Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

Postoperative Peripheral Nerve Injury in Patients Receiving Cross-Sex Hormone Therapy and Undergoing Gender-Affirming Surgery

Student Investigator's Name

Kevin Harriman

Date of Submission *(mm/dd/yyyy)*

03/17/2022

Graduation Year

2022

Project Course *(Indicate whether the project was conducted in the Scholarly Projects Curriculum; Physician Scientist Experience; Combined Degree Program [MD/MPH, MD/PhD]; or other course.)*

Scholarly Projects Curriculum

Co-Investigators *(Names, departments; institution if not OHSU)*

Mentor's Name

Brandon Togioka, MD

Mentor's Department

Anesthesiology & Perioperative Medicine

Scholarly Project Final Report

Concentration Lead's Name

David Buckley, MD

Project/Research Question

What is the rate of new postoperative peripheral nerve injuries in patients on cross-sex hormone therapy and undergoing gender-affirming surgery?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

Retrospective descriptive clinical research study

Key words *(4-10 words describing key aspects of your project)*

Postoperative peripheral nerve injury, cross-sex hormone therapy, gender-affirming surgery, general anesthesia, general anesthesia complications,

Meeting Presentations

If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

OHSU Annual Anesthesiology & Perioperative Medicine Research and Quality Day 2021 – virtual event, June 7th, poster submission

Publications *(Abstract, article, other)*

If your project was published, please provide reference(s) below in JAMA style.

Submission to Archive

Final reports will be archived in a central library to benefit other students and colleagues. Describe any restrictions below (e.g., hold until publication of article on a specific date).

Please hold until publication (no date currently available)

Scholarly Project Final Report

Next Steps
What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

I think this project prepares the way for comparative research studies attempting to identify the risk factors or even potentially causes of an increased rate of postoperative peripheral nerve injuries in patients undergoing gender-affirming surgery. Another interesting question would be looking back and trying to determine the clinical severity and duration of these nerve injuries, although I'm afraid that this would be very difficult to accomplish retrospectively. I cannot think of any obvious way that this data might be helpful for other research questions not directly related to this line of inquiry.

Please follow the link below and complete the archival process for your Project in addition to submitting your final report.

https://ohsu.ca1.qualtrics.com/jfe/form/SV_3ls2z8V0goKiHZP

Student's Signature/Date *(Electronic signatures on this form are acceptable.)*
This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

X _____
Student's full name

Mentor's Approval *(Signature/date)* ****Email from mentor acknowledging receipt of the final report and approving archiving was forwarded to Will Ragan****

X _____
Mentor Name

Scholarly Project Final Report

Report*: Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

This project arose out of a clinical observation among anesthesiologists taking care of gender-affirming surgery patients that these patients seemed to be experiencing postoperative peripheral nerve injuries at rates higher than they ordinarily expect to see. This, admittedly anecdotal, observation immediately poses several questions. Are these patients genuinely at higher risk? If so, what might be responsible for the increased risk? These questions carry with them equity considerations as well. Patients undergoing gender-affirming surgery belong to a marginalized group by virtue of their gender identity. Considerations of justice oblige us to understand differential anesthetic or surgical complications that these patients may be experiencing.

Peripheral nerve injuries are a known complication in patients undergoing anesthesia care.[1] These injuries can become a significant problem for patients and result in dissatisfaction with their care. Indeed, peripheral nerve injuries are one of the greatest contributors to malpractice litigation against anesthesia providers.[2] These injuries can have a range of severities and affect both sensory and motor function. They are though to arise from a variety of mechanisms occurring in the setting of anesthesia including local compression, stretch, and ischemia, as well as systemic factors such as hypotension and inflammation.[1]

Gender-affirming surgeries constitute a wide class of surgical procedures carried out with the aim of alleviating gender dysphoria. Procedures falling under this category range from genital surgery to breast/chest surgery to face and voice surgery. It is not known why patients undergoing specifically gender-affirming surgeries would be at risk for higher rates of nerve injury, if they indeed are. However, given the wide variety in surgical technique, one might look to other similarities among the patient population. One way in which patients undergoing gender-affirming surgery are relatively unique is that virtually all of them are receiving hormone therapy for gender dysphoria (sometimes referred to as “cross-sex hormone therapy”). Some literature in the obstetric anesthesia literature has found that hormone-related changes in pregnancy are associated with increased sensitivity of peripheral nerves to blockade.[3-4] One possible hypothesis for any increased rate of nerve injury could be that hormonal alterations associated with hormone therapy are sensitizing peripheral nerves.

