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Startle sign events induced by mechanical manipulation during surgery for neuroma localization: a retrospective cohort study

Jonathan M. Gorky[1], Sarah J. Karinja[2], Sylvia L. Ranjeva[1], Lingshan Liu[1], Matthew R. Smith[1], Ariel L. Mueller[1], Timothy T. Houle[1], Kyle R. Eberlin[2] and Katarina J. Ruscic[1*]

Abstract

Background Chronic pain from peripheral neuromas is difficult to manage and often requires surgical excision, though intraoperative identification of neuromas can be challenging due to anatomical ambiguity. Mechanical manipulation of the neuroma during surgery can elicit a characteristic "startle sign", which can help guide surgical management. However, it is unknown how anesthetic management affects detection of the startle sign.

Methods We performed a retrospective cohort study of 73 neuroma excision surgeries performed recently at Massachusetts General Hospital. Physiological changes in the anesthetic record were analyzed to identify associations with a startle sign event. Anesthesia type and doses of pharmacological agents were analyzed between startle sign and no-startle sign groups.

Results Of the 64 neuroma resection surgeries included, 13 had a startle sign. Combined intravenous and inhalation anesthesia (CIVIA) was more frequently used in the startle sign group vs. no-startle sign group (54% vs. 8%), while regional blockade with monitored anesthetic care was not associated with the startle sign group (12% vs. 0%), $p = 0.001$ for anesthesia type. Other factors, such as neuromuscular blocking agents, ketamine infusion, remifentanil infusion, and intravenous morphine equivalents showed no differences between groups.

Conclusions Here, we identified hypothesis-generating descriptive differences in anesthetic management associated with the detection of the neuroma startle sign during neuroma excision surgery, suggesting ways to deliver anesthesia facilitating detection of this phenomenon. Prospective trials are needed to further validate the hypotheses generated.

Keywords Peripheral nerve blockade, Startle reaction, Startle response, Startle sign, Neuroma startle sign, Neuroma surgery, Combined intravenous and inhaled anesthesia (CIVIA), Intraoperative monitoring, Chronic pain management, Neuroma identification

*Correspondence:
Katarina J. Ruscic
kruscic@mgh.harvard.edu
[1]Department of Anesthesia, Critical Care and Pain Medicine, The Massachusetts General Hospital, 55 Fruit Street, GRB444, Boston, MA 02114, USA
[2]Division of Plastic and Reconstructive Surgery, The Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

Background

Chronic neuropathic pain is defined as 'pain caused by a lesion or disease of the somatosensory system' [1, 2]. It is maintained in part by central sensitization driven by neuroinflammation leading to synaptic plasticity and long-term potentiation [3], while 'top-down' cognitive and emotional modulation as well as 'bottom-up' sensory inputs impact the perception of neuropathic pain [4]. Neuromas arise from abnormal regeneration of peripheral nerves after injury and are characterized histologically by disorganized nerve fiber tangles, decreased myelination, scar tissue, and myofibroblast burden [5]. Neuromas cause persistent pain, disability, increased opioid use, and delayed return to work. Non-surgical options for treating traumatic neuroma include desensitization techniques, neuromodulation, radiofrequency ablation, and pain medications. Despite this, treatments like pharmacotherapy or other symptom-focused strategies often provide limited relief for neuropathic pain. Conventional previous surgical interventions primarily focused on removing the damaged nerve segment or targeting the autonomic nervous system through sympathectomy [6]. More recent surgical techniques for managing neuromas have shifted towards active approaches that foster a functional designation to the regenerating nerve, such as autograft or allograft nerve reconstruction, targeted muscle reinnervation, and/or the use of regenerative peripheral nerve interfaces [6–8]. In patients surgically treated for symptomatic neuromas, these methods have been found to reduce pain and opioid use while improving function and quality of life [9–11].

Despite advances in surgical technique, identifying neuromas intraoperatively remains challenging and may limit surgical efficiency and outcomes. We previously defined the "neuroma startle sign" [11] and were the first to describe that when surgically dissecting near or on a symptomatic neuroma, patients sometimes have a characteristic increased physiological response, despite general anesthesia. The "startle" reaction may represent brief stimulation or pain from nerve manipulation. Observed responses include tachycardia, hypertension, tachypnea, elevated peak inspiratory pressures, ventilator dyssynchrony, Masimo processed electroencephalogram (EEG) Sedline patient safety index alterations, generalized patient movement, or withdrawal of the limb. Recognizing this phenomenon helps accurately localize neuromas and confirm symptomatic nerve identification without the use of advanced nerve monitoring techniques. Furthermore, this observed phenomenon has the potential to drive advancements in perioperative optimization and anesthetic planning for neuroma and other peripheral nerve surgeries. We wanted to learn how often the neuroma startle sign occurs, and under what conditions.

We hypothesized that eliciting a startle response may be affected by anesthetic technique and that regional anesthesia would not be associated with eliciting this response. Patients with neuromas often have chronic pain for which they have received treatment, resulting in higher baseline opioid tolerance, which can make perioperative analgesia more challenging [12]. Like in other patient populations suffering from chronic pain, an emphasis has historically been placed in neuroma surgery on regional anesthesia and multimodal antinociceptive adjuncts with the goal of optimizing and decreasing postoperative pain [13]. However, with a goal to elicit the neuroma startle sign, regional anesthesia may be unfavorable due to blockade of pain transmission from the surgical site.

The aim of this study was to explore anesthetic factors related to detection or blunting of the intra-operative neuroma startle sign in a retrospective cohort of patients undergoing neuroma excision surgery. We hypothesized that the mode of anesthesia and anesthetic adjuncts would be associated with differences in detection of the neuroma startle response.

Methods

The study was approved by the appropriate Institutional Review Board (IRB), and the requirement for written informed consent was waived by the IRB. Sequential sampling was used to extract all neuroma excision surgeries performed by a single surgeon (KRE) over a 34-month period (from 1/1/2019 through 10/31/2021) at Massachusetts General Hospital and were examined for inclusion in the study. There were 73 such surgeries, of which 64 were included for this retrospective review. Nine cases were excluded due to multiple procedures performed within the same operation in addition to neuroma excision, urgent or emergent surgery, operations performed on patients admitted for other medical problems (e.g. sepsis, decompensated heart failure, or respiratory failure), an intensive care unit admission, or failure to meet established criteria for symptomatic neuroma diagnosis [7]. No a-priori power calculation was performed as all available data during the study period were included. This manuscript adheres to all applicable Strengthening the Reporting of Observations Studies in Epidemiology (STROBE) guidelines.

Identification of the neuroma startle sign

The neuroma startle sign occurs with routine surgical stimulation of the neuroma. No exogenous stimulation was used to elicit the sign. No advanced nerve monitoring methods were used in any operations. Cases were retrospectively reviewed for the presence or absence of the startle sign by two anesthesiologists, using intraoperative physiological variables and documented interventions as

proxy indicators, including: intraoperative provider notes documenting unexpected patient changes or movement, changes in vital signs (increase in heart rate > 10 beats per minute or > 10%, increase in systolic blood pressure > 30 mm Hg or > 20%, increase in respiratory rate > 5 breaths per minute or > 40%), changes in ventilator settings (increase in peak inspiratory pressure > 4 cm H2O, ventilator dysysnchrony, or change in ventilator mode), Masimo processed EEG patient safety index increase (> 5 units or > 20%), patient movement (generalized movement or withdrawal of the operative limb) or administration of otherwise unexplained boluses of anesthetic medications (most often intravenous propofol). Possible startle sign events were examined contextually in the anesthetic record and timing of abnormalities and number of abnormalities were considered in relation to the specific timepoint within the surgery and anesthetic, and in relation to corresponding provider notes in the chart. For each patient, a rating scale of certainty was applied by an anesthesiologist ranging from 1 to 5, with 1 representing strong suspicion that no startle sign was present and 5 indicating a strong suspicion that a startle sign event occurred. Cases with a rating of >=4 were included in the positive startle sign group. A detailed rationale for the rating for each case is provided in Supplemental Table 1.

