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Safety and Efficacy of Fixed-dose Heparin in Carotid Endarterectomy

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Abstract

OBJECTIVE—Although fixed dosage of heparin is frequently used during vascular surgery, there are very few studies that document the appropriateness of this type of dosing. We have undertaken a prospective study to determine the physiological response to a fixed dose of heparin, using a conventional measure of anticoagulation, and have correlated this measure with complications.

METHODS—We studied 140 consecutive patients undergoing elective carotid endarterectomy. Serial activated clotting times (ACT values) were obtained in duplicate before administration of heparin, 15 minutes after application of a carotid artery cross-clamp, and 1 hour after administration of 5000 U of heparin by intravenous bolus. Postoperatively, patients were assessed for new neurological deficits (transient ischemic attack and stroke) and neck hematomas. A battery of neuropsychometric tests was performed in 49 patients at baseline and on the day after carotid endarterectomy to identify subtle new neurological deficits.

RESULTS—ACT values were found to be highly reproducible, with less than a 1.5% difference between duplicate baseline samples. Although all patients received 5000 U of heparin, the dose received per kilogram of body weight varied considerably (44–116 U/kg), as did ACT values at both 15 minutes (178–423 s) and 1 hour (173–390 s). Nevertheless, there was a significant correlation between heparin dose per kilogram and ACT values at 15 minutes ($r = 0.45$) and at 1 hour ($r = 0.38$) postinfusion, as well as ACT ratios (final ACT/initial ACT) at 15 minutes ($r = 0.43$) and at 1 hour ($r = 0.34$) after heparin bolus. Eight patients (5.7%) developed postoperative wound hematomas, one of which (0.7%) required reoperation. No patient had a stroke, but one patient had a transient ischemic attack, and 19 (39%) of 49 patients demonstrated significant early postoperative neuropsychometric deficits. Although the incidence of neck hematoma was not influenced by the heparin dose ($P = 0.23$), the ACT value at 15 minutes ($P = 0.71$) or 1 hour ($P = 0.61$), or the ACT ratio ($P = 0.68$), the only severe hematoma requiring reoperation occurred when the maximal ACT value was more than 400 seconds. Although performance on neuropsychometric tests did not appear to be statistically influenced by heparin dosing, the ACT value, or the degree of ACT elevation, there was a trend for deficits to be associated with lower heparin doses.

CONCLUSION—Fixed heparin dosing achieves safe and efficacious anticoagulation in the great majority of patients having carotid endarterectomy, with 5000 U expected to result in 15-minute and 1-hour ACT values of 175 to 425 seconds and 170 to 390 seconds, respectively. Although weight-based heparin dosing may reduce the incidence of subtle complications (hematoma formation or decline on neuropsychometric tests) and may result in more predictable 15-minute and 1-hour ACT

values (85 U/kg; 225-375 and 200-340 s, respectively), no statistically compelling clinical advantage could be demonstrated. Therefore, either weight-based or fixed dosing is acceptable, with both obviating the need for routine pre-clamp ACT confirmation, thereby saving operative time and expense.

Keywords

Activated clotting time; Carotid endarterectomy; Heparin; Monitoring

Since heparin was first used in humans in 1935, it has been widely used as an anticoagulant for the management of various disorders of arterial and venous circulation (3,17). The activated clotting time (ACT) has been used since the early 1970s to quantify the degree of anticoagulation induced by large doses of heparin during procedures requiring extracorporeal bypass (16). ACT monitoring has been shown to be simple and inexpensive and to correlate reliably with both serum heparin concentration and partial thromboplastin time (11,15). Furthermore, several studies have suggested that the ACT value is more effective than partial thromboplastin time for monitoring the level of intraoperative anticoagulation (9,22). Nonetheless, whereas therapeutic ACT values have been established for cardiac surgery, appropriate anticoagulation for patients undergoing carotid endarterectomy (CEA) is not entirely clear (2,21).

To evaluate the safety of a fixed heparin dosing strategy, we prospectively examined a large consecutive series of patients undergoing CEA to determine the variability in the degree of ACT elevation. We also examined these patients for neck hematoma and adverse cerebrovascular events, namely transient ischemic attack (TIA) and stroke. Because the latter were expected to occur with low frequency, a neuropsychometric battery was given to a subset of patients to determine the incidence of more subtle neurological injury (12,24). We sought to evaluate the hypotheses that although fixed dosing is apparently safe, it results in marked variability in the degree of ACT elevation, and also that extremes of ACT elevation could be associated with either an increased incidence of bleeding complications, in the case of excessive anticoagulation, or more subtle cerebral dysfunction, in the case of insufficient anticoagulation.

