Protamine reduces bleeding complications associated with carotid endarterectomy without increasing the risk of stroke

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Objectives: **Controversy persists regarding the use of protamine during carotid endarterectomy (CEA) based on prior conflicting reports documenting both reduced bleeding as well as increased stroke risk. The purpose of this study was to determine the effect of protamine reversal of heparin anticoagulation on the outcome of CEA in a contemporary multistate registry.**

Methods: **We reviewed a prospective regional registry of 4587 CEAs in 4311 patients performed by 66 surgeons from 11 centers in Northern New England from 2003-2008. Protamine use varied by surgeon (38% routine use, 44% rare use, 18% selective use). Endpoints were postoperative bleeding requiring reoperation as well as potential thrombotic complications, including stroke, death, and myocardial infarction (MI). Predictors of endpoints were determined by multivariate logistic regression after associated variables were identified by univariate analysis.**

Results: **Of the 4587 CEAs performed, 46% utilized protamine, while 54% did not. Fourteen patients (0.64%) in the protamine-treated group required reoperation for bleeding compared with 42 patients (1.66%) in the untreated cohort ($P = .001$). Protamine use did not affect the rate of MI (1.1% vs 0.91%, $P = .51$), stroke (0.78% vs 1.15%, $P = .2$), or death (0.23% vs 0.32%, $P = .57$) between treated and untreated patients, respectively. By multivariate analysis, protamine (odds ratio [OR] 0.32, 95% confidence interval [CI], 0.17-0.63; $P = .001$) and patch angioplasty (OR 0.46, 95% CI, 0.26-0.81; $P = .007$) were independently associated with diminished reoperation for bleeding. A single center was associated with a significantly higher rate of reoperation for bleeding (OR 6.47, 95% CI, 3.02-13.9; $P < .001$). Independent of protamine use, consequences of reoperation for bleeding were significant, with a four-fold increase in MI, a seven-fold increase in stroke, and a 30-fold increase in death.**

Conclusion: **Protamine reduced serious bleeding requiring reoperation during CEA without increasing the risk of MI, stroke, or death, in this large, contemporary registry. In light of significant complications referable to bleeding, liberal use of protamine during CEA appears warranted. (J Vasc Surg 2010;51:559-64.)**

Thromboembolic events are a significant cause of perioperative stroke during carotid endarterectomy (CEA).[1] In an attempt to minimize this and other periprocedural complications, details of surgical technique have been the focus of considerable attention.[2-7] One area of continued controversy is whether to reverse heparin anticoagulation with protamine sulfate during CEA.

Protamine proponents cite the benefit of diminished bleeding complications without increasing the risk of stroke or other thrombotic complications.[8-10] Surgeons who do not use protamine cite the potential for increased thrombotic complications including stroke or myocardial infarction (MI), or anaphylactic reactions to protamine,[11] with an acceptably low incidence of bleeding complications without using protamine.[12,13]

Despite substantial literature devoted to CEA, data remain conflicted about the safety and efficacy of protamine use. Two reports addressing the use of protamine during CEA documented an increased association of stroke with protamine administration.[12,13] By comparison, three reports document diminished bleeding associated with protamine use during CEA without an increased risk of stroke.[8-10] Differences in these studies may reflect relatively small sample sizes from single-center experiences. Given the low incidence of both bleeding complications and stroke during CEA, these studies may have been underpowered to reach definitive conclusions. The purpose of this study was to use a large multistate registry to examine the impact of protamine use during CEA. Specifically, we sought to determine whether protamine had an effect on the incidence of bleeding complications, measured as reoperation for bleeding, as well as an impact on the incidence of thrombotic complications, measured as MI, stroke, and death.

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METHODS

Subjects and database. This study reflects data collected in the prospectively compiled registry of the Vascular Study Group of Northern New England (VSGNNE). This effort represents a regional cooperative quality improvement initiative started in 2003 to study vascular surgery outcomes.[14,15] Patients were treated at 11 academic and community centers (Appendix I, online only) by 66 participating surgeons. Trained clinical data abstractors, nurses, and surgeons entered data prospectively for over 70 clinical, operative, and demographic variables. All analysts were blinded to patient, surgeon, and center identification.