Description of anesthetic regimen and surgical procedure

Surgical characteristics of cases were reviewed and described by a plastic surgeon (SK) under the guidance of a senior plastic surgeon (KRE). All cases were reviewed to describe the anesthetic regimen and quantify the pharmacological agents used. We quantified doses and timing of drugs delivered, which were categorized into three time periods: induction, intraoperative period, and case closure. Induction was defined as the time from the first medication given in the operating room until surgical procedure start, the intraoperative period spanned from procedure start until 15 min before procedure end, and case closure was the period 15 min prior to procedure end until leaving the room. We assumed that neuroma manipulation, neuroma identification, and startle signs occurred during the intraoperative period.

For intraoperative medications in which both boluses and infusions were used (propofol, ketamine), a single composite average variable in mcg/kg/min was determined for the medication. For ketamine, boluses given during induction were included in the intraoperative calculation, as the drug is long-acting. For opioids, we report total intravenous morphine equivalents during maintenance anesthesia, combining: hydromorphone given at least 15 min prior to closure (and thus prior to neuroma localization), fentanyl outside of induction and at least 15 min prior to closure, and total remifentanil. Intravenous morphine equivalents were calculated using standard conversion units [14]. Because of substantial differences in cumulative dose over the course of surgery, remifentanil infusions were analyzed separately from bolus doses of opioids as an independent variable. Inhaled anesthetics were compared by adding the age-adjusted mean alveolar concentration for each inhaled agent during the intraoperative period, averaged over time. Combined intravenous and inhalation anesthesia (CIVIA) was defined as a maintenance anesthetic combining inhaled volatile anesthetics and a propofol infusion. To qualify a case for inclusion in the CIVIA group, propofol infusion must have been used throughout most of the anesthesia maintenance phase.

Continuous variables were reported as the median and interquartile range and categorical variables were reported as frequency and percentage. The Mann-Whitney U test was used to compare continuous variables between the event group and the non-event group. Pearson's Chi-squared test was used to compare categorical variables between the event group and the non-event group. All tests were performed as two-sided. The analysis was completed using the latest version of R (4.2.2) and RStudio (2022.07.02) available at the time of analysis.

Results

Patient demographics and preoperative characteristics

Of the 64 neuroma resection surgeries meeting inclusion criteria for the study, 13 cases exhibited the neuroma startle sign (Table 1). Demographic characteristics were similar between the groups in this middle-aged, overweight population, with age (median, [interquartile range]) 50 [35, 59] years in the no-startle sign group and 46 [34, 56] years in the startle sign group, female sex in 47% in the no-startle sign group and 39% in the startle sign group, and body mass index (BMI) 27 [23, 33] kg/m^2 in both groups. Surgical and clinical variables were similar between the groups. Neuroma locations included the lower extremity, upper extremity, and trunk, with lower extremity as the most prevalent location (74% in no-startle sign and 69% in the startle sign group). The median duration of pain preoperatively was 2 [1, 3] years for no-startle sign and 2 [2, 3] years for startle sign cases ($p=0.12$), with inciting events similar between groups and including unknown etiologies, infection, surgery and trauma. We examined preoperative medications that could impact detection of a startle sign, which mostly did not vary between the groups, including antihypertensives, beta-blockers, narcotics, and nonsteroidal anti-inflammatory drugs. Preoperative gabapentinoid medications (primarily gabapentin) were notably used in 31% of the no-startle sign group and 0% in the startle sign group ($p=0.05$). Among patients using gabapentin, the median duration of outpatient use was 2.7 [1.1–4.1] years, with a median total daily dose of 1200 [400–1900]

Table 1 Patient Demographic, Clinical, Operative, and Anesthetic Details for Startle Sign and Non-Startle Sign Cases

