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General anaesthesia versus local anaesthesia in carotid endarterectomy: a systematic review and meta-analysis

Amer Harky[a*], Jeffrey Shi Kai Chan[b*], Thompson Ka Ming Kot[b], Dilan Sanli[c], Rashad Rahimli[d], Zlatka Belamaric[e], Marcus Ng[b], Ian Yu Yeung Kwan[b], Christiana Bithas[f], Ragai Makar[a], Ramasubramanyan Chandrasekar[a], Sameh Dimitri[a]

a. Department of Vascular Surgery, Countess of Chester, Chester, UK

b. Faculty of Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

c. Gundogmus State Hospital, Antalya, Turkey

d. Faculty of Medicine, Bulent Ecevit University, Zonguldak, Turkey

e. Department of Perioperative Medicine, Barts Heart Centre, St Bartholomew's Hospital, London, UK

f. School of Medicine, University of Liverpool, Liverpool, UK

[*] These authors contributed equally to this study

Correspondence to:

Dr Amer Harky

Department of Vascular Surgery, Countess of Chester, Chester, CH2 1UL, UK

aaharky@gmail.com

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Key words: Local anaesthesia, General anaesthesia, carotid endarterectomy, anaesthetic technique

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Contributors

AH: study design, literature search, data analysis, writing of manuscript, tables, figures

JSKC: study design, data extraction, data analysis, writing of manuscript, tables, figures

TKMK: data extraction, writing of manuscript, tables

DS: literature search, writing of manuscript

RR: literature search, writing of manuscript

ZB: revision, writing of manuscript

CB: revision, writing of manuscript

MN: data extraction, writing of manuscript, tables

IYYK: data extraction, writing of manuscript, tables

RC: revision, study design, critical appraisal of the manuscript

RM: revision, study design, critical appraisal of the manuscript

SD: study design, critical appraisal of the manuscript, writing of manuscript

Abstract

Objective: The choice of anaesthetic technique in carotid endarterectomy (CEA) has been controversial. This study compared the outcomes of general anaesthesia (GA) and local anaesthesia (LA) in CEA.

Design: This is a systematic review and meta-analysis of comparative studies.

Setting: Hospitals.

Participants: Adult patients undergoing carotid endarterectomy using either local or general anaesthesia

Interventions: The effects of general and local anaesthesia on carotid endarterectomy outcomes were compared.

Measurements and main results: PubMed, OVID, Scopus, and Embase were searched to June 2018. 31 studies with 152,376 patients were analysed. Random effect model was used, and heterogeneity was assessed by I^2, and Chi^2 test. LA was associated with shorter operative time (weighted mean difference -9.15 minutes [-15.55, -2.75], p=0.005), and less stroke (odds ratio (OR) 0.76 [0.62, 0.92], p=0.006), cardiac complications (OR 0.59 [0.47, 0.73], p<0.00001), and in-hospital mortality (OR 0.72, [0.59, 0.90], p=0.003). TND rates were similar (OR 0.69 [0.46, 1.04], p=0.07). Heterogeneity was significant for operative time (I^2=0.99, Chi^2=1336.04, p<0.00001), TND (I^2=0.41, Chi^2=28.81, p=0.04) and cardiac complications (I^2=0.42, Chi^2=43.32, p=0.01), but not for stroke (I^2=0.22, Chi^2=30.72, p=0.16) and mortality (I^2=0.00, Chi^2=21.69, p=0.65). RCTs subgroup analysis was done, in which all the above variables were not significantly different or heterogeneous.

Conclusion: The results from our study showed no inferiority of using local anaesthesia to general anaesthesia in patients undergoing carotid endarterectomy. Future investigations should be reported more systematically, preferably with randomisation or propensity-matched analysis and thus registries will facilitate investigation of this subject. Anaesthetic choice in CEA should be individualised and encouraged where applicable.

Key words: Local anaesthesia, General anaesthesia, carotid endarterectomy, anaesthetic technique

Introduction

Carotid endarterectomy (CEA) was first described in 1954 by Eastcott et al[1] and gained popularity in the 1960 – 1970s for stroke prevention. It has been shown that combined CEA and medical therapy is superior to isolated medical therapy for treating and preventing stroke in patients with symptomatic carotid stenosis,[2–4] with smaller but significant benefits in asymptomatic patients.[5,6] According to the guidelines, the main indications for CEA included symptomatic internal carotid artery stenosis of > 50%, and asymptomatic internal carotid artery stenosis of > 60%.[7,8]

However, the choice of anaesthetic technique has been widely debated over the years, mainly due to the advantages and disadvantages of using general anaesthesia (GA) or local anaesthesia (LA; cervical plexus block) in terms of neurological complications and monitoring. While GA had been the mainstay for anaesthesia which allowed optimal patient positioning with excellent control of oxygenation and ventilation; however, intraoperative neurological monitoring remained difficult and yet, no highly sensitive and specific technique for such purpose exists. LA had been proposed to overcome this issue, but it requires a cooperative patient with risk of delayed or difficult airway access in emergencies that necessitates GA.[9]

In 2008, the General Anaesthesia vs Local Anaesthesia (GALA) trial, a large-scale multicentre randomised controlled trial (RCT), was conducted to investigate the choice of anaesthesia in CEA. The results showed no significant difference in rates of stroke, myocardial infarction, or mortality rates.[10] However, several non-randomised studies, including some recently published analyses with large sample sizes, found significant, albeit small differences in outcomes between GA and LA.[11,12] As such, this systematic review and meta-analysis aimed to investigate the choice of anaesthesia in CEA with consideration of new evidence.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis is conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[13] Electronic searches were performed on PubMed, OVID, Scopus, and Embase to identify all comparative studies comparing the use of local or general anaesthetic in carotid endarterectomy (CEA). All databases were searched from their inception till June 2018. A search was also conducted on ClinicalTrials.gov to identify ongoing or unpublished clinical trials. Search string used was ((“local anaesthesia” OR local OR anaesthesia) AND (“general anaesthesia” OR general OR anaesthesia)) AND (carotid OR endarterectomy OR “carotid endarterectomy”). Reference lists of papers found in the literature search were manually searched to assess suitability for inclusion in this review. Articles were first screened by four reviewers (AH, DS, CB and RR) based on their titles and abstracts. All identified articles were systematically assessed using the inclusion and exclusion criteria for further study. Conflicts over inclusion were resolved by an independent reviewer (JSKC). Articles were deemed eligible for inclusion if the authors described comparison between local and general anaesthetic techniques for CEA. Only studies written in the English language were included. Non-comparative studies or articles were excluded. Summary estimates were extracted from included studies by five reviewers (JSKC, TKMK, MN, SB and IYYK). Study authors were contacted where necessary. Conflicts over data extraction were resolved by an independent reviewer (AH).

Data analysis

Data were extracted manually. Where there were duplicate data, only the most up-to-date ones were included. Odds ratios (OR [95% confidence interval (CI]) or weighted mean differences (WMD [95% CI]) were used as the main summary measures for the main outcomes. All included studies were critically appraised using the Newcastle-Ottawa scale (Table 1).

Pre-operative variables extracted included mean patient age, proportion of males and females, and rates of diabetes mellitus (DM), hypertension, chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD), smoking, previous stroke, transient ischaemic attack (TIA), and amaurosis fugax. The extracted operative variables included operative urgency, operative indications, rate of conversion to general anaesthesia in LA cohorts, mean operative duration, shunt use, type of LA or GA used, and the number of patients using specific LA or GA. Primary outcomes analysed were total operative time, 30-day mortality rates, stroke, transient neurological deficit (TND), and cardiac complication (including infarctions, ischaemia, arrhythmias, or systolic or diastolic dysfunctions) rates. Secondary outcomes analysed included rates of all neurological complications, vascular complications, pulmonary complications, wound infection, requirement for inotropic support, cranial nerve injury, and mean length of hospital and intensive care unit stay.

In addition to analysing the overall data, we also pre-planned RCTs data subgroup analysis, as well as a sensitivity analysis by screening, that is, by excluding non-randomized studies with one arm's sample size being at least twice as big as the other arm and which had high chances of bias.

Random effects model was used through Mantel-Haenszel test or inverse variance analysis as appropriate. Chi^2 test was used to assess heterogeneity, as well as the I^2 statistic for which a cut-off threshold of 40% was chosen, with values exceeding this considered to signify substantial heterogeneity. Funnel plots were generated for variables which were not significantly heterogeneous. All p values were two-sided, and $p<0.05$ was considered significant. Statistical analyses were performed using Review Manager V.5.2.1 (Cochrane Collaboration, Oxford, UK).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

4,130 non-duplicate articles were screened and 31 articles were included in the analysis (Figure 1),[10,11,14–42] of which six were randomised controlled trials (RCTs).[10,19,20,23,30,40] Study characteristics were summarized in Table 2.

