The Effectiveness of Different Nerve Transfers in the Restoration of Elbow Flexion in Adults Following Brachial Plexus Injury: A Systematic Review and Meta-Analysis

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Purpose Restoration of elbow flexion is an important goal in the treatment of patients with traumatic brachial plexus injury. Numerous studies have described various nerve transfers for neurotization of the musculocutaneous nerve (or its motor branches); however, there is uncertainty over the effectiveness of each method. The aim of this study was to summarize the published evidence in adults with traumatic brachial plexus injury.

Methods Medline, Embase, medRxiv, and bioRxiv were systematically searched from inception to April 12, 2021. We included studies that reported the outcomes of nerve transfers for the restoration of elbow flexion in adults. The primary outcome was elbow flexion of grade 4 (M4) or higher on the British Medical Research Council scale. Data were pooled using random-effects meta-analyses, and heterogeneity was explored using metaregression. Confidence intervals (CIs) were generated to the 95% level.

Results We included 64 articles, which described 13 different nerve transfers. There were 1,335 adults, of whom 813 (61%) had partial and 522 (39%) had pan-plexus injuries. Overall, 75% of the patients with partial brachial plexus injuries achieved ≥M4 (CI, 69%−80%), and the choice of donor nerve was associated with clinically meaningful differences in the outcome. Of the patients with pan-plexus injuries, 45% achieved ≥M4 (CI, 31%−60%), and overall, each month delay from the time of injury to reconstruction reduced the probability of achieving ≥M4 by 7% (CI, 1%−12%).

Conclusions The choice of donor nerve affects the chance of attaining a British Medical Research Council score of ≥4 in upper-trunk reconstruction. For patients with pan-plexus injuries, delay in neurotization may be detrimental to motor outcomes. *(J Hand Surg Am. 2023;48(3):236−244. Copyright © 2023 by the American Society for Surgery of the Hand. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).)*

Type of study/level of evidence Therapeutic IV.

Key words Brachial plexus injury, meta-analysis, nerve transfer, neurotization.

Additional Material at jhandsurg.org

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Received for publication June 21, 2022; accepted in revised form November 22, 2022.

Dr Wade is a Doctoral Research Fellow funded by the National Institute for Health Research (NIHR, DRF-2018-11-ST2-028). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. No benefits in any form have been received or will be received by the other authors related directly or indirectly to the subject of this article.

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0363-5023/23/4803-0003
https://doi.org/10.1016/j.jhsa.2022.11.013

Restoration of elbow flexion is an important goal in the treatment of patients with traumatic brachial plexus injury (BPI).[1] The majority of patients with traumatic BPIs have injuries to the proximal elements of the spinal nerve roots or rootlets, which precludes interposition nerve grafting.[2] To restore elbow flexion in patients with preganglionic or avulsion injuries or in those who fail to improve following nerve grafting of postganglionic injuries, nerve transfers are a valuable option. A recent study suggested that for patients eligible for both interposition nerve grafting and nerve transfers, neurotization is more often associated with restoration of the ability to (at least) flex the elbow against gravity.[3] Consequently, neurotization is frequently used as the primary reconstruction option in patients with deficient elbow flexion following traumatic BPIs.

There are several donor nerves available for neurotization of the musculocutaneous nerve or its branches to the biceps brachii and brachialis. These donors may originate from within the brachial plexus (intraplexal, eg, a fascicle of the ulnar nerve) or outside (extraplexal, eg, intercostal nerves). The choice between intraplexal versus extraplexal donors is complex but largely driven by availability. For patients with partial BPIs (involving the upper and/or middle trunks or their spinal roots), there are many intraplexal and extraplexal donors available. However, patients with pan-plexus injuries (involving all roots, trunks, cords, or divisions) typically have fewer reconstructive options, with donors only originating outside the plexus. There have been numerous studies comparing the outcomes of different nerve transfers for the restoration of elbow flexion; however, there is uncertainty over which method is most effective for patients with partial and pan-plexus injuries.

