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Clinical Study

Anaesthesia during Carotid Endarterectomy and Urinary Neopterin

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Recent systematic reviews of randomized controlled trials show that the rate of postoperative complications after carotid endarterectomy (CEA) was not significantly different between operations performed under general anesthesia (GA) or local anesthesia (LA). However, these studies were not large enough to draw meaningful conclusions about any difference in mortality. This study therefore aimed to compare a surrogate endpoint of postoperative mortality between GA and LA by using urinary neopterin. 68 consecutive patients admitted electively for CEA were studied. Urinary neopterin levels were assayed preoperatively, immediately postoperatively (PO), 4, 6, 12, and 24 hrs PO. This study compared the level of urinary neopterin between GA and LA. Of the 68 CEAs, 48 operations were performed under GA. Urinary neopterin concentration in LA group increased PO and reached a peak at 6 hrs PO. At this point, the urinary neopterin levels in the GA group (85.3 μmol/mol creatinine) were significantly lower than those under the LA group (123.4 μmol/mol creatinine) ($P = 0.02$). We found that the level of urinary neopterin level after operation in LA was significantly higher than those under GA. More studies are needed.

1. Introduction

Atherosclerosis at the carotid bifurcation is a recognized cause of stroke, and surgical removal of the disease—carotid endarterectomy (CEA)—can decrease the chance of stroke in selected patients. Our pooled analyses of large prospective, randomized controlled trials (RCTs), that is, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), have clearly shown that in patients with recent symptomatic severe carotid stenosis, CEA can prevent further strokes more often than medical treatment alone [1–3]. CEA can be performed under general anesthesia (GA) or local anesthesia (LA). LA has the benefit of assessing patients' response following clamping of the carotid artery, avoidance of inappropriate shunt insertion, and preservation of cerebral autoregulation [4].

In our previous Cochrane review, the non-RCTs showed consistently lower risks of operative death when CEA was done under LA (41 studies, 20195 CEAs, odds ratio 0.63, 95% confidence interval 0.45–0, 89, $P = 0.008$) [5]. Our recent Cochrane review of 10 RCTs showed that there was a trend toward lower operative mortality with LA (10 RCTs, 4084 CEAs, odds ratio 0.62, 95% confidence interval 0.36–1.07, $P = 0.08$) [6]. However, although this systematic review had some 4 thousand CEAs, the sample size was not enough to detect the effect on mortality [6]. Large new RCTs are needed. In the mean time, to try to determine if one technique had an advantage over another in terms of mortality, we compared LA and GA using a biomarker (urinary neopterin) in our patients.

Neopterin is produced by mononuclear cells in plasma during elective surgery or trauma. The level of neopterin has been used as a marker of the inflammatory process in many surgical studies [7–9]. In critical care patients, high levels of urinary neopterin are associated with high mortality [10, 11]. In the current study the effects of GA and LA on urinary neopterin were determined in CEA patients. It was

Table 1: Baseline characteristics of patients between GA and LA.

Characteristics	Anesthetics technique		P value
	GA $N = 48$	LA $N = 20$	
Mean age (years) (range)	66.9 (50–76)	69.1 (55–79)	0.49
Male (%)	22 (45.8)	14 (70)	0.11
Indication			
Stroke (%)	20 (41.7)	4 (20)	
TIA (%)	10 (20.8)	9 (45)	0.08
No symptom (%)	14 (29.2)	4 (20)	
DM (%)	9 (18.8)	7 (35)	0.34
Current smoker (%)	10 (20.8)	1 (5)	0.22
Hypertension (%)	35 (72.9)	14 (70)	1.0
Dyslipidemia (%)	14 (32.6)	3 (15)	0.35
IHD (%)	15 (31.3)	7 (35)	0.08
PVD (%)	13 (29.5)	5 (26.3)	1.00
Intraluminal shunting (%)	34 (79.1)	4 (20)	<0.01
Mean clamping time (mins)	10.15 (1.5)	23.45 (3.6)	<0.01
Mean operative time (mins)	125.87 (4.1)	98.95 (7.2)	0.01

N: total number, GA: general anesthesia, LA: local anesthesia, DM: diabetic mellitus, MI: myocardial infarction, IHD: ischemic heart disease, PVD: peripheral vascular disease, mins: minutes.

hypothesized that LA and GA would have a different effect on urinary neopterin, which in turn may be an indicator of the potential risk of mortality following surgery.

2. Materials and Methods

A prospective, nonrandomised study was conducted of 68 consecutive patients, admitted electively to the Vascular Unit at the University Hospital of Southampton for CEA. The indications in this symptomatic group were moderate to severe carotid stenosis on duplex scan (50–99%). In equivocal cases, CT angiograms were performed. Patients under LA were sedated and the neck was blocked by using superficial cervical nerve block together with local infiltration. The requirement for a shunt in patients under LA was if the patient developed a contralateral hemiparesis or became uncooperative following temporary carotid artery clamping, ("awake testing"). In the GA group shunts were used routinely by some surgeons and selectively by others based on cerebral monitoring with transcranial Doppler ultrasound. All procedures were performed by one of the four consultant vascular surgeons or surgical trainees under supervision. Surgical techniques used were at the discretion of the individual consultant. The majority of operations were performed by conventional procedures with selective patching. A minority used eversion techniques.

Urine samples (20 mls) were collected from all patients during the preoperative, immediate postoperative (PO), 6-hour PO, 12-hour PO, and 24-hour PO and stored at −20°C. The urinary neopterin was measured by isocratic reverse-phase liquid chromatography with a fluorescence detector at a wavelength of 353 nm for excitation and 438 nm for emission. Creatinine levels were determined at the same time by using an ultraviolet detector at a wavelength of 235 nm. Neopterin was expressed as micromoles of neopterin per mole of creatinine. All baseline clinical data was recorded. The postoperative 30-day outcome including stroke, myocardial infarction (MI), and death were recorded.