Table 3 summarizes the preoperative characteristics of included patients. There was no significant difference in the mean age among LA against GA patients (70.7±9.31 years in GA vs 69.5±9.09 years in LA, p=0.09), as well as hypertension rate (86.5±5.71%, n=79,948 in GA vs 75.3±15.1%, n=14,941 in LA, p=0.08). The proportions of patients with DM and COPD were higher in GA cohort (32.5±3.76%, n=40,668 in GA vs 27.5±5.79%, n=6922 in LA, p=0.03; and 21.8±2.07%, n=15,659 in GA vs 20.0±5.55%, n=1893 in LA, p=0.01, respectively). However, higher rates of IHD (30.7±5.00%, n=15,659 in GA vs 35.5±8.35%, n=1893 in LA, p=0.04), previous stroke (28.3±8.86%, n=561 in GA vs 24.1±5.38%, n=1171 in LA, p=0.001), and TIA (32.4±13.2%, n=1371 in GA vs 41.9±17.6%, n=2805 in LA, p=0.02) were noted in the LA cohort.

Tables 4 and 5 summarizes the operative data and postoperative outcomes respectively while table 6 summarizes the indications for CEA in each cohort. LA usage was associated with shorter total operative time (WMD -9.15 minutes [-15.55, -2.75], p=0.005, figure 2), and lower rates of stroke (OR 0.76 [0.62, 0.92], p=0.006, figure 3), cardiac complications (OR 0.59 [0.47, 0.73], p<0.00001, figure 4), and 30-day mortality (OR 0.72 [0.59, 0.90], p=0.003, figure 5). However, the rate of TND was not significantly different between the two cohorts (OR 0.69 [0.46, 1.04], p=0.07, figure 6).

Additionally, the rate of vascular complications was higher in GA cohort (26.3±7.51%, n=19651 in GA vs 17.8±7.46%, n=1603 in LA, p=0.0001). The mean length of stay in intensive care and total hospital stay were both shorter in LA cohorts (1.51±0.734 days in GA vs 0.624±0.340 day in LA, p<0.0001; and 2.58±5.17 days in GA vs 2.30±5.07 days in LA, p=0.001, respectively). Heterogeneity was significant for total operative time (I^2=0.99, Chi^2=1336.04, p<0.00001), TND

(I^2=0.41, Chi^2=28.81, p=0.04) and cardiac complications (I^2=0.42, Chi^2=43.32, p=0.01), but not for stroke (I^2=0.22, Chi^2=30.72, p=0.16) and mortality (I^2=0.00, Chi^2=21.69, p=0.65). Henceforth, funnel plots were generated for 30-day mortality (supplementary figure 1) and stroke (supplementary figure 2) yielding a largely symmetrical plot for 30-day mortality but an asymmetrical plot for stroke.

Subgroup analysis of RCTs data was performed, including 1969 patients in the GA cohort and 1987 patients in the LA cohort. Between GA and LA cohorts, there was no difference in the mean age (69.9±8.40 years in GA vs 68.9±8.77 years in LA, p=0.33), DM rate (24.4±3.67%, n=481 in GA vs 24.2±3.75%, n=480 in LA, p=0.09), IHD rate (37.9±4.42%, n=735 in GA vs 36.1±4.51%, n=707 in LA, p=0.09), COPD rate (12.8%, n=224 in GA vs 12.4%, n=219 in LA, p=0.045), hypertension rate (75.6±4.81%, n=1489 in GA vs 77.7±3.40%, n=1543 in LA, p=0.65), and preoperative stroke rate (28.6%, n=8 in GA vs 37.9%, n=11 in LA, p=0.11) and TIA rate (20.8±3.72%, n=371 in GA vs 20.9±3.15%, n=376 in LA, p=0.99). However, COPD rate was only reported by one study. There was no significant difference in total operative time (WMD -3.46 minutes [-8.11, 1.19], p=0.14, figure 7), and rates of stroke (OR 0.97 [0.42, 2.23], p=0.95, figure 8), cardiac complications (OR 0.95 [0.50, 1.78], p=0.87, figure 9), and 30-day mortality (OR 0.67 [0.38, 1.17], p=0.16, figure 10). TND rates were also not significantly different (1.60±0.858%, n=3 in GA vs 1.99±1.84%, n=3 in LA, p=0.99). Heterogeneity was not significant for all these variables (total operative time: I^2=0.00, Chi^2=1.56, p=0.46); stroke: I^2=0.17, Chi^2=2.42, p-0.30; cardiac complications: I^2=0.01, Chi^2=4.03, p=0.40; 30-day mortality: I^2=0.00, Chi^2=1.52, p=0.68).

Seven non-randomized studies with one arm's sample size being at least twice as big as the other arm and which had high chances of bias were excluded.[11,12,14,26,28,29,32] The 24 remaining studies were analysed, yielding similar results: LA was associated with shorter total operative time (WMD -8.77 minutes [-16.84, -0.69], p=0.03, supplementary figure 3), lower stroke rate (OR 0.64 [0.38, 0.89], p=0.01, supplementary figure 4), cardiac complications (OR 0.48 [0.32, 0.72], p=0.004, supplementary figure 5), 30-day mortality (OR 0.66 [0.45, 0.96], p=0.03, supplementary figure 6), and TND rates (OR 0.58 [0.38, 0.89], p=0.01, supplementary figure 7). Heterogeneity was significant for total operative time (I^2=0.99, Chi^2=1214.45, p<0.00001) and cardiac complications (I^2=0.43, Chi^2=29.79, p=0.03), but not for stroke (I^2=0.15, Chi^2=18.88, p=0.28), TND (I^2=0.24, Chi^2=18.33, p=0.19) and 30-day mortality (I^2=0.00, Chi^2=11.72, p=0.86).

Discussion

Carotid endarterectomy has been established as an important intervention in the prevention of stroke and treatment of extracranial carotid artery disease. While three major guidelines [7,8,43] have described the indications and timing for carotid endarterectomy in great detail, the choice between general and local anaesthesia remained inconclusive with all guidelines stating no significant difference in clinical outcome between the two and, in practice, leaving the decision to surgeons' and anaesthetists' discretion. Three major meta-analyses had been performed in an effort to resolve this issue.[44–46] Two of these studies[44,46] concluded that LA was associated with significantly lower stroke and mortality rates, but the remaining study by Vaniyapong et al.[45], which included only RCTs, found no significant difference in outcomes between LA and GA. This study, with a total sample size of 152,376, represented a much bigger population than any of these previous meta-analyses. Overall, our result revealed differences between RCTs and non-randomised data which suggested bias in the later, and that no clearly significant differences in outcome between LA and GA in CEA were demonstrated.

Cardiac complications occurred significantly less frequently in LA group than in GA group. This goes along with findings from previous meta-analyses that included non-randomised studies.[44,46] However, the non-significant difference in the RCTs subgroup analysis suggested possible bias in non-randomised studies that were eliminated in the RCTs. Even though DM and hypertension were well-established cardiovascular risk factors in general, and that a significantly higher proportion of GA group patients had DM with a trend of higher portion of patients with hypertension that approached significance (p=0.08), a prospective cohort study had failed to demonstrate any statistically significant differences between the morbidities in patients with or without these risk factors.[47] In addition, the significantly higher proportion of patients in the LA group with ischaemic heart disease added to the suggestion that there were other factors contributing to the significant difference in cardiac complications between the two groups. The heterogeneity for cardiac complications was significant, likely due to differences in patient selection and operative procedures between different papers. It was also possible that the variable experience of different centres and surgeons could have had major effects on the outcomes.

Interpretation of the analysis results for 30-day mortality and postoperative stroke rates was less straightforward. Meta-analysis of 30-day mortality rate showed an overall odds ratio of 0.72 [0.59, 0.90] which favours LA, but taking the event count and total sample size for calculation gave a higher 30-day mortality rates in LA (0.593%) than GA (0.482%). Similarly, meta-analysis of postoperative stroke rate showed an overall odds ratio of 0.76 (95% CI 0.62, 0.92) which favours LA, while the percentage calculation gave a higher stroke rate in LA (1.32%) than GA (1.03%). This reversal of effect, also referred to as Simpson's paradox, was well documented in literature, and had been attributed to large discrepancy in sample sizes between the two arms of treatments.[48,49] In this study, the sample sizes of LA and GA exhibited extreme discrepancies, with 25,311 patients and 125,825 patients having 30-day mortality recorded in LA and GA groups respectively, and 25,204 patients and 125,622 patients having postoperative stroke recorded in LA and GA groups respectively. As noted by Rücker et al,[49] this discrepancy in sample sizes occurred much less frequently and was thus less frequently a problem in meta-analysis of RCTs – this held true in this study, where 1910 patients and 1886 patients had 30-day mortality recorded in LA and GA groups respectively in RCTs, and 1958 patients and 1941 patients had postoperative stroke recorded in LA and GA groups respectively in RCTs. This idea that the reversal in effect was caused by the imbalance of sample sizes in the two arms was supported by further analysis excluding studies in which the sample size of one arm was at least twice as big as the other arm. Such exclusion in the mortality meta-analysis left 5770 patients in the LA group and 5865 in the GA group. Similarly, the exclusion left 5403 patients in the LA group and 5539 patients in the GA group for postoperative stroke meta-analysis. Such exclusion corrected the effect reversal.

