similar across all study groups with a few exceptions. There was a statistically-significant difference between populations in their ages and BMI. In the bivariate analysis, route of hysterectomy, smoking status, morcellation, gravidity/parity, previous pap smear, use of HRT, and ovarian presence were not statistically significant as risk factors in increased cervical nerve count.

Increased average nerve counts (Table 2) are noted in both trachelectomy groups (groups 1 and 2) when compared to control (group 3). When adjusted for confounders in the multivariate analysis, the statistical significance remains ($p=0.02$). The differences in average nerve counts by population is depicted graphically in Figure 2. Notably, among trachelectomy groups alone, there were increased numbers of nerve fibers in those with pain vs. those without pain (group 1 vs. group 2, $p=0.02$).

When comparing only patients who underwent trachelectomy, those with an intra-operative diagnosis of endometriosis ($n=8$) had more cervical nerve fibers present than those without an endometriosis diagnosis ($n=27$), 17.7 (95% CI 13.4, 22.0) vs. 14.6 (95% CI 12.2, 17.1). However, this did not reach statistical significance, likely due to the small number of patients in this category (Table 3). Of note, among the 8 patients with endometriosis diagnosed at time of trachelectomy, 6 (75%) reported pain as the indication for their surgery. Those 6 patients had an average of 22.4 (95% CI 4.5, 40.3) nerve fibers/HPF. Table 4 divides patients by pain indication and diagnosis of endometriosis and gives average nerve counts for each group. Patients with both documented endometriosis and pain had the highest nerve counts, while those with no endometriosis and no pain had the lowest.

Discussion

Similar to what was demonstrated in the myometrium of the lower uterine segments of hysterectomy specimens studied by Atwal, et al, our study shows a higher proportion of nerve fibers in the cervixes of women undergoing trachelectomy for chronic pain (9). A subgroup analysis also identifies the presence of endometriosis as a possible separate and independent risk factor for increased nerve proliferation.

Not surprisingly, those patients who underwent trachelectomy for non-pain indications also had increased cervical nerve counts when compared to controls. Simply having had a previous surgery in this area (subtotal hysterectomy) exposes the remaining tissue to an array of inflammatory processes that recruits local innervation. For this reason, a control group of normal cervixes (removed with the uterus during hysterectomy) was added to our analysis in order to include a baseline comparator. We hypothesize that the greater the inflammation (i.e. endometriosis), the greater the nerve proliferation. Our results would

argue that, not only does the cervix contain significant nerve fibers, but the amount of innervation is variable and dynamic, probably depending on multiple factors.

The connection between endometriosis and nerve growth has previously and repeatedly been demonstrated. In one study, Tulandi, et al. found increased presence of nerve fibers in the peritoneum of women with endometriosis compared to controls without endometriosis (10). The relationship between reinnervation, pain, and endometriosis is well-outlined by Howard (8). The major mediator in this relationship is nerve growth factor (NGF), which initiates the development of new sensory neurons and also acts directly as a pain mediator. NGF has been identified in endometriosis lesions and in the uterus, and is modified by the amount of circulating estrogen and progesterone. This relationship is so strong that Al-Jefout, et al. showed that higher nerve counts in the endometrial biopsies of patients correlated strongly (sensitivity 83%, specificity 98%) with a diagnosis of pelvic endometriosis (11). Tokushige, et al, looked at patients with endometriosis who had undergone hysterectomy, and found decreased nerve densities in the endometrium and myometrium in those patients who had been previously treated with hormone therapies (oral contraceptives, progesterone, etc.) (12). This potential protective effect of hormone-based therapies on tissue nerve in-growth was accounted for in our study design, as we included hormone replacement therapy and ovarian presence in our analysis.

