REVIEW

Carotid Sinus Nerve Blockade to Reduce Blood Pressure Instability Following Carotid Endarterectomy: A Systematic Review and Meta-analysis

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Objectives. Local anaesthetic infiltration into the carotid sinus during carotid endarterectomy (CEA) has been recommended to minimise blood pressure fluctuations but its use remains controversial. The aim of this meta-analysis was to determine whether intra-operative administration of local anaesthetic reduces the incidence of haemodynamic instability following CEA.

Materials and methods. A search of the Medline, Pubmed and Embase databases and the Current Controlled Trials register identified four trials, which met the pre-defined inclusion criteria for data extraction. Pooled odds ratios with 95 per cent confidence intervals (c.i.) for the development of post-operative hypotension and hypertension were calculated using a random-effects model.

Results. Outcomes of 432 patients were studied. Local anaesthetic blockade of the carotid sinus was associated with a pooled odds ratio of 1.25 (95 per cent c.i. 0.496 to 3.15; \( p = 0.216 \)) and 1.28 (95 per cent c.i. 0.699 to 2.33; \( p = 0.428 \)) for the development of post-operative hypotension and hypertension respectively. Although none reach significance there was a trend towards increased risk of developing a complication in those patients who received local anaesthetic.

Conclusions. There are insufficient data to determine the role of intra-operative local anaesthetic administration in reducing post-operative blood pressure lability following CEA. Conversely, the possibility of harm cannot be excluded on the basis of the currently available data.

Introduction

Carotid endarterectomy (CEA) is performed to improve the cerebrovascular prognosis of patients with a significant symptomatic carotid artery stenosis by removing atheroma from the carotid bifurcation and internal carotid artery.\(^1,2\) Post-endarterectomy haemodynamic instability, including hypotension and hypertension,\(^3–5\) which has been attributed to collateral damage of the baroreceptor mechanism\(^6\) is common and is associated with an increased risk of cardiovascular morbidity and mortality not only in the immediate post-operative period but also in the long-term.\(^3,5,7,8\) Hypertension has been noted in up to 56% of patients,\(^3,4\) which may lead to wound haematoma, hyperperfusion syndrome, stroke and myocardial infarction. Hypotension has been documented in up to 50% patients,\(^3,9\) which can reduce the blood flow through the newly endarterectomised artery and cause thrombus formation and subsequent stroke. Also systemic hypotension can reduce coronary perfusion leading to myocardial infarction in patients who are likely to have a high incidence of co-existing coronary artery disease.\(^10\)

Post CEA hypotension has been attributed to alteration of the carotid sinus baroreceptors, specialised neurons located in the adventitia of the carotid artery, which are stimulated when a small rise in blood pressure is sensed. This initiates a reflex arc
to the upper brainstem and produces a compensatory bradycardia and a subsequent lowering in blood pressure.11

Some vascular surgeons advocate nerve-sparing dissection and/or local anaesthetic blockade of the carotid sinus nerve at the time of CEA to minimise fluctuations in blood pressure,12 although the purported benefits are based primarily on animal studies13 and several randomised studies have refuted this assertion.14,15

Therefore the role of local anaesthetic infiltration into the carotid sinus during CEA to prevent post-operative haemodynamic instability remains unclear. The aim of this meta-analysis was to determine if routine injection of local anaesthetic during CEA is of benefit to the patient in preventing post-operative haemodynamic instability within the first 24 hours of surgery.

Materials and Methods

This meta-analysis was conducted according to recommendations of the QUORUM statement.16

The Pubmed and Embase databases were searched between 1966 and October 2006. Combinations of the search terms ‘carotid sinus nerve’, ‘local anaesthetic’, ‘carotid’, ‘endarterectomy’, ‘hypotension’, ‘hypertension’ and ‘outcome’ were used to identify randomised controlled trials of intra-operative local anaesthetic injection of the carotid sinus nerve. The abstracts of publications identified by the primary search were then assessed for eligibility. Studies were included if they met each of four criteria: randomised controlled trial published as an original article in the English language, subjects undergoing carotid endarterectomy, comparison of patients receiving intra-operative local anaesthetic with controls and an explicit definition of post-operative hypotension and hypertension. The electronic search was supplemented by a manual search of the reference lists of relevant articles and abstract books of major national vascular and general surgical meetings for the past 10 years to ensure inclusion of all possible studies and exclude duplicates. In addition, the Current Controlled Trials register (www.controlled-trials.com) was searched. Review articles and retrospective analyses were excluded. Eligible studies were assessed for quality using the Jadad scoring system (maximum score 5).17 Differences in assessment were discussed among all authors until agreement was achieved and data were analysed on an intention-to-treat basis.

