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Systematic Review and Meta-analysis

What Is the Risk of Postoperative Neurologic Symptoms After Regional Anesthesia in Upper Extremity Surgery? A Systematic Review and Meta-analysis of Randomized Trials

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Abstract

Background The risk of neurologic symptoms after regional anesthesia in orthopaedic surgery is estimated to approach 3%, with long-term deficits affecting 2 to 4 per 10,000 patients. However, current estimates are derived from large retrospective or observational studies that are subject to important systemic biases. Therefore, to harness the highest quality data and overcome the challenge of small numbers of participants in individual randomized trials, we undertook this systematic review and meta-analysis of contemporary randomized trials.

Questions/purposes In this systematic review and meta-analysis of randomized trials we asked: (1) What is the aggregate pessimistic and optimistic risk of postoperative neurologic symptoms after regional anesthesia in upper extremity surgery? (2) What block locations have the highest and lowest risk of postoperative neurologic symptoms? (3) What is the timing of occurrence of postoperative neurologic symptoms (in days) after surgery?

Methods We searched Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, Web of Science, Scopus, and PubMed for randomized controlled trials (RCTs) published between 2008 and 2019 that prospectively evaluated postoperative neurologic symptoms after peripheral nerve blocks in operative procedures. Based on the Grading of Recommendations, Assessment, Development, and Evaluation guidance for using the Risk of Bias in Non-Randomized Studies of Interventions tool, most trials registered a global rating of a low-to-intermediate risk of bias. A total of 12,532 participants in 143 trials were analyzed. Data were pooled and interpreted using two approaches to calculate the aggregate risk of postoperative neurologic symptoms: first according to the occurrence of each neurologic symptom, such that all reported symptoms were considered mutually exclusive

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(pessimistic estimate), and second according to the occurrence of any neurologic symptom for each participant, such that all reported symptoms were considered mutually inclusive (optimistic estimate).

Results At any time postoperatively, the aggregate pessimistic and optimistic risks of postoperative neurologic symptoms were 7% (915 of 12,532 [95% CI 7% to 8%]) and 6% (775 of 12,532 [95% CI 6% to 7%]), respectively. Interscalene block was associated with the highest risk (13% [661 of 5101] [95% CI 12% to 14%]) and axillary block the lowest (3% [88 of 3026] [95% CI 2% to 4%]). Of all symptom occurrences, 73% (724 of 998) were reported between 0 and 7 days, 24% (243 of 998) between 7 and 90 days, and 3% (30 of 998) between 90 and 180 days. Among the 31 occurrences reported at 90 days or beyond, all involved sensory deficits and four involved motor deficits, three of which ultimately resolved.

Conclusion When assessed prospectively in randomized trials, the aggregate risk of postoperative neurologic symptoms associated with peripheral nerve block in upper extremity surgery was approximately 7%, which is greater than previous estimates described in large retrospective and observational trials. Most occurrences were reported within the first week and were associated with an interscalene block. Few occurrences were reported after 90 days, and they primarily involved sensory deficits. Although these findings cannot inform causation, they can help inform risk discussions and clinical decisions, as well as bolster our understanding of the evolution of postoperative neurologic symptoms after regional anesthesia in upper extremity surgery. Future prospective trials examining the risks of neurologic symptoms should aim to standardize descriptions of symptoms, timing of evaluation, classification of severity, and diagnostic methods.

Level of Evidence Level I, therapeutic study.

Introduction

Postoperative neurologic symptoms are a distressing and potentially devastating complication of regional anesthesia and orthopaedic surgery for patients and providers alike. A reliable and valid estimation of risk of postoperative neurologic symptoms after a peripheral nerve blockade in orthopaedic surgery is essential to inform routine clinical care, risk-benefit discussions, choice of peripheral nerve blockade technique, and medicolegal matters. Because nerve injury associated with peripheral nerve blockade is uncommon, large numbers of patients are required for a study to estimate risk. As such, our current understanding of the risk stems from large retrospective or observational studies [24, 26, 105, 106], which estimate that the risk of neurologic symptoms after regional anesthesia in orthopaedic surgery approaches 3%, with long-term injury affecting 2 to 4 per 10,000 patients. Although these methods offer the distinct advantages of feasibility and cost efficiency, retrospective and observational studies are also subject to important systemic biases leading to incomplete risk estimates.

Although prospective clinical randomized controlled trials (RCTs) are the most favorable study design to mitigate against bias and yield the highest quality evidence, the quantity of study participants, time, and costs required for an adequately powered RCT to definitively determine the risk of neurologic complications associated with peripheral nerve blockade, compared with no peripheral nerve blockade, is prohibitively large [105]. Therefore, to accurately estimate the true risk and timing of postoperative neurologic symptoms using the highest quality data, and to overcome the challenge of relatively small numbers of participants in individual RCTs, we undertook this systematic review and meta-analysis of contemporary RCTs in which postoperative neurologic symptoms associated with peripheral nerve blockade and upper extremity surgery were prospectively investigated.