The aim of this project however was merely to establish a starting point for investigating this question. Namely, to answer the first of two questions posed above – are these patients genuinely at higher risk of postoperative peripheral nerve injury? In order to answer this question, a retrospective chart review was performed to determine the rate of postoperative peripheral nerve injury among gender-affirming surgery patients. This rate was then compared to the available literature on postoperative peripheral nerve injury rates among general and other specific surgical populations.

Methods *(≥250 words)*

In order to determine the rate of postoperative peripheral nerve injuries following gender-affirming procedures, we conducted a descriptive retrospective cohort study without a comparator group. The cohort was constructed from all adult patients undergoing gender-affirming surgical procedures at OHSU in

the year 2019. Patients were included if they were on cross-sex hormone therapy at the time of the procedure and underwent the procedure under general anesthesia.

Once this cohort was defined, a trained and approved analyst from the Clinical Research Division of OHSU's Department of Anesthesiology and Perioperative Medicine pulled patient data from the EMR, including demographic information, procedure type and length, preoperative labs (most recent up to 30 days prior to surgery), and patient comorbidities (from Problem Lists and History).

Patient electronic records were then individually reviewed to verify that they met inclusion criteria, to gather additional information about the anesthesia care (including method of blood pressure measurement and frequency of blood pressure checks), and to identify and, if present, characterize postoperative peripheral nerve injuries. Procedures were considered gender-affirming if the surgical diagnoses included gender dysphoria or if the name of the procedure performed, as indicated by the surgeon, included the expression "gender affirming". Patients were considered to be on cross-sex hormone therapy if they were either (1) assigned male at birth and receiving estrogen or progesterone therapy or (2) assigned female at birth and receiving testosterone therapy. The use of general anesthesia was verified by looking at the anesthesia record. The use of non-invasive blood pressure monitoring (NIBPM) versus arterial line was determined from the anesthesia record. The frequency of blood pressure measurements for NIBPM was recorded as either every three minutes or every five minutes based on the frequency that predominated throughout the case. Postoperative peripheral nerve injuries were defined as new onset numbness, paresthesia, neuropathic pain, or weakness in the upper and/or lower extremities recorded in the medical record within 30 days of the procedure. Peripheral nerve injuries were categorized according to location (upper vs lower extremity) and type (sensory, motor, both, undetermined). Injuries obviously related to the surgical procedure, such as pain or sensory changes occurring at a skin graft donor site, were excluded.

Descriptive statistics were used to characterize the cohort's baseline demographic data, procedure types and characteristics, lab values, and comorbidities. The rate of postoperative peripheral nerve injuries among patients meeting inclusion criteria was determined.

Given the availability of baseline patient data broken down by the occurrence or non-occurrence of postoperative peripheral nerve injury, a limited case-control analysis was attempted to identify any statistically significant covariates of nerve injury. This was attempted by means of binomial logistic regression with nerve injury status as a binary dependent variable and other gathered covariates serving as independent variables.[5] Statistical analysis was performed using Intel SPSS software.

Results *(≥500 words)*

A total of 232 patients were included in the final analysis. Two patients were excluded due to not taking cross-sex hormone therapy and one patient was excluded for not receiving general anesthesia. Among these patients, nine were found to have experienced postoperative peripheral nerve injury within the first 30 days post-op. This represents an annual incidence of 3.88%. The following two tables show data characterizing the identified nerve injuries and baseline patient characteristics respectively.

Table 1: Characteristics of identified nerve injuries

Nerve Injury Characteristic	**No. (%)**
Location	
Upper extremity	5 (55.5)
Lower extremity	4 (44.4)

Type	
Sensory	9 (100)
Motor	0 (0)

Table 2: Baseline patient characteristics (in some cases not all percentages add up to 100 due to incomplete data)