The aim of this study was to summarize the safety and effectiveness of different nerve transfers in the restoration of elbow flexion of (at least) grade 4 or higher (≥M4) on the British Medical Research Council (BMRC) scale in adults following BPI.

MATERIALS AND METHODS

This review is registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (ID CRD42019142880). It was designed and conducted in accordance with the Cochrane Handbook of Systematic Reviews and has been authored in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[4,5]

Studies, participants, and interventions

This review included studies that reported the outcomes of any recognized nerve transfer for neurotization of the motor components of the musculocutaneous nerve (or its branches directly in the biceps brachii or brachialis muscles) for the restoration of elbow flexion in adults (defined as individuals aged 16 years or above) with BPI. Neurotization must have been performed within 1 year of injury. We excluded studies concerning neurotization of free tissue transfers (eg, free gracilis muscle transfer), participants with congenital or acquired neuromuscular disorders, and case reports.

Outcomes

The primary outcome was the attainment of elbow flexion graded as ≥M4 on the BMRC scale, which agrees with operator-independent techniques such as dynamometry and surface electromyography.[6] If studies reported the elbow flexion strength per patient, captured using a dynamometer (for example), then M4 was back calculated for all patients who could pull >0 kg against gravity. For studies that further categorized BMRC grades by the addition of + or − symbols, we used numeric grades, eg, M3+ and M3− were both categorized as M3, assuming that the authors meant that M3+ was stronger in class M3 and stronger than M3/M3− but not strong enough to merit M4. We selected a BMRC score of ≥M4 as the threshold (rather than ≥M3, for example) based on a poll completed by peripheral nerve surgeons in the protocol phase (64% voted for a BMRC score of ≥M4), which is concordant with a recent international Delphi study that showed that although imperfect and incomplete, BMRC was a clinically practical and widely accepted measurement of motor outcomes.[7,8]

Search strategy

The National Institute for Health and Care Excellence (NICE) databases were searched according to Supplementary Data (SD) Appendix 1 (available online on the *Journal*'s website at www.jhandsurg.org).[9] The medRxiv and bioRxiv preprint archives were searched with the same strategy using the R package medrxivr.[10] No language restrictions were applied. Our searches yielded 640 hits in PubMed, 671 in Embase, and none in the preprint archives on the April 12, 2021. After removal of duplicates, there were 866 citations.

Titles and abstracts were independently screened by 4 review authors (C.Y.V.L., E.C., M.C., and R.G.W.). The full texts of all potentially relevant articles were obtained. The reference lists of included articles were also scrutinized. The final lists of the included articles were compared, and disagreements were resolved by discussion.

Data extraction

Data were dual extracted by 3 independent review authors (C.Y.V.L., E.C., and M.C.) and checked for accuracy by R.G.W.. Studies reporting the "Oberlin procedure" were categorized into 3 discrete entities: neurotization involving a single donor from the median nerve was classified as "Oberlin (median)"; a single ulnar donor fascicle was classified as "Oberlin (ulnar)"; and when both an ulnar and median fascicle was used, we termed this as "double Oberlin." When data were missing or unclear, we contacted the corresponding author by email. There was no evidence of duplication of patients across the articles by the same authors. The authors of 5 articles provided additional information upon request.[11−15]

Risk of bias assessment

The risk of methodologic bias was assessed by 3 review authors (C.Y.V.L., E.C., and M.C.) independently using the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool, and their judgments were displayed graphically using robvis.[16,17] Disagreements were resolved by discussion with R.G.W.

