## Supplemental Table 1: PRISMA checklist

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Page 1 line 1 |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Page 2 line 1-page 3 line 4 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Page 4 line 1-page 5 line 15 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Page 4 line 1-page 5 line 15 |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Page 6 lines 2-5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Page 6 lines 6-16 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Page 7 lines 3-9 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Appendix A2 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Page 7 lines 7-17 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Page 7 line 17 – page 8 line 12 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Page 7 line 17 – page 8 line 12 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Page 7 lines 20 - 22 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Page 8 line 13 – page 9 line 2 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | Page 8 line 13 – page 9 line 2 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

## Supplemental Table 2a: Search terms used for MEDLINE database

|  |  |  |
| --- | --- | --- |
|  | Search terms (MESH/ and free text) | Results |
| 1 | Anesthesia/ or anesthesia, conduction/ or anesthesia, general/ or anesthesia, endotracheal/ or anesthesia, intravenous/ or anesthesia, Inhalation/ or anesthetics, Inhalation/137319 | 137319 |
| 2 | TIVA.ab,ti. | 912 |
| 3 | ("inhalation\* an?esthesia" or "intravenous an?esthesia").ab,ti. | 4872 |
| 4 | Propofol.ab,ti. | 20658 |
| 5 | Sevoflurane.ab,ti. | 8886 |
| 6 | Immunoassay/ | 29472 |
| 7 | Interleukins/ or cytokines/ | 161660 |
| 8 | (Biomarker\* or Tau or ?Tau or "Neurofilament light" or NFL or amyloid or S100\* or S-100\* or CRP or TNF\* or interleukin or IL-\* or (NSE or neuron specific enolase) or prostaglandin).ab,ti. | 871932 |
| 9 | randomi?ed.ab,ti. | 630289 |
| 10 | Randomized Controlled Trial/ | 510971 |
| 11 | 1 or 2 or 3 or 4 or 5 | 153427 |
| 12 | 6 or 7 or 8 | 982309 |
| 13 | 9 or 10 | 831417 |
| 14 | 11 and 12 and 13 | 431 |

## Supplemental Table 2b: Search terms used for EMBASE database

|  |  |  |
| --- | --- | --- |
|  | Search terms (MESH/ and free text) | Results |
| 1 | Anesthesia/ or anesthesia, conduction/ or anesthesia, general/ or anesthesia, endotracheal/ or anesthesia, intravenous/ or anesthesia, Inhalation/ or anesthetics, Inhalation/137319 | 243608 |
| 2 | TIVA.ab,ti. | 1620 |
| 3 | ("inhalation\* an?esthesia" or "intravenous an?esthesia").ab,ti. | 6900 |
| 4 | Propofol.ab,ti. | 30440 |
| 5 | Sevoflurane.ab,ti. | 12017 |
| 6 | Immunoassay/ | 69956 |
| 7 | Interleukins/ or cytokines/ | 207046 |
| 8 | (Biomarker\* or Tau or ?Tau or "Neurofilament light" or NFL or amyloid or S100\* or S-100\* or CRP or TNF\* or interleukin or IL-\* or (NSE or neuron specific enolase) or prostaglandin).ab,ti. | 1238275 |
| 9 | randomi?ed.ab,ti. | 905502 |
| 10 | Randomized Controlled Trial/ | 617577 |
| 11 | 1 or 2 or 3 or 4 or 5 | 26661 |
| 12 | 6 or 7 or 8 | 1420264 |
| 13 | 9 or 10 | 1092851 |
| 14 | 11 and 12 and 13 | 721 |

**Supplemental Table 3: IL-6 Meta Regressions**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **IL-6 – T1** | | | | |
|  | Estimate | SE | *p* | 95% CI |
| Surgery | 35.27 | 20.94 | 0.12 | -11.39 – 81.922 |
| Duration | -4.09 | 15.65 | 0.80 | -38.95 – 30.77 |
| Age | 31.26 | 20.86 | 0.17 | -15.22 – 77.74 |
| Surgery: Duration | -20.34 | 18.11 | 0.29 | -60.70 – 20.02 |
| Surgery: Age | -61.43 | 15.34 | 0.003 | -95.62 – -27.24 |
| Duration: Age | 45.11 | 23.92 | 0.09 | -8.19 – 98.42 |
| **IL-6 – T2** | | | | |
|  | Estimate | SE | *p* | 95% CI |
| Surgery | 30.90 | 24.75 | 0.25 | -26.17 – 87.97 |
| Duration | -7.51 | 14.88 | 0.63 | -41.83 – 26.80 |
| Age | 26.94 | 1.04 | 0.33 | -32.66 – 86.54 |
| Surgery: Duration | -15.89 | 22.80 | 0.51 | -68.48 – 36.69 |
| Surgery: Age | -65.12 | 17.18 | -0.005 | -104.73 – -25.51 |
| Duration: Age | 47.74 | 25.25 | 0.10 | -10.47 – 105.96 |

**Supplemental Table 4: GRADE quality assessment**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome (N RCTs)** | **Limitations (RoB2)** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Quality** |
| **IL-6 T1 (19)** | No serious limitations | No serious inconsistency1 | No serious indirectness | Serious3 | Not detected | Moderate |
| **IL-6 T2 (16)** | No serious limitations | No serious inconsistency1 | No serious indirectness | Serious3 | Not detected | Moderate |
| **IL-6 T3 (6)** | No serious limitations | Serious2 | No serious indirectness | Serious4 | Not detected | Low |
| **IL-10 T1 (9)** | No serious limitations | Serious2 | No serious indirectness | Serious3 | Not detected | Low |
| **IL-10 T2 (7)** | No serious limitations | Serious2 | No serious indirectness | No serious imprecision5 | Not detected | Moderate |
| **TNF-a T1 (10)** | No serious limitations | Serious2 | No serious indirectness | No serious imprecision5 | Not detected | Moderate |
| **TNF-a T2 (9)** | No serious limitations | Serious2 | No serious indirectness | Serious3 | Not detected | Low |
| **TNF-a T3 (4)** | No serious limitations | Serious2 | No serious indirectness | Serious4 | Not detected | Low |
| **CRP T2 (4)** | No serious limitations | Serious2 | No serious indirectness | Serious3 | Not detected | Low |

IL = interleukin; TNF-a = tissue necrosis factor alpha; CRP = C-reactive protein; ROB2 = Cochrane risk of bias 2 tool

1Statistical heterogeneity was largely accounted for by patient characteristics in meta-regression

2Inconsistency due to significant statistical heterogeneity

3Confidence intervals range from showing reduced inflammatory biomarker levels associated with use of propofol or sevoflurane

4Confidence intervals range from showing reduced inflammatory biomarker levels associated with use of propofol to showing no clinically significant difference

5Confidence intervals range shows no clinically significant change in inflammatory biomarker levels associated with propofol or sevoflurane use