	No startle sign (*n* = 51)		**Startle sign (*n* = 13)**		
	No.	**%**	**No.**	**%**	***P* Value**
Demographic Characteristics					
Age, years	50 [35, 59]	-	46 [34, 56]	-	0.42
Female Sex	24	47%	5	39%	0.81
Race	-	-	-	-	0.51
White	38	74%	10	77%	
Black	3	6%	1	8%	
Asian	2	4%	2	15%	
Other	6	12%	0	0%	
Declined	1	2%	0	0%	
Unavailable	1	2%	0	0%	
BMI, kg/m^2	27 [23, 33]	-	27 [23, 33]	-	0.83
Clinical History					
Neuroma Location	-	-	-	-	0.77
Lower extremity	38	74%	9	69%	
Upper extremity	12	24%	4	31%	
Trunk	1	2%	0	0%	
Neuroma Pain Duration, years	2 [1, 3]	-	2 [2, 3]	-	0.12
Inciting Event	-	-	-	-	0.78
Infection	1	2%	0	0%	
Surgery	32	63%	9	69%	
Trauma	15	29%	4	31%	
Unknown	3	6%	0	0%	
Pre-operative Medications	-	-	-	-	
Anti-hypertensives	6	12%	2	15%	1.00
Beta-blockers	6	12%	0	0%	0.44
Narcotics	12	23%	3	23%	1.00
Gabapentinoids	16	31%	0	0%	0.05
NSAIDs	10	19%	4	31%	0.62
Pre-operative Success of Diagnostic Nerve Block	-	-	-	-	0.40
Yes	25	49%	4	31%	
No	1	2%	0	0%	
Not performed	25	49%	9	69%	
ASA Physical Status	-	-	-	-	0.31
1	8	16%	4	31%	
2	32	63%	8	61%	
3	11	21%	1	8%	
Operative Characteristics					
Operation	-	-	-	-	0.83
Excision +/- burying	10	20%	3	23%	
Excision & allograft recon	29	57%	8	62%	
Excision & targeted muscle reinnervation	9	17%	2	15%	
Excision & regenerative peripheral nerve interface	3	6%	0	0%	
Operative Duration, minutes	76 [60, 95]	-	88 [70, 119]	-	0.35
Tourniquet	40	78%	10	77%	1.00
Tourniquet Time, minutes[a]	54 [34, 66]	-	67 [15, 85]	-	
Anesthesia Variables					
Airway Management					
Laryngeal Mask Airway	22	43%	6	54%	0.36
Endotracheal Tube	22	43%	7	46%	
Natural Airway	7	14%	0	0%	
Induction Medications					

Table 1 (continued)

	No startle sign (*n* = 51)		**Startle sign (*n* = 13)**		
	No.	**%**	**No.**	**%**	***P* Value**
Propofol	48	94%	13	100%	0.87
mg[a]	200 [150, 220]	-	200 [200, 250]	-	
Ketamine	15	29%	3	23%	0.91
mg[a]	50 [40, 50]	-	30 [25, 40]	-	
Fentanyl	45	88%	11	85%	1.00
mcg[a]	100 [50, 100]	-	100 [50, 100]	-	
Lidocaine	40	78%	9	69%	0.74
mg[a]	100 [80, 100]	-	80 [60, 100]	-	
Long-acting Paralytic	8	16%	3	23%	0.83
Use of Any Inhaled Anesthetics	38	75%	12	92%	0.31
Total Age-Adjusted Mean Alveolar Concentration[a]	1.2 [0.9, 1.6]	-	1.0 [0.7,1.2]	-	
Primary Anesthesia Mode					0.001
Inhaled Anesthesia	33	64%	5	38%	
TIVA	8	16%	1	8%	
CIVIA	4	8%	7	54%	
Monitored Anesthetic Care	6	12%	0	0%	
Maintenance Anesthesia		-		-	
Sevoflurane	38	75%	10	77%	1.00
Expired, percent[a]	1.8 [1.4, 1.9]	-	1.4 [1.2, 1.8]	-	
Nitrous Oxide	20	39%	5	39%	1.00
Expired, percent[a]	43.4 [39.3, 56.2]	-	49.8 [41.8, 52.0]	-	
Isoflurane	0	0%	1	8%	0.46
Dexmedetomidine	0	0%	1	8%	0.46
Propofol	20	39%	8	62%	0.26
mcg/kg/min[a]	96.6 [84.5, 114.4]	-	104.8 [62.4, 137.4]	-	
Ketamine	7	14%	2	15%	1.00
mcg/kg/min[a]	10.6 [10.4, 12.1]	-	18.2 [15.1, 21.4]	-	
Remifentanil	6	12%	1	8%	1.00
mcg/kg/min[a]	0.10 [0.08, 0.10]	-	0.10 [0.10, 0.10]	-	
Use of Opioids					
Hydromorphone	16	31%	4	31%	1.00
Fentanyl	13	26%	6	46%	0.27
Local Anesthesia					0.84
Local (administered by surgeon at surgical site)	40	78%	11	84%	
Regional Block	4	8%	1	8%	
None	7	14%	1	8%	
Intravenous Morphine Equivalents	29	57%	9	70%	0.62
mg/kg (all patients)	0.04 [0.00, 0.11]	-	0.08 [0.00, 0.10]	-	0.36
mg/kg[a]	0.09 [0.05, 0.16]	-	0.10 [0.08, 0.14]	-	
mg (all patients)	3.35 [0.00, 7.50]	-	5.00 [0.00, 9.96]	-	0.37
mg[a]	6.67 [3.37, 13.29]	-	8.31 [5.00, 15.00]	-	