Statistical analysis

The raw data are available via the Open Science Framework.[18] The pooled prevalence of ≥M4 was estimated using metaprop in Stata/MP, version 16.1.[19] Data pertaining to partial BPIs (injuries involving the upper and/or middle trunk or any combination of injuries to the spinal nerve roots of C5−C7) and pan-plexus injuries (C5-T1 inclusively) were pooled separately. Given the clinical heterogeneity, the between-study variance (tau^2) was estimated using the Dersimonian and Laird method.[20] The Freeman−Tukey arcsine transformation was used to stabilize the variance, and 95% confidence intervals (CIs) were computed based on the score-test statistic. Heterogeneity in the primary outcome was explored in 2 univariable meta-regression models, 1 for patients with partial injuries and the second for patients with pan-plexus injuries. The dependent variable in both the models was the proportion of patients who attained ≥M4. The moderator variable was time from injury to neurotization, handled as a continuous covariable. The Restricted Maximum Likelihood (REML) estimator for random effects was used throughout. Statistical heterogeneity was quantified using I^2.[21] To investigate the possibility of small-study effects, a funnel plot was constructed with pseudo-CIs contoured by tau^2.[22]

RESULTS

Study selection

Ultimately, 64 articles were included (SD eFig. 2, available online on the *Journal*'s website at www.jhandsurg.org).[11,13−15,23−83]

Study characteristics

The characteristics of the included studies are presented in SD eTable 3 (available online on the *Journal*'s website at www.jhandsurg.org). Overall, we included data from 1,335 adults, of whom 813 (61%) had partial BPIs and 522 (39%) had pan-plexus injuries. Thirteen different nerve transfers were described. The male-to-female ratio was approximately 13:1. The mean age of the patients was 26 years (range, 16−72; CI, 25−28; I^2, 57%). The mean time from injury to neurotization was 4.8 months (CI, 4.4−5.3; I^2, 82%). The mean follow-up duration was 24 months (CI, 21−27; I^2, 100%). The median sample size of the included studies was 12 (interquartile range, 8−26; range, 2−205). The median length of recruitment was 4 years (interquartile range, 2−7; range, 1−28). The studies originated from China (n = 10), Brazil (n = 8), India (n = 8), Thailand (n = 7), France (n = 6), the United States of America (n = 6), Japan (n = 6), Iran (n = 3), Taiwan (n = 2), and others.[11,14,15,23−35,37−39,41,43−48,50−54,57−67,71−80,82,83] The risk of bias within the studies is summarized in SD eFigure 4 (available online on the *Journal*'s website at www.jhandsurg.org). No study was free of methodologic bias, and generally, the risk of bias was determined to be moderate. Almost all the studies were at a critical risk of bias due to potential confounding. Again, almost all the studies were at an unclear risk of bias due to lack of reporting related to missing data and measurement of the outcomes. The risk of bias was almost entirely low in the classification of the intervention (type of neurotization). Because there is no opportunity for patients to deviate from the allocated intervention, the fourth domain of the ROBINS tool was universally at a low risk of bias.

Synthesis of results

The outcomes in the patients with partial BPIs were reported in 52 studies.[11,14,15,24−30,32−37,39−44,46,47,49−55,57,58,60,61,63,65,67,69−71,73,74,76−83] Overall, 75% of the patients achieved ≥M4 during surveillance (CI,

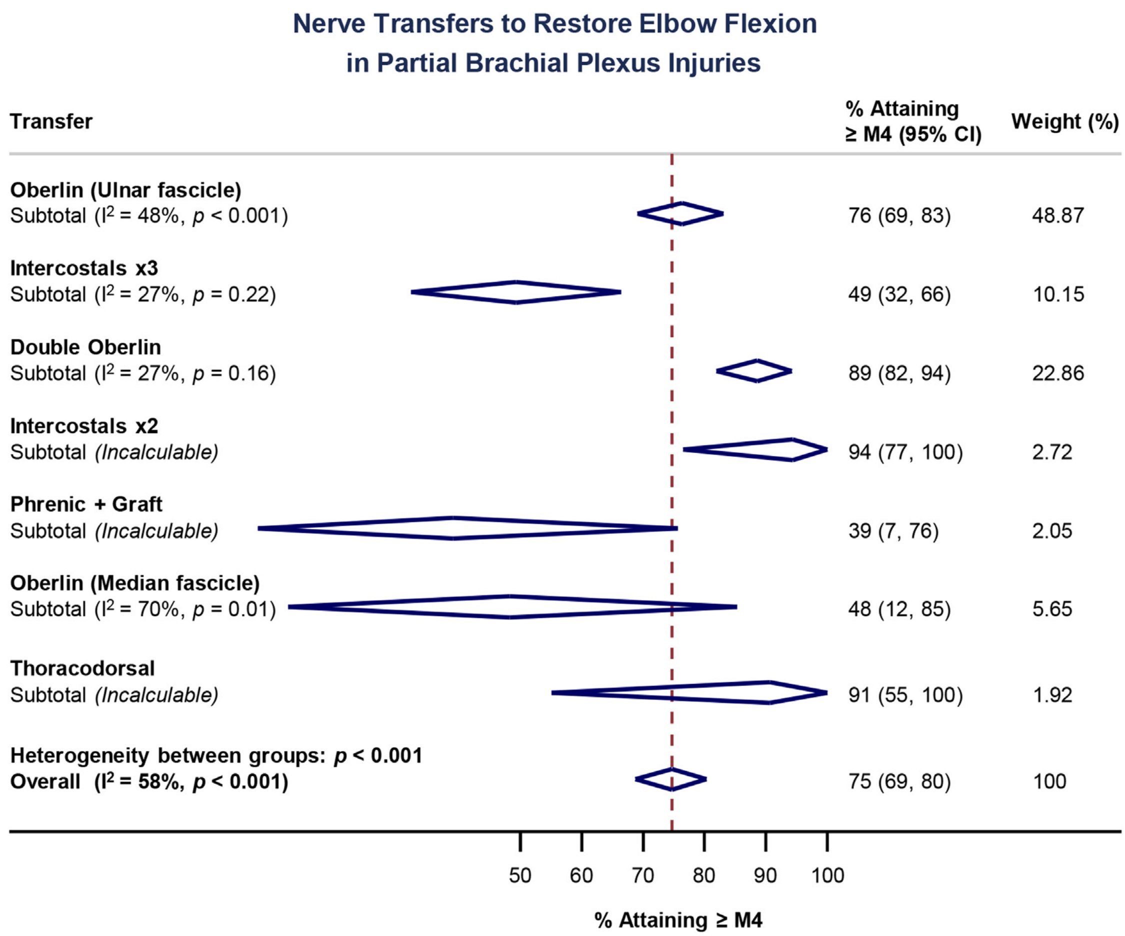

FIGURE 1: A summary forest plot showing the proportion (%) of patients with partial BPIs who attained a BMRC score of ≥M4 after different nerve transfers. The full forest plot showing the study-level estimates is shown in SD eFigures 5 and 6.

69%−80%; I^2, 57%). It appeared that double Oberlin transfer or 2 intercostal nerve (ICN) transfers were associated with consistently better chances of attaining ≥M4 compared with other transfers (eg, single Oberlin, thoracodorsal, phrenic, or other ICN variants; Fig. 1). Although the pooled proportion of patients who attained ≥M4 was slightly lower with double Oberlin transfers than with 2 intercostal nerves (89% vs 94%), double Oberlin transfers were associated with considerably less variability and minimal statistical heterogeneity (Fig. 1), which means that the findings are more reliable, and real-world replications are likely to be similar. The full forest plot showing the study-level estimates is shown in SD eFigures 5 and 6 (available online on the *Journal*'s website at www.jhandsurg.org).

The outcomes in the patients with pan-plexus injuries were reported in 23 studies.[11,13,15,23,29,31,32,36,40,45−48,59,60,62,64,66,68,70,72,75,77] For the patients with pan-plexus injuries, 45% achieved ≥M4 during follow-up (CI, 31%−60%; I^2, 87%). It appeared that the spinal accessory via an interposition nerve graft donor was associated with the best chance of attaining ≥M4 (88% [CI, 69%−99%]; 3 studies), whereas other nerve transfers were associated with lower chances of attaining ≥M4 (Fig. 2). There were insufficient data to explore which combination of ICNs (eg, 2 ICNs [third and fourth] vs 3 ICNs [third, fourth, and fifth]) was associated with better recovery.

Meta-regression showed that for the patients with pan-plexus injuries, the time from injury to neurotization was associated with a linear reduction in the probability of attaining ≥M4, whereby each month reduced the overall probability of attaining ≥M4 by 7% (CI, 1%−12%; I^2, 84%; Fig. 3). However, for the patients with partial BPIs, there was no association between time from injury to neurotization and recovery for those treated up to 12 months from the time of injury (Fig. 3). There was no association between age (16−72 years) and the probability of attaining ≥M4 in the patients with partial (β, 0.01 [CI, −0.01 to 0.01]) or pan-plexus injuries (β, 0.002 [CI, −0.01 to 0.01]; SD eFig. 7, available online on the *Journal*'s website at www.jhandsurg.org).

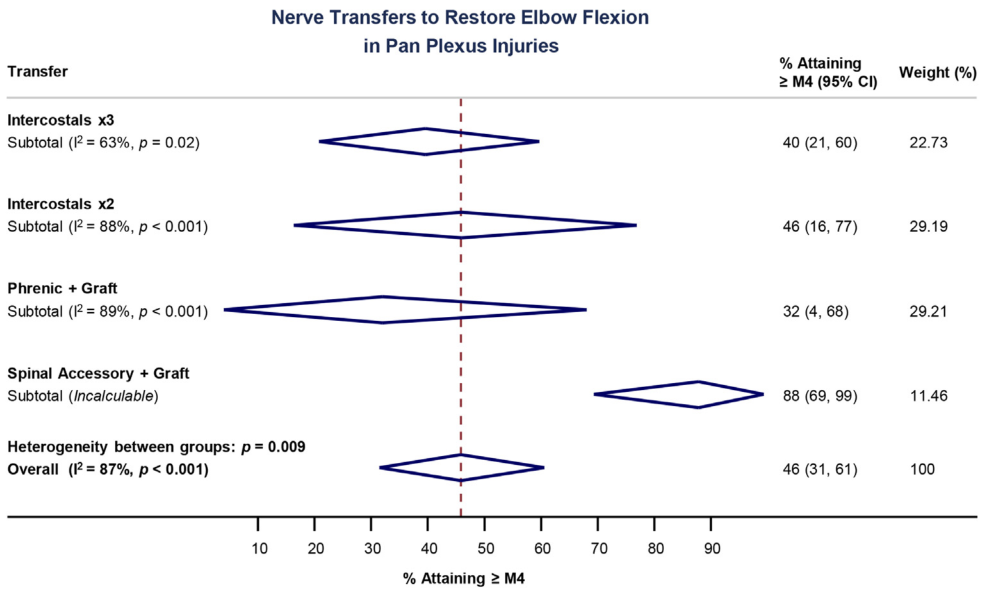

FIGURE 2: A forest plot showing the proportion of patients with pan-plexus injuries who attained ≥M4 after different nerve transfers. The full forest plot showing the study-level estimates is shown in SD eFigure 11.