As noted by Altman et al,[50] aggregating data from different studies and analysing it as if it were from one single study was much more prone to bias than using standard meta-analytical approaches. Hence, in this case, the odds ratios should be used to interpret the overall effect, which means that LA was associated with significantly lower 30-day mortality and postoperative stroke rates. These findings were echoed by other previously published meta-analyses.[44,46] Considering that LA was associated with lower rates of vascular complication, postoperative stroke, and cardiac complications, shorter mean length of stay in hospital and in intensive care unit; the finding regarding the mortality rate should not be surprising. The significantly shorter length of stay in LA group was likely due to the higher proportion of patients in the GA group having diabetes and postoperative complications, both of which had been demonstrated to be risk factors for prolonged length of stay.[51]

In view of the statistically homogeneous data for 30-day mortality and postoperative stroke rates, funnel plots were generated. The plot for 30-day mortality (supplementary figure 1) was largely symmetrical implying a relatively low risk of publication bias. The plot for postoperative stroke rate (supplementary figure 2), however, was asymmetrical and suggested possible bias against data of positive odds ratios (i.e. favouring GA). Other causes of asymmetrical funnel plot were also possible,[52] prominently selective outcome reporting, since only 17 out of the 31 included studies reported the postoperative stroke rate. Most other outcomes were also only reported in some of the included studies. This called for more consistent outcome reporting and possibly study design in future studies. The importance of heterogeneity was also illustratable in the significantly lower rates of temporary neurological deficits after removing seven non-randomized studies with one arm's sample size being at least twice as big as the other arm and which had high chances of bias. The post-removal analysis not only gave a statistically significant difference in TND rates, but also a strongly non-significant heterogeneity. This also suggested the possibility of the effects being distorted and heterogeneity arising from the imbalances in sample sizes.

The indications for CEA in each study have been summarized in Table 6. While the indications were limited to symptomatic or asymptomatic carotid artery disease, stroke, TIA, amaurosis fugax and neurological deficit; however, it was likely that the definition of these indications varied widely between different studies. There was significant overlap between the abovementioned indications, and few studies reported the numbers of all these indications. Some studies did not report indications at all. This again called for more consistent reporting of study design and procedures in order to achieve better uniformity and allow more comprehensive analyses.

Even though RCTs data controls for most preoperative characteristics, the data was predominated by the GALA trial which accounted for 89.2% of LA RCT sample population and 89.0% of GA RCT sample population. This called for larger RCTs which may better delineate the differences in clinical outcomes between LA and GA for CEA. In addition, none of the RCTs were blinded, meaning that the data were also prone to bias on the surgeon's and the data collector's parts.

The discrepancies between the overall data and that from RCTs suggested systematic biases. While RCTs are gold standards for eliminating these biases, propensity-matched analysis might be done for the same purpose, albeit with more problems and limitations. Several studies had done so, including (but not limited to) those by Liu et al,[12] Schechter et al,[53] Leichtle et al,[54] and the much more recently published analysis by Malik et al.[55] Nevertheless, this type of analysis required a large sample size, and notably, all the above-mentioned studies deploying propensity-matched analysis worked on data from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database from different periods (except Liu et al who also included data from the New York State Inpatient Database (NY-SID)). While other databases exist, such as the Michigan Surgical Quality

Collaborative (MSQC) database as utilized by Hussain et al,[14] there are not enough of them globally for the data to represent populations from different parts of the world. A way forward would be to establish an international registry, much like the International registry of Acute Aortic Dissection (IRAD).[56,57] Nevertheless, given that CEA is much more commonly done than the occurrence of aortic dissections, the information recorded may not be as complete, and setting up such a large-scaled database would involve immense financial input and manpower which would severely limit its feasibility.

It was important to note that the included studies did not always report all the analysed outcomes. This selective outcome reporting might cause bias. Moreover, meta-analysis of several variables showed significant heterogeneity which suggested inconsistency or bias in included studies, reducing the quality of the presented evidence. In addition, the lack of blinding in RCT, as discussed above, was a source of bias. The wide range of publication time of the included studies might contribute to bias and errors in the final outcome data as well. In addition, at the review level, our search terms and the limited number of databases searched might have led to incomplete retrieval of articles, and the exclusion of non-English articles might have omitted relevant studies that were not written in English and thus affected the results. The high likelihood of significant inconsistency between included studies was another limitation of this study. It was unfortunate only very few studies reported outcomes for different surgical techniques or indications separately. This rendered the relevant subgroup analyses and thus delineation of possible biases in these areas to be impossible. In addition, inconsistencies in surgical techniques and sedation were possible sources of bias in this study. Lastly, trial sequential analysis had not been done for the study, limiting its clinical and academic relevance and implications.

Conclusion

In conclusion, RCTs data with small sample sizes showed no significant difference between the outcomes of GA and LA use in CEA. When non-randomised data with much larger sample sizes were also considered, small but significant differences were demonstrated favouring LA. As such, larger and more systematically reported studies are required to conclude the debate surrounding the use of GA and LA in CEA. Use of randomisation or propensity-matched analysis should be encouraged, and registries should facilitate investigation of this subject. As of now, the choice of anaesthetic technique should be considered very carefully to cater to individual patients' needs. Morbidities and surgeon's / anaesthetist's or institutional experience should be taken into account in an attempt to optimize outcomes.

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Figure legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Figure 2. Forest plot of meta-analysis of mean operative time in all included studies. CI, confidence interval. IV, inverse variance. SD, standard deviation.

Figure 3. Forest plot of meta-analysis of postoperative stroke rate in all included studies. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Figure 4. Forest plot of meta-analysis of postoperative cardiac complication rate in all included studies. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Figure 5. Forest plot of meta-analysis of 30-day mortality rate in all included studies. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Figure 6. Forest plot of meta-analysis of transient neurological deficit rate in all included studies. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Figure 7. Forest plot of meta-analysis of mean operative time in randomised controlled trial data. CI, confidence interval. IV, inverse variance. SD, standard deviation.

Figure 8. Forest plot of meta-analysis of postoperative stroke rate in randomised controlled trial data. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Figure 9. Forest plot of meta-analysis of postoperative cardiac complication rate in randomised controlled trial data. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Figure 10. Forest plot of meta-analysis of postoperative 30-day mortality rate in randomised controlled trial data. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Supplementary material

Supplementary figure 1. Funnel plot for all-cause 30-day mortality for all included studies. OR, odds ratio. SE, standard error.

Supplementary figure 2. Funnel plot for postoperative stroke rate for all included studies. OR, odds ratio. SE, standard error.

Supplementary figure 3. Forest plot of meta-analysis of mean operative time in sensitivity analysis. CI, confidence interval. IV, inverse variance. SD, standard deviation.

Supplementary figure 4. Forest plot of meta-analysis of postoperative stroke rate in sensitivity analysis. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Supplementary figure 5. Forest plot of meta-analysis of postoperative cardiac complication rate in sensitivity analysis. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Supplementary figure 6. Forest plot of meta-analysis of postoperative 30-day mortality rate in sensitivity analysis. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Supplementary figure 7. Forest plot of meta-analysis of cumulative transient neurological deficit rate in sensitivity analysis. CI, confidence interval. M-H, Mantel-Haenszel. SD, standard deviation.

Table 1. Newcastle-Ottawa Quality Assessment Scale.

Author	**Selection**				**Comparability**	**Outcomes**		
	Representation of patients receiving LA	Selection of patients receiving GA	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	History of stroke or TIA = ✷ History of MI or angina = ✷	Assessment of outcomes	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Allen et al[14]	✷	✷	✷	✷	✷	✷	✷	✷
Aridi et al[11]	✷	✷	✷	✷	✷✷	✷	✷	✷
Bowyer et al[15]	✷	✷	✷		✷✷	✷	✷	✷
Corson et al[16]	✷	✷	✷		✷✷	✷	✷	✷
Ferrero et al[17]	✷	✷	✷		✷	✷	✷	✷
Fiorani et al[18]	✷	✷	✷		✷	✷	✷	✷
Forssell et al[19]			✷		✷✷	✷	✷	✷
Gabelman et al[20]	✷	✷	✷		✷✷	✷	✷	✷
GALA Trial Collaborative Group et al[10]	✷	✷	✷	✷	✷✷	✷	✷	✷
Gurer et al[21]	✷	✷	✷		✷✷	✷	✷	✷
Hussain et al[22]	✷	✷	✷			✷	✷	✷
Kalko et al[23]	✷	✷	✷	✷	✷✷	✷	✷	✷
Liu et al[12]	✷	✷	✷	✷	✷	✷	✷	✷
Love et al[25]	✷	✷	✷			✷	✷	✷
Lutz et al[26]	✷	✷	✷		✷✷	✷	✷	✷
Mazul-Sunko et al[27]	✷	✷	✷		✷✷	✷	✷	✷
McCarthy et al (2001)[28]	✷	✷	✷		✷✷	✷	✷	✷
McCarthy et al (2002)[29]	✷	✷	✷		✷✷	✷	✷	✷
Mofidi et al[30]	✷	✷	✷		✷✷	✷	✷	✷
Moritz et al[31]	✷	✷	✷		✷✷	✷	✷	✷
Mracek et al[32]	✷	✷	✷	✷		✷	✷	✷
Palmar[33]		✷	✷		✷✷	✷	✷	✷
Prough[34]		✷	✷			✷	✷	✷
Rockman et al[35]	✷	✷	✷		✷✷	✷	✷	✷
Santamaria et al[36]	✷	✷	✷			✷	✷	✷
Sbarigia et al[37]	✷	✷	✷	✷	✷✷	✷	✷	✷
Shah et al[38]	✷	✷	✷		✷	✷	✷	✷
Sideso et al[39]	✷	✷	✷	✷	✷✷	✷	✷	✷
Sternbach et al[40]	✷	✷	✷	✷	✷	✷	✷	✷
Takolander et al[41]	✷	✷	✷		✷	✷	✷	✷
Watts et al[42]	✷	✷	✷	✷	✷✷	✷	✷	✷

GA, general anaesthesia. LA, local anaesthesia. MI, myocardial infarction. TIA, transient ischaemic attack.

