Appendix A

Literature search strategy

Database searches were performed for the period 1975-2015.

The MEDLINE search used a combination of the following medical subject headings: nerve injury, neurological injury, peripheral nerve injury, neurological deficit, paresthesia, neurological sequelae, pathology, ultrastructure, anatomy, transient neurological deficit, transient neurological symptoms, paralysis, nerve block, peripheral nerve block, local anesthetic, local anesthesia, conduction anesthesia, and regional anesthesia. Subsequent searches combined the keywords intraneural injection, epineurium, subepineurial injections, perineurium, intrafascicular injection, extrafascicular injection, injection pressure, ultrasound, neurostimulation, and needles.

The EMBASE and OVID database searches included the following search strategy steps:

1. (motor or nerve or peripheral).ab,hw,kf,ot,ti,ui.
2. (injur$ adj3 (motor or nerve or peripheral)).ab,hw,kf,ot,ti,ui.
3. (deficit$ adj3 (motor or nerve or peripheral)).ab,hw,kf,ot,ti,ui.
4. (complicat$ adj3 (motor or nerve or peripheral)).ab,hw,kf,ot,ti,ui.
5. 2 or 3 or 4
6. (nerve adj5 (inject$ or anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.
7. (regional adj5 (inject$ or anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.
8. (sensory adj5 (inject$ or anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.
9. (local adj5 (inject$ or anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.
10. (conduction adj5 (inject$ or anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.
11. (conduct$ adj5 (inject$ or anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.
12. 6 or 7 or 8 or 9 or 10
13. 5 and 12
14. neuro$.ab,hw,kf,ot,ti,ui.
15. (group$ or blind$ or trial$ or prospective or retrospective or random$ or group$ or study or systematic$ or control$ or meta$ or cohort).ab,hw,kf,ot,ti,ui.
16. 14 and 15
17. 13 and 16
18. (nerve adj5 (anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.
19. (conduction adj5 (anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.
20. (regional adj5 (anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.
21. (sensory adj5 (anesthe$ or anaesthe$ or block$ or analges$)).ab,hw,kf,ot,ti,ui.

**Assessment of methodological quality and data synthesis**

We adopted the criteria for assessing observational studies as reported by Agency for Healthcare Research and Quality (AHRQ) evidence reports and other similar reviews on risk factor exposures. Essentially, these included the method of selecting a cohort (unbiased/biased), sample size estimation, methods of measuring exposure and outcomes, adequacy of follow-up period, analysis and reporting of results. We assigned a "yes," "no," or "can't tell" score for each item, as reported by other similar articles. We did not attempt to use summary quality score for each study since there is little evidence to indicate a substantial effect of such quality scoring on the results of the systematic review and, secondly, rather than relying on global quality scores, many AHRQ evidence reports indicate that it is more helpful to identify consistent and specific quality issues affecting the majority of literature to guide future research. Only one systematic review
was included in the summary and was assessed for the comprehensiveness of the search strategy, the description of inclusion criteria, quality assessment, whether heterogeneity and publication bias were assessed, and whether the conclusions were supported by the data presented.

The GRADE approach to summarize the quality of evidence grades the quality of evidence as low, moderate, or high which can be further modified based on study design, risk of bias, indirectness of evidence, inconsistency, or imprecision of results (Table 1). A high rating usually means that further research is unlikely to change the confidence in the estimate of effect, while moderate rating indicates moderate confidence that the observed effect reflects the true effect and that future research may change the confidence of the estimate of the effect. A low rating indicates low confidence that the observed effect represents the true effect, and future research is necessary.

**Data synthesis and generation of evidence tables**

We summarized the findings of individual studies in an MS Excel spreadsheet, including study design, study size, type(s) of blocks, outcome measures, definition and time point of neurological assessment, selection and measurement bias, duration of follow-up, and adjustment of confounders. We evaluated the evidence as high, moderate, low, or very low depending on the adequacy of evidence and whether future research is likely to change the current estimates. These were determined using the approach used by other systematic reviews on risk factor association in complex diseases.\(^{21,22}\) We assessed for consistency of association, where the presence of two or more high quality studies (well conducted RCTs of adequate size/systematic review) showing the same direction of association indicated high evidence, whereas it was considered moderate evidence when one high quality study and one or more medium quality
studies showed same direction of association. Insufficient evidence meant low number of trials (in a small overall population) of low or very low quality. Inconsistent evidence meant the presence of contrary evidence for the measured outcome.