Specifically, we asked: (1) What is the aggregate pessimistic and optimistic risk of postoperative neurologic symptoms after regional anesthesia in upper extremity surgery? (2) What block locations have the highest and lowest risk of postoperative neurologic symptoms? (3) What is the timing of occurrence of postoperative neurologic symptoms (in days) after surgery?

Materials and Methods

Search Strategy and Criteria

This manuscript was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [111]. Beginning in May 2018 and updated once in August 2019, we searched for all contemporary RCTs that prospectively assessed or reported postoperative neurologic symptoms as a primary or secondary outcome after peripheral nerve blockade in the setting of operative procedures for the upper extremity. When assessing the occurrence of postoperative neurologic symptoms associated with peripheral nerve blockade, RCTs minimize bias by balancing risk factors and confounders, blinding providers and/or patients, and systematically following study participants. Indeed, the structure and timing of follow-up are the key factors to mitigate variance in reported rates of postoperative neurologic symptoms. Moreover, RCTs offer granular details regarding block technique, injectate, and block procedure-related events, which are often lacking in larger retrospective and observational trials. A systematic search strategy was created for Ovid MEDLINE, MEDLINE in-process and other non-indexed citations, Embase, Cochrane Central Register of Controlled Trials and

Cochrane Database of Systematic Reviews, Web of Science, Scopus, and PubMed (not MEDLINE). Non-peer-reviewed sources, including preprint servers and abstracts from national meetings, were not included in our search. We searched the databases from January 2008 (corresponding to the widespread adoption of real-time ultrasound guidance) [65, 133] to August 2019. This search was developed using a combination of medical subject headings and keywords relating to the following key domains: regional anesthesia, upper extremity, and neurologic complications (Supplementary Table 1; http://links.lww.com/CORR/A931). Citations and bibliographies from systematic reviews and meta-analyses identified through our search, as well as all included randomized trials, were further searched manually for additional relevant trials.

Eligibility Criteria

RCTs that prospectively assessed or reported postoperative neurologic symptoms in adult participants (aged 18 years or older) receiving any upper extremity peripheral nerve blockade in the setting of any operative procedure in at least one study arm were included. All variations in block locations and techniques were accepted, provided blocks were performed by a qualified physician and the details of block performance were recorded. Feasibility studies, abstracts, non-English-language articles, and clinical trials not assessing or reporting postoperative neurologic symptoms were excluded.

Selection of Included Studies

Two authors (JMA, MMA) independently reviewed titles and abstracts. The same two authors subsequently independently retrieved and reviewed the full-text articles of potentially eligible studies. If a disagreement regarding study eligibility could not be resolved after discussion between the two reviewers, consultation with a third reviewer (FWA) was sought to make the final decision.

Our search yielded 9268 studies, 554 of which were retrieved for full-text review based on title and abstract screening (Fig. 1). After the full-text review, 433 additional