The connection between endometriosis, pain, and the cervical stump has also been demonstrated. Okaro, et al. performed a retrospective review of 70 women who underwent supracervical hysterectomy to measure the prevalence of cervical stump symptoms and the need for reoperation (13). In their cohort, 13/70 (18.6%) of women reported pain and/or dyspareunia related to the remaining cervix. Another 4 patients reported bleeding only. Interestingly, 14 of these 17 patients (82.3%) had been treated for endometriosis in the past. Their results suggest that a previous diagnosis of endometriosis is a risk factor for post-operative pain after subtotal hysterectomy. The cervical stump was later removed in 16 of these patients.

Without the presence of endometriosis, it is unclear exactly why the cervix would initiate new nociceptive nerve growth on its own, thus becoming a primary source of pain. One hypothesis is the idea that subtotal hysterectomy acts as an “amputation” of sorts, leaving the remaining stump to act as the “limb” in a phantom limb-like scenario. Post-operative neuropathic pain is not a new phenomenon, but most clinicians would not consider the cervix to be vulnerable to this process. However, the inflammatory and healing processes that occur after amputation of a limb or mastectomy or hysterectomy are essentially the same. Risk factors for the development of chronic post-operative pain include pre-operative pain, type of surgery, above-normal post-operative pain, and genetic and psychosocial factors (14). Thus, those patients who undergo subtotal hysterectomy for chronic pelvic pain would be at higher risk for developing cervical stump pain.

In our study, we found increased nerve fiber densities in the cervixes of patients with a diagnosis of endometriosis and in patients who underwent trachelectomy for pain. We did not have access to the pre-operative indications for their original supracervical hysterectomies. Thus, we cannot determine an association between pre-hysterectomy pelvic

pain and the need for future trachelectomy due to pain or elevated nerve counts. However, based on previous literature, we can postulate that those patients would be at greatest risk for re-operation. Based on our findings, patients with a history of endometriosis and those undergoing surgery for pain indications could be at increased risk for future trachelectomy; and these diagnoses may lead the surgeon to recommend total hysterectomy rather than supracervical.

The two main advantages of this study are its novelty and its consistency with similar studies. This study is the first to address the issue of nerve fiber density in the cervix, with results similar to previous findings in painful pelvic structures, including the uterus and peritoneum (9-12). This study also demonstrates histopathologic evidence for chronic pain in an organ (cervix) that is typically considered static in its innervation. Left unanswered to date is the important question of sequence: do nerve fibers appear first, then pain develops, or vice versa? Similarly, in the patient with pain at the time of hysterectomy, are they also more vulnerable to the development of intrinsic vaginal apex pain, and if so, are they better served by removing the cervix or not?

This study is limited by several factors. The first is missing information regarding the presence of pre-hysterectomy pelvic pain in these patients. The majority of patients were referred for trachelectomy and underwent the original hysterectomy at an outside facility, where the charts were unavailable for our abstraction. This study is also limited by the small numbers of patients and the extended duration of time to collect this sample size. Even at two large referral centers, it required almost 10 years to collect this sample size.

Trachelectomy is not a common procedure. It is plausible that, over 10 years, practice patterns change and evolve, which could influence outcomes. However, it would require multiple centers with a longer study duration to collect more data, which would introduce more heterogeneity in the sample. Thus, we chose to limit our sample to two institutions and 10 years, which ultimately did meet our power analysis. The smaller sample size does widen the confidence intervals around our findings, introduce bias, and limit the conclusions that can be made regarding our findings. Our conclusions are most limited in the population with endometriosis. Because of the small numbers in that category, our results are mostly hypothesis-generating. However, we still believe the results are notable and can inform further research in this area.

In conclusion, women undergoing trachelectomy after supracervical hysterectomy had a higher cervical nerve fiber count if they had an intra-operative diagnosis of endometriosis, or were undergoing trachelectomy for pain rather than another non-pain indication. These observations provide histopathologic evidence possibly supporting the performance of total hysterectomy for women with chronic pelvic pain or endometriosis.

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Work source: Chart review and re-processing of pathology specimens from two institutions.