PATIENTS AND METHODS

Study population

One hundred forty-nine consecutive patients undergoing elective CEA for "critical" (>70%) carotid artery stenosis were recruited to participate in this institutional review board-approved study. Nine patients were excluded from the study; full anticoagulation was achieved preoperatively in five patients, and not all ACT levels were obtained for four patients. The demographic characteristics of the study group are summarized in Table 1. The average age was 70.1 ± 8.8 years (standard deviation). The male-to-female ratio was 55%:45%, and the ratio of left-to-right carotid endarterectomy was also 55%:45%. Most of the patients were hypertensive (68.9%), and many had diabetes mellitus (20.4%). Nearly half had had a previous stroke or TIA (47.9%), and almost one-quarter had sustained a previous myocardial infarction (22.8%). Twelve percent had undergone previous CEA on the opposite side, but none had undergone a prior CEA on the same side.

Anesthesia

No patient was premedicated. Standard monitors, including an intra-arterial catheter, were applied. All hemodynamic data and temperature were monitored continuously and recorded every minute by a personal computer-based data acquisition system (Lifelog; Modular Instruments, Rosemont, PA) or manually in a small number of cases. In addition, continuous

eight-channel electroencephalographic (EEG) monitoring was performed on all patients (Neurotrac II; Telefactor Corp., West Conshohocken, PA). After the internal carotid artery was cross-clamped, a significant EEG change was defined as a 50% or greater decrease in amplitude in the alpha or beta frequencies and a similar increase in the delta or theta frequencies, or complete loss of all cerebral electrical activity. General anesthesia was induced exclusively with fentanyl/midazolam (average total doses [standard deviation], $2.3 \pm 0.9 \mu\text{g/kg}$ and $0.05 \pm 0.14 \text{ mg/kg}$, respectively) and vecuronium ($6.5 \pm 4.9 \text{ mg}$) or rocuronium ($82.5 \pm 27.5 \text{ mg}$); and maintained with isoflurane $[0.2\text{-}0.5]_{\text{exp}}$ as tolerated. The doses of fentanyl and midazolam were $3.3 \pm 0.9 \mu\text{g/kg}$ and $0.04 \pm 0.01 \text{ mg/kg}$, respectively. The same team of anesthesiologists (EJH, DCA) performed the administration of all anesthesia.

Surgery

All operations were performed by one of three surgeons (DOQ, RAS, ESC) using a similar technique. A shunt was used only if significant EEG changes were noted, as described above. After intravenous administration of heparin (5000 U), the common, internal, and external carotid arteries were occluded. All vessels were repaired primarily with backbleeding of the common, internal, and external carotid arteries before placing the final running 6-0 Prolene sutures (Ethicon, Inc., Somerville, NJ). During the repair, irrigation with heparinized saline was used. Clamps were sequentially removed from the external, common, and internal carotid arteries. The duration of surgery and cross-clamp times were recorded as 147.1 ± 45.5 minutes and 36.0 ± 10.4 minutes, respectively.

ACT

For measurement of ACT, fresh whole blood was added to a Celite-containing test tube for surface activation of factors XII and XI. The time to clot was then measured using Hemochron 8000 (Technidyne Corp., Edison, NJ). All samples (2 ml each) were drawn from the radial arterial line after removal of 10 ml of "waste." Samples were drawn at three time points. Two baseline samples were drawn at some time before the administration of heparin; one sample was obtained 15 minutes after clamping of the carotid artery, and one sample was obtained 1 hour after administration of a 5000-U heparin dose. The degree of ACT elevation was expressed both as an ACT ratio and as an actual ACT value. The ACT ratio was calculated as the ACT value at 15 minutes or 1 hour (ACT_i), divided by the baseline value (ACT_b).

Cervical hematoma identification

All patients were examined in the early postoperative period and again at 1 week for the presence of a neck hematoma. Hematomas were considered significant if they were large enough to cause symptoms such as pain, resulted in more than one postoperative dressing change, or required reoperation.