Characteristic	Nerve Injury Absent (N=223)	Nerve Injury Present (N=9)
Age – yr		
Average	38.1	40.8
Weight – lbs		
Average	182.5	190.8
BMI		
<40 – no. (%)	207 (92.8)	8 (88.9)
>40 – no. (%)	10 (4.5)	0 (0)
Procedural Type		
Genital surgery – no. (%)	179 (80.3)	7 (77.8)
Chest/breast surgery – no. (%)	30 (13.5)	0 (0)
Face/skull surgery – no. (%)	14 (6.3)	2 (22.2)
Procedure Length – hh:mm		
Average	04:54	07:43
Blood pressure monitoring		
Non-invasive – no. (%)	210 (94.2)	9 (100)
Arterial line – no. (%)	13 (5.8)	0 (0)
Frequency of blood pressure checks		
q3 minutes – no. (%)	125 (56.1)	3 (33.3)
q5 minutes – no. (%)	85 (38.1)	6 (66.7)
Estimated blood loss – mL		
Average	207	289
Pre-op creatinine – mg/dL		
Average	0.87	0.82
Pre-op hematocrit - %		
Average	42.4	42.3
Tobacco use – no. (%)	16 (7.2)	0 (0)
Diabetes mellitus – no. (%)	16 (7.2)	0 (0)
Asthma – no. (%)	19 (8.5)	2 (22.2)

The attempted binomial logistic regression resulted in models lacking statistical significance.

Discussion *(≥500 words)*

The demonstration of an annual incidence of postoperative peripheral nerve injury of 3.88% is not in itself sufficient to determine whether these injuries are occurring at higher rates than in other surgical populations. This requires comparison to other surgical populations. Unfortunately, as this was not a comparative study, this project did not itself contain this comparison. However, this incidence of nerve injury was compared to available literature on postoperative peripheral nerve injuries, which I will briefly

summarize.

The largest study performed to date on all types of postoperative peripheral nerve injuries reviewed nearly 400,000 cases over a 10-year period at a single institution and found a rate of peripheral nerve injury of approximately 0.04%.[6] In that study, the surgical specialties with the highest rates of postoperative peripheral nerve injuries (general, cardiac, neurosurgery, orthopedics) had rates ranging from 0.05-0.08%.[6] Several other large studies with greater than one thousand cases have observed postoperative nerve injury rates of between 0.03-0.72%.[7-9] These are rates approximately one to two orders of magnitude less than we observed.

However, several surgical contexts have received special attention as presenting higher risks for postoperative nerve injuries and have reported nerve injury rates closer to what we are reporting. These include studies of urologic surgery (1.3-6.6%)[10-11], shoulder arthroplasty (4.3-8.2%)[12-13], hip procedures (0.72-2%)[8,14], cardiac surgery (6.1%)[15], and surgeries performed in the lithotomy position (0.03-1.5%)[7,16].

Overall, it would seem that the postoperative nerve injury rate that we observed is notably higher than what is reported in a general surgical population and in some of the largest studies of the phenomenon. But the incidence we observed was quite similar to findings in other high-risk surgical populations. This suggests that the population of individuals undergoing gender-affirming surgery may represent another previously-unidentified high-risk population for postoperative peripheral nerve injury.

Of course, comparing rates across different studies presents a whole host of problems. The populations in these studies almost certainly differ across a number of other domains, in addition definitions of nerve injuries and methods for detecting them differ across studies. Without direct comparisons of different populations using a shared methodology, it is very difficult to make strong claims. At best, we can say that our observations, when compared with available literature, suggest a possibility that this may be a higher-risk population.

With regards to our attempted case control analysis, we were not able to identify associations between nerve injury and any of our covariables with statistical significance. This is almost certainly due to the small absolute number of nerve injuries in our cohort providing insufficient statistical power. Larger studies detecting greater numbers of injuries would be required to begin testing for risk factors. Nonetheless, it may be worthwhile to point out just one trend observed in our data, though it cannot be known whether this trend was statistically significant. Procedural length was nearly eight hours on average among patients experiencing nerve injuries compared with less than five hours on average among patients without identified nerve injuries. Given what is known about the suspected mechanisms of postoperative nerve injury, it is certainly plausible that this could be a risk factor for injury. This may be another avenue of further research.

Before concluding, it is worth explicitly pointing out the significant limitations of the project, some of which have been touched upon above. This was not a designed or intended as a comparative study and thus not set-up to test hypotheses about risk factors or causes of any trend. The study was overall small with a small absolute number of nerve injuries. Finally, the study did not gather data on the severity or duration of nerve injuries, which would be useful in better evaluating the clinical significance of these injuries.

Conclusions *(2-3 summary sentences)*

In a descriptive retrospective cohort study of 232 patients undergoing gender-affirming surgical procedures at OHSU in 2019, the annual incidence of postoperative peripheral nerve injury was 3.88%. As far as can be

determined by comparison to incidences reported in the literature, this is a high rate of postoperative peripheral nerve injury, comparable to other surgical populations which are considered to be at high risk for postoperative peripheral nerve injury. Additional research is needed to validate this observation in direct comparative studies and to begin assessing the risk factors and possible etiologies of this trend.