The primary outcome for the meta-analysis was development of post-operative hypotension and hypertension, clearly pre-defined in each trial. The secondary outcomes were incidence of any post-operative complication, arrhythmia, myocardial infarction and cerebrovascular accident (CVA). Correlating the type of local anaesthetic used with outcome could not be performed because of the relative small numbers. The incidence of intra-operative haemodynamic lability was not looked for between the two groups as intra-operative factors could not be as well controlled for and the heterogeneity of the data presented was large.

Data from eligible papers were reviewed independently by two authors (TT & SRW) and abstracted into an Excel spreadsheet. Pooled odds ratios (OR) with 95 per cent confidence intervals (C.I.) were calculated for each outcome using a random effects model as described by DerSimonian and Laird.18 Heterogeneity across the studies was evaluated using the Cochran’s Q statistic. The level of significance was set at $p < 0.05$. The statistical analysis was performed using Statsdirect 2.5.3 (Statsdirect Ltd., UK).

Results

The search strategy initially identified 7 randomised controlled trials of local anaesthetic infiltration of carotid sinus during CEA. After scrutinising the abstracts and where necessary the full reports of these trials, two trials were identified as having only measured the haemodynamic effects of carotid sinus anaesthesia intra-operatively.19,20 One trial only compared actual blood pressure variability between the two groups with no mention of development of post-operative hypotensive and hypertensive events.21 This left four randomised trials conducted on patients who underwent carotid sinus nerve blockade during CEA where the incidence of post-operative hypotension and hypertension was documented.11,14,15,22 Data from these four trials were abstracted for meta-analysis.

The four trials included a total of 432 patients (Table 1). Forest plots were constructed comparing development of post-operative hypotension and hypertension, any post-operative complication, arrhythmia, myocardial infarction and CVA for those patients who had their carotid sinus injected with local anaesthetic against placebo (Figs. 1–6). Heterogeneity between studies was not significant (data shown in figures).

Post-operative hypotension occurred in 31.8% of patients who received local anaesthetic intra-operatively and in 23.0% who were given placebo or no injection (pooled odds ratio 1.25 (95 per cent c.i. 0.496 to 3.15); $p = 0.634$) (Fig. 1). Post-operative hypoten-
hypertension occurred in 34.5% and 33.0% of patients who received local anaesthetic infiltration and placebo respectively (pooled odds ratio 1.28 (95 per cent c.i. 0.70 to 2.33); \( p = 0.428 \)) (Fig. 2).

One trial\textsuperscript{15} did not mention the development of any post-operative arrhythmias and hence only three studies were meta-analysed for this outcome. Arrhythmias occurred in 24.1% patients who received local anaesthetic and in 15.6% who were given placebo (pooled odds ratio 1.34 (95 per cent c.i. 0.541 to 3.31); \( p = 0.527 \)) (Fig. 3). Similarly only two trials\textsuperscript{14,22} mention the development of any post-operative complication, myocardial infarction and CVA. Number of events for each is discussed in the respective figure (Figs. 4–6). Although none reach statistical significance there was a trend towards increased risk of developing a complication in those patients who received local anaesthetic to block the carotid sinus nerve during surgery.

**Discussion**

This study depended on 4 randomised controlled trials comparing the use of local anaesthetic to reduce blood pressure lability post CEA. Despite CEA being

<table>
<thead>
<tr>
<th>Number</th>
<th>Carotid nerve of hering conserved</th>
<th>Treatment groups</th>
<th>Shunt used</th>
<th>Patch closure</th>
<th>Number of surgeons</th>
<th>General anaesthetic</th>
<th>Primary outcome: Definition of post-operative hypotension</th>
<th>Definition of post-operative hypertension</th>
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<tr>
<td>Elliott 1986</td>
<td>Yes</td>
<td>0.25% bupivacaine vs. no injection</td>
<td>Yes</td>
<td>Unclear</td>
<td>4</td>
<td>Yes</td>
<td>Decrease &gt; 20 mmHg in SBP</td>
<td>Decrease &gt; 20 mmHg in SBP</td>
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<tr>
<td>Gottlieb 1997</td>
<td>Yes</td>
<td>0.25% bupivacaine vs. NaCl</td>
<td>Yes</td>
<td>Yes</td>
<td>1</td>
<td>Yes</td>
<td>Decrease of &gt; 30% from the average pre-operative SBP or SBP &lt; 100 mmHg</td>
<td>Increase &gt; 20 mmHg in SBP</td>
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<td>Fardo 1999</td>
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<td>1% xylocaine vs. bupivacaine vs. NaCl</td>
<td>Yes</td>
<td>Yes</td>
<td>1</td>
<td>Yes</td>
<td>Decrease in SBP of &gt; 40 mmHg or absolute SBP &lt; 90 mmHg</td>
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<td>Maher 2002</td>
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<td>Selective</td>
<td>Yes</td>
<td>SBP &lt; 100 mmHg</td>
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**Table 1. Baseline characteristics of included studies**

**Fig. 1.** Forest plot for the effect of local anaesthetic infiltration on the development of post-operative hypotension following CEA.
a common operation and hypotension and hypertension complicating up to 50% cases\(^3\)–\(^5\),\(^9\) all the trials were relatively small; only one study randomised more than 50 patients to each arm.\(^{15}\) A significant risk of a Type II error is likely to exist with each individual trial and no attempt has been made to calculate a power estimation in any study. Assuming that 10% (a conservative estimate) of the control patients...
Fig. 4. Forest plot for the effect of local anaesthetic infiltration on the development of post-operative myocardial infarction following CEA.