References

1. Mathias S, Kupperman M, Liberman R, Lipschultz R, Steege J. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. *Obstet Gynecol.* 1996; 87:321–7. [PubMed: 8598948]
2. Zonderman KT, Yudkin PL, Vessey MP, Dawes MG, Barlow DH, Kennedy SH. Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database. *BJOG.* 1999; 106:1149–55.
3. Wilcox LS, Koonin LM, Pokras R, et al. Hysterectomy in the United States 1988–1990. *Obstet Gynecol.* 1994; 83:549–555. [PubMed: 8134065]
4. Brandsborg B, Dueholm M, Nikolajsen L, Kehlet H, Jensen T. A prospective study of risk factors for pain persisting 4 months after hysterectomy. *Clin J Pain.* 2009; 25:263–68. [PubMed: 19590472]
5. Stovall T, Ling F, Crawford D. Hysterectomy for Chronic Pelvic Pain of Presumed Uterine Etiology. *Obstet Gynecol.* 1990; 75:676–679. [PubMed: 2248635]
6. Nisolle M, Donnez J. Subtotal hysterectomy in patients with endometriosis-an option. *Fertil Steril.* 1997; 67:1185–7. [PubMed: 9176472]
7. Lieng M, Qvigstad E, Istre O, Langebrekke A, Ballard K. Long-term outcomes following laparoscopic supracervical hysterectomy. *BJOG.* 2008; 115:1605–1610. [PubMed: 18752588]
8. Howard F. Endometriosis and mechanisms of pelvic pain. *JMIG.* 2009; 16:540–50.
9. Atwal G, Plessis D, Armstrong G, Slade R, Quinn M. Uterine innervation after hysterectomy for chronic pelvic pain with, and without, endometriosis. *Am J Obstet and Gynecol.* 2005; 193:1650–5. [PubMed: 16260205]
10. Tulandi T, Felemban A, Chen MF. Nerve fibers and histopathology of endometriosis-harboring peritoneum. *J Am Assoc Gynecol Laparosc.* 2001; 8:95–98. [PubMed: 11172122]
11. Al-Jefout M, Dezarnaulds G, Cooper M, et al. Diagnosis of endometriosis by detection of nerve fibers in an endometrial biopsy: a double blind study. *Human Reproduction.* 2009; 24:3019–24. [PubMed: 19690352]
12. Tokushige N, Markham R, Russell R, Fraser I. Effects of hormonal treatment on nerve fibers in endometrium and myometrium in women with endometriosis. *Fertil Steril.* 2008; 90:1589–98. [PubMed: 18061173]
13. Okaro E, Jones K, Sutton C. Long term outcome following laparoscopic supracervical hysterectomy. *BJOG.* 2001; 108:1017–1020. [PubMed: 11702830]
14. Kehlet H, Jensen T, Woolf C. Persistent postsurgical pain: risk factors and prevention. *Lancet.* 2006; 367:1618–25. [PubMed: 16698416]

Figure 1.

Representative tissue sections of histologic examination for nerves in cervical specimens.

A) a well-defined large peripheral nerve fiber (objective magnification 40×); B) Nerve fibers of this caliber (arrow) were also counted, but individual thinner fibers in the background stroma were not counted (objective magnification 40×); C, A Microneuroma, consisting of a central nerve trunk and surrounding smaller nerves associated with it (objective

magnification 20×) D) A microneuroma, consisting of a disorganized cluster of peripheral nerves (objective magnification 20×) E) a perivascular nerve fiber proliferation, in the form of small nerves at the periadventitial regions of an artery ((objective magnification 20×); F) a perivascular nerve fiber proliferation, in the form of a dense perivascular proliferation of small nerve fibers, often involving the outer adventitia of the vessels.