References *(JAMA style format)*

1. Chui J, Murkin JM, Posner KL, Domino KB. Perioperative Peripheral Nerve Injury After General Anesthesia: A Qualitative Systematic Review. *Anesth Analg*. 2018;127(1):134-143. doi:10.1213/ANE.0000000000003420
2. Kovacheva VP, Brovman EY, Greenberg P, Song E, Palanisamy A, Urman RD. A Contemporary Analysis of Medicolegal Issues in Obstetric Anesthesia Between 2005 and 2015. *Anesth Analg*. 2019;128(6):1199-1207. doi:10.1213/ANE.0000000000003395
3. Flanagan HL, Datta S, Lambert DH, Gissen AJ, Covino BG. Effect of pregnancy on bupivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesth Analg*. 1987;66(2):123-126.
4. Butterworth JF 4th, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. *Anesthesiology*. 1990;72(6):962-965. doi:10.1097/00000542-199006000-00002
5. Logistic regression carried out as per SPSS Statistics Tutorials and Statistical Guides | Laerd Statistics. https://statistics.laerd.com/.
6. Welch MB, Brummett CM, Welch TD, et al. Perioperative peripheral nerve injuries: a retrospective study of 380,680 cases during a 10-year period at a single institution. *Anesthesiology*. 2009;111(3):490-497. doi:10.1097/ALN.0b013e3181af61cb
7. Warner MA, Martin JT, Schroeder DR, Offord KP, Chute CG. Lower-extremity motor neuropathy associated with surgery performed on patients in a lithotomy position. *Anesthesiology*. 1994;81(1):6-12. doi:10.1097/00000542-199407000-00004
8. Jacob AK, Mantilla CB, Sviggum HP, Schroeder DR, Pagnano MW, Hebl JR. Perioperative nerve injury after total hip arthroplasty: regional anesthesia risk during a 20-year cohort study. *Anesthesiology*. 2011;115(6):1172-1178. doi:10.1097/ALN.0b013e3182326c20
9. Navarro-Vicente F, García-Granero A, Frasson M, et al. Prospective evaluation of intraoperative peripheral nerve injury in colorectal surgery. *Colorectal Dis*. 2012;14(3):382-385. doi:10.1111/j.1463-1318.2011.02630.x
10. Koç G, Tazeh NN, Joudi FN, Winfield HN, Tracy CR, Brown JA. Lower extremity neuropathies after robot-assisted laparoscopic prostatectomy on a split-leg table. *J Endourol*. 2012;26(8):1026-1029. doi:10.1089/end.2011.0653
11. Mills JT, Burris MB, Warburton DJ, Conaway MR, Schenkman NS, Krupski TL. Positioning injuries associated with robotic assisted urological surgery. *J Urol*. 2013;190(2):580-584. doi:10.1016/j.juro.2013.02.3185
12. Lynch NM, Cofield RH, Silbert PL, Hermann RC. Neurologic complications after total shoulder arthroplasty. *J Shoulder Elbow Surg*. 1996;5(1):53-61. doi:10.1016/s1058-2746(96)80031-0
13. Ho E, Cofield RH, Balm MR, Hattrup SJ, Rowland CM. Neurologic complications of surgery for anterior shoulder instability. *J Shoulder Elbow Surg*. 1999;8(3):266-270. doi:10.1016/s1058-2746(99)90140-4
14. Pailhé R, Chiron P, Reina N, Cavaignac E, Lafontan V, Laffosse JM. Pudendal nerve neuralgia

after hip arthroscopy: retrospective study and literature review. *Orthop Traumatol Surg Res*. 2013;99(7):785-790. doi:10.1016/j.otsr.2013.07.015

15. Gavazzi A, de Rino F, Boveri MC, Picozzi A, Franceschi M. Prevalence of peripheral nervous system complications after major heart surgery. *Neurol Sci*. 2016;37(2):205-209. doi:10.1007/s10072-015-2390-z
16. Warner MA, Warner DO, Harper CM, Schroeder DR, Maxson PM. Lower extremity neuropathies associated with lithotomy positions. *Anesthesiology*. 2000;93(4):938-942. doi:10.1097/00000542-200010000-00010