Table 2: Mean neopterin (standard error of the mean) in 5 different periods in perioperative CEA (μmol/mol creatinine).

Timing	GA $N = 48$	LA $N = 20$	P value
Before operation	107.7 (9.2)	104.4 (7.1)	0.81
After operation			
(i) Immediate	89.8 (7.9)	63.5 (6.2)	0.62
(ii) 4 hours	87.1 (8.8)	120.4 (39.7)	0.28
(iii) 6 hours	85.3 (8.5)	123.4 (11.5)	0.02
(iv) 12 hours	116.9 (16.0)	118.11 (13.9)	0.97
(v) 24 hours	102.0 (6.8)	116.1 (8.4)	0.24

Results for the GA and LA group were compared using the chi-squared test (or Fisher's exact test) for categorical data and the student t-test for continuous data. A P value less than 0.05 was considered statistically significantly. All analyses were carried out with SPSS version 17.0 software. The Local Research Ethics Committee approved the study.

3. Results

During the study period, 68 CEAs were performed, with 48 operations (66.3%) carried out under GA. The baseline clinical data was not different between groups (Table 1). The rate of intraluminal shunting in GA was significantly higher than those under LA (79.1% and 21.1%, resp.). In this study, there was 1 postoperative stroke (in GA group) and no deaths. The stroke/death rate was not different between GA and LA. Immediately after CEA, the level of urinary neopterin tended to be higher in GA than those under the LA group. However after this, the level of urinary neopterin rose more quickly in the LA group and reached a peak at 6 hours after CEA. At this point, the level of urinary neopterin was significantly higher in LA than in GA (Figure 1). The urinary neopterin levels in the GA group (85.3 μmol/mol creatinine) were significantly lower than those under the LA group (123.4 μmol/mol creatinine) ($P = 0.02$) (Table 2). Also at this point, when analyses only in the LA group, the level of urinary neopterin levels in patients with shunting insertion (positive awake testing group) was lower than that in those without shunting (105.9 and 131.1 μmol/mol creatinine resp.). However this trend were not reach statistically significant.

4. Discussion

We found as was expected that the level of urinary neopterin levels rose in patients after CEA. In the LA group the postoperative rise in neopterin was significantly greater than the GA group at 6 hours PO. A strong association between

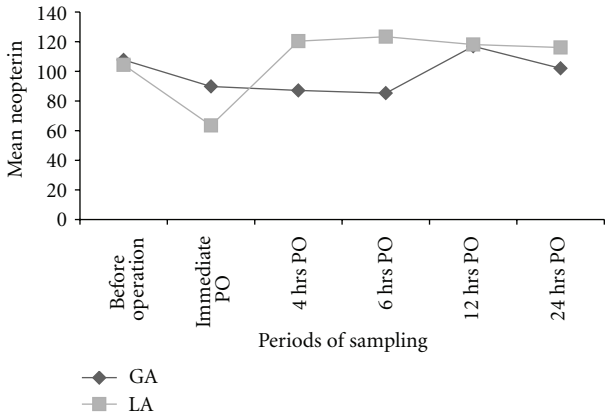

Figure 1: Graph showed the mean neopterin (μmol/mol creatinine) in 5 different periods (before operation, immediate postoperative period (PO), 4 hrs PO, 6 hrs PO, 12 hrs PO, and 24 hrs PO).

urinary neopterin levels and multiple organ failure and death has been reported in other studies [10, 11].

The mechanism of the elevation of urinary neopterin in LA is unclear. Neopterin is a pteridine derivative and is released by mononuclear white blood cells into plasma and body fluid during or after surgery [10]. It is recognized as a marker of cell mediated immunity [10]. The production of neopterin is stimulated mostly by interferon γ and tumor necrotic factor α following various stressors, such as severe trauma, elective surgery, and sepsis [8]. Neopterin is a stable substance and can be found easily in various body fluids including urine. Therefore it has been used as an important tool to monitor activated cellular immune response and disease progression [9]. Kaufmann and colleagues studied the association between the levels of plasma neopterin and the severity of pancreatitis. They found that the neopterin levels were significantly higher in severe pancreatitis, such as pancreatic necrosis, than in those were in a milder form of the disease. Also the levels of neopterin with a positive correlation with the acute physiology score. Neopterin levels may be useful in predicting prognoses of patients. The high level of urinary neopterin in patients undergoing CEA under LA is surprising. It may be related to stress and pain during the operation. However, other than the anesthesia the major difference between the groups was the frequency of the use of a shunt. In the LA group, we found that the levels of urinary neopterin in shunting group (positive awake test group) tend to be lower than those in nonshunting group. Perhaps the increased neopterin levels in LA group may indicate that negative awake testing may not be sensitive enough to detect more subtle periods of relative cerebral ischemia; however this point needs further investigation.

5. Limitations

Although the differences between the 2 groups were marked, this is a small study and conclusions are limited due to this. The effect of the different anesthetic agents on urinary neopterin levels is not fully understood.

6. Conclusion

We found that the levels of urinary neopterin after operations in LA during CEA were significantly higher than those under GA. This may suggest that other factors affect patients undergoing CEA under LA which increase the immunological response to the surgical procedure. Greater understanding of these effects may allow surgeons to reduce the risk of postoperative complications.

Conflict of Interests

The authors declared that there are no conflict of interests.

Authors' Contribution

All authors made substantial contributions from designing, data collection and analysis, and drafting of the paper.

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