Table 2. Study characteristics

Author	Year	Country	Type	No of patients	GA (n)	LA (n)	Primary end points	Comments / Conclusion
Gabelman et al[20]	1983	United States	Retrospective cohort	100	46	54	Hospitalization duration and costs	The use of LA in carotid endarterectomy is indicative of significant reductions in operating and postoperative stay durations and medical costs. No significant differences between local and GA in terms of stroke and mortality rates were reported.
Prough et al[34]	1985	United States	Prospective cohort	23	10	13	Systolic and diastolic arterial pressure, and pulmonary artery occlusion pressure	GA was associated with reduced mean arterial pressure solely due to reduced systemic vascular resistance, but the ultimate haemodynamic result is dependent on the postoperative intravascular volume status and on the conventional management of post-endarterectomy hypotension.
Corson et al[16]	1987	United States	Prospective cohort	399	242	157	Perioperative mortality, stroke, cardiovascular complications	Regional anaesthesia can be safely performed without using an intraluminal shunt. A higher rate of permanent stroke deficits was noted in patients under GA without a shunt.
Forssell et al[19]	1989	Sweden	Randomised controlled trial	103	55	48	Perioperative mortality, neurological deficits	The perioperative complications of LA and GA are comparable. The perioperative blood pressure is significantly higher in LA than in GA.
Palmer et al[33]	1989	United States	Prospective cohort	221	37	184	Mortality, cardiac and neurological morbidities	No significant difference in morbidity and mortality was demonstrated in patients receiving general and LA for carotid endarterectomy.
Takolander *et al*[41]	1990	Sweden	Non-randomized controlled trial	75	47	28	Perioperative plasma adrenaline and noradrenaline levels, blood pressure, heart rate, and complications.	No statistical analysis was reported for clinical outcomes including mortality and complications. LA was associated with sympathetic nervous system activation with significantly more frequently induced marked hypertensive responses. GA was associated with significantly more frequently induced marked hypotensive responses.
Allen et al[14]	1994	United States	Retrospective cohort	679	361	318	Perioperative mortality, stroke, and cardiopulmonary complication rates	The use of LA in carotid endarterectomy is indicative of lower perioperative mortality and cardiopulmonary complication rates, shorter operative and hospitalization durations, and higher efficacy in the use of hospital resources when compared to the use of GA.
Shah *et al*[38]	1994	United States	Retrospective cohort	1073	419	654	Perioperative rates of mortality, cardiac and neurological complications	No statistical analysis was reported. The authors concluded LA might be associated with a decrease in perioperative stroke and mortality rates, and that it was an acceptable alternative to GA with routine shunt usage.
Rockman *et al*[35]	1996	United States	Retrospective cohort	3975	593	3382	Perioperative mortality, stroke and myocardial infarction rates	Regional anaesthesia was safe for carotid endarterectomy in most patients, without any demonstrable difference in mortality, stroke and myocardial infarction rates as compared to GA.
Fiorani et al[18]	1997	Italy	Retrospective cohort	1020	337	683	Perioperative mortality, neurological or cardiac complications	Regional anaesthesia (cervical block) gives better perioperative performance than GA, in terms of the need of ICA shunting, and stroke rate.
Sbarigia *et al*[37]	1999	Italy	Randomized controlled trial	107	52	55	Perioperative rate of cardiac complications	The rates of perioperative cardiac complications are not significantly different between the two modes of anaesthesia. GA caused more hypodynamic events while LA caused more hyperdynamic events.
Bowyer et al[15]	2000	United States	Retrospective cohort	500	228	272	Perioperative mortality and neurologic complication rates	There are no significant differences in the rates of mortality and neurologic complications in patients after undergoing carotid endarterectomy under local or GA, but LA provides distinct benefits over GA, such as shorter operative and hospitalization durations, and continuous neurological monitoring.
Love et al[25]	2000	Australia	Prospective cohort	443	243	200	Perioperative mortality, stroke	LA was associated with lower rate of mortality and stroke, probably due to the ability of assessing cerebral perfusion level in patients with LA

McCarthy et al[28]	2001	United Kingdom	Prospective cohort	240	140	100	30 days mortality and stroke rates	Carotid endarterectomy performed under LA, compared to GA, was associated with better monitoring and selectivity for intraoperative shunting. Shorter hospital stay and reduced cost was also observed with LA.
McCarthy et al[29]	2002	United Kingdom	Randomized controlled trial	67	33	34	Mean middle cerebral artery velocity and mean arterial pressure	Carotid endarterectomy performed under LA showed better preservation in ipsilateral cerebral circulation and tolerance to carotid clamping over that under GA.
Sternbach *et al*[40]	2002	United States	Retrospective cohort	550	324	226	Perioperative rates of mortality, cardiovascular and neurological complications	Despite having no significant difference in the rate of neurological complications, LA was associated with significantly less perioperative haemodynamic instability, cardiac complications, requirement for ICU admission, and shorter hospital stay.
Santamaria *et al*[36]	2004	Italy	Retrospective cohort	259	56	203	Perioperative mortality and neurological complication rates	No statistical analysis was reported. The authors concluded that the duration of intervention, hospital stay, and rates of neurological complications, shunt insertion and intensive care unit admission were reduced with LA, albeit with worse blood pressure control as compared to GA
Watts *et al*[42]	2004	United States	Retrospective cohort	503	268	235	Treatment outcome, and perioperative mortality and morbidity (cardiac, neurological, pulmonary and surgical complications)	There was no significant difference in the rates of neurological complication and mortality between the two modes of anaesthesia. LA was associated with significantly less cases of haemodynamic instability and cardiopulmonary complications compared to GA. The former also allowed better intraoperative neurological monitoring.
Mofidi et al[30]	2006	United Kingdom	Prospective cohort	371	179	192	Mortality, neurological and cardiac complication rates	Reduction in intraoperative shunting requirement, perioperative stroke rate and hospital stay duration were observed in carotid endarterectomies performed under LA when compared to that of GA.
Kalko et al[23]	2007	Turkey	Retrospective cohort	405	105	300	Perioperative mortality, stroke, MI	LA usage is associated with lower morbidity rate, fewer shunt usage and operative time compared to GA.
GALA trial collaborative group[10]	2008	United Kingdom	Randomized controlled trial	3526	1753	1773	Perioperative stroke (including retinal infarction), myocardial infarction, and mortality rates	There are no significant differences in the rates of mortality, stroke, and myocardial infarction in patients after undergoing carotid endarterectomy under local or GA, but patients who underwent the operation under GA were slightly more likely to suffer from postoperative complications. There is no evidence to support the preference of one type of anaesthetic over the other.
Lutz et al[26]	2008	Germany	Prospective cohort	1341	876	465	Perioperative neurological outcome	The use of LA in carotid endarterectomy may provide better neurological outcome than GA, where it shows significantly lower rates of neurological complications and death.
Ferrero et al[17]	2010	Italy	Retrospective cohort	428	219	209	Perioperative mortality, stroke, TIA	There was no significant difference in the morbidity or mortality between patients using LA and GA respectively, as were perioperative neurological and cardiopulmonary complications. Surgical techniques instead of type of anaesthesia are more significant in long term patency of the vessels.
Mazul-Sunko et al[27]	2010	Croatia	Randomized controlled trial	57	28	29	Cognitive function (Digit symbol, perceptual speed, attention, working memory, spatial working memory and verbal fluency) assessed by psychometric tests and S100-beta levels	Carotid endarterectomy patients receiving intraoperative shunts showed lower perceptual speed and spatial working memory, while the type anaesthetic technique employed did not show clinically significant difference in their respective effect on cognitive function.
Moritz et al[31]	2010	Germany	Randomized controlled trial	96	48	48	Stump pressure	Carotid artery clamping results in similar stump pressure changes for patients receiving local and GA in carotid endarterectomy.
Sideso *et al*[39]	2011	United Kingdom	Prospective cohort	389	129	260	30-day rates of mortality and stroke, separately and combined	There was no significant difference in clinical outcomes between local and GA. The choice of anaesthesia should be chosen based on local expertise and rate of complications.
Mracek et al[32]	2012	Czech Republic	Prospective cohort	60	30	30	Cognitive function assessed by auditory event related potentials,	GA negatively influenced cognitive performance in post-carotid endarterectomy patients transiently but was restored in six postoperative

							P3 response	days. It was therefore considered a side-effect rather than a negative effect when compared with LA.
Gurer et al[21]	2013	Turkey	Retrospective cohort	329	150	179	Perioperative mortality and stroke	LA is preferable to GA due to reduced shunt use, shorter hospitalization stays, and lower rate of permanent stroke in short term, with long term rates comparable to GA.
Liu et al[12]	2014	United States	Retrospective cohort (NY-SID data)	17,058	13,913	3145	Perioperative mortality, stroke, paraplegia, new neurological disorder, aspiration, respiratory failure, pulmonary resuscitation procedure (including intubation), cardiac arrest, cardiac resuscitation procedure, MI, CHF	Postoperatively, GA was associated with a higher risk of unexpected intubation, and pulmonary resuscitation procedure as compared to LA
			Retrospective cohort (NSQIP data)	38,102	32,718	5384	30-days postoperative complications: mortality, stroke, coma, unplanned intubation, on ventilator > 48 hours, cardiac arrest, MI	
Hussain et al[22]	2017	United States	Retrospective cohort	4558	4008	550	Perioperative mortality, MI, stroke	LA has been associated with lower rates of morbidity, unplanned intubation, readmission and resource utilization.
Aridi et al[11]	2018	United States	Prospective cohort	75319	68635	6684	Perioperative mortality, stroke, and myocardial infarction rates	There are no significant differences in the rates of mortality and cardiac complications in patients after undergoing carotid endarterectomy under local or GA, but patients who underwent the operation under GA were slightly more likely to suffer from postoperative myocardial infarction and required longer periods of hospitalization than the other group.

CHF, congestive heart failure. GA, general anaesthesia. ICA, internal carotid artery. ICU, intensive care unit. LA, local anaesthesia. MI, myocardial infarction. NSQIP, National Surgical Quality Improvement Program. NY-SID, New York State Inpatient Database. RA, regional anaesthesia. TIA, transient ischaemic attack.

Table 3: Pre-operative characteristics

Characteristics	All included studies			RCTs		
	GA (N=126282)	LA (N=26094)	p value	GA (N=1969)	LA (N=1987)	p value
Mean age (years)	70.7±9.31	69.5±9.09	0.09	69.9±8.40	68.9±8.77	0.33
Male	74796 (59.9±2.87)	14178 (64.2±6.39)	NA	1390 (70.6±4.23)	1429 (71.9±4.30)	NA
Diabetes	40668 (32.5±3.76)	6922 (27.5±5.79)	0.03	481 (24.4±3.67)	480 (24.2±3.75)	0.09
Hypertension	79948 (86.5±5.71)	14941 (75.3±15.1)	0.08	1489 (75.6±4.81)	1543 (77.7±3.40)	0.65
COPD	15659 (21.8±2.07)	1893 (20.0±5.55)	0.01	224 (12.8)*	219 (12.4)*	0.45
Ischaemic heart disease	32782 (30.7±5.00)	7273 (35.5±8.35)	0.04	735 (37.9±4.42)	707 (36.1±4.51)	0.09
Smoking	56402 (71.9±12.7)	9987 (60.2±19.4)	NA	1450 (78.9±7.50)	1459 (78.4±9.44)	NA
Previous stroke	561 (28.3±8.86)	1171 (24.1±5.38)	0.001	8 (28.6)*	11 (37.9)*	0.11
Transient ischaemic attack	1371 (32.4±13.2)	2805 (41.9±17.6)	0.02	371 (20.8±3.72)	376 (20.9±3.15)	0.99
Amaurosis fugax	270 (11.3±6.08)	303 (11.5±6.13)	NA	155 (8.84)*	173 (9.76)*	NA

Percentages are in brackets where applicable. ASA, American Society of Anaesthesiologists. COPD, chronic obstructive pulmonary disease. GA, general anaesthesia. LA, local anaesthesia. RCTs, randomised controlled trials.

*Standard deviations not available due to the statistic only being reported by one study.

Table 4: Operative data

Characteristics	All included studies			RCTs		
	GA (N=126282)	LA (N=26094)	p value	GA (N=1969)	LA (N=1987)	p value
Operative urgency						
Elective	60165 (87.5±0.674)	6259 (89.2±2.92)	NA	28 (100) †	29 (100) †	NA
Non-elective	8570 (12.5±0.672)	743 (10.6±2.88)	NA	0 (0.00) †	0 (0.00) †	NA
Conversion to general anaesthesia	NA	125 (2.48±2.42)	NA	NA	77 (4.23±2.89)	NA
Mean operative duration (minutes)	141±66.2	127±57.4	0.005	83.9±15.3	80.3±20.2	0.14
Shunt use	43047 (56.9±8.98)	2274 (13.4±3.27)	NA	819 (41.6±9.93)	272 (13.7±1.80)	NA
LA used*						
Lidocaine	NA	1792 (56.7)	NA	NA	34 (26.2)	NA
Bupivacaine	NA	3073 (75.5)	NA	NA	137 (74.1)	NA
Intravenous sedation	NA	504 (23.0)	NA	NA	0 (0.00)	NA
GA used*						
Propofol	795 (47.6)	NA	NA	116 (61.7)	NA	NA
Thiopental	842 (59.0)	NA	NA	75 (70.1)	NA	NA

Percentages are in brackets where applicable. GA, general anaesthetic. LA, local anaesthetic. NA, not applicable. RCTs, randomised controlled trials.
*Standard deviations are not reported. The medications were predefined by the studies’ authors and thus the standard deviations carry no practical meaning.
†Standard deviations not available due to the statistic only being reported by one study.

Table 5: Postoperative outcomes.

Characteristics	All included studies			RCTs		
	GA (N=126282)	LA (N=26094)	p value	GA (N=1969)	LA (N=1987)	p value
Stroke	1287 (1.02±0.746)	332 (1.32±0.954)	0.007	73 (3.76±0.966)	69 (3.52±1.17)	0.95
Transient neurologic defect	335 (0.462±1.55)	160 (1.48±3.84)	0.07	3 (1.60±0.858)	3 (1.99±1.84)	0.99
All neurology complications	1134 (1.59±0.906)	217 (1.64±1.80)	0.99	2 (3.85)*	14 (13.6±15.1)	0.54
Vascular complication	19651 (26.3±7.51)	1603 (17.8±7.46)	0.0001	NA	NA	NA
Cardiac complications	3226 (2.57±1.34)	444 (1.74±0.155)	<0.00001	25 (1.29±5.60)	25 (1.28±3.99)	0.87
Pulmonary complications	388 (2.01±0.569)	48 (1.04±0.517)	NA	NA	NA	NA
Wound infection	28 (0.510±0.391)	20 (0.881±1.36)	NA	NA	NA	NA
Requirement for inotropic support	151 (35.2±3.03)	157 (21.5±23.7)	NA	NA	NA	NA
Cranial nerve injury	42 (3.17±3.59)	60 (4.08±3.93)	NA	NA	NA	NA
Mean length of stay (days)	2.58±5.17	2.30±5.07	0.001	NA	NA	NA
Mean intensive care unit stay (days)	1.51±0.734	0.624±0.340	<0.0001	NA	NA	NA
30-day mortality	606 (0.482±0.362)	150 (0.576±0.494)	0.008	31 (1.64±0.842)	20 (1.05±0.406)	0.16

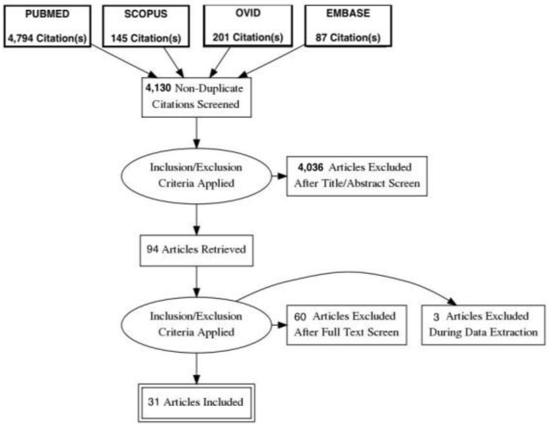
Percentages are in brackets where applicable. GA, general anaesthetic. LA, local anaesthetic. NA, not available. RCTs, randomised controlled trials.
*Standard deviation is not available due to the statistic only being reported by one study.