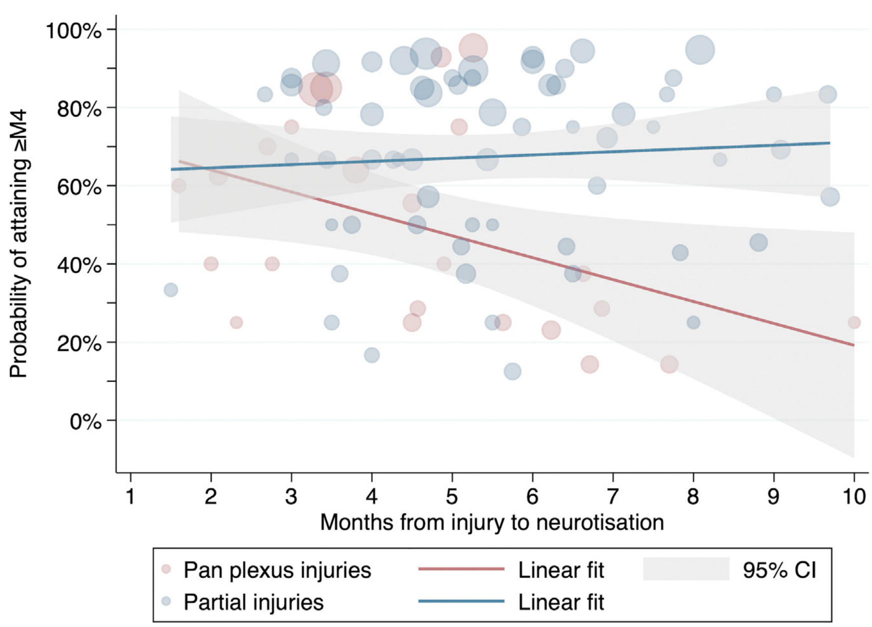

FIGURE 3: A scatter plot showing the proportion of patients who attained ≥M4 based on the time from injury to neurotization, with linear fits and 95% CIs. Data points are colored by injury type and scaled by the inverse variance (size) of the study.

There were insufficient data to explore the relationship between body mass index and the probability of attaining a BMRC score of ≥M4. There were insufficient data to meta-analyze the complications of different transfers. There was no evidence of small-study effects (SD eFig. 8, available online on the *Journal*'s website at www.jhandsurg.org). Data on outcomes per country are limited and displayed as a heatmap in SD eFigure 9 (available online on the *Journal*'s website at www.jhandsurg.org) and a summary forest plot in SD eFigure 10 (available online on the *Journal*'s website at www.jhandsurg.org).

DISCUSSION

This review summarizes the evidence regarding the effectiveness of different nerve transfers in the restoration of elbow flexion (a score of ≥M4 on the BMRC scale) for patients with BPIs. The choice of donor nerve(s) appears to affect the chance of recovering elbow flexion to a BMRC score of ≥M4, and for patients with pan-plexus injuries, any delay in neurotization is detrimental. Phrased another way, neurotization should be performed as soon as possible to provide the best chance of meaningful recovery. This information may help clinicians and patients to reach shared decisions about the choice of donor nerve(s) and the timing of surgery.

Our findings broadly agree with prior studies on the topic. A meta-analysis of 9 studies by Texakalidis et al[3] showed that nerve transfers were associated with a score of ≥M3 in 78% of patients. However, the meta-analytical methods used to calculate the pooled prevalence were not presented, and there were no corresponding CIs, meaning that fractions might have simply been summed. Additionally, the patterns of injuries were not described, which makes it difficult to appreciate whether the populations from which the samples were drawn were similar to those in our study and, therefore, how their estimates could be applied to clinical practice. We agree with Donnelly et al,[84] who showed that for adults with partial BPIs, 84% of those who underwent double Oberlin transfer achieved elbow flexion with a BMRC score of ≥4 compared with 63% of those who underwent single (median or ulnar) transfers; however, the statistical methods used to pool aggregate data were also unclear in that study. Similarly, our analyses both corroborate and build upon the work by Sneiders et al,[85] who showed that in patients with partial injuries, double Oberlin transfers were associated with a 11% increase in the proportion of patients attaining ≥M4 compared with single fascicular transfers (84% vs 73%, respectively). Furthermore, Sneiders et al[85] showed that for patients with partial injuries who underwent reconstruction within 6 months, a trend toward better BMRC scores was seen with earlier surgery, and our findings both agree and go further to quantify the linear relationship between surgical delay and the probability of ≥M4 recovery. Overall, our findings show that for patients with partial BPIs, nerve transfers are associated with favorable outcomes, and some donor nerve(s) appear to be better than others.

