



Is Heparin Reversal with Protamine after Carotid Endarterectomy Dangerous?

D. Dellagrammaticas^a, S.C. Lewis^b, M.J. Gough^{a,*},
On behalf of the GALA Trial Collaborators

^a Leeds Vascular Institute, The General Infirmary at Leeds, United Kingdom

^b Division of Clinical Neurosciences, University of Edinburgh, United Kingdom

Submitted 28 October 2007; accepted 21 January 2008

Available online 11 April 2008

KEYWORDS

Carotid
endarterectomy;
Heparin;
Protamine sulphate

Abstract *Objective:* Although systemic heparinisation is routine during CEA, reversal with protamine is controversial with 3 studies suggesting increased peri-operative stroke rates and 3 no effect. None included independent peer-review.

Design: Non-randomised observational study of data derived from a randomised controlled study of anaesthetic technique for CEA.

Methods: Data on heparin and protamine use and risk factors potentially influencing CEA outcome were collected prospectively. Stroke, death, MI, wound haematoma and re-operation rates were recorded following independent peer-review.

Results: 1513/2107 patients received heparin alone (H) and 594/2107 had heparin reversed with protamine (H+P). Risk factors for outcome were similar in both groups. The frequency of outcome events (H v H+P) were: stroke: 67/1513 (4.4%) v 17/594 (2.9%), $p = 0.098$; non stroke or MI death: 10/1513 (0.7%) v 5/594 (0.8%), $p = 0.657$; MI: 6/1513 (0.4%) v 3/594 (0.5%), $p = 0.718$; haematoma: 157/1513 (10.4%) v 44/594 (7.4%), $p = 0.037$; re-operation: 51/1380 (3.7%) v 18/565 (3.2%), $p = 0.581$.

Conclusions: These results show a non-significant increase in stroke rate in patients receiving heparin alone refuting suggestions that protamine is harmful. Conversely post-operative haematoma was more frequent when protamine was withheld but re-operation rates were no different. Thus protamine use appears safe and should remain a matter for individual surgeon preference.

© 2008 European Society for Vascular Surgery. Published by Elsevier Ltd. All rights reserved.

* Corresponding author. Mr. M. J. Gough, Leeds Vascular Institute, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, United Kingdom. Tel.: +44 113 39 22823; fax: +44 113 39 22624.

E-mail address: michael.gough@leedsth.nhs.uk (M.J. Gough).

Introduction

Administration of heparin to achieve a systemic anticoagulation prior to application of the vascular clamps during carotid endarterectomy is routine. However its subsequent

reversal with protamine sulphate is controversial. The decision to use protamine depends on the perceived risk of bleeding from the wound or suture line and subsequent haematoma formation, against the potential risk of promoting thrombosis at the endarterectomy site and ischaemic stroke. Other side-effects of protamine use (anaphylaxis, transient hypotension, pulmonary hypertension) are rare and appear to be related to the much higher doses of the drug that are given following cardio-pulmonary bypass.

Three studies have associated the use of protamine with an increased stroke risk. The randomised prospective study by Fearn *et al.*,¹ whilst investigating the effect of protamine on the development of wound haematoma noted 2 strokes in the patients receiving protamine and none in those who did not. The study was discontinued early after recruiting 63 patients. This was prompted in part by the publication of a retrospective study of 348 patients² which reported a significantly increased risk of stroke when protamine was given. A further retrospective study by Levison *et al.*³ also suggested an association between protamine and stroke risk, although no statistical significance was demonstrated. Stroke risk notwithstanding, the study by Fearn *et al.*¹ demonstrated a significant decrease in wound drainage with protamine use and that of Levison *et al.*³ identified a significant reduction in the incidence of wound haematoma. Treiman *et al.*,⁴ in another retrospective study, found a significant reduction in haematoma rates without associated stroke risk. Two further retrospective studies from the USA reporting on the association of processes of care with outcome following carotid endarterectomy did not find an association between protamine use and adverse outcome.^{5,6}

In an attempt to clarify the role of protamine in CEA, the effect of its use on outcome was examined in an analysis of data from 2158 patients participating in the ongoing GALA Trial, a multicentre prospective randomised trial of general (GA) versus local (LA) anaesthesia in carotid endarterectomy.

Methods

In the GALA Trial ~ (multicentre international randomised trial of general versus local anaesthetic for carotid endarterectomy) centres perform CEA according to their normal practice; the Trial is prescriptive only in that the use of a shunt in patients randomised to receive LA should be determined by awake neurological testing.

Data regarding demographics, indication for surgery and details of each procedure were collected prospectively. The 30-day outcome was independently assessed by a stroke physician or neurologist. Data on the main outcome events, including stroke, death, myocardial infarction, haematoma and re-operation were forwarded to the Trial office. Unblinded data (excluding the type of anaesthetic and shunt use) was provided for this study. Statistical analysis was performed using the chi-squared test (or Fisher's exact test for small samples where appropriate) for nominal data and the Mann-Whitney U test for non-normal distributions of continuous data, using a proprietary statistics software package (SPSS 12.0.1). Multivariable logistic regression was

performed using SAS version 9.1.3, with all variables of interest being added to the model concurrently.