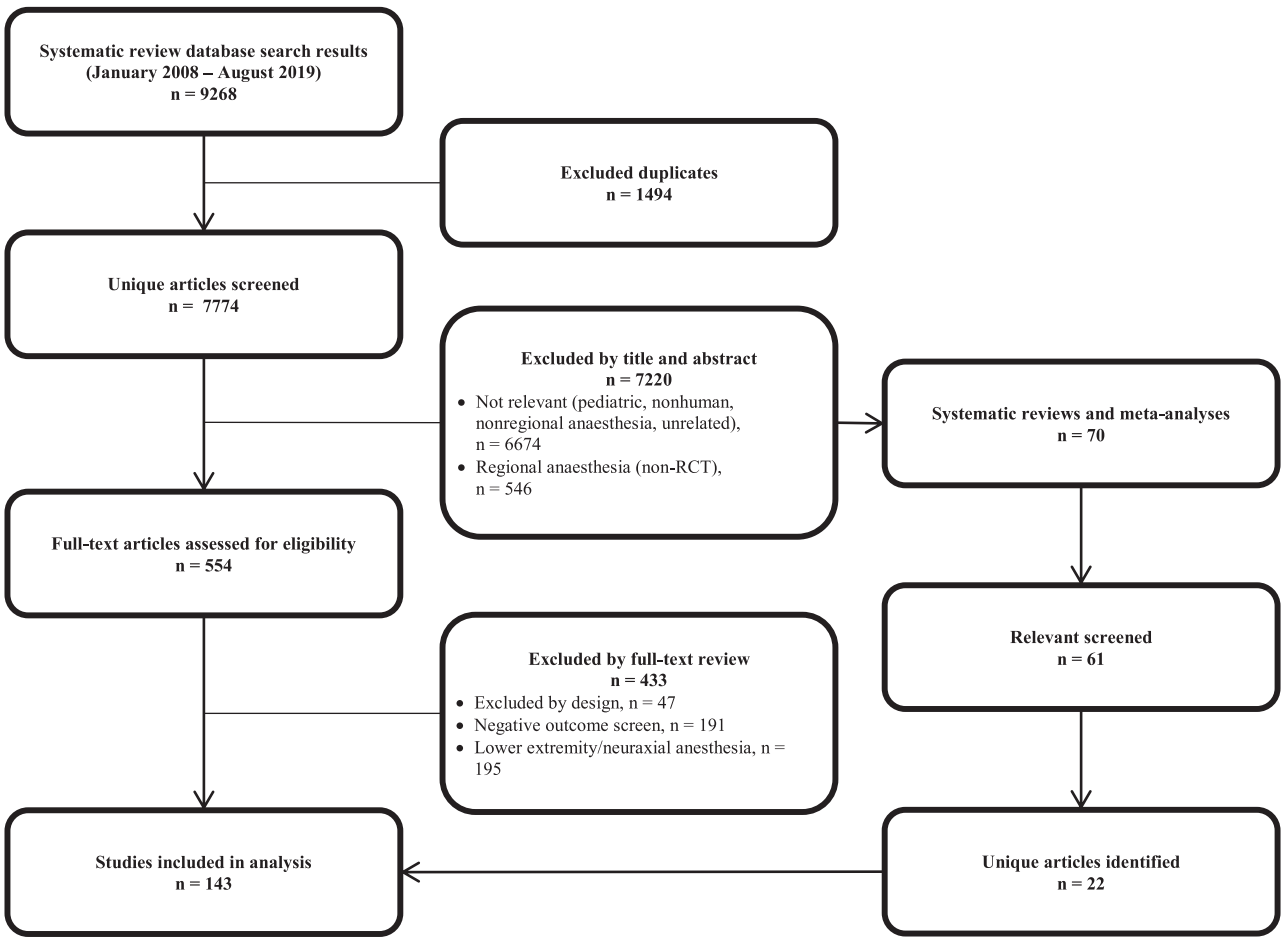

Fig. 1. This flowchart shows the studies that were included in this systematic review.

articles were excluded: 47 did not meet study design criteria, 191 did not prospectively assess or report postoperative neurologic symptoms, and 195 were RCTs of peripheral nerve blockades related to lower extremity surgical procedures. Subsequently, we captured and included 22 additional articles following manual search of citations and bibliographies from 70 systematic reviews and meta-analyses. In total, we identified 143 RCTs with 329 unique study arms published between January 2008 and August 2019, yielding a total of 12,532 participants with data available for analysis [1-3, 5-21, 23, 25, 27-44, 48-64, 66, 68, 70, 71, 74-102, 104, 108-110, 112-132, 134-138, 140, 141, 143-151, 153-162, 164, 165]. The four most common brachial plexus blocks were interscalene (5417 participants), axillary (3301), infraclavicular (2445), and supraclavicular (1840 participants). Ultrasound guidance was used for block performance in 71% of participants (including 23% in combination with nerve stimulation) (Table 1).

Table 1. Study characteristics

Study characteristic	Total (n = 13,707)[a]
Brachial plexus block location	
Axillary	24 (3301)
Interscalene	40 (5417)
Supraclavicular	13 (1840)
Infraclavicular	18 (2445)
Other upper extremity[b]	3 (441)
Nonregional comparator group	2 (263)
Needle guidance	
Ultrasound (with or without peripheral nerve stimulator)	71 (9781)
Peripheral nerve stimulator	23 (3201)
Anatomic landmark	3 (432)
Not applicable	2 (293)
Block technique	
Single injection only	86 (11,820)
Catheter	11 (1547)
Not applicable or reported	2 (340)
Maximum follow-up	
0 to 7 days	39 (5301)
> 7 to 90 days	39 (5321)
> 90 to 180 days	10 (1416)
> 180 days	1 (95)
Not reported	11 (1574)

Data presented as % (n).
[a]Baseline characteristics for all randomized participants (12,532 participants were available for analysis).
[b]Forearm, wrist, subacromial, suprascapular, or undefined brachial plexus block.