Figure 2.
Adjusted cervical nerve counts by trachelectomy indication and control

Table 1

Patient demographics

Patient demographic	Pain indication N=25 Median (range) or N (%)	Non-pain indication N=10 Median (range) or %	Control N=15 Median (range) or %	P-value
Age	33 (22-46)	40 (28-54)	45 (30-55)	P=0.001*
BMI	25 (19-44)	36 (23-45)	28 (20-44)	P=0.02 [†]
Gravidity/Parity	2 (0-4)/2 (0-3)	2 (0-5)/1 (0-4)	2 (0-5)/1 (0-3)	NS
Route of trachelectomy				
Vaginal	3 (12%)	1 (10%)	–	NS
Laparoscopic	21 (84%)	7 (70%)	---	
Abdominal	1 (4%)	2 (20%)	–	
Route of hysterectomy [‡]				
Open	11 (44%)	5 (50%)	2 (13%)	NS
Laparoscopic	14 (56%)	5 (50%)	7 (47%)	
Vaginal	–	–	6 (40%)	
Endometriosis [‡]	6 (24%)	2 (20%)	0 (0%)	NS
Morcellation [‡]	14 (56%)	5 (50%)	0 (0%)	NS
Tobacco use	9 (36%)	2 (20%)	2 (13%)	NS
HRT	2 (8%)	1 (10%)	1 (7%)	NS
Ovaries present	20 (80%)	8 (80%)	10 (67%)	NS
Previous pap smear				
Normal	16 (64%)	7 (70%)	11 (73%)	NS
ASCUS	0 (0%)	0 (0%)	0 (0%)	
LSIL	1 (4%)	0 (0%)	0 (0%)	
HSIL	0 (0%)	0 (0%)	0 (0%)	
AGUS	0 (0%)	1 (10%)	0 (0%)	
unknown	8 (32%)	2 (20%)	4 (27%)	
Previous cervical procedure [§]				
None	15 (60%)	6 (60%)	10 (67%)	NS
Biopsy	1 (4%)	1 (10%)	0 (0%)	
LEEP	3 (12%)	2 (20%)	1 (7%)	
CKC	0 (0%)	0 (0%)	0 (0%)	
Dilation	5 (20%)	2 (20%)	4 (27%)	

Patient demographic	Pain indication N=25 Median (range) or N (%)	Non-pain indication N=10 Median (range) or %	Control N=15 Median (range) or %	P-value
Other	1 (4%)	0 (0%)	0 (0%)	

* when comparing entire group; individual pairings: pain vs non-pain (p=0.04); pain vs. control (p=0.003); non-pain vs control (p=0.64)

† when comparing entire group; individual pairings: pain vs non-pain (p=0.005); pain vs. control (p=0.25); non-pain vs control (p=0.11)

‡ Analysis only includes trachelectomy groups (not controls due to lack of representation)

§ numbers do not add to 100% as some patients had several cervical procedures

Table 2

Unadjusted and adjusted average cervix nerve counts by group

Indication for trachelectomy	Unadjusted average nerve count (median with 95% CI)	Referent	p-value [*]	Adjusted average nerve count (median with 95% CI)	p-value [†]
Group 1 (Pain)	17.8 (14.0, 21.6)	Group 2	0.02	17.8 (13.2, 22.3)	0.02
		Group 3	<0.01		
Group 2 (Non-pain)	12.5 (6.7, 18.3)	Group 1	0.02	11.5 (4.8, 18.2)	---
		Group 3	0.04		
Group 3 (Control)	6.1 (1.2, 10.9)	—	---	6.3 (0.8, 11.8)	---

* Kruskal-Wallis test

† ANCOVA with all groups

Table 3

Average (median) nerve counts by endometriosis.

	Unadjusted average nerve count Median (95% CI)	Adjusted average nerve count Median (95% CI)
Endometriosis (n=8)	16.8 (9.5, 24.0)	17.7 (13.4, 22.0)
No endometriosis (n=27)	13.6 (9.5, 17.7)	14.6 (12.2, 17.1)

Table 4

Average nerve counts by indication and findings of endometriosis.

Indication for trachelectomy	Endometriosis Median (95% CI)	No endometriosis Median (95% CI)
Pain	N=6 22.4 (4.5, 40.3)	N=19 17.0 (6.6, 27.4)
Non-pain	N=2 18.1 (-3.6, 39.9)	N=8 9.6 (-19.3, 38.5)