Clinical neurological examination

Any new neurological finding was determined independently by the surgeon and a board-certified neurologist. These new neurological deficits were in turn confirmed by at least one other observer. Deficits were coded as strokes if they persisted for more than 24 hours or as transient ischemic attacks if they resolved within this time period. No reversible ischemic neurological deficit ("RIND") designation was used.

Neuropsychometric evaluation

A battery of neuropsychometric tests (NPMTs) was administered before and 24 hours after surgery. Eight scores were generated from this battery of four NPMTs, each of which was chosen to evaluate a different cognitive domain: Halstead-Reitan trail-making test (Parts A and B), finger-tapping test for dominant and nondominant hands, grooved pegboard test for

dominant and nondominant hands, and Buschke selective reminding test scored for long-term retrieval and consistency of long-term retrieval (1,5,14). Using “event rate” analysis, each patient’s overall neuropsychometric performance was assessed by comparing preoperative and postoperative scores for each test (difference scores). Significant decline for any individual test was present if there was a 25% or greater decrease in postoperative performance, compared with preoperative performance. On the basis of previous work by our group, we considered decreases in three or more tests to be a sign of significant subclinical cerebral injury, as corroborated by serum markers of neuronal injury (namely, neuron-specific enolase) (12). Others have confirmed these findings and have shown that significant subclinical injury can be correlated with new magnetic resonance imaging evidence of stroke (6). In addition, our group has recently shown that age-, sex-, anesthetic-, and risk factor-matched operative controls do not exhibit these severe testing abnormalities (8).

Statistical analysis

The relationship of heparin dosage (in units per kilogram of body weight) to the ACT values and the number of significantly decreased NPMTs was evaluated, using linear regression analysis. The analysis of wound hematoma incidence and ACT levels was performed using Student’s *t* test. Statistical analyses were performed and graphs were generated using Microsoft Excel software (Microsoft, Inc., Redmond, WA). ACT values are expressed as means $\pm$ standard deviation.

RESULTS

The baseline ACT values were 142 ± 13 seconds (range, 96-203 s). Paired baseline values differed by 1.5%. Mean heparin doses were 72 ± 13 U/kg (range, 44-116 U/kg).

Intraoperative ACT elevation: dose response

The average ACT value increased to 273 ± 44 seconds (1.94 ± 0.31 times baseline; range, 1.26-3.00 times baseline) at 15 minutes and then declined to 245 ± 37 seconds (1.72 ± 0.32 times baseline; range, 1.24-2.86 times baseline) at 1 hour after the administration of heparin (Fig. 1). There was a dose-dependent relationship between the amount of heparin administered (per kilogram) and the ACT values at both 15 minutes ($r = 0.45$) (Fig. 2A) and 1 hour ($r = 0.38$) (Fig. 2B) after heparin administration. Although this dose-dependent relationship still existed when the heparin dose was correlated to the degree of ACT elevation ($r = 0.43$ at 15 min, and $r = 0.34$ at 1 h) (Fig. 3), it is clear that individual patient responses to similar doses could vary dramatically.

Owing to the extreme variability in individual response to heparin and the marked variation in the dose received, both excessive and insufficient anticoagulation were observed, as measured by ACT values. At 15 minutes, 4 to 6% of patients had ACT values more than 2.5 times control levels or more than 350 seconds. Even at 60 minutes, this excessive anticoagulation was present in 2 to 5% of patients (as defined by an ACT level >2.5 times control levels or >300 s). On the other hand, at 15 minutes, ACT values of less than 200 seconds or 1.5 times control levels were found in 3 to 6% of patients, and by 60 minutes, the proportion had increased to 11 to 18% of patients.