Table 6: Indication(s)/ presenting symptom(s) for carotid endarterectomy in included studies

Author	Local anaesthesia	General anaesthesia
Allen et al.[14]	Symptomatic CA disease: 180 Asymptomatic CA disease: 138	Symptomatic CA disease: 247 Asymptomatic CA disease: 114
Aridi et al.[11]	Symptomatic CA disease: 1831 Asymptomatic CA disease: 4853	Symptomatic CA disease: 21260 Asymptomatic CA disease: 47375
Bowyer et al.[15]	Symptomatic CA disease: 239 Asymptomatic CA disease: 33 Stroke: 60 TIA: 112 Amaurosis fugax: 63 Neurological deficit: 5	Symptomatic CA disease: 196 Asymptomatic CA disease: 32 Stroke: 46 TIA: 103 Amaurosis fugax: 43 Neurological deficit: 5
Corson et al.[16]	NA	NA
Ferrero et al.[17]	Symptomatic CA disease: 63 Asymptomatic CA disease: 146	Symptomatic CA disease: 79 Asymptomatic CA disease: 140
Fiorani et al.[18]	Symptomatic CA disease: 621 Asymptomatic CA disease: 62	Symptomatic CA disease: 312 Asymptomatic CA disease: 25
Forssell et al.[19]	Symptomatic CA disease: 48 Asymptomatic CA disease: 8 Stroke:22 TIA: 16 Amaurosis fugax: 8 Neurological deficit: 2	Symptomatic CA disease: 48 Asymptomatic CA disease: 7 Stroke: 26 TIA: 15 Amaurosis fugax: 6 Neurological deficit: 1
Gabelman et al.[20]	Symptomatic CA disease: 54 Asymptomatic CA disease: 0 TIA: 37 Amaurosis fugax: 12 Neurological deficit: 12	Symptomatic CA disease: 38 Asymptomatic CA disease: 8 TIA: 29 Amaurosis fugax: 11 Neurological deficit: 11
GALA trial collaborative group[10]	Symptomatic CA disease:1096 Asymptomatic CA disease: 677 Stroke: 346 TIA: 375 Amaurosis fugax: 173	Symptomatic CA disease: 1068 Asymptomatic CA disease: 685 Stroke: 346 TIA: 371 Amaurosis fugax: 155
Gurer et al.[21]	Symptomatic CA disease: 151 Asymptomatic CA disease: 28 Stroke: 37 TIA: 125 Neurological deficit: 4	Symptomatic CA disease: 122 Asymptomatic CA disease: 28 Stroke: 23 TIA: 99 Neurological deficit: 5
Hussain et al.[22]	NA	NA
Kalko et al.[23]	Symptomatic CA disease: 102 Asymptomatic CA disease: 193 Stroke: 22 TIA: 77 Amaurosis fugax: 11	Symptomatic CA disease: 44 Asymptomatic CA disease: 61 Stroke: 11 TIA: 20 Amaurosis fugax: 2
Liu et al.[12]	NA	NA
Love et al.[25]	NA	NA
Lutz et al.[26]	Symptomatic CA disease: 203 Asymptomatic CA disease: 238 Stroke: 91 TIA: 112 Neurological deficit: 22	Symptomatic CA disease: 508 Asymptomatic CA disease: 322 Stroke: 208 TIA: 300 Neurological deficit: 52
Mazul-Sunko et al.[27]	Stroke: 11 TIA: 1	Stroke: 8 TIA: 0
McCarthy et al. (2001)[28]	Symptomatic CA disease: 83 Asymptomatic CA disease: 17 Stroke: 19 TIA: 46 Amaurosis fugax: 13	Symptomatic CA disease: 133 Asymptomatic CA disease: 7 Stroke: 33 TIA: 73 Amaurosis fugax: 21
McCarthy et al. (2002)[29]	Symptomatic CA disease: 26 Asymptomatic CA disease: 8 Stroke: 11 TIA: 8 Amaurosis fugax: 7	Symptomatic CA disease: 31 Asymptomatic CA disease: 2 Stroke: 13 TIA: 13 Amaurosis fugax: 5
Mofidi et al.[30]	Symptomatic CA disease: 191 Asymptomatic CA disease: 1 Stroke: 68 TIA: 73 Amaurosis fugax: 50	Symptomatic CA disease: 168 Asymptomatic CA disease: 11 Stroke: 65 TIA: 65 Amaurosis fugax: 35
Moritz et al.[31]	Symptomatic CA disease: 24 Asymptomatic CA disease: 24 Stroke: 4 TIA: 11 Amaurosis fugax: 11	Symptomatic CA disease: 28 Asymptomatic CA disease: 20 Stroke: 7 TIA: 16 Amaurosis fugax: 16

	Neurological deficit: 1	Neurological deficit: 2
Mracek et al.	Symptomatic CA disease: 30 Asymptomatic CA disease: 0	Symptomatic CA disease: 30 Asymptomatic CA disease: 0
Palmer et al.[33]	Symptomatic CA disease: 171 Asymptomatic CA disease: 13 Stroke: 48 TIA: 123	Symptomatic CA disease: 32 Asymptomatic CA disease: 5 Stroke: 13 TIA: 6
Prough et al.[34]	NA	NA
Rockman et al.[35]	Symptomatic CA disease: 2773 Asymptomatic CA disease: 609 Stroke: 893 TIA: 1880	Symptomatic CA disease: 490 Asymptomatic CA disease: 103 Stroke: 214 TIA: 276
Santamaria et al.[36]	NA	NA
Sbarigia et al.[37]	Symptomatic CA disease: 44 Asymptomatic CA disease: 11 Stroke: 8 TIA: 36	Symptomatic CA disease: 42 Asymptomatic CA disease: 11 Stroke: 7 TIA: 34
Shah et al.[38]	Symptomatic CA disease: 508 Asymptomatic CA disease: 146 Stroke: 86 TIA: 311 Amaurosis fugax: 106	NA
Sideso et al.[39]	NA	NA
Sternbach et al.[40]	Symptomatic CA disease: 85 Asymptomatic CA disease: 141 Stroke: 15 TIA: 35 Amaurosis fugax: 19	Symptomatic CA disease: 146 Asymptomatic CA disease: 178 Stroke: 29 TIA: 55 Amaurosis fugax: 30
Takolander et al.[41]	Symptomatic CA disease: 27 Asymptomatic CA disease: 1 Stroke: 14 TIA: 8 Amaurosis fugax: 5	Symptomatic CA disease: 42 Asymptomatic CA disease: 5 Stroke: 23 TIA: 14 Amaurosis fugax: 5
Watts et al.[42]	Symptomatic CA disease: 187 Asymptomatic CA disease: 73 Stroke: 57 TIA: 86 Amaurosis fugax: 44	Symptomatic CA disease: 218 Asymptomatic CA disease: 65 Stroke: 51 TIA: 108 Amaurosis fugax: 59
Total	Symptomatic CA disease: 10391 Asymptomatic CA disease: 9812 Stroke: 3631 TIA: 5743 Amaurosis fugax: 522 Neurological deficit: 46	Symptomatic CA disease: 34465 Asymptomatic CA disease: 60691 Stroke: 14988 TIA: 17002 Amaurosis fugax: 388 Neurological deficit: 76

When the indication for surgery is not explicitly stated, the presenting symptoms are reported instead. CA, carotid artery. NA, not available. TIA, transient ischaemic attack.



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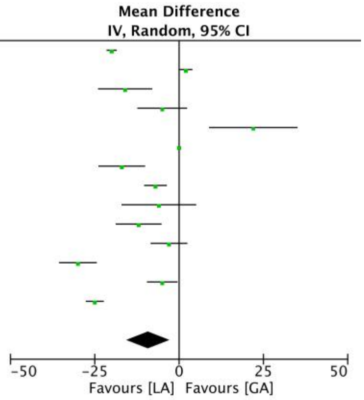
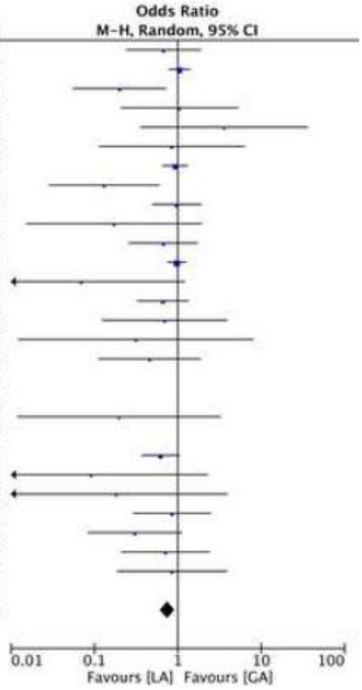
Study or Subgroup	Local Anaesthesia Mean	SD	Total	General Anaesthesia Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Allen et al 1994	102	12	318	122	2.4	361	7.6%	−20.00 [−21.34, −18.66]
Aridi et al 2018	145	71	6684	143	68	68635	7.6%	2.00 [0.22, 3.78]
Bowyer et al 2000	141	39	272	157	49	228	6.9%	−16.00 [−23.87, −8.13]
Forssell et al 1989	80	18	48	85	13	25	7.0%	−5.00 [−12.20, 2.20]
Gabelman et al 1983	162	36	54	140	30	46	5.8%	22.00 [9.06, 34.94]
GALA trial collaborative group 2008	93	5.5	1773	93	4.6	1753	7.7%	0.00 [−0.33, 0.33]
Gurer et al 2013	105	24	179	122	36	150	7.1%	−17.00 [−23.75, −10.25]
Lutz et al. 2008	104	27	465	111	31	876	7.5%	−7.00 [−10.20, −3.80]
Mazul-Sunko et al. 2010	74	22	29	80	20	28	6.3%	−6.00 [−16.91, 4.91]
McCarthy et al 2001	98	32	100	110	13	140	7.1%	−12.00 [−18.63, −5.37]
Palmer et al 1989	84	29	184	87	10	37	7.3%	−3.00 [−8.29, 2.29]
Santamaria et al 2004	90	25	203	120	16	56	7.3%	−30.00 [−35.42, −24.58]
Sternbach et al 2001	79	31	226	84	15	324	7.4%	−5.00 [−9.36, −0.64]
Watts et al 2004	63	10	235	88	18	268	7.6%	−25.00 [−27.51, −22.49]
Total (95% CI)			**10770**			**72927**	**100.0%**	**−9.15 [−15.55, −2.75]**