Continuous variables are reported as median and interquartile range. Categorical variables are summarized as frequency and percentage. Three patients are missing data for neuroma pain duration. The Mann-Whitney U test was used to compare continuous variables between the event group and the non-event group. Pearson's Chi-squared test was used to compare categorical variables between the event group and the non-event group

[a]Median and interquartile range are calculated for the subset of cases with non-zero values of the variable

mg. American Society of Anesthesiologists (ASA) physical status score did not differ between the groups ($p=0.31$).

Operative characteristics

The types of neuroma surgery included neuroma excision with or without burying, excision and allograft reconstruction, excision with targeted muscle reinnervation, and excision with regenerative peripheral nerve interface surgery. The operative time was 76 [60–95] minutes in the no-startle sign group and 88 [70–119] minutes in the startle sign group, with similar tourniquet use (78% vs. 77%) and tourniquet time in the use group (54 [34–66] minutes vs. 67 [15–85] minutes) between no-startle sign vs. startle sign groups.

Anesthetic variables

The mode of anesthesia maintenance differed between no-startle sign and startle sign cases ($p=0.001$) (Table 1). There were more CIVIA anesthetics in the startle sign cases compared to the no-startle sign cases (54% vs. 8%). The other modes of anesthetic maintenance included inhaled anesthesia (64% no-startle sign vs. 38% startle sign), total intravenous anesthesia (TIVA, 16% no-startle sign vs. 8% startle sign), and monitored anesthesia care in combination with peripheral nerve block (12% no-startle sign vs. 0% startle sign). Other anesthetic management variables were similar between the groups. For airway management, laryngeal mask airway (LMA) and endotracheal tube (ETT) were used for most cases while a natural airway was used in a minority of cases in both groups. The use of propofol, fentanyl, and intravenous lidocaine on induction was nearly universal, with similar doses of the drugs between groups (Table 1). A ketamine bolus on induction was used in 29% of no-startle sign cases vs. 23% of startle sign cases, with 50 [40–50] mg used in no-startle sign vs. 30 [25–40] mg used in startle sign cases ($p=0.91$). While the minority of cases used long-acting neuromuscular blocking agents (rocuronium, cisatracurium) on induction, use between cases was similar (16% no-startle sign vs. 23% startle sign cases). Startle sign cases versus no-startle sign cases had similar utilization of ketamine infusion (14% vs. 15%, $p=1.00$), dexmedetomidine infusion (0% vs. 8%, $p=0.46$), and remifentanil infusion (12% vs. 8%, $p=1.00$) (Table 1). Use of opioids in the maintenance phase of anesthesia was similar between no-startle sign and startle sign groups across multiple agents, including hydromorphone (31% vs. 31%), fentanyl (26% vs. 46%), and intravenous morphine equivalents per kg (0.09 [0.05–0.16] mg/kg vs. 0.10 [0.08–0.14] mg/kg).