All CEAs performed between 2003 and 2008 were identified (n = 4672). Combined CABG/CEA procedures (n = 85) were excluded from the analysis, resulting in a study cohort of 4587 CEAs performed in 4311 patients. Heparin and protamine use during surgery were at the discretion of the operating surgeon.

Outcomes and variable definitions. The endpoints of this study were postoperative bleeding requiring reoperation (to determine a potential benefit of protamine) and postoperative MI, stroke, or death (to reflect thrombotic complications potentially associated with protamine). Anaphylactic reactions to protamine were not specifically recorded, but mortality, length of stay, and hypotension requiring intravenous (IV) medication at any time during hospitalization were recorded and were analyzed as potential surrogates for other potential serious complications of protamine administration. All endpoints were restricted to the hospitalization for CEA. The stroke endpoint included both major (defined as disability causing non-independent living status) and minor (defined as non-disabling) events. MI was defined by either troponin level or EKG changes detected during routine clinical care.

Statistical analysis. Variables associated with endpoints were initially identified by univariate analysis of potentially relevant variables using Pearson chi-square (Fisher's exact correction). Variables found to be significant at $P < .10$ were then entered into a multivariate model using backwards stepwise logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were generated for significant endpoint predictors.

To further investigate outcomes of our multivariate model, surgeon-specific cluster analysis was performed. Protamine use, stroke, and cranial nerve injury were stratified by both low and high rates of surgeon-associated reoperation for bleeding. Crainial nerve injury was selected as a proxy measure of a less "technically careful" surgeon to better identify whether these surgeons accounted for increased reoperation for bleeding. The study was conducted in compliance with the Institutional Review Board at Dartmouth Medical School.

RESULTS

During the 4587 CEAs performed, 46% (n = 2087) of the patients received intraoperative protamine while 54% (n = 2500) did not. Most procedures were performed electively, using general anesthesia, patch angioplasty, and intraoperative shunting. The majority of patients in both the protamine-treated and untreated groups were taking antiplatelet therapy (90% vs 87%, P = NS) at the time of CEA. Additional demographic details, comorbidities, and preoperative medications of the study cohort are depicted in Table I.

Table I. Demographic variables, comorbidities, and preoperative medications of protamine-treated and untreated patients

Protamine	*Yes (%)*	*No (%)*	P *value*
Age (years)	69.2	70.0	NS
Gender (male)	60	60	NS
DM	33	30	.03
HTN	87	86	NS
CAD	36	32	.01
CHF	9	7	.005
Smoking	81	80	NS
COPD	25	22	.02
Creatinine > 1.8	7	6	.1
Aspirin	87	82	.02
Plavix	21	13	.0001
Anti-platelet	90	87	NS
Statin	72	69	.07
β-blocker	83	85	NS
Elective	93	88	.0001
Any preoperative symptoms	34	38	.01
Ipsilateral preoperative symptoms	25	27	.1
Patch	91	76	.0001
General anesthesia	48	52	.001

CAD, Coronary artery disease; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *DM,* diabetes mellitus; *HTN,* hypertension.

Protamine use varied by surgeon. When stratified by frequency of use, 38% (n = 25) of surgeons used protamine routinely (defined as during more than 80% of their CEAs), 44% (n = 29) used it rarely (defined as <10% of their CEAs), and 18% (n = 12) used protamine selectively during surgery (defined as use between 10% and 80% of CEAs performed. These cutpoints were chosen to best separate the three groups based on inspection of the distribution.

Reoperation for bleeding was performed in 1.66% (n = 42) of patients who did not receive protamine compared with 0.64% (n = 14) of those who did (Fig 1). Clinical predictors that showed univariate association with diminished bleeding requiring reoperation (at $P < .10$) included intraoperative protamine use, intraoperative shunting, patch angioplasty, and general anesthesia. A history of renal insufficiency (Cr >1.8 mg/dL) and baseline low hemoglobin (defined as <9 gm/dL) were univariately associated with increased bleeding requiring reoperation. Four specific centers also demonstrated a univariate association with reoperation for bleeding. The complete univariate analysis is available as Appendix II (online only).