Fig. 5. Forest plot for the effect of local anaesthetic infiltration on the development of post-operative CVA following CEA.
develop post-operative haemodynamic complications, 365 patients would be required in each arm of the trial to demonstrate a 50% reduction in complication rates with 80% power at the 5% significance level (Table 2).

The results of the present analysis suggest that at present there is no conclusive evidence to support the routine use of local anaesthetic to block the carotid sinus nerve in patients undergoing CEA to reduce post-operative blood pressure fluctuation, which has been associated with increased incidence of complications (i.e. myocardial infarction or stroke). In fact, there was a trend towards increased risk of developing a complication in those patients who received local anaesthetic, although none of the mentioned complications reached statistical significance.

The included trials were analysed on an intention-to-treat basis as this reduces bias and tends to answer a question of clinical relevance. However it is important to consider the inclusion criteria for each of the studies when applying the results to clinical practice. Although there was no statistical significant evidence of heterogeneity between the trials in our analysis the sample size (four trials) is relatively small and moreover scrutiny of the study designs does reveal some important differences in the trial methodology. Definitions of the primary outcomes hypotension and hypertension are all different in the four trials (Table 1). The treatment arms are also different in terms of different types and concentrations of local anaesthetic used and the use of no placebo. In addition, no nerve sparing technique is mentioned in one trial. Carotid sinus denervation could have had a blunting effect on the haemodynamic changes accompanying the nerve blockade and may also reduce the incidence of hypotension episodes in the control group.

**Table 2. Quality indicators of included studies**

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<td>Power calculation</td>
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<td>No/No</td>
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<td>Yes</td>
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<td>No</td>
<td>No</td>
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The answer to reducing post-operative blood pressure lability may not simply lie at the carotid sinus baroreceptor reflex level. There is evidence to suggest that carotid sinus baroreceptors functioning before CEA suddenly deteriorate at the point when the athromatous plaque is removed from the carotid sinus region. This sudden deterioration closely resembles the situation seen in animal experiments in which the carotid sinus nerve is deliberately cut. Histological studies have shown that unmyelinated nerves penetrate the artery wall as far as the intima and because CEA removes part of the muscular media of the internal carotid artery and hence damages these nerves. This novel theory of intramural denervation to explain the disruption of the baroreceptor mechanism is supported by the fact that the baroreflex response to intraluminal stretch stimulation is abolished by infiltration of local anaesthetic into the peri-adventitial tissue around the carotid sinus.25

Although recent work demonstrated universal deterioration of the baroreceptor function following CEA, not every patient develops blood pressure instability. Why might this be? The experimental literature on sino-aortic denervation, a reasonably close animal model of CEA suggests that there is redundancy in the system, and that one functioning baroreceptor may be sufficient to maintain function.27 Furthermore, marked paroxysmal hypertension and blood pressure lability develops after bilateral carotid sinus denervation in humans.28,29 Also, patients undergoing staged (i.e. bilateral) CEA surgery were noted to be twice more likely to develop blood pressure instability than those with unilateral endarterectomy.30 Taken together, these observations point to the presence of a “baroreceptor reserve”, which, if diminished due to the presence of pre-existing baroreceptor impairment (e.g. contralateral carotid artery disease) may predispose patients to haemodynamic instability. Recent observations seem to confirm this hypothesis in the short term: patients with severe contralateral carotid disease have a marked increase in blood pressure immediately following endarterectomy compared with those with normal contralateral vessels.26

Also more than one site is likely to be involved in the baroreflex control of systemic blood pressure e.g. aortic arch.31 However, it has been argued that aortic arch baroreceptors are not as important in humans as in animals, owing to the greater sensitivity of the carotid baroreceptors to orthostatic changes, although blood pressure instability has been observed after thoracic aortic surgery and paroxysms of severe hypertension are among the most feared complications of thoracic aortic surgery, as they can put the suture line under severe stress with fatal consequences.

Conclusions

There are insufficient data to determine the role of intra-operative local anaesthetic administration in reducing post-operative blood pressure lability following CEA with reasonable certainty. Conversely, the possibility of harm cannot be excluded on the basis of the currently available data. Large-scale, double-blind, placebo-controlled trials are required.

Acknowledgements

SRW receives funding from the Moulton Charitable Foundation.

References

1 MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists’ Collaborative Group. Lancet 1991;337(8752):1235—1243.
Carotid Sinus Nerve Blockade does not Reduce Haemodynamic Instability Following CEA


