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A Pilot Trial of Low-Dose Intravenous Abciximab and Unfractionated Heparin for Acute Ischemic Stroke: Translating GP IIb/IIIa Receptor Inhibition to Clinical Practice

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Abstract Thrombolysis remains a mainstay in the treatment of ischemic stroke. While not usually considered in the spectrum of clot lysis, experimental data show that inhibition of the platelet glycoprotein (GP) IIb/IIIa receptor can reduce as well as reverse thrombus formation and improve microvascular flow in stroke models. However, a recent clinical trial of GP IIb/IIIa inhibition in stroke did not demonstrate clinical benefit and was associated with increased hemorrhage. Based on an understanding of the relationship between GP IIb/IIIa receptor inhibition, efficacy and hemorrhage, we hypothesized that a lower dose of abciximab would achieve a favorable range of platelet inhibition and potentially good clinical outcomes. Forty-four patients with suspected large vessel occlusion, who were not eligible for rt-PA were offered treatment with approximately 30% lower total dose of intravenous abciximab if within 6 h for anterior circulation or 24 h for posterior circulation stroke (later modified to 12 h). Concomitant anticoagulation, usually with unfractionated heparin was employed. The extent of platelet inhibition was measured in 21 patients. Hemorrhage rate and 90-day functional outcomes and mortality were obtained. A matching algorithm involving finding the nearest neighbor from individual subjects in the control arm of the NINDS rt-PA database was used to compare outcomes at similar baseline characteristics and gender. Mean platelet inhibition was 92.1±6.7% vs inhibition reported with percutaneous coronary intervention (PCI) of 96±10; p=0.08. Successful matching to NINDS controls was accomplished: after outlier elimination, median and mean NIHSS of the abciximab subjects compared to NINDS controls was 16.5 vs 15.5 (p=0.92) and 16.3 vs 16.0 (p=0.86). Mean age was 67.2 vs 67.1 (p=0.97). Mean glucose was 141 vs 142 (p=0.92). There was one symptomatic hemorrhage; minor hemorrhages occurred in 9%. The percent of patients who achieved an mRS 0–2 or died in the treated vs matched NINDS control patients was 63 vs 38 (p=.02) and 23 vs 23 (p=1.0). Our pilot results indicated that a lower dose of abciximab results in platelet inhibition similar to that achieved in the coronary vascular bed during PCI. Comparison to matched historical controls suggests that this lower dose in combination therapy may be safe and effective therapy for thrombotic stroke and a randomized trial is warranted.

Keywords Glycoprotein IIB/IIIA receptor antagonists · GP IIB/IIIA inhibitors · Abciximab · Platelet aggregation units · Platelet function inhibition · Ischemic stroke · Matching algorithm

Disclosures Drs. Mandava and Kent hold the copyright for PPREDICTS© and a patent application has been submitted on their behalf for PPREDICTS©.

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Background

Thrombolysis remains the primary approach to treating acute stroke. Its limitations, including reduced time window, risk of hemorrhage, ineffective recanalization as well as molecular events that may contribute to worsening outcome [1], have led to extensive efforts to finding more effective treatments. These include neuroprotectant therapies, direct clot lysis or mechanical clot retraction. Neuroprotection has yet to be translated to clinical effectiveness and our data suggest that while endovascular approaches may improve outcome in some, higher mortality at later time points limits its overall effectiveness [2–4]. Therefore, new approaches are needed.

Inhibitors of the GP IIb/IIIa receptor have proven to be safe and effective in acute coronary syndromes and when combined with percutaneous coronary intervention (PCI) [5, 6]. Its usefulness in stroke has been more mixed. While showing early promise, intravenous abciximab in Phase III was not found to be safe and effective. It was associated with lack of improvement in functional outcome and increased bleeding [7, 8]. However, in experimental stroke models, GP IIb/IIIa antagonists were shown to have beneficial effects in both the proximal and distal circulation [9–11] suggesting that it may be worthwhile to try to understand these discrepancies.

Our review of the preclinical and clinical literature on GP IIb/IIIa antagonists suggests several reasons why clinical trials for stroke have failed [8]. GP IIb/IIIa receptor occupancy by 7e3 (the non-chimeric version of abciximab) has a sigmoid relationship to efficacy for reduction in embolic events [12]. Receptor occupancy between 70% and 100% produced complete abolition of thromboembolic events. On the other hand, the relationship between receptor occupancy and bleeding time was linear with monotonic increase in bleeding time. Two other groups have shown [10, 13], employing different animal models of stroke and different GP IIb/IIIa receptor antagonists (TP9201 and JON/A), that intracerebral hemorrhages increase with increasing doses. The disparity between reduction of thromboembolic events and prolongation of bleeding time suggest that an antithrombotic effect can be achieved without a significant prolongation of bleeding time. Many clinically effective antithrombototic drugs such as aspirin have a minimal effect on bleeding time [14]. Notably, in key acute stroke trials, e.g., AbESTT I/II [7, 15], platelet inhibition was not monitored.

In addition to lack of platelet inhibition monitoring, concomitant anticoagulation was prohibited in AbESTT I/II, presumably due to concerns of increased risk of hemorrhage. However, in the coronary circulation, there is considerable evidence that addition of GP IIb/IIIa inhibitors to aspirin and unfractionated heparin improves efficacy [16–19].

Based on the preceding lines of evidence and the high rate of hemorrhage in AbESTT II, we hypothesized that the dose in AbESTT I/II may have been too high for stroke patients, and that a lower dose would achieve platelet inhibition levels comparable to the PCI literature. We also hypothesized that addition of concomitant anticoagulation may improve effectiveness without an increase in hemorrhagic transformation when combined with this lower dose. We sought to investigate whether we could translate preclinical data on optimal range of platelet inhibition in a subset of patients by measuring platelet inhibition using this lower dose strategy.

Given the pilot nature of this study, a control arm was not included. In order to determine how outcomes compare to other treatments, we adapted our novel matching method based on weighted-Euclidean distance [20], to find matches between our consecutive series of abciximab-treated patients to control subjects in the placebo arm of the NINDS rt-PA trial

Methods

Abciximab Treatment Protocol, Subject Selection, and Assessment

The protocol was approved by the Institutional Review Board of Human Subjects at Baylor College of Medicine, the Michael E. DeBakey VA Medical Center and the University of Texas Medical Branch at Galveston. Patients suspected of suffering an acute ischemic stroke due to a large vessel occlusion, within 6 h for anterior circulation or 24 h for posterior circulation (later changed to 12 h) were offered low-dose intravenous abciximab along with time-limited unfractionated heparin (or continuation of warfarin if INR was therapeutic). Inclusion and exclusion criteria had to be met (Table 1). The bolus (0.2 mg/kg, max of 16 mg) and infusion dose (0.05ug/kg/min over 12 h, max of 2.9 mg over 12 h) resulted in a maximal bolus dose approximately 80% and infusion dose approximately 40% of AbESