Meta-Analysis and Systematic Review of the Relationship between Hospital Volume and Outcome Following Carotid Endarterectomy

P.J.E. Holt,1* J.D. Poloniecki,2 I.M. Loftus1 and M.M. Thompson1

1St George’s Vascular Institute, 4th floor, St James’ Wing, St George’s Hospital, London SW17 0QT, UK, and 2Community Health Sciences, St George’s University of London, London SW17 0QT, UK

Introduction

Carotid endarterectomy is undertaken to reduce the risk of stroke in both symptomatic and asymptomatic patients with carotid artery stenosis.1–3 CEA has been shown to be superior to medical management in defined sub-groups of patients with carotid stenosis.4 With prompt surgery following a carotid territory event, highly significant absolute risk reductions in subsequent stroke may be attained5 with low numbers of patients requiring treatment to prevent a neurological event.

The absolute risk reduction in stroke depends upon the natural history of the disease and the peri-procedural risk of stroke and death. The lower the peri-operative event rate, the greater the absolute risk reduction. Selected single centre series and trial participants have produced very low 30-day stroke rates, but there have been some studies that have questioned whether these results are reproducible in the community.6

It has been suggested that the number of adverse events related to CEA may be associated with the annual hospital volume undertaken. If a volume-outcome relationship existed for CEA, then it may be expected to inform health policy, and direct health economists in the planning of vascular services.

This article reviews the published evidence for the relationship between annual hospital volume and outcomes of CEA.

Methods

PubMed, EMBASE and the Cochrane library medical databases were searched for articles investigating the
hospital-volume of CEA, and outcome from this procedure, using broad terms. The search terms employed were “carotid endarterectomy and volume-outcome relationship,” “carotid endarterectomy and mortality,” “carotid endarterectomy and post-operative stroke,” “carotid endarterectomy and outcome measures,” “carotid endarterectomy and hospital volume,” “carotid endarterectomy and provider volume.” A final search “vascular surgery and mortality” was included to increase the sensitivity, though not specificity of the search.

**Article selection**

The searches identified forty-five potentially relevant articles to which exclusion criteria were applied. Articles investigating the relationship between surgeon-operative volume and outcomes were excluded. Relevant citations were identified from scrutiny of retrieved articles in order to collect any articles missed by the searches.

**Validity assessment**

Having met the inclusion criteria, articles were assessed for quality and their findings. In-hospital death and post-operative stroke were the principal outcome measures. The presence, or absence, of case-mix adjustment was recorded, along with the impact of case-mix where adjusted and unadjusted data were presented. Case-mix adjusted data were used for the meta-analysis where available.

**Data abstraction**

Data abstraction was performed independently by PH. In-hospital death, post-operative stroke, or combined stroke/death rates were extracted from the original articles, along with the odds ratios and 95% confidence intervals for higher- and lower-volume hospitals. Where only annual volumes and adverse event rates were presented for the different hospital volumes, the number of affected patients was calculated, within the error of the published results. This allowed the generation of confidence intervals for these studies.

The threshold value for the number of CEA repairs performed per annum between higher- and lower-volume hospitals was recorded, as stated in the original articles. Datasets were dichotomised to higher- and lower-volume categories where articles published a series of volume groupings (e.g. higher-, moderate- and lower-volume hospitals).

**Study characteristics**

Analysis of the data was by meta-analysis and systematic review. Four articles were included in a systematic review, as the data could not be meta-analysed, due to inadequate published data.

**Quantitative data synthesis**

Weighted averages were calculated for fixed effect meta-analyses by the inverse variance method. The inverse variance method of meta-analysis is a widely applicable approach to meta-analysis and is based on a mathematical assumption that every study evaluated a common effect i.e. chance was the only factor effecting the results other than the effect investigated.

It involved a weighted average of the effect estimates from the separate studies. The weight for each study was taken to be the inverse of the variance (one divided by the square of the standard error) of the effect estimate."
Forest plots were used to illustrate the information from the individual studies used in the meta-analyses, in terms of odds ratios and 95% confidence intervals. The plots demonstrated the variation between studies and a pooled point estimate of the overall result, which represented the volume-outcome relationship in CEA.

Publication bias

Publication bias was assessed through separate funnel plots for each outcome variable investigated. Symmetry of the funnel plots indicated no publication bias.

Heterogeneity

Clinical heterogeneity may account for part of the effect seen in meta-analysis. Although the estimates of treatment effect at high-volume hospitals varied by chance between studies, the assessment of heterogeneity assessed whether there was more variation than expected by chance alone. By testing for heterogeneity, the validity of the combined effect estimate was assessed.

This described whether the effects found in the individual studies were similar enough to be confident that the combined estimate was a meaningful description of the set of studies. The test of heterogeneity was not the sole determinant of model choice in meta-analysis, and clinical insight was relevant to both the investigation and interpretation of heterogeneity.

The Q-statistic was calculated along with the degrees of freedom of the study (number of individual studies minus one) and compared using a chi-squared distribution. As a second test of heterogeneity the I-squared value was calculated.

Sensitivity analysis

Sensitivity analyses were performed by comparing the results obtained through both fixed and random effects meta-analyses. Furthermore, the exclusion of the largest trial in each sub-group, followed by recalculation of the meta-analyses, determined whether the results were being heavily determined by that trial.

Results

After exclusions, twenty-five articles (935 156 cases) provided information on the annual hospital volume and outcome of CEA. The mean death rate was 1.6% (range 0.3 to 5.2%), and the mean disabling stroke rate was 2.7% (0.23 to 6.1%).

The results from 885 034 CEA were suitable for meta-analysis and were sub-divided into three groups depending on the focus of the published article. The pooled effects for each group were (odds ratio [95% confidence intervals], threshold value):

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio [95% CI]</th>
<th>Threshold Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke rate</td>
<td>0.84 [0.79–0.88]</td>
<td>72 CEA p.a.</td>
</tr>
<tr>
<td>Death rate</td>
<td>0.76 [0.74–0.81]</td>
<td>81 CEA p.a.</td>
</tr>
<tr>
<td>Combined stroke/death rate</td>
<td>0.73 [0.68–0.78]</td>
<td>84 CEA p.a.</td>
</tr>
</tbody>
</table>

Overall, stroke and death attributable to CEA occurred less frequently in higher-volume hospitals (0.78 [0.64–0.92]; Fig. 1D). The critical volume threshold between higher- and lower-volume hospitals was 79 CEA per annum, defined by weighting the threshold values stated in the included articles.

Four articles (50 122 cases) were presented as a systematic review (Table 1). Two articles found significant improvements in outcomes with volume, and two did not.

Study validity

No significant heterogeneity was found in any of the sub-group analyses by either the Q-statistic or I-squared method. The funnel plots showed good symmetry indicating insignificant publication bias (Fig. 2a–c). Exclusion of the largest study in each sub-group did not change the pooled effect estimate for each sub-group. This indicated that the results were not influenced by a single large trial, supporting the validity of these results.

In comparing the pooled effect estimates from the three sub-group analyses, the results in terms of effect and volume threshold were consistent between the mortality, and stroke-mortality sub-groups. The stroke-only sub-group had a more conservative pooled effect estimate at a higher volume threshold compared to the other two sub-groups.

Discussion

The articles utilised in this review were largely based on retrospective, administrative data from the USA, and demonstrated significant relationships between the annual hospital volume and outcomes of CEA in terms of stroke and mortality.

For these data, all-cause post-operative mortality was accurately quantified through discharge...
Only two outcomes were investigated in this meta-analysis (stroke and death), therefore it is highly likely that the total complication rate was higher than presented here. Furthermore, as these studies included symptomatic and asymptomatic patients, the overall stroke and death rates were lower than expected, especially when compared to European data that are based on performing the majority of procedures on symptomatic patients.