Assessment of Methodologic Quality Across Trials

We used the Cochrane Collaboration's tool for assessing the risk of bias to critically appraise the methodologic quality of all included studies [69]. This tool assesses various components of study methodology and bias in RCTs, including selection (randomization and allocation), performance (blinding), detection, attrition, and reporting bias. One author (MMA) assigned a risk rating to each study, which was independently verified by another author (JMA). Randomization, allocation, and blinding were assessed on a scale from 1 to 4 (1 = definitely low risk, 2 = probably low risk, 3 = probably high risk, 4 = definitely high risk), and attrition and reporting bias were assessed dichotomously (1 = low risk and 2 = high risk) based on previously defined criteria. In our assessment, we assigned a grade of intermediate risk of bias for studies that were neither definitely high nor definitely low risk. Certainty of evidence for estimates derived from each outcome from RCTs was assessed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). Based on the GRADE guidance for using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool [139], studies started at high certainty and were downgraded by one level when most of the evidence came from studies at moderate risk of bias, two levels when most of the evidence came from studies at high risk of bias, and three levels when most of the evidence came from studies rated at critical risk of bias. Overall, the methodologic quality of included trials was acceptable, with most trials registering a global rating of a low-to-intermediate risk of bias (Table 2 and Supplementary Table 2; http://links.lww.com/CORR/A932).

Data Extraction

Data extraction began in December 2018. We used a standardized, predetermined data extraction form, and one author (JMA) abstracted and summarized relevant study characteristics, while another author (MMA) verified the data. In instances of discrepancy after discussion, a third reviewer (FWA) assessed the data and determined the outcome. All methodologic and block performance data were retrieved from study text, and numerical data were extracted from the primary source of reporting (table or text where applicable).

Primary and Secondary Study Outcomes

The primary outcome of this systematic review and meta-analysis was the aggregate risk of postoperative neurologic symptoms at any time after peripheral nerve blockade in the setting of upper extremity surgery. We broadly defined

Table 2. Risk of bias assessment summary (n = 143)

Bias type	Low risk	Intermediate risk	High risk
Selection bias			
Random sequence generation	89 (127)	11 (16)	0 (0)
Allocation concealment	20 (29)	80 (114)	0 (0)
Performance bias			
Blinding of participants and personnel	28 (40)	52 (75)	20 (28)
Blinding of outcome assessment	69 (99)	18 (26)	13 (18)
Attrition bias			
Incomplete outcome data	100 (143)		0 (0)
Reporting bias			
Selective outcome reporting	100 (143)		0 (0)

Data presented as % (n).

postoperative neurologic symptoms to include any new postoperative neurologic sign, symptom, or dysfunction, thus ensuring the greatest capture rate to generate the most prudent risk estimates. Postoperative neurologic symptom descriptors were abstracted verbatim. Secondary outcomes included the type of neurologic deficit (motor versus sensory) and timing of occurrences of postoperative neurologic symptoms after upper extremity peripheral nerve blockade.

Assumptions and Interpretation of Outcomes

For the present systematic review, we aimed to determine the aggregate risk of postoperative neurologic symptoms at any time postoperatively. For studies that evaluated postoperative neurologic symptoms at more than one time interval postoperatively, we included only the highest rate of symptoms reported among all measured time intervals to calculate the aggregate risk. Because all included studies followed participants prospectively for complications, studies that did not report the occurrence of any neurologic symptoms were assumed to have a rate of 0. We conducted two approaches to calculating the aggregate risk of postoperative neurologic symptoms, the first according to the occurrence of each neurologic symptom irrespective of the total number of participants (symptom-based occurrence), and the second according to the occurrence of any neurologic symptom (binary: yes or no) for each participant, irrespective of the total number of neurologic symptoms (participant-based occurrence). Symptom-based occurrence assumes the worst-case scenario (pessimistic assessment); that is, all reported occurrences of postoperative neurologic symptoms were considered mutually exclusive, such that one participant could suffer more than one occurrence (type; motor or sensory) of postoperative neurologic symptoms. For example, if a source study reported that six participants suffered numbness and four participants suffered weakness, we calculated 10 (6 + 4) occurrences of postoperative neurologic symptoms. Participant-based occurrence assumes the best-case scenario (optimistic assessment); that is, all occurrences were mutually inclusive such that the number of occurrences could not exceed the number of participants who suffered any neurologic symptom. As in the example, if a source study reported that six participants suffered numbness and four suffered weakness, we calculated that six participants suffered any type of postoperative neurologic symptom (four participants experienced numbness and weakness and two additional participants who experienced numbness only).

Type of Postoperative Neurologic Symptom

The type of postoperative neurologic symptom was abstracted verbatim from each study and categorized as sensory (numbness, tingling, paresthesia, dysesthesia, other sensory deficit), motor (weakness, paralysis, or other motor deficit), or undefined neurologic symptom (reported in studies as postoperative neurologic symptom, neurologic complication, complication, or adverse effects). As for the aggregate risk of postoperative neurologic symptoms, we then calculated the risk of postoperative neurologic symptoms according to symptom type using the highest rate of motor and/or sensory symptoms reported in each study.

Timing of Occurrences

The timing of occurrences of postoperative neurologic symptoms was abstracted verbatim based on the timing of evaluation from each individual study. For studies where postoperative neurologic symptoms were evaluated at more than one timepoint postoperatively, we included data from

each timepoint. For each study, the timing of evaluation was converted to postoperative days (1 week = 7 days; 1 month = 30 days) and categorized as follows: 0 to 7 days, > 7 to 90 days, > 90 to 180 days, and more than 180 days postoperatively. For any occurrence of postoperative neurologic symptoms reported beyond 90 days, we sought additional data related to block performance including surgical indication and duration, tourniquet use, block location, guidance (such as ultrasound or a peripheral nerve stimulator), needle type, and local anesthetic dose and concentration. Any details related to diagnosis, such as specialist referrals or nerve conduction studies, were also noted.

Statistical Analysis

We summarized participant, study, and peripheral nerve blockade characteristics using descriptive statistics. We estimated the aggregate risk with 95% confidence intervals (CIs) for all postoperative neurologic symptoms according to block location. All statistical analyses were performed using Comprehensive Meta-Analysis Version 2.0 statistical software (Biostat) and Review Manager (RevMan 5.4, Cochrane). For quantitative reviews of rare events [142], the Cochrane guidelines (Version 6.2) recommend using the Peto OR option in RevMan software. This method is powerful for addressing rare outcomes and provides a nonbiased estimate of event rates and an accurate confidence interval [163]. The Peto method is recognized to perform well when the quantity of trials and participants is robust, the sizes of the comparator groups (such as block locations) are balanced, and the treatment effects are small.

Results

Aggregate Pessimistic and Optimistic Risk of Postoperative Neurologic Symptoms

The aggregate risk of postoperative neurologic symptoms after regional anesthesia in upper extremity surgery was 7% (915 of 12,532 [95% CI 7% to 8%]) using the pessimistic approach and 6% (775 of 12,532 [95% CI 6% to 7%]) using the optimistic approach (Table 3). Sensory deficits were identified in 5% (636 of 12,532 [95% CI 5% to 5%]), and motor deficits were identified in 2% (248 of 12,532 [95% CI 2% to 2%]) (Table 4).

Block Locations With the Highest and Lowest Risk of Postoperative Neurologic Symptoms

Among upper extremity peripheral nerve blockades, the highest risk of postoperative neurologic symptoms was associated with interscalene brachial plexus blocks at 13% (661 of 5101 [95% CI 12% to 14%]), and the lowest risk was associated with axillary blocks at 3% (88 of 3026 [95% CI 2% to 4%]) (Table 3). Sensory and motor symptoms were most reported with interscalene brachial plexus blocks (7% [356 of 5101] and 5% [234 of 5101], respectively) (Table 4).

Timing of Occurrence of Postoperative Neurologic Symptoms (in Days) After Surgery

Overall, 73% (724 of 998) of all occurrences of postoperative neurologic symptoms were reported between 0 and 7 days postoperatively, 24% (243 of 998) were reported between 7 and 90 days postoperatively, and 3% (30 of 998) were reported between 90 and 180 days postoperatively (Table 5). Among the 87 studies that evaluated postoperative neurologic symptoms occurring between 0 and 7 days, 9% (724 of 8297) of participants reported postoperative neurologic symptoms. Among the 48 studies that evaluated postoperative neurologic symptoms occurring between 7 and 90 days, 4% (243 of 6313) of participants reported symptoms. Among the seven studies that evaluated postoperative neurologic symptoms between 90 and 180 days, 2% (30 of 1416) of participants reported symptoms. Only one study systematically evaluated the rates of postoperative neurologic symptoms persisting

Table 3. Aggregate rate of postoperative neurologic symptom occurrences at any time, stratified by block location

Brachial plexus block location	Pessimistic approach	95% CI	Optimistic approach	95% CI
Axillary	3 (88 of 3026)	2-4	2 (75 of 3026)	2-3
Infraclavicular	3 (77 of 2264)	3-4	3 (76 of 2264)	3-4
Interscalene	13 (661 of 5101)	12-14	11 (539 of 5101)	10-11
Supraclavicular	4 (67 of 1703)	3-5	4 (63 of 1703)	3-5
Other upper extremity[a]	5 (22 of 438)	3-7	5 (22 of 438)	3-7
Total	7 (915 of 12,532)	7-8	6 (775 of 12,532)	6-7

Data presented as % (n).
[a]Forearm, wrist, subacromial, suprascapular, or undefined brachial plexus block.