Verification of CIVIA classification

A descriptive analysis of anesthetic medications stratified by mode of anesthesia showed that total age-adjusted mean alveolar concentration for the inhaled anesthetic group was 1.3 [1.0, 1.6], while that of the CIVIA group was 0.7 [0.6, 0.9]. All CIVIA cases also used a propofol infusion, with median dose 96.6 [60.5–109.6] mcg/kg/min. IV morphine equivalents in patients who received opioids during the maintenance phase of anesthesia were much higher in the TIVA group (1.19 [0.06, 1.14]) due to remifentanil infusions. Opioid use in the maintenance phase of anesthesia was similar between the inhaled anesthetic and CIVIA groups (63% vs. 74%, respectively) with similar doses given (0.08 [0.05, 0.13] mg/kg IV morphine equivalents and 0.11 [0.09, 0.20] mg/kg IV morphine equivalents, respectively). An additional exploratory breakdown of the modes of anesthesia by startle sign and non-startle cases is given in Supplemental Table 2. The CIVIA cases which achieved a startle sign received less opioid in the maintenance phase of anesthesia than CIVIA no-startle sign cases (0.10 [0.08,0.11] vs. 0.24 [0.18,0.30] IV mg/kg morphine equivalents), though we are cautious with interpretation and did not calculate statistical differences due to low total case numbers in these sub-categories.

Discussion

Recognizing the neuroma startle sign as a useful intraoperative indicator for neuroma localization necessitates reevaluating the optimal anesthesia approach for neuroma excision surgery. Identification of the neuroma startle sign can be helpful in cases where the localization of the injured nerve is not obvious. Here, we characterize anesthetic factors related to eliciting the neuroma startle sign, providing the first steps towards tailored anesthetic management.

Our findings suggest a previously unknown association between the primary mode of anesthesia and presence of the neuroma startle sign. Startle sign cases were associated with higher use of CIVIA as the primary anesthetic strategy compared to controls, while inhaled anesthesia, TIVA, and regional anesthesia with monitored anesthetic care were less associated with the neuroma startle sign. While further prospective research is required to establish a causal link between anesthetic mode and startle sign presence, several possible explanations for our descriptive findings are plausible. The overall anesthetic plane may be different between CIVIA and pure inhaled volatile anesthesia, and the balance of lack of awareness, immobility, and antinociception may differ between CIVIA and other anesthetic modes. CIVIA may permit adequate hypnosis without as much immobility and antinociception as a pure inhaled anesthetic [15]. Propofol, the main intravenous component of CIVIA anesthetics, provides excellent hypnosis, but less immobility and antinociception than volatile inhaled anesthesia [16]. When remifentanil infusion is used with propofol (common in

a TIVA), immobility and antinociception are increased. With the use of CIVIA, some hypnosis comes from inhaled volatile anesthetics and some from propofol. However, the immobility and antinociception are not as well covered by a partial mean alveolar concentration of inhaled anesthetics [17]. Our findings generate the hypothesis that CIVIA provides a balance of general anesthesia that permits a good surgical field while also not fully blocking the nociception and motor reactivity needed to observe a neuroma startle sign.

Neuromuscular blockade limits physical movement, remifentanil restricts movement and suppresses respiratory indicators of 'startle', while ketamine is a potent adjunct modulator of pain. Thus, prior to analysis, we hypothesized that neuromuscular blockade, remifentanil, and ketamine were likely to suppress the startle sign. Long-acting neuromuscular blockers given on induction may not be present at the neuromuscular junction at the time of neuroma localization and startle sign. Even with light redosing of paralytics, there may not be complete patient immobility. The use of long-acting paralytics was low across patients in both of our groups, and we did not have consistent documentation of train-of-four monitoring to systematically quantify the level of patient paralysis. Furthermore, some 'startle sign' patients had physiological changes in hemodynamics, which would not be blunted by paralysis. These may be reasons why the use of neuromuscular blockade did not emerge in our study as a difference between no-startle sign and startle sign groups, despite the obvious fact that paralyzed patients cannot produce the physical movements helpful in recognizing a 'startle' event. We did not see differences between groups with ketamine boluses or infusions, but small sample size may limit detection of differences.