It is unclear why the probability of attaining elbow flexion of ≥M4 in the patients with partial BPIs was not related to delays in neurotization; however, we offer the following hypotheses. It is plausible that some patients with partial BPIs (in the included studies) had preserved brachioradialis function at baseline. Alternatively, there may have been heterogeneity of baseline function, whereby some may have had less-severe middle-trunk injury (or no C7 injury), which could have influenced both the timing of neurotization and how much the patients might improve later. The net effect of this disparity in the timing of neurotization might have been that the clinical trajectories merged. Ultimately, this observation is impossible to explain using the present data, and future studies should aim to collect dynamometry data (not just BMRC scores) at baseline and serially over time to understand this relationship. These efferent measurements of muscular function could be complemented by electrodiagnostic data as well as data on modalities of imaging (ultrasound, magnetic resonance imaging, and tomography, as available) and afferent muscular functions, such as muscular fatigue, cocontraction, proprioception, and pain, which are more important to patients.[86] A large amount of data captured in a standardized manner would be needed to model this relationship mathematically. As such, we believe that a study of this nature would be best delivered through international collaboration and by collecting both objective and patient-reported data in a centralized registry.

For the patients with pan-plexus injuries, the meta-analysis (Fig. 2) suggested that neurotization using the spinal accessory nerve and an interposition graft was associated with the highest chance of attaining ≥M4. This is difficult to explain biologically given the presence of 2 coaptations and the distance that the donor axons would have to travel compared with other donors. The subgroup meta-analysis concerning the spinal accessory nerve and interposition grafting was based on just 3 heterogenous studies, and this may have resulted in biased findings (SD eFig. 11, available online on the *Journal*'s website at www.jhandsurg.org). Overall, we have low confidence in the data concerning neurotization for elbow flexion in patients with pan-plexus injuries, and further studies must be conducted on this topic.

It is inappropriate for us to comment on the ideal transfer for the restoration of elbow flexion because this review was unable to address an important secondary outcome, namely complications. When selecting a surgical treatment option, it is necessary to weigh the potential risks and benefits such that a joint decision can be reached with patients. Owing to variable reporting at the study level, we were unable to make a meaningful assessment of the risk of complications for the neurotizations performed, which is an important limitation of this study and should be part of future data capture and reporting. There are limited data on adults aged over 50 years, and so our findings may not be generalizable to older adults. Moreover, this review only considers the restoration of elbow flexion, a small part of the overall care of adults with BPIs and should be interpreted in a wider context. We elected not to repeat the analyses for ≥M3 because this would represent a deviation from protocol, ignoring the community consensus on ≥M4 and the findings of a recent international Delphi study.[7,8] Still, it is plausible that the patterns we observed may be different at the M3 threshold, and so, we discourage extrapolation. We expect that our analyses of partial injuries were biased by heterogeneity of baseline function, and it is plausible that there were measurement biases in the patient data (eg, patients may have had compensatory movements that facilitated elbow flexion that could not be measured or adjusted for); therefore, we suggest that future research activities include serial standardized measurements of limb function, including a preoperative, baseline assessment. Finally, there were insufficient data for multivariable meta-regression; therefore, we cannot be sure that the detrimental effect of surgical delay is independent of the donor nerve choice for patients with pan-plexus injuries.

ACKNOWLEDGMENTS

We thank Ana-Marija Ljubenković, MD, Nephrologist at the General Hospital, and Ivo Pedišić Sisak, in Sisak, Croatia, for kindly translating 2 articles from Serbian to English; Samriti Sharma, MS, an independent bilingual pharma consultant in International Health Economics and Pharmaconomics, Tokyo, for translating 1 article from Japanese to English; and Frédérique Thonon, PhD, National Institute of Health and Medical Research (INSERM), for translating 1 article from French to English.

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