Results

Of 2158 randomised patients, 2107 received heparin, of whom 594 had this reversed with protamine. Demographic details and the indication for surgery for each group are shown in Table 1. Details of surgery are shown in Table 2.

The groups were well matched for age, sex, endarterectomy technique, patch use, duration of surgery, grade of operating surgeon and severity of contralateral carotid stenosis. The severity of the ipsilateral stenosis (assessed primarily by duplex ultrasound based on NASCET criteria) was greater in patients who did not receive protamine (median $\pm$ IQR: 84.5% (75.0–90.0) v 80.0% (75.0–90.0), $p = 0.029$ and there were more asymptomatic patients in the protamine group (255/594 v 418/1513 $p < 0.001$).

The stroke rate in the protamine group was 2.9%, compared to 4.4% in the group receiving heparin only (Table 3). This difference was not statistically significant, and the effect remained in the same direction, and non-statistically significant after adjusting for potential confounding variables (Table 4). Similarly protamine administration had no impact on non-stroke or MI death, MI, and re-operation rates (Table 3) but was associated with a lower frequency of wound haematoma (7.4% vs. 10.4% $p = 0.037$).

Data regarding the precise dose of heparin and protamine was available in 1824/2107 (86.6%) and 519/594 (87.4%) patients respectively; the median dose of heparin was 5000 iu (IQR 3000–5000) whilst that of protamine was 25 mg (IQR 15–50 mg). Patients who had a stroke (69/1824) received a lower median dose of heparin (4000 iu [3000–5000] vs. 5000 iu [3000–5000], $p = 0.026$), whilst those requiring re-operation (17/491) had received a lower dose

Table 1 Comparison of demographic characteristics and indication for surgery

	Protamine	No Protamine	<i>p</i> value
Age in years (mean)	70.0	70.4	0.335 [†]
Median (IQR)	71.0 (64.0–76.0)	71.5 (64.6–76.9)	
Sex			
Male	403	1067	0.229*
Female	191	446	
% ipsilateral carotid stenosis			
Median (IQR)	80.0 (75.0–90.0)	84.5 (75.0–90.0)	0.029 [†]
% contralateral carotid stenosis			
Median (IQR)	40.0 (10.0–67.5)	40.0 (0.0–70.0)	0.860 [†]
Contralateral occlusion (%)	58 (9.8)	152 (10.1)	0.846*
Asymptomatic (%)	255 (42.9)	418 (27.6)	<0.001*

* chi-squared test.

[†] Mann-Whitney U test.

Table 2 Comparison of details of procedure

	Protamine	No protamine	<i>p</i> value
Type of surgery (%) (<i>n</i> = 1835)			
Conventional	408 (78.4)	1053 (80.1)	0.438*
Eversion	104 (20.0)	250 (19.0)	
Other	8 (1.5)	12 (0.9)	
Grade of surgeon (%)			
Consultant	510 (85.9)	1257 (83.1)	0.119*
Trainee	84 (14.1)	256 (16.9)	
Use of patch (%)	296 (50.0)	699 (46.5)	0.146*
Duration of surgery (mean)	96.2 min	94.7 min	0.860 [†]
Median (IQR)	90.0 (70.0–113.5)	90.0 (70.0–120.0)	

* chi-squared test.

[†] Mann-Whitney U test.

of protamine than those who did not (25 mg [10–25] v 25 mg [15–50], *p* = 0.046, Mann-Whitney U test).

Discussion

Although this is not a randomised study assessing the risks and benefits of protamine use during carotid endarterectomy, it is a large observational study of patients undergoing surgery in Europe during the last 5 years. Thus we believe that the results are applicable to current practice. Further, the occurrence of stroke, death and MI were monitored by an independent neurologist, which adds further weight to the validity of these results.

We have found no association between the use of protamine and serious adverse events. In particular, stroke rates were slightly lower in patients receiving protamine. This group also had a significant reduction in the frequency of wound haematoma. These data challenge earlier suggestions that protamine increases the thromboembolic complications of carotid endarterectomy^{1–3} and is in agreement with data from the USA which reported no association between protamine administration and an adverse outcome.^{5,6} Further, it should be noted that the studies reporting an adverse effect of protamine were flawed for

Table 3 Summary of major outcome data

	Protamine	No Protamine	<i>p</i> value
Stroke or Retinal Infarction (%)	17 (2.9)	67 (4.4)	0.098*
Non-stroke death (%)	5 (0.8)	10 (0.7)	0.657*
Myocardial infarction (%)	3 (0.5)	6 (0.4)	0.718 [†]
Stroke, Death or MI (%)	25 (4.2)	83 (5.5)	0.232*
Haematoma (%)	44 (7.4)	157 (10.4)	0.037*
Re-operation (%)	18 (3.2)	51 (3.7)	0.581*

* chi-squared test.