A further problem identified was in the coding of post-operative stroke, as patients may have been admitted to hospital due to cerebrovascular disease, or have suffered a stroke post-operatively. In the process of generating the data, either of these may be miscoded.

There was significant variation in the way in which “stroke” was defined in the different articles ranging from a focal neurological deficit present for two or...
more consecutive days, to a deficit unresolved by discharge or fatal stroke. A number of articles specified the use of ICD-9 code (997.x) to determine the rate of post-operative stroke, with no further assessment of severity, or duration. One study stated that in the presence of a code relating to stroke, it was “assumed to be post-operative.” The difficulty of interpreting ‘post-operative stroke’ was supported in the sensitivity analyses, where the pooled effect estimate for this sub-group was of a lesser extent than the other sub-groups.

The heterogeneous way that ‘post-operative stroke’ was interpreted suggested that the most valid measure for CEA outcome is post-operative death. Fig. 1a and b did show similarities in the impact of volume on outcome. Therefore, post-operative death may be a valid outcome surrogate for the hospital post-operative stroke-rate.

The impact on the results of these confounding factors was impossible to quantify, and these differences will be difficult to rectify in the future without increasing clinician involvement in the coding process in parallel with the continued development of diagnostic coding systems, such as ICD-10.

The results demonstrated that CEA performed at higher-volume hospitals had improved outcome quantified through significantly lower stroke and death rates. The key factors underlying this complex relationship related to hospital infrastructure (cardiology, specialist anaesthetists and neurology support on-site), the provision of suitable intensive care facilities where necessary, and concomitant provision of high-volume surgeons with vascular sub-specialisation. For CEA, lower-volume surgeons achieved results similar to higher-volume surgeons when operating in higher-volume hospitals. This supported the concept that hospital infrastructure was as a major component of the volume-outcome relationship, and acted independently to a relationship between surgeon operative volume and outcome. Death and stroke rate for CEA are lowest for high-volume vascular specialist surgeons, operating in high-volume hospitals.

It has been suggested that differences in case-mix between higher- and lower-volume hospitals may underlie the volume-outcome relationship observed.
with higher-volume hospitals taking on a larger number of asymptomatic cases, and lower-risk patients. However, this was not supported by articles in this study, with significant crude results remaining significant after case-mix adjustment, whether those results showed a volume-outcome relationship or not.18 The studies utilised in this analysis varied in the way the data were presented, with some presenting an in-hospital death or stroke rate, and others a combined stroke/death rate. In order to more easily assess the data for CEA, it would be advisable that all future studies make an assessment of both primary outcome measures for this procedure, and present a combined stroke/death rate. Further risk adjustment would be made possible through the routine inclusion of physiological parameters, including a pre-operative neurological scoring system and functional assessment, whether the patient was symptomatic or asymptomatic, and the degree of carotid artery stenosis.

The evidence presented here demonstrated that the relationship between hospital volume and outcome was consistent and reproducible. We suggest that all healthcare systems should establish volume criteria for CEA. The volume threshold will need individual assessment in each system, as different policies regarding the proportion of asymptomatic carotid artery stenoses operated will have an effect on the threshold.

Conclusion

CEA is the gold standard therapy in the prevention of neurological symptoms secondary to carotid artery stenosis. This study demonstrated that adverse outcome from CEA was reduced as the annual hospital volume of surgery increased. Volume criteria should be established in every healthcare system for CEA, to reduce the incidence of these events.

References

4 Rothwell PM. ACST: which subgroups will benefit most from carotid endarterectomy? Lancet 2004 Sep 25–Oct 1;364(9440):1122–1123 [author reply 5–6].
32 Feasby TE, Quan H, Gali WA. Hospital and surgeon determinants of carotid endarterectomy outcomes. Arch Neurol 2002 Dec;59(12):1877–1881.

Accepted 21 January 2007
Available online 30 March 2007