Heterogeneity: $Tau^2 = 139.32$; $Chi^2 = 1336.04$, df = 13 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: Z = 2.80 (P = 0.005)



	Local Anaesthesia		General Anaesthesia			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Allen et al 1994	6	318	10	361	3.3%	0.68 [0.24, 1.88]
Aridi et al 2018	50	6684	490	68635	16.3%	1.05 [0.78, 1.40]
Bowyer et al 2000	3	272	12	228	2.2%	0.20 [0.06, 0.72]
Ferrero et al 2010	3	209	3	219	1.4%	1.05 [0.21, 5.25]
Forssell et al 1989	3	48	1	55	0.7%	3.60 [0.36, 35.82]
Gabelman et al 1983	2	54	2	46	0.9%	0.85 [0.11, 6.26]
GALA trial collaborative group 2008	66	1771	70	1753	14.4%	0.93 [0.66, 1.31]
Gurer et al 2013	2	179	12	150	1.6%	0.13 [0.03, 0.59]
Hussain et al 2017	10	550	75	4008	6.5%	0.97 [0.50, 1.89]
Kalko et al 2016	1	300	2	105	0.7%	0.17 [0.02, 1.92]
Liu et al 1 2014	5	3154	33	13913	3.8%	0.67 [0.26, 1.71]
Liu et al 2 2014	77	5384	481	32718	18.4%	0.97 [0.76, 1.24]
Love et al 2000	0	200	8	243	0.5%	0.07 [0.00, 1.20]
Lutz et al. 2008	11	465	31	876	6.1%	0.66 [0.33, 1.33]
McCarthy et al 2001	2	100	4	140	1.3%	0.69 [0.12, 3.86]
McCarthy et al 2002	0	34	1	33	0.4%	0.31 [0.01, 7.99]
Mofidi et al 2006	3	192	6	179	1.8%	0.46 [0.11, 1.86]
Moritz et al 2010	0	48	0	48		Not estimable
Mracek et al 2012	0	30	0	30		Not estimable
Palmer et al 1989	1	184	1	37	0.5%	0.20 [0.01, 3.22]
Prough et al 1985	0	13	0	10		Not estimable
Rockman et al 1996	68	3382	19	593	9.3%	0.62 [0.37, 1.04]
Santamaria et al 2004	0	203	1	56	0.4%	0.09 [0.00, 2.26]
Sbarigia et al 1999	0	55	2	52	0.4%	0.18 [0.01, 3.88]
Shah et al 1994	8	654	6	419	3.0%	0.85 [0.29, 2.47]
Sideso et al 2011	4	260	6	123	2.2%	0.30 [0.08, 1.10]
Sternbach et al 2001	4	226	8	324	2.4%	0.71 [0.21, 2.39]
Watts et al 2004	3	235	4	268	1.6%	0.85 [0.19, 3.85]
Total (95% CI)		**25204**		**125622**	**100.0%**	**0.76 [0.62, 0.92]**
Total events	332		1288			

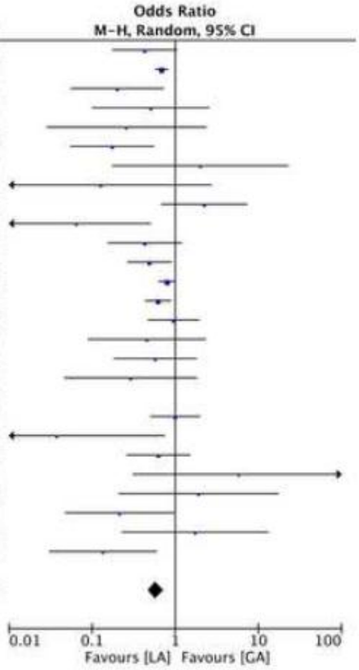
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 30.72$, df = 24 ($P = 0.16$); $I^2 = 22\%$
Test for overall effect: $Z = 2.77$ ($P = 0.006$)



	Local Anaesthesia		General Anaesthesia			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Allen et al 1994	7	318	18	361	4.6%	0.43 [0.18, 1.04]
Aridi et al 2018	144	6684	2136	68635	14.5%	0.69 [0.58, 0.81]
Bowyer et al 2000	3	272	12	228	2.6%	0.20 [0.06, 0.72]
Corson et al 1987	2	157	6	242	1.7%	0.51 [0.10, 2.55]
Ferrero et al 2010	1	209	4	219	1.0%	0.26 [0.03, 2.33]
Fiorani et al 1997	4	683	11	337	3.1%	0.17 [0.06, 0.55]
Forssell et al 1989	2	56	1	55	0.8%	2.00 [0.18, 22.72]
Gabelman et al 1983	0	54	2	36	0.5%	0.13 [0.01, 2.72]
GALA trial collaborative group 2008	9	1773	4	1753	3.0%	2.23 [0.69, 7.26]
Gurer et al 2013	1	179	12	150	1.1%	0.06 [0.01, 0.50]
Hussain et al 2017	4	550	67	4008	3.8%	0.43 [0.16, 1.19]
Kalko et al 2016	34	330	20	105	7.4%	0.49 [0.27, 0.89]
Liu et al 1 2014	90	3154	494	13913	13.6%	0.80 [0.64, 1.00]
Liu et al 2 2014	35	5384	341	32718	11.5%	0.62 [0.44, 0.88]
Love et al 2000	15	200	19	243	6.2%	0.96 [0.47, 1.93]
McCarthy et al 2001	2	100	6	140	1.7%	0.46 [0.09, 2.31]
Mofidi et al 2006	5	192	8	179	3.1%	0.57 [0.18, 1.78]
Palmer et al 1989	3	184	2	37	1.4%	0.29 [0.05, 1.80]
Prough et al 1985	0	13	0	10		Not estimable
Rockman et al 1996	57	3382	10	593	6.5%	1.00 [0.51, 1.97]
Santamaria et al 2004	0	203	3	56	0.5%	0.04 [0.00, 0.74]
Sbarigia et al 1999	12	55	16	52	4.7%	0.63 [0.26, 1.50]
Shah et al 1994	4	654	0	419	0.6%	5.80 [0.31, 108.08]
Sideso et al 2011	4	260	1	123	1.0%	1.91 [0.21, 17.24]
Sternbach et al 2001	2	226	13	324	2.0%	0.21 [0.05, 0.96]
Takolander et al 1989	2	28	2	47	1.1%	1.73 [0.23, 13.03]
Watts et al 2004	2	235	16	268	2.0%	0.14 [0.03, 0.59]
Total (95% CI)		**25535**		**125251**	**100.0%**	**0.59 [0.47, 0.73]**
Total events	444		3224			

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 43.32$, $df = 25$ ($P = 0.01$); $I^2 = 42\%$

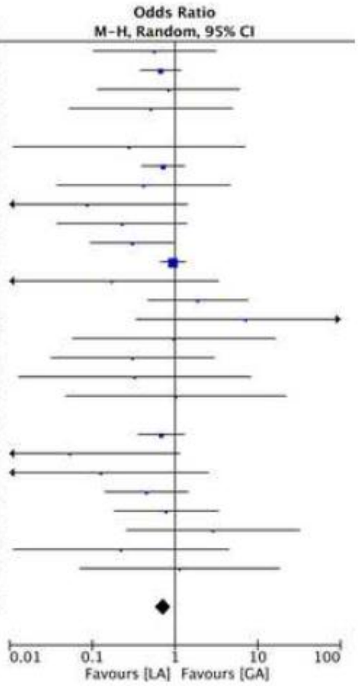
Test for overall effect: $Z = 4.66$ ($P < 0.00001$)



Study or Subgroup	Local Anaesthesia Events	Local Anaesthesia Total	General Anaesthesia Events	General Anaesthesia Total	Weight	Odds Ratio M-H, Random, 95% CI
Allen et al 1994	2	318	4	361	1.6%	0.56 [0.10, 3.10]
Aridi et al 2018	13	6684	199	68635	14.4%	0.67 [0.38, 1.18]
Bowyer et al 2000	2	272	2	228	1.2%	0.84 [0.12, 5.99]
Corson et al 1987	1	157	3	242	0.9%	0.51 [0.05, 4.95]
Ferrero et al 2010	0	209	0	219		Not estimable
Gabelman et al 1983	0	54	1	46	0.4%	0.28 [0.01, 7.00]
GALA trial collaborative group 2008	19	1771	26	1752	12.8%	0.72 [0.40, 1.31]
Gurer et al 2013	1	179	2	150	0.8%	0.42 [0.04, 4.63]
Hussain et al 2017	0	550	41	4008	0.6%	0.09 [0.01, 1.41]
Kalko et al 2016	2	300	3	105	1.4%	0.23 [0.04, 1.38]
Liu et al 1 2014	3	3154	43	13913	3.3%	0.31 [0.10, 0.99]
Liu et al 2 2014	37	5384	238	32718	37.5%	0.94 [0.67, 1.34]
Love et al 2000	0	200	3	243	0.5%	0.17 [0.01, 3.34]
Lutz et al. 2008	4	465	4	876	2.3%	1.89 [0.47, 7.60]
McCarthy et al 2001	2	100	0	140	0.5%	7.13 [0.34, 150.18]
McCarthy et al 2002	1	34	1	33	0.6%	0.97 [0.06, 16.17]
Mofidi et al 2006	1	192	3	179	0.9%	0.31 [0.03, 2.98]
Moritz et al 2010	0	48	1	48	0.4%	0.33 [0.01, 8.22]
Palmer et al 1989	2	184	0	37	0.5%	1.03 [0.05, 21.84]
Prough et al 1985	0	13	0	10		Not estimable
Rockman et al 1996	47	3382	12	593	11.1%	0.68 [0.36, 1.29]
Santamaria et al 2004	0	203	2	56	0.5%	0.05 [0.00, 1.13]
Sbarigia et al 1999	0	55	3	52	0.5%	0.13 [0.01, 2.53]
Shah et al 1994	5	654	7	419	3.4%	0.45 [0.14, 1.44]
Sideso et al 2011	5	260	3	123	2.2%	0.78 [0.18, 3.34]
Sternbach et al 2001	2	226	1	324	0.8%	2.88 [0.26, 32.00]
Takolander et al 1989	0	28	3	47	0.5%	0.22 [0.01, 4.48]
Watts et al 2004	1	235	1	268	0.6%	1.14 [0.07, 18.34]
Total (95% CI)		**25311**		**125825**	**100.0%**	**0.72 [0.59, 0.90]**
Total events	150		606			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 21.69$, $df = 25$ ($P = 0.65$); $I^2 = 0\%$