Table 4. Type of postoperative neurologic symptom occurrences at any time, stratified by block location

Brachial plexus block location	Sensory deficit	95% CI	Motor deficit	95% CI
Axillary	4 (109 of 3026)	3-4	0 (5 of 3026)	0-0
Infraclavicular	4 (95 of 2264)	3-5	0 (0 of 2264)	0-0
Interscalene	7 (356 of 5101)	6-8	5 (234 of 5101)	4-5
Supraclavicular	3 (57 of 1703)	2-4	0 (7 of 1703)	0-0
Other upper extremity[a]	4 (19 of 438)	2-6	0 (2 of 438)	0-0
Total	5 (636 of 12,532)	5-5	2 (248 of 12,532)	2-2

Data presented as % (n).
[a]Forearm, wrist, subacromial, suprascapular, or undefined brachial plexus block.

beyond 180 days, and it did not identify any among 95 participants [164]. One additional study that followed all postoperative neurologic symptoms to completion [44] identified a single participant with persistent sensory deficit 3 years after axillary peripheral nerve blockade. Among participants with symptoms occurring or persisting at 90 days or beyond, all received either an axillary or interscalene peripheral nerve blockade (Table 6), and all participants reported sensory symptoms, with motor symptoms concurrently reported in 13% (4 of 31). Of those with motor symptoms, all but one ultimately resolved (Table 7).

Discussion

Postoperative neurologic symptoms are a distressing and potentially devastating complication of regional anesthesia and orthopaedic surgery. Our current understanding of neurologic symptoms after regional anesthesia in the setting of orthopaedic surgery is based upon large retrospective or observational studies, which are subject to important systemic biases. We conducted this systematic review and meta-analysis of contemporary RCTs, the largest to date for any systematic review examining regional anesthesia, to harness the highest quality data to estimate and characterize the risk of postoperative neurologic symptoms. We found that the aggregate risk of postoperative neurologic symptoms associated with peripheral nerve blockade and upper extremity surgery is greater than the traditional rates described by large retrospective and observational studies. Most occurrences were reported within the first week and associated with interscalene block, whereas few occurrences were reported after 90 days and primarily involved sensory deficits.

Limitations

Chief among the limitations of the present review is the heterogeneity in our source dataset. Much of this variability stems from highly variable definitions of postoperative neurologic symptoms, limited use of laboratory neurologic testing, financial-related and time-related restrictions limiting the duration of follow-up, and missing details surrounding the nature and severity of presenting symptoms, occurrence of multiple symptoms, duration of symptoms, and causation of symptoms. Many orthopaedic surgical procedures carry an inherent risk of neurologic symptoms [46, 47, 152], and studies reporting postoperative neurologic symptoms immediately postoperatively may overestimate the true risk of postoperative neurologic symptoms attributable to peripheral nerve blockade. Moreover, patients undergo many other physiologic insults perioperatively that can cause postoperative neurologic symptoms. Distinguishing the relative contributions of

Table 5. Proportion of postoperative neurologic symptom occurrences according to timing of occurrence, stratified by block location

Timing of occurrence	Axillary (n = 89)	Infraclavicular (n = 85)	Interscalene (n = 741)	Supraclavicular (n = 60)	Other upper extremity (n = 23)[a]	Total (n = 998)
0 to 7 days	46 (41)	72 (61)	75 (556)	73 (44)	96 (22)	73 (724)
> 7 to 90 days	26 (23)	28 (24)	24 (179)	27 (16)	4 (1)	24 (243)
> 90 to 180 days	27 (24)	0 (0)	1 (6)	0 (0)	0 (0)	3 (30)
> 180 days	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (1)

Data presented as % (n).
[a]Forearm, wrist, subacromial, suprascapular, or undefined brachial plexus block.

Table 6. Procedural details related to postoperative neurologic symptom occurrences at 90 days or longer

Patient	Author	Block type	Guidance	Local anesthetic	Needle type	Surgical procedure (duration)	Tourniquet use, yes or no
1	Desmet et al. [38]	Interscalene	US and PNS	Ropivacaine (30 mL, 0.5%)	Stimuplex (50 mm, 22 G)	Arthroscopic shoulder surgery (NR)	NR
2	Holland et al. [70]	Interscalene	US	Bupivacaine (30 mL, 0.5%)	Pajunk (50 mm, 22 G)	Arthroscopic shoulder surgery (1.1 hours)	NR
3	Holland et al. [70]	Interscalene	US	Bupivacaine (30 mL, 0.5%)	Pajunk (50 mm, 22 G)	Arthroscopic shoulder surgery (1.1 hours)	NR
4	Holland et al. [70]	Interscalene	US	Bupivacaine (30 mL, 0.5%)	Pajunk (50 mm, 22 G)	Arthroscopic shoulder surgery (1.1 hours)	NR
5	Holland et al. [70]	Interscalene	US	Bupivacaine (30 mL, 0.5%) and perineural dexamethasone (8 mg)	Pajunk (50 mm, 22 G)	Arthroscopic shoulder surgery (1.0 hour)	NR
6	Holland et al. [70]	Interscalene	US	Bupivacaine (30 mL, 0.5%)	Pajunk (50 mm, 22 G)	Arthroscopic shoulder surgery (28.5 hours)	NR
7	Clement et al. [32]	Axillary	US and PNS	Ropivacaine (0.125 mL/kg^{1}, 0.475%) and intravenous dexamethasone (8 mg)	Locoplex (50 mm)	Hand or forearm surgery (37 minutes)	Yes
8-17	Dhir et al. [44]	Axillary	US and PNS	Ropivacaine (40 mL, 0.5%)	Pajunk (50 mm, 22 G)	Upper limb surgery (NR)	Yes
18-31	Dhir et al. [44]	Axillary	US and PNS	Ropivacaine (40 mL, 0.5%)	Pajunk (50 mm, 22 G)	Upper limb surgery (NR)	Yes