[†] Fisher's Exact test.

a number of reasons. The studies by Mauney *et al*² and Levison *et al*³ were both retrospective historical studies in single-centre institutions. Mauney *et al*,² whilst showing a statistically significant increase in stroke rate associated with protamine use, reported only 5 strokes in 348 patients, and acknowledged the limited statistical power of their findings. Similarly Levison *et al*³ reported only 10 strokes out of 407 CEAs, and their suggestion of increased risk with protamine use failed to reach statistical significance. The study by Fearn *et al*,¹ although prospective and randomised, was also small (only 64 CEAs). It showed a non-significant risk of ICA thrombosis with protamine use although interestingly, in these patients a patch was used less often. Finally, none of these studies employed independent postoperative assessment of patients by a stroke physician or neurologist.

Because this is a non-randomised study some inconsistencies are inevitable. Thus, surgery for an asymptomatic stenosis was more common in the group receiving protamine and, as expected, stroke rates were lower in asymptomatic compared to symptomatic patients in the study as a whole (2.4% vs 4.7% *p* = 0.01 chi-squared test). The impact of this on the results has been assessed by multivariate analysis of potential confounding variables (Table 4). In contrast, other factors that might influence the outcome of surgery (type of surgery, duration of surgery, patch use, grade of surgeon, contralateral occlusion)

Table 4 The relationship between stroke outcome and protamine use with adjustment for other potentially confounding variables using multivariable logistic regression analysis

Variable	Stroke (<i>N</i> = 84)	No Stroke (<i>N</i> = 2023)	Odds ratio (95% confidence interval)	Wald <i>p</i> value
Protamine used (<i>N</i> and %)	17 (20%)	577 (29%)	0.79 (0.40, 1.56)	0.505
Heparin dose [IU] (mean and s.d.)	4486 (2494)	4992 (2890)	1.00 (1.00, 1.00)	0.538
Age (mean and s.d.)	70.5 (8.5)	70.3 (8.8)	0.99 (0.97, 1.02)	0.741
% contralateral carotid stenosis (mean and s.d.)	82.9 (10.7)	81.6 (10.3)	1.01 (0.99, 1.04)	0.269
Duration of surgery in minutes (mean and s.d.)	94.2 (40.4)	95.1 (34.8)	1.00 (0.99, 1.01)	0.988
Asymptomatic (<i>N</i> and %)	16 (19%)	657 (32%)	0.51 (0.28, 0.93)	0.027

were equally distributed between the heparin only and heparin + protamine groups (Table 2).

Although protamine use did not impact on stroke, MI and death rates its omission did increase the incidence of wound haematoma (Table 3) although this was not reflected by an increased need for re-operation. Whilst a strict definition of haematoma was not used, the need for re-operation is more likely to be of clinical relevance. The influence, if any, of pre-operative antiplatelet drugs on wound haematoma rates has not been assessed since this data was not collected during the pilot phase of the Trial when approximately 700 of these patients were recruited.

It is not known whether the study groups were equally matched for the use of a shunt. This data was not made available for the analysis due to the concern that it might partially unblind the allocation of anaesthesia, especially in centres which routinely shunted during GA. Nevertheless a recent meta-analysis has failed to identify a relationship between a policy of never, selectively or routinely shunting and the risk of stroke during CEA.⁷

In conclusion this study shows no association between the use of protamine and adverse outcome following carotid endarterectomy. These findings should reassure surgeons who use protamine during surgery that it appears safe to do so.

Acknowledgements

The GALA Trial is funded by the Health Foundation and has received financial support from the European Society for Vascular Surgery.

Details of the GALA Trial protocol and participating centres can be viewed online at www.galatrial.com.

References

- 1 Fearn SJ, Parry AD, Picton AJ, McCollum CN. Should heparin be reversed after carotid endarterectomy? A randomised prospective trial. *Eur J Vasc Endovasc Surg* 1997;13: 394–7.
- 2 Mauney MC, Buchanan SA, Lawrence WA, Bishop A, Sinclair K, Daniel TM, et al. Stroke rate is markedly reduced after carotid endarterectomy by avoidance of protamine. *J Vasc Surg* 1995; 22:264–9.
- 3 Levison JA, Faust GR, Halpern VJ, Theodoris A, Nathan I, Kline RG, et al. Relationship of protamine dosing with postoperative complications of carotid endarterectomy. *Ann Vasc Surg* 1999;13:67–72.
- 4 Treiman RL, Cossman DV, Foran RF, Levin PM, Cohen JL, Wagner WH. The influence of neutralizing heparin after carotid endarterectomy on postoperative stroke and wound haematoma. *J Vasc Surg* 1990;12:440–6.
- 5 Hannan EL, Popp AJ, Feustel P, Halm E, Bernardini G, Waldman J, et al. Association of surgical specialty and processes of care with patient outcomes for carotid endarterectomy. *Stroke* 2001; 32:2890–7.
- 6 Kresowik TF, Bratzler DW, Kresowik RA, Hendel ME, Grund SL, Brown KR, et al. Multistate improvement in processes and outcomes of carotid endarterectomy. *J Vasc Surg* 2004; 39:372–80.
- 7 Bond R, Rerkasem K, Rothwell PM. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). *Cochrane Datab Syst Rev* 2001;(Issue 4). Art. No.: CD000190. doi:10.1002/14651858.CD000190.