Multivariate logistic regression confirmed that protamine administration was an independent predictor of diminished reoperation for bleeding, after accounting for other variables, including center variation, surgical tech-

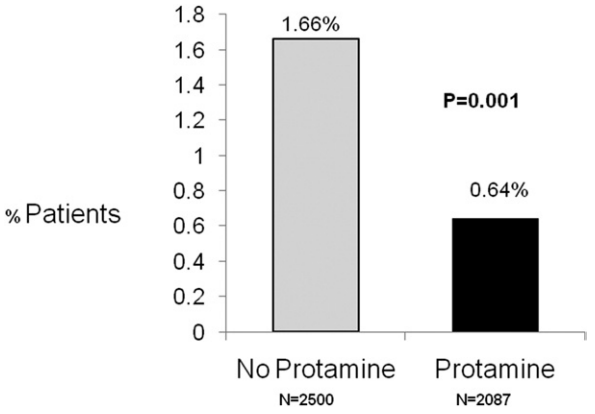

Fig 1. Reoperation for bleeding. Reoperation for bleeding was reduced three-fold in patients receiving protamine.

Table II. Significant independent predictors associated with reoperation for bleeding

		95% CI for OR		
	Odds ratio	*Lower*	*Upper*	P *value*
Protamine	0.32	0.17	0.63	.001
Patch	0.46	0.26	0.81	.007
One center	6.47	3.02	13.9	<.001

CI, Confidence interval; *OR,* odds ratio.

Table III. Surgeon-specific sub-analyses comparing the incidence of stroke and cranial nerve injury stratified by surgeons with low and high rates of reoperation for bleeding

Reoperation for bleeding	*Stroke*	*Cranial nerve injury*
Low rate (0%-3%)	0.9%	5.7%
High rate (5%-12%)	1.4%	4.8%

nique, and antiplatelet therapy (OR 0.32, $P < .001$). In addition, patch angioplasty demonstrated a significant association with diminished reoperation for bleeding (OR 0.46, $P < .007$), while a single center, with a protamine utilization rate of 63%, was associated with an increased incidence of reoperation for bleeding (OR 6.47, $P < .001$; 95% CI are listed in Table II).

The above observation that both protamine and patching reduced bleeding led to the question of whether these variables might be a proxy for more careful or expert surgeons. This led to further surgeon-specific cluster analysis (Table III). When stratified by either a low rate (0%-3%) of reoperation for bleeding versus a high rate (5%-12%) of reoperation for bleeding, there were no significant differences in the incidence of either transient cranial nerve injury (5.7% vs 4.8%) or stroke (0.9% vs 1.4%).

Thrombotic complications were not significantly affected by protamine administration. There were no significant differences in the incidence of stroke, death, or clinically apparent MI among patients who received protamine versus those who did not (Fig 2). Regardless of protamine treatment, however, the observed consequences of reoperation for bleeding were significant. There was an observed increase in the incidence of clinically significant MI among patients requiring reoperation compared with those patients who did not (3.6% vs 0.9%, $P < .05$). In addition, the incidence of stroke was greater among patients who required reoperation for bleeding (7.1% vs 0.9%, $P < .001$). Lastly, the incidence of in-hospital death among patients who required re-exploration for bleeding was notably higher compared with patients who did not require reoperation for bleeding (7.1% vs 0.19%, $P < .001$; Fig 3).

In order to identify any other potential complications of protamine use, several additional variables were examined. Protamine use was associated with a slightly higher risk of hypotension requiring IV medication by univariate analysis (11.8% vs 9.0%; $P = .008$). However, this association was not significant in our multivariate model when adjusted for potentially confounding variables (OR 0.92; 95% CI, 0.7-1.2; $P = .53$). Observed length of stay was over two-fold greater among patients who underwent reoperation for bleeding versus those who did not (2.0 vs 4.6 days, $P = .001$).