While most moderate physiological perturbations during surgery are manageable for anesthesiologists, sudden patient movement could pose a safety concern. Typically, we observe limb withdrawal, which is not problematic as access lines are on the contralateral side and the airway is distant. However, generalized movement introduces a theoretical risk of airway loss (e.g., extubation), underscoring the need for excellent communication between the surgical and anesthesia teams. It is essential that the anesthesia team is aware of potential movement and informs the surgeons if it occurs, especially if it may indicate the neuroma startle sign. Importantly, we saw no evidence of bronchospasm or laryngospasm in any cases. Clear preoperative discussion between surgeons and anesthesiologists is necessary to determine if the startle sign is desirable in each case and to formulate an optimal plan to achieve this goal.

The no-startle sign group had more patients with use of outpatient gabapentinoids compared to the startle sign group. Experimental models in humans have demonstrated that gabapentinoids can reduce central sensitization of pain [18]; indeed, this is the reason that neuroma patients are prescribed these drugs. It is plausible that the mechanism underlying the startle sign involves central sensitization, possibly even as a potentiator, and the use of gabapentinoids could modify this effect. Considering the approximately six-hour half-life of gabapentin and pregabalin, optimizing the startle sign may involve discontinuing these medications for 24–48 h before surgery, but needs further validation and study.

Some limitations of our work include a limited sample size, which does not allow us to detect small differences between variables. A small sample size also precludes modeling with variable adjustment for hypothesis testing, limiting us to a descriptive analysis. Keeping the sample set to a single surgeon ensures uniformity in surgical procedure and expertise between the case and startle sign groups but contributes to a small sample and may limit generalizability of our results. Due to the retrospective design of the study, we used proxy variables to identify cases with a startle sign, as this sign was not routinely documented in real time in the electronic health record. Given the variability in surgical and anesthetic approaches between cases, we relied on the context-specific interpretation of physiological changes in the anesthetic record and the expertise of anesthesiologists to determine which cases exhibited a startle sign. Some cases used long-acting neuromuscular blockade, while others did not, and train-of-four monitoring was not uniformly available for review across all surgeries. While we have age-adjusted mean alveolar concentration for inhalational anesthesia cases, we have no universal metric to assess the depth of anesthesia across all cases. This limits our ability to explore whether CIVIA cases simply had a lower depth of anesthesia compared to other modes of anesthesia in the study. Importantly, there were no reports of recall in any patient records or during surgical follow-up visits. It is unknown whether the neuroma startle sign represents a moment of hyperalgesia. If this response allows for more accurate identification of the patient's neuroma and potentially allows for cure of chronic pain, a brief hyperalgesic event under general anesthesia may be justifiable and result in a net benefit for the patient. Although visible startle reactions were brief, physiological changes such as blood pressure elevation persisted for up to 20 min in cases where additional anesthetics were not administered. These questions warrant further investigation in a future prospective study designed to address the limitations of this retrospective analysis.

Conclusions

Effective communication between the anesthesia and surgical teams is critical both before and during surgery. This ensures a shared understanding of the objectives for eliciting the startle sign, including achieving a balance between patient unawareness and pain control, allowing for slight patient reactivity, and maintaining overall safety. Regular intraoperative check-ins are essential to assess if the preoperative goals are being met. In these early stages of the description of a neuroma startle sign, we present evidence that there may be ways to deliver anesthesia to patients safely that still permit detection of this phenomenon by using CIVIA. In the future, prospective studies are needed to validate the hypotheses generated in this work.

Abbreviations

CIVIA	Combined Intravenous and Inhalational Anesthesia
EEG	Electroencephalogram
IRB	Institutional Review Board
TIVA	Total Intravenous Anesthesia
LMA	Laryngeal Mask Airway
ETT	Endotracheal Tube
BMI	Body Mass Index
ASA	American Society of Anesthesiologists
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02758-5.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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None.

Author contributions

JG – Data collection, data analysis, manuscript writing and editing. SK – Data collection, manuscript writing and editing. SR – Data analysis, manuscript writing and editing. LL – Data collection. MS – Data analysis. AM – Data analysis. TH – Data analysis. KE – Conceptualization, manuscript editing. KR – Conceptualization, data analysis, manuscript writing and editing.