NR = not reported; PNS = peripheral nerve stimulator; US = ultrasound.

peripheral nerve blockade from that of surgery (such as iatrogenic injury, orthopaedic trauma, and tourniquet time) and patient comorbidities (such as smoking, hypertension, and diabetes) is challenging and often presumptive at best. Furthermore, we did not disaggregate data based on sex as to the best of our knowledge and clinical experience, there are no differences in risk of postoperative neurologic symptoms by sex. Although heterogeneity and related confounders are shared by prospective and retrospective studies investigating uncommon outcomes such as postoperative neurologic symptoms after regional anesthesia, we aimed to mitigate variability by preserving the descriptions of postoperative neurologic symptoms to the greatest possible extent and present data as multiple cross-sectional analyses that provide a snapshot in time. Missing details regarding risk disclosure practices in the context of RCTs may also undermine the reliability and validity of prospectively collected data. Our results may also not be generalizable to lower extremity peripheral nerve blockade; however, clinical practice patterns and the relative quantity of published RCTs favor upper extremity blockade. We did not include non-English-language studies, feasibility studies, or published abstracts, and as such, we may have missed relevant data. Unfortunately, we did not have the resources for language translation services or search of the grey literature. The latter notwithstanding, it remains our preference that the reproducibility of our search strategy is endured. Finally, and importantly, our findings do not and cannot elucidate causation of postoperative neurologic symptoms as a function of upper extremity peripheral nerve blockade, surgical technique, or positioning.

Aggregate Pessimistic and Optimistic Risk of Postoperative Neurologic Symptoms

The overall risk of developing postoperative neurologic symptoms after regional nerve block is approximately one in 15 patients. These results stand in contrast to our 2007 review of the largest retrospective and observational trials, in which we found the aggregate risk of any postoperative neurologic symptoms after peripheral nerve blockade to be 3%, with only one occurrence reported at 12 months postoperatively [26]. Unfortunately, the clinically important risk of neurologic symptoms lasting beyond 12 months postoperatively could not be ascertained in the present review. Although advances in regional anesthesia practice (formal training programs, new block techniques, ultrasound guidance) aim to reduce the incidence of neurologic complications [4, 22, 67, 103], there has also been an increase in the prevalence of risk factors (obesity, diabetes,

Table 7. Characteristics of postoperative neurologic symptom occurrences at 90 days or longer

Patient	Type of postoperative neurologic symptom	Duration	Method of identification	Remarks
1	Chronic regional pain syndrome (Type 1)	> 3 months	Investigator-probed (telephone), magnetic resonance imaging, electromyography	One participant had intractable shoulder pain without evidence of brachial plexus conditions on magnetic resonance imaging and electromyography. A diagnosis of chronic regional pain syndrome (Type 1) was made, and the patient was referred to a chronic pain specialist for further treatment. Exact duration was not reported.
2	Numbness, paresthesia	6 months	Investigator-probed (telephone)	A 49-year-old man with preexisting multiple sclerosis. Right acromioplasty and debridement of labrum and rotator cuff without general anesthetic. Hand-grip weakness with numbness and paresthesia over most of the arm on POD 14. At 6 months, symptoms persist only in the thumb and two adjacent fingers.
3	Paresthesia, numbness, and weakness	6 months	Investigator-probed (telephone), nerve conduction studies	A 56-year-old man. Acromioplasty with general anesthetic. Nonspecific numbness, paresthesia, and weakness in the surgical arm on POD 14. Nerve conduction studies led to ulnar nerve release at the elbow with resolution of weakness but persistent sensory symptoms at 6 months.
4	Numbness, weakness	6 months	Investigator-probed (telephone)	A 43-year-old woman. BMI of 37 kg/m^2. Left rotator cuff repair and subacromial decompression without general anesthetic. Numb, weak fingers on POD 14. At 6 months, finger symptoms resolved but shoulder numbness persisted.
5	Paresthesia, numbness, and weakness	6 months	Investigator-probed (telephone), nerve conduction studies	A 61-year-old woman. Patient smoked cigarettes. Right rotator cuff repair with general anesthetic. Numbness and paresthesia in median nerve distribution of the hand with weak grip on POD 14. At 6 months, nerve conduction studies showed a median nerve injury between the elbow and shoulder. Paresthesia had resolved, but other symptoms persisted without alleviation.
6	Paresthesia	6 months	Investigator-probed (telephone)	A 67-year-old male. Right rotator cuff repair and biceps tenotomy without general anesthetic. Block duration of 21.8 hours with 8 mg perineural dexamethasone. Mild grip weakness with associated numbness and paresthesia of thumb and index finger on POD 7. At 6 months, carpal tunnel syndrome was diagnosed. Only paresthesia persists.
7	Hypoesthesia	< 6 months	Investigator-probed (telephone)	Distribution in territory of the lateral cutaneous nerve of the forearm. Resolved by 6 months.
8-17	Nonspecific tingling, no motor or sensory deficit	Up to 14 weeks	Investigator-probed (telephone), formal in-person evaluation, referrals, and/or investigations as needed	Initial presentation at 3 days to 2 weeks. No actual sensory or motor deficits could be found during clinical assessment. Follow-up indicated resolution at 1 to 14 weeks, but no individual-level data reported by study. Possible or probable association with nerve block reported as equivocal.