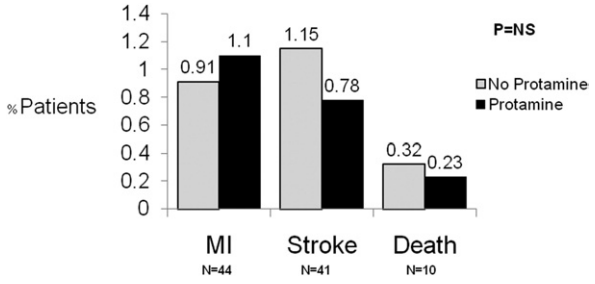

Fig 2. Thrombotic complications. There were no observed significant differences in the incidence of major thrombotic complications, including MI, stroke, and death between protamine-treated and untreated patients.

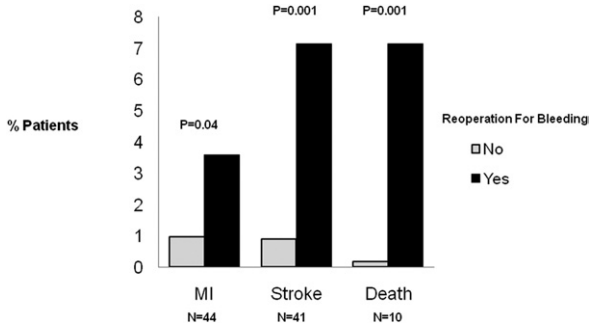

Fig 3. Consequences of reoperation for bleeding. Regardless of protamine use, the consequences of reoperation for bleeding were significant. Patients who required reoperation for bleeding had a significantly higher risk of MI, stroke, and death, compared with patients without this bleeding complication.

Table IV. Studies examining the use of protamine during carotid endarterectomy to date

Author	*Year*	*Treated patients (N)*	*Bleeding complications*	*Thrombotic complications*
Treiman et al.[10]	1990	328	Increased wound hematoma in untreated patients (6.5% vs 1.8%, $P = .004$)	No effect on CVA (1.8% vs 2.7%, $P = .6$)
Mauney et al.[13]	1995	348	No effect on significant hematoma (1.0% vs 1.9%, $P =$ NS)	Increased CVA with protamine (2.6% vs 0%, $P < .05$)
Fearn et al.[12]	1997	64	Decreased wound drainage with protamine (69 mL, vs 35 mL, $P < .001$); no change in neck swelling	Increased CVA with protamine (3 patients with ICA thrombosis)
Levison et al.[9]	1999	407	Decreased wound hematoma with protamine (1.9% vs 9.5%, $P = .02$)	Increased CVA with protamine (2.7% vs 0%, $P = .33$)
Dellagrammaticas et al.[8]	2008	594	Decreased wound hematoma with protamine (7.4% vs 10.4%, $P = .04$); no difference in reoperation with protamine (3.7% vs 3.2%, $P = .58$)	No effect on CVA (4.4% vs 2.9%, $P = .1$)
Stone et al.	2009	2087	Decreased reoperation for bleeding with protamine (0.64% vs 1.66%, $P = .001$)	No effect on CVA (0.78% vs 1.15%, $P = .2$) No effect on MI (1.1% vs 0.91%, $P = .51$) No effect on death (0.23% vs 0.32%, $P = .57$)

CVA, Cerebral vascular accident; *ICA,* internal carotid artery; *MI,* myocardial infarction.

As noted above, protamine was not associated with an increased incidence of MI, stroke, or death, which could also represent surrogate endpoints for adverse protamine reactions. Consistent with this finding, there was no observed difference in the incidence of combined MI, stroke, and death among insulin-dependent diabetic patients who received protamine versus those who did not (4.8% vs 2. 8%, $P = .3$).