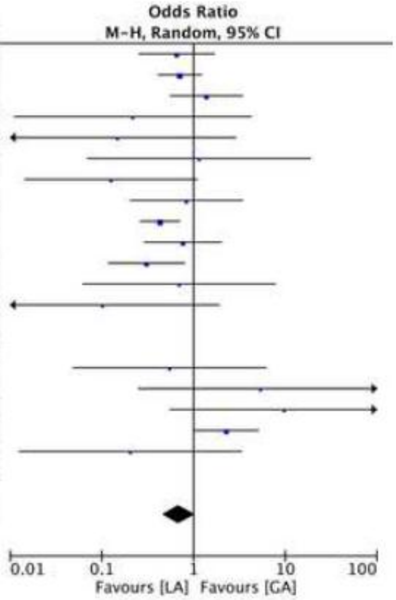
Test for overall effect: $Z = 2.96$ ($P = 0.003$)



Study or Subgroup	Local Anaesthesia Events	Local Anaesthesia Total	General Anaesthesia Events	General Anaesthesia Total	Weight	Odds Ratio M-H, Random, 95% CI
Allen et al 1994	7	318	12	361	9.0%	0.65 [0.25, 1.68]
Aridi et al 2018	14	6684	203	68635	13.6%	0.71 [0.41, 1.22]
Bowyer et al 2000	13	272	8	228	9.5%	1.38 [0.56, 3.39]
Corson et al 1987	0	157	3	242	1.7%	0.22 [0.01, 4.23]
Ferrero et al 2010	0	209	3	219	1.7%	0.15 [0.01, 2.88]
Forssell et al 1989	1	48	1	55	1.8%	1.15 [0.07, 18.88]
Gabelman et al 1983	1	54	6	46	2.9%	0.13 [0.01, 1.09]
Gurer et al 2013	4	179	4	150	5.6%	0.83 [0.21, 3.39]
Kalko et al 2016	59	300	38	105	14.2%	0.43 [0.26, 0.70]
Love et al 2000	7	200	11	243	8.8%	0.76 [0.29, 2.01]
Lutz et al. 2008	5	465	30	876	8.9%	0.31 [0.12, 0.80]
McCarthy et al 2001	1	100	2	140	2.4%	0.70 [0.06, 7.79]
Mofidi et al 2006	0	192	4	179	1.7%	0.10 [0.01, 1.89]
Moritz et al 2010	0	48	0	48		Not estimable
Palmer et al 1989	0	184	0	37		Not estimable
Santamaria et al 2004	2	203	1	56	2.4%	0.55 [0.05, 6.15]
Sbarigia et al 1999	2	55	0	57	1.6%	5.37 [0.25, 114.51]
Shah et al 1994	7	654	0	419	1.8%	9.72 [0.55, 170.60]
Sideso et al 2011	34	260	8	129	10.5%	2.28 [1.02, 5.07]
Sternbach et al 2001	1	226	1	47	1.9%	0.20 [0.01, 3.33]
Takolander et al 1989	2	28	0	0		Not estimable
Total (95% CI)		**10836**		**72272**	**100.0%**	**0.69 [0.46, 1.04]**
Total events	160		335			

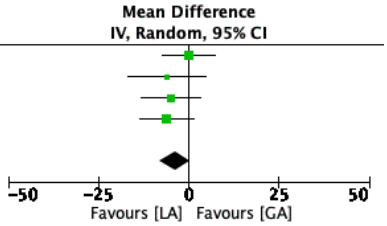
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 28.81$, df = 17 (P = 0.04); $I^2 = 41\%$

Test for overall effect: Z = 1.79 (P = 0.07)



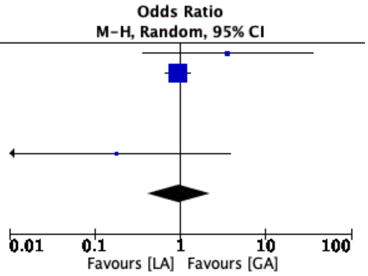
Study or Subgroup	Local Anaesthesia Mean	SD	Total	General Anaesthesia Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Forssell et al 1989	80	18	48	80	19	55	32.1%	0.00 [−7.15, 7.15]
Mazul-Sunko et al. 2010	74	22	29	80	20	28	13.8%	−6.00 [−16.91, 4.91]
Mracek et al 2012	76	13	30	81	19	30	24.2%	−5.00 [−13.24, 3.24]
Sbarigla et al 1999	84	21	55	90	18	52	30.0%	−6.00 [−13.40, 1.40]
Total (95% CI)			162			165	100.0%	−3.83 [−7.88, 0.22]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.66$, $df = 3$ ($P = 0.65$); $I^2 = 0\%$
Test for overall effect: $Z = 1.86$ ($P = 0.06$)



Study or Subgroup	Local Anaesthesia Events	Local Anaesthesia Total	General Anaesthesia Events	General Anaesthesia Total	Weight	Odds Ratio M-H, Random, 95% CI
Forssell et al 1989	3	48	1	55	11.5%	3.60 [0.36, 35.82]
GALA trial collaborative group 2008	66	1773	70	1753	81.6%	0.93 [0.66, 1.31]
McCarthy et al 2002	0	34	0	33		Not estimable
Moritz et al 2010	0	48	0	48		Not estimable
Mracek et al 2012	0	30	0	30		Not estimable
Sbarigia et al 1999	0	55	2	52	6.9%	0.18 [0.01, 3.88]
Total (95% CI)		1988		1971	100.0%	0.97 [0.42, 2.23]
Total events	69		73			

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.42$, $df = 2$ ($P = 0.30$); $I^2 = 17\%$
Test for overall effect: $Z = 0.07$ ($P = 0.95$)

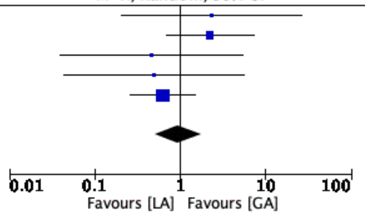


Study or Subgroup	Local Anaesthesia Events	Local Anaesthesia Total	General Anaesthesia Events	General Anaesthesia Total	Weight	Odds Ratio M-H, Random, 95% CI
Forssell et al 1989	2	48	1	55	6.7%	2.35 [0.21, 26.73]
GALA trial collaborative group 2008	9	1773	4	1753	28.4%	2.23 [0.69, 7.26]
Mazul-Sunko et al. 2010	1	29	2	28	6.6%	0.46 [0.04, 5.43]
Moritz et al 2010	1	48	2	48	6.7%	0.49 [0.04, 5.58]
Sbarigia et al 1999	12	55	16	52	51.6%	0.63 [0.26, 1.50]
Total (95% CI)		1953		1936	100.0%	0.95 [0.50, 1.78]
Total events	25		25			

Heterogeneity: Tau² = 0.00; Chi² = 4.03, df = 4 (P = 0.40); I² = 1%

Test for overall effect: Z = 0.17 (P = 0.87)

Odds Ratio
M-H, Random, 95% CI



Study or Subgroup	Local Anaesthesia Events	Local Anaesthesia Total	General Anaesthesia Events	General Anaesthesia Total	Weight	Odds Ratio M-H, Random, 95% CI
GALA trial collaborative group 2008	19	1773	26	1753	89.4%	0.72 [0.40, 1.30]
McCarthy et al 2002	1	34	1	33	4.0%	0.97 [0.06, 16.17]
Moritz et al 2010	0	48	1	48	3.0%	0.33 [0.01, 8.22]
Sbarigia et al 1999	0	55	3	52	3.5%	0.13 [0.01, 2.53]
Total (95% CI)		1910		1886	100.0%	0.67 [0.38, 1.17]
Total events	20		31			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.52$, $df = 3$ ($P = 0.68$); $I^2 = 0\%$

Test for overall effect: $Z = 1.40$ ($P = 0.16$)