Association with complications

Cervical hematoma—Eight patients (6%) had significant postoperative hematomas, one of which required evacuation (0.7%). Although hematomas occurred relatively infrequently, patients receiving heparin at doses of 90 U/kg or more ($n = 12$) demonstrated a threefold increase (16% versus 5%; $P = 0.1$) in incidence compared with those receiving less than 90 U/kg (Table 2A). Furthermore, although there were no hematomas in patients receiving 80 to 89

U/kg, hematomas did occur at doses of less than 80 U/kg, suggesting that the degree of heparinization is probably only one factor in their occurrence. In fact, the multifactorial nature of cervical hematoma formation and the small overall sample size made further comparisons statistically nonsignificant; only trends to higher absolute ACT values were observed for hematoma patients in comparison to nonhematoma patients, and no difference was observed in relation to dose received or ACT ratios (Fig. 4). It is notable, however, that the highest ACT level at both 15 minutes (423 s) and 1 hour (390 s) resulted in the one hematoma requiring reoperation. Interestingly, this patient presented with a normal baseline ACT value (141 s) and received a reasonable heparin dose (92 U/kg). This patient also developed neuropsychological dysfunction in the early postoperative period.

Neuropsychometric deficit—No deaths, no strokes, and only one instance of clinical cerebral TIA in the immediate postoperative period occurred; therefore, no meaningful analysis regarding the effect of varying doses of heparin could be made. Cerebral dysfunction, as defined by more than two abnormal NPMTs, occurred in 39% of the patients tested (19 of 49 patients). Although the heparin dose as well as the ACT level at both 15 minutes and 1 hour were similar for those with and without cerebral dysfunction, the incidence of deficits in singly operated patients was 14% (1 of 7 patients) in those receiving heparin at a dose of 80 U/kg or more, compared with 40% (17 of 42 patients) in those receiving less (*P* not significant) (Table 2B). Furthermore, patients receiving 60 to 79 U/kg had a 37% incidence versus a 50% incidence for those receiving 44 to 59 U/kg (*P* not significant). Finally, it is notable that the one patient who had a cerebral TIA also demonstrated neuropsychological decline and was found to have received a somewhat reduced dose of heparin (68 U/kg); despite adequate ACT levels (289 s at 15 min; 240 s at 1 h), his ACT ratios were much lower than are thought to be ideal (1.6 at 15 min; 1.3 at 1 h).

DISCUSSION

A fixed heparin dose of 5000 U achieves a safe and effective level of anticoagulation in all patients, as evidenced by low rates of clinically significant neurological injury (stroke/TIA, 0.7%) and adverse outcomes (hematoma requiring reoperation, 0.7%) in our study group. Heparin works primarily by acceleration and potentiation of the action of antithrombin III, to which it binds, producing a conformational change in the antithrombin III complex (22). This complex inactivates clotting factors of the intrinsic coagulation cascade (thrombin, Xa, XIIa, XIa, and IXa). In addition, heparin inhibits coagulation by inducing thrombin inactivation via heparin cofactor II at extremely high concentrations and inhibits the function of platelets by binding to them (22). ACT and activated partial thromboplastin time (aPTT) are the two common methods of measuring the degree of anticoagulation due to heparin administration. Both tests measure the intrinsic and common pathways of coagulation. Although either of these assays can be used to monitor the effects of heparin on anticoagulation, both have limitations and may be affected by binding of heparin to platelets, macrophages, fibrin, protein, and endothelial surfaces (13). There is some controversy regarding which test accurately predicts the degree of anticoagulation. However, numerous studies suggest that ACT, as opposed to aPTT, maintains accuracy at higher heparin concentrations, such as those encountered during cardiopulmonary bypass and CEA, and that determinations of ACT can be obtained more rapidly (4,4a,7,18-20). Furthermore, a linear relationship exists between ACT and heparin plasma concentrations, as opposed to a log-linear relationship between aPTT and heparin concentrations (7). Empirically, this should allow for tighter control of dose response changes when ACT is used than when aPTT is used (22).

Individual responses to given amounts of heparin vary greatly from person to person. There are many known causes for this variability. Heparin acts on all three stages of clot formation: generation of thromboplastin, conversion of prothrombin to thrombin, and enzymatic

conversion of fibrinogen to fibrin. The degradation of heparin is thought to occur through several enzymatic pathways in the liver as well as the reticuloendothelial system. Any alteration or variation in these enzymatic networks will cause either active heparin consumption or resistance (10). Although ACT levels varied substantially in response to a given dose of heparin in our study, an overall dose-dependent rise in ACT level was observed. The range of maximal ACT levels observed in our study group was consistent with findings in previous reports (21).