DISCUSSION

This study is among the first to definitively demonstrate that protamine was associated with diminished reoperation for bleeding during CEA in a large prospective registry, without an observed increase in associated thrombotic complications, including MI, stroke, or death. Furthermore, the present study demonstrates a nearly three-fold increased rate of serious bleeding requiring reoperation among those who do not receive protamine during CEA.

As noted, controversy persists regarding the use of protamine during CEA. Previous studies on this topic are summarized in Table IV. There has been only a single randomized trial that has addressed whether protamine administration is safe during CEA.[12] In this study, 64 patients were randomized to undergo reversal of heparin anticoagulation versus no pharmacologic treatment. A total of 31 patients received intraoperative protamine and subsequently had diminished wound drainage with no impact on neck swelling compared with the untreated cohort. Perhaps more striking, however, was the finding that two protamine-treated patients acutely thrombosed their respective operated internal carotid arteries and died. Based on these findings, the authors concluded that protamine use may predispose to internal carotid artery (ICA) thrombosis and subsequent stroke. This study, however, consisted of only 64 patients, making it difficult to extrapolate definitive conclusions regarding protamine use.[12]

By comparison, a post-hoc analysis from the GALA trial (General Anesthetic Versus Local Anesthetic for Carotid Surgery Trial) examined outcomes of patients treated with protamine versus those who were untreated.[8] Specifically, the authors documented a 4.4% stroke rate among untreated patients versus 2.9% among protamine-treated patients ($P = .098$). Furthermore, the study demonstrated a statistically lower incidence of associated neck hematoma in the protamine-treated group compared with the untreated cohort (7.4% vs 10.4%; $P = .037$). The authors concluded that their findings refute the perception that protamine is associated with deleterious outcomes during CEA.

The above finding of diminished neck hematomas among treated patients in the GALA trial and the observed diminished incidence of reoperation for bleeding in our study have significant clinical implications. Historically, many surgeons have advocated CEA using aggressive anticoagulation with a tacit willingness to accept an increased associated incidence of bleeding complications.[16,17] Indeed, LaMuraglia et al, among others, note that significant hematomas were the most common complication observed in their CEA experience, although only a minority of patients required reoperation for bleeding.[16] Our study demonstrates that the sequelae of reoperation for bleeding were significant. Indeed, patients requiring reoperation for bleeding demonstrated an increased incidence of MI, stroke, and death, although the cause for this observation remains undefined. Return to the operating room with its

ensuing additional anesthetic may have an associated physiologic impact on cardiac physiology, perhaps partly accounting for the observed increased incidence in MI, although this remains speculative. An increased incidence in stroke upon return to the operating room may reflect the need for reclamping and/or operative revision with its inherent transient cerebral ischemia; however, the timing of these associated neurologic events is not recorded in this dataset, thereby limiting our conclusions regarding this association. Furthermore, the observed increase in death may reflect a myriad of etiologies including a second anesthetic, potential reclamping, and ongoing bleeding in a high-risk patient cohort. These findings highlight the importance of adequate hemostasis and we believe justify a more liberal stance toward intraoperative heparin reversal during CEA. Although protamine did not decrease the incidence of MI, stroke, or death by multivariate analysis, our study was not powered to detect such an effect, given the multiple clinical causes of these more severe endpoints. However, diminished reoperation for bleeding was significantly associated with protamine use, so by extrapolation, a beneficial effect on more severe complications related to reoperation is likely. A novel observation made by our multivariate analysis was that patch angioplasty, utilized in 91% and 76% of the treated and untreated patients, in addition to protamine, was independently associated with diminished reoperation for bleeding. To better account for this observation, surgeon-specific analyses were performed to assess whether patch angioplasty served as a proxy measure for a "careful," technically expert surgeon. When surgeon-associated reoperation for bleeding rates were subdivided into both low rates (0%-3%) and high rates (5%-12%), there was no observed statistical correlation with transient cranial nerve injury or stroke rate. This finding suggests that patch angioplasty is not likely a proxy for the more "careful" surgeon, although the explanation for a beneficial effect of patching is not clear and requires further study.