Table 7. continued

Patient	Type of postoperative neurologic symptom	Duration	Method of identification	Remarks
18-29	Nonspecific tingling, no motor or sensory deficit	Up to 14 weeks	Investigator-probed (telephone), formal in-person evaluation, referrals, and/or investigations as needed	Initial presentation at 3 days to 2 weeks. No actual sensory or motor deficits could be found during clinical assessment. Follow-up indicated resolution at 1 to 14 weeks, but no individual-level data reported by study. Possible or probable association with nerve block reported as equivocal.
30	Sensory deficit	13 weeks	Investigator-probed (telephone), formal in-person evaluation, referrals, and/or investigations as needed	Initial presentation on POD 10. Possible or probable association with nerve block reported as likely.
31	Motor and sensory deficit	3 years	Investigator-probed (telephone), formal in-person evaluation, referrals, and/or investigations as needed	Initial presentation at 2 weeks. Nerve injury because of initial trauma unlikely. Electromyography at 8 weeks showed involvement of sensory and motor fascicles of the ulnar and median nerves at the level of the wrist. At 3 years after injury, motor deficit had settled; mild sensory deficit (2-point discrimination 4 mm) continued. Possible or probable association with nerve block reported as unlikely.

POD = postoperative day.

use of anticoagulant medications, and continuous catheter-based analgesia) that increase susceptibility to neurological complications [45, 72, 73, 107] and may help to explain the relatively higher risk identified in our study. Our results may also reflect the change in practice from traditional blind techniques of needle-nerve localization to widespread ultrasound guidance because more than 75% of studies in our review used ultrasound guidance for nerve localization, which contrasts with most existing large-scale retrospective and observational trials. Our findings might at least partially reflect our modern tendency to perfect needle-nerve approximation under direct sonographic visualization, inadvertently contributing to nerve irritation or injury.

Block Locations With the Highest and Lowest Risk of Postoperative Neurologic Symptoms

Importantly, in keeping with the results of our 2007 review [26], we found that interscalene block is also associated with the highest risk of postoperative neurologic symptoms among all upper extremity peripheral nerve blockades investigated prospectively in contemporary RCTs. One postulated explanation for this observation is the high-density neural architecture that characterizes the nerve roots of the proximal brachial plexus compared with the peripheral nerve tissue targeted by more distal approaches to brachial plexus blockade. This relatively lower amount of nonneural connective tissue creates a higher fascicle-to–connective tissue content that may theoretically pose a greater risk of mechanical nerve injury [24].

Timing of Occurrence of Postoperative Neurologic Symptoms (in Days) After Surgery

Although we could not classify postoperative neurologic symptoms according to severity, we did assess both timing of occurrence and type of symptoms to help inform the measure of severity, with persistent motor deficit(s) arguably considered most severe. To that end, only a very small proportion of reported neurologic symptoms occurred or persisted beyond 90 days, and fortunately, these primarily involved sensory deficits. All but one occurrence of motor symptoms reported at or beyond 90 days ultimately resolved.

Conclusion

When assessed prospectively in randomized trials, the aggregate risk of postoperative neurologic symptoms

associated with peripheral nerve block in upper extremity surgery was approximately 7%, which is greater than previous estimates described in large retrospective and observational trials. Most occurrences were reported within the first week and were associated with interscalene block. Only a few occurrences were reported after 90 days, and they primarily involved sensory deficits. Although these findings cannot inform causation, taken together with existing large retrospective and observational trials, they can help inform risk discussions and support clinical decisions among surgeons, anesthesiologists, and patients, as well as bolster our understanding of the evolution of postoperative neurologic symptoms after regional anesthesia in upper extremity surgery. Future prospective trials examining the risks of neurologic symptoms after regional anesthesia should aim to standardize descriptions of symptoms, timing of evaluation, classification of severity, and diagnostic methods to reduce heterogeneity, improve reliability, and help our patients make the most informed and meaningful decisions regarding their perioperative care.

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