Although neurological examination may reveal a great deal of information about injury to the brain, subtle changes in neurological functioning can be overlooked. Batteries of NPMTs are becoming increasingly accepted as more detailed assessments of higher cortical functioning. In our study, NPMT performance was not clearly influenced by either heparin dosing or ACT. Furthermore, there were no TIAs or strokes, and no patient developed acute restenosis attributable to thrombosis. We therefore conclude that the degree of anticoagulation alone does not affect the incidence of either subtle or clinically significant cerebral injury after CEA. Any trends suggesting an association between subtle neuropsychological deficits and decreasing heparin doses should be viewed with caution, as statistical significance is lacking.

This is particularly true in light of the fact that excessive anticoagulation may result in serious bleeding complications. In our patient population, the incidence of wound hematoma was 5.7% (with 0.7% reoperation rate for hematoma), which is consistent with findings in previously published reports (23,25). Although this incidence was not influenced by heparin dosing, ACT, or ACT ratio, the only patient who developed a wound hematoma requiring evacuation had a normal baseline ACT level but had 15-minute and 1-hour ACT values that were more than 3 standard deviations above the mean for our study population. This patient received a somewhat higher than normal heparin dose (92 U/kg), and there seems to be a trend for higher doses to be associated with an increased incidence of hematoma formation. Nonetheless, this trend was not statistically significant.

According to previous reports, a serum level of heparin in the range of 0.2 to 0.5 U/ml is suggested as the therapeutic range in vascular surgery, and ACT values of twice the baseline level have been calculated to fall within this range (11). We found that 40 to 60% of our patients fell below this proposed level of anticoagulation, with 15-minute ACT ratios and absolute values as low as 1.26 times baseline and 178 seconds, respectively. Nevertheless, the rates of adverse effects (neuropsychological decline and hematoma) in this group were similar to those with ACT ratios of more than 2 and ACT values of more than 250 seconds. On the basis of these findings alone, we cannot advocate routine ACT measurement before cross-clamping aimed at achieving specific ACT ratios or values.

Furthermore, as hematoma and NPMT deficits were evenly distributed throughout the range of heparin doses, conclusions regarding an appropriate weight-based dose are also difficult; but if these data were to support any weight-based dosing paradigm (albeit based on nonstatistical trends and limited by sample size), 85 U/kg would seem most reasonable. On the basis of the available data, this level of anticoagulation might be expected to balance the adverse effects of excessive and insufficient anticoagulation, potentially minimizing hematoma formation and possibly reducing the rate of subclinical neuropsychometric demise (Fig. 5). This dose should produce ACT values of 225 to 375 seconds at 15 minutes and 200 to 340 seconds at 1 hour.

Using either fixed-dose or weight-based paradigms, anticoagulation monitoring, if desired, may then be limited to just one ACT determination at 1 hour after heparin administration. This value can be used to decide whether or not to reverse heparin with protamine in the rare case that a patient has an overly exuberant response. This management strategy avoids delaying

arteriotomy for additional heparinization or ACT confirmation and also allows surgeons opposed to protamine reversal to simply wait an additional period of time before closing.

CONCLUSION

Fixed-dose heparinization with 5000 U appears safe and efficacious for patients undergoing CEA. Retrospective review suggests that weight-based dosing may also be safe, with preliminary analysis suggesting a dose of 85 U/kg as a reasonable alternative. Either paradigm avoids the time and expense of routine pre-clamp ACT monitoring.

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COMMENTS

Poisik et al. describe a regimen for fixed-dose heparin, obviating the need for activated clotting time (ACT) measurements. Much of the current vascular literature recommends dosing in the range of 80 to 100 U/kg to address the issue of extremes of anticoagulation, as the authors have discussed. When we originally reported on the use of ACT during carotid endarterectomy (CEA) in 1981, standard dosing for CEA was not routinely used; furthermore, in certain difficult cases, ACT may still be of value. In cases in which significant carotid reconstruction and placement of a shunt is indicated, perhaps adequate anticoagulation may be ensured by the use of this test. I agree with the authors that the routine use of ACT is not necessary during CEA, but rather than recommend a standard bolus of 5000 U per case, I would advocate dosing on a per kilogram basis.

Robert H. Rosenwasser

Philadelphia, Pennsylvania

Poisik and colleagues report a nicely done investigation on the safety and efficacy of using fixed-dose heparin for CEA. Briefly, 140 consecutive patients undergoing CEA with the use of general anesthesia, electroencephalographic monitoring, and selective shunting were given a standard dose of 5000 U of heparin before cross-clamping. ACT values were obtained before, 15 minutes after, and 1 hour after heparin administration. Only one patient (0.7%) required evacuation of a neck hematoma, and no patient had a clinically documented stroke. A subset of 49 patients were given neuropsychometric tests (NPMTs) before and after surgery, and 39% of this group were found to have an early decline in test scores. There was no statistically significant correlation between ACT values and either hematoma formation or decline in NPMT scores. On the basis of these findings, one can conclude that fixed-dose heparin is safe and efficacious for CEA. Because of the relatively small number of patients and the commendably small number of adverse outcome events in the study, the power to find a statistically significant association between ACT values and postoperative complications is limited. The authors suggest that there may be benefits to weight-based heparin dosing, but no statistically valid data in this study substantiate that belief.

My practice has been to use a fixed-dose heparin regimen, with administration of 5000 U at the time that dissection in the carotid sheath commences. No ACT levels are obtained. In preparation for a presentation at the Congress of Neurological Surgeons meeting in Seattle, I reviewed 501 consecutive CEAs performed on my service from July 7, 1994, through July 21,

1998. The postoperative incidence of ipsilateral stroke in this group was 1.79%, and only one patient (0.2%) required evacuation of a postoperative neck hematoma.

With regard to the 39% incidence of postoperative NPMT score decline, there was no significant correlation between ACT value and NPMT scores. Microembolization during CEA is a possible cause of early NPMT score decline that might be reduced by higher heparin doses. This is, of course, pure speculation, and a number of other reasons for the early decline in NPMT scores could be postulated. I wonder about the effects of general anesthesia in this patient population. We are beginning a study in patients undergoing CEA using regional anesthesia to evaluate the contribution of anesthetic agents to postoperative NPMT score decline.

In summary, the authors present a meticulously documented study demonstrating that, in their hands, the use of fixed-dose heparin during CEA results in a very low incidence of adverse postoperative clinical outcomes. Further studies by this group and others may lead to making CEA an even safer and more efficacious procedure than it already is.

Robert E. Harbaugh

Lebanon, New Hampshire

Poisik et al. provide a thoughtful approach and an elegant scientific solution to a small but important clinical problem. They demonstrate that fixed-dose heparin use in carotid artery surgery is adequate, but they recommend administration of a tailored dose of 85 U/kg instead, to avoid the pitfalls of excessive anticoagulation in lightweight patients or insufficient anticoagulation in larger individuals. They carefully and eloquently document the pitfalls (with care) of each type of error.

I was taught the 5000-U dosing schedule at The Neurological Institute, as were these authors in their training. I intend to modify my own practice on the basis of these data. I would point out one additional observation that I have made in the practice of carotid surgery: patients who are brought to the operating room already heparinized (whether for crescendo transient ischemic attacks or high-grade stenosis, or both), and who customarily do not receive a bolus dose, will often prove to be insufficiently anticoagulated if the ACT level is checked. This observation came as a surprise to me when I first began to use intraoperative ACT; we now routinely find that patients brought from the ward to the operating room require a bolus dose in addition to their underlying anticoagulation.

In summary, the current body weight-tailored dosing schedule for heparin is well supported and worthy of adoption in clinical practice. Obtaining an intraoperative ACT level as a check on either heparin bolus or preoperative heparinization likewise probably has value in clinical practice.

Christopher M. Loftus

Oklahoma City, Oklahoma

The authors have undertaken an initiative to examine the safety and efficacy of fixed-dose versus weight-dosed heparin during CEA. I must admit that my colleagues and I have used fixed-dose heparin as a matter of routine in our practice, and although we examine ACT values intraoperatively, only rarely do the reported values cause us to alter our routine (for example, by administering an additional dose of heparin as the ACT level begins to normalize in a case involving prolonged repair). The results reported here reassure me that our past practice has

been appropriate, but they also challenge me to think more about the possible advantages of weight-based dosing in the future.

The findings of the neuropsychometric studies reported here and in a previous article are of interest, inasmuch as there are a number of studies in the cerebrovascular literature that report improved psychometrics after CEA. The depth of neuropsychometric testing in the previous reports was not as detailed as in the authors' study. The finding of deterioration of psychometrics, at least acutely, in the majority of their CEA patients is of some concern. It will be of interest to follow the authors' further studies with regard to the patient and intraoperative factors that may correlate with these changes.

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FIGURE 1.

A, response of activated clotting time (ACT) to a 5000-U heparin bolus measured before heparin administration (baseline) and at 15 and 60 minutes after the heparin bolus. ACT values are measured in seconds and presented as means and standard deviations (*bars*). B, response of ACT ratio (ACT_f/ACT_i) to a 5000-U heparin bolus measured before heparin administration (baseline) and at 15 and 60 minutes after the heparin bolus. ACT ratios are given as means and standard deviations (*bars*).

FIGURE 2.

A, correlation ($r = 0.45$) between heparin dose (units per kilogram of body weight) and activated clotting time (ACT) measured at 15 minutes after heparin administration. *Squares*, patients with neck hematomas; *circles*, patients with significant decline on neuropsychometric tests (NPMTs) (subclinical cerebral injury). B, correlation ($r = 0.38$) between heparin dose (units per kilogram of body weight) and ACT measured at 60 minutes after heparin administration. *Squares*, patients with neck hematomas; *circles*, patients with significant NPMT decline.

FIGURE 3.

A, correlation ($r = 0.43$) between heparin dose (units per kilogram of body weight) and activated clotting time (ACT) ratios (ACT_t/ACT_i) measured at 15 minutes after heparin administration. *Squares*, patients with cervical hematomas; *circles*, patients with significant decline on neuropsychometric tests (NPMTs) (subclinical cerebral injury). *Vertical bars* mark the interval of heparin dose (80-90 U/kg) at which no adverse effects occurred. B, correlation ($r = 0.34$) between heparin dose (units per kilogram of body weight) and ACT ratios (ACT_t/ACT_i) measured at 60 minutes after heparin administration. *Squares*, patients with cervical hematomas; *circles*, patients with significant NPMT decline (subclinical cerebral injury).

Vertical bars mark the interval of heparin dose (80-90 U/kg) at which no adverse effects occurred.

FIGURE 4.

Heparin dose (units per kilogram of body weight), activated clotting time (ACT) levels at 15 minutes after heparin administration, and ACT levels at 60 minutes after heparin administration for patients with and without cervical hematoma. Values are given as mean $\pm$ standard deviation (*bars*) (*P* not significant).

FIGURE 5.

Percentage of patients with complications (including both neck hematoma and neuropsychometric decline) per heparin dose interval. *, $P < 0.05$ for 80-89 U/kg interval versus all other groups.

TABLE 1
Demographic and Intraoperative Parameters^a

Age (yr)	70.1 (8.8)
Operative side (right:left)	55%:45%
Sex (male:female)	55%:45%
Handedness (right:left)	91.9%:8.1%
Height (cm)	165.9 (24.0)
Weight (kg)	71.4 (14.4)
Education (yr)	15.2 (6.6)
Hypertension	68.9%
Diabetes mellitus	20.4%
Previous stroke or TIA	47.9%
Previous MI	22.8%
Previous CEA	12.0%
Duration of surgery (min)	147.1 (45.5)
Cross-clamp time (min)	36.0 (10.4)
Fentanyl ($\mu\text{g/kg}$)	3.3 (0.9)
Midazolam (mg/kg)	0.04 (0.01)

^aTIA, transient ischemic attack; MI, myocardial infarction; CEA, carotid endarterectomy. Means with standard deviations in parentheses and percentages are given.

TABLE 2A
Incidence of Wound Hematoma in Patients Receiving Different Heparin Doses

Heparin Dose Intervals (U/kg)	No. of Patients Examined for Hematoma	No. of Hematomas Observed	Incidence of Hematoma (%)
44-59	22	0	0
60-69	47	3	6
70-79	40	3	8
80-89	19	0	0
≥90	12	2	17
Total	140	8	6

TABLE 2B
Incidence of Subclinical Cerebral Injury in Patients Receiving Different Heparin Doses

Heparin Dose Intervals (U/kg)	No. of Patients with NPMT ^a	No. of Patients with NPMT Deficits	Incidence of Subclinical Injury (%)
44-59	10	5	50
60-69	17	6	35
70-79	15	6	40
>80	6	1	17
Total	48	18	38

^a Singly operated patients only. NPMTs, neuropsychometric tests.