Previous reports have documented the potential for hypotension to be associated with protamine use.[18-21] It remains difficult to draw definitive conclusions regarding protamine and hypotension requiring IV medication, since blood pressure thresholds warranting therapy remained at the discretion of the attending physicians. Multivariate analysis, however, indicated that protamine was not associated with increased hypotension requiring treatment, and more severe sequelae of hypotension, such as MI, were not increased by protamine use.

This study has several limitations. First, it does not provide Level I evidence of a randomized controlled trial. However, it was adequately powered to detect a difference in low frequency complications in a "real world" practice experience that reflects both academic and community practices. Second, the dosing of protamine and heparin was not standardized, which could potentially confound outcomes. As noted by Levison et al, excessive protamine dosing may paradoxically lead to increased bleeding/hematoma formation.[9] In addition, 90% of patients receiving protamine were on antiplatelet therapy at the time of surgery, which could potentially reduce the incidence of observed thrombotic complications among patients receiving protamine. In addition, the VSGNNE registry does not record data regarding anaphylactic reactions to protamine. Although other reports have documented the incidence of significant anaphylactic protamine reactions to be quite low (0.19%-0.69%), we could only infer that this complication was rare, since it did not detract from the observed beneficial results of protamine treatment.[11] Finally, recorded strokes in this study were not neurologist-adjudicated as they were in the GALA trial report by Dellagrammaticas et al.[8] However, both studies demonstrate similar conclusions that protamine is not statistically associated with increased stroke rates. Despite these limitations, this study reports real practice outcomes among surgeons who by chance were nearly evenly split in their use of protamine, thereby approximating a random comparison, since our analysis demonstrated that the benefit of protamine persisted when controlled for individual surgeon or center effects.

CONCLUSIONS

Based on the analysis of nearly 5,000 patients, this study demonstrates that protamine is associated with significantly diminished reoperation for bleeding during CEA, without increasing thrombotic risk, as practiced in a large regional registry, reflecting both academic and community practices. Currently, further analysis is underway to examine details of heparin and protamine dosing, but in the interim, these data support the use of protamine during carotid endarterectomy, given the major consequences of reoperation for bleeding.

AUTHOR CONTRIBUTIONS

Conception and design: DS, JC, BN
Analysis and interpretation: DS, JC, BN
Data collection: DS, BN
Writing the article: DS, JC
Critical revision of the article: DS, JC, BN, DW, PG, DL, AS, RC
Final approval of the article: DS, JC, BN, DW, PG, DL, AS, RC
Statistical analysis: BN, PG
Obtained funding: JC
Overall responsibility: DS, JC

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Additional material for this article may be found online at www.jvascsurg.org.

Appendix: I, online only. Participating centers of the Vascular Study Group of Northern New England

Center	*Location*
Catholic Medical Center	Manchester, NH
Central Maine Medical Center	Lewiston, Me
Concord Hospital	Concord, NH
Cottage Hospital	Woodsville, NH
Dartmouth-Hitchcock Medical Center	Lebanon, NH
Eastern Maine Medical Center	Bangor, Me
Fletcher Allen Health Care	Burlington, Vt
Lakes Region General Hospital	Laconia, NH
Maine Medical Center	Portland, Me
Mercy Hospital	Portland, Me
UMASS Memorial Medical Center	Worcester, Mass

Appendix II, online only. Univariate predictors associated with reoperation for bleeding

	Reoperation for bleeding if present	*Reoperation for bleeding if not present*	P *value*
Center 2	1.9	0.9	.004
CHF	2.0	1.1	.1
Cr>1.8	2.2	1.1	.09
Center 8	4.8	1.0	<.001
Low Hb (<9)	6.3	1.2	.06
Center 9	0.0	1.3	.01
Center 10	0.6	1.3	.1
Protamine	0.6	1.6	.001
Shunt	0.8	1.5	.02
Patch	0.9	2.5	<.001
Statin	1.0	1.5	.10
GETA	1.0	2.2	.03

CHF, Congestive heart failure; *Cr,* creatinine; *GETA,* general endotracheal anesthesia; *Hb,* hemoglobin.