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Data availability

Data supporting the findings of this study are available from the corresponding author, Katarina J Ruscic, upon reasonable request. The release of deidentified data is subject to the establishment of appropriate data transfer agreements and approvals from both the requesting and sending institutions.

Declarations

Ethics approval and consent to participate

The study was approved and waived by the Massachusetts General Hospital Institutional Review Board (IRB), protocol 2021P002542, "Retrospective Chart Review to Assess Neuroma Hypersensitivity Reaction." The requirement for written informed consent from patients was waived by the IRB.

Consent for publication

Not applicable. As the requirement for written informed consent was waived by the IRB, there is no consent needed for publication. No identifying images or personal or clinical details of participants are presented in this study.

Competing interests

KRE is a consultant for AxoGen, Integra, Checkpoint, Tissium, Tulavi, and Biocircuit.

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References

1. Finnerup NB, et al. Neuropathic pain: an updated grading system for research and clinical practice. Pain. 2016;157(8):1599–606.
2. Attal N, Bouhassira D, Colvin L. Advances and challenges in neuropathic pain: a narrative review and future directions. Br J Anaesth. 2023;131(1):79–92.
3. Ji R-R, et al. Neuroinflammation and Central Sensitization in chronic and widespread Pain. Anesthesiology. 2018;129(2):343–66.
4. Chen Q, Heinricher MM. Shifting the balance: how top-down and Bottom-Up Input Modulate Pain via the Rostral Ventromedial Medulla. Front Pain Res (Lausanne). 2022;3:932476.
5. Hwang CD, et al. Biology and pathophysiology of symptomatic neuromas. Pain. 2024;165(3):550–64.
6. Eberlin KR. I. Ducic 2018 Surgical Algorithm for Neuroma Management: a changing treatment paradigm. Plast Reconstr Surg Glob Open 6 10 e1952.
7. Arnold DMJ, et al. Diagnostic criteria for symptomatic neuroma. Ann Plast Surg. 2019;82(4):420–7.
8. Ducic I, Yoon J, Eberlin KR. Treatment of Neuroma-induced Chronic Pain and Management of nerve defects with processed nerve allografts. Plast Reconstr Surg Glob Open. 2019;7(12):e2467.
9. Drinane JJ, et al. A longitudinal assessment of the surgical treatment of symptomatic neuromas and their surgical management in the American College of Surgeons National Surgical Quality Improvement Program database. J Plast Reconstr Aesthet Surg. 2021;74(9):2392–442.
10. Poppler LH, Mackinnon SE. The role of the peripheral nerve surgeon in the treatment of Pain. Neurotherapeutics. 2019;16(1):9–25.
11. Karinja SJ, et al. The Neuroma Startle sign: A Surgical Indicator of Proximity to an injured nerve. Plast Reconstr Surg Glob Open. 2023;11(3):e4890.
12. Brown EN, Pavone KJ, Naranjo M. Multimodal General Anesthesia: theory and practice. Anesth Analg. 2018;127(5):1246–58.
13. Chen YK, Boden KA, Schreiber KL. The role of regional anaesthesia and multimodal analgesia in the prevention of chronic postoperative pain: a narrative review. Anaesthesia. 2021;76(Suppl 1):8–17.
14. Santa Cruz Mercado LA, et al. Association of Intraoperative Opioid Administration with Postoperative Pain and Opioid Use. JAMA Surg. 2023;158(8):854–64.
15. Yang J, et al. Further proof that the spinal cord, and not the brain, mediates the immobility produced by inhaled anesthetics. Anesthesiology. 2009;110(3):591–5.
16. Matute E, Rivera-Arconada I, López-García JA. Effects of propofol and sevoflurane on the excitability of rat spinal motoneurones and nociceptive reflexes in vitro. Br J Anaesth. 2004;93(3):422–7.
17. Grasshoff C, Antkowiak B. Propofol and sevoflurane depress spinal neurons in vitro via different molecular targets. Anesthesiology. 2004;101(5):1167–76.

18. Gottrup H, et al. Chronic oral gabapentin reduces elements of central sensitization in human experimental hyperalgesia. Anesthesiology. 2004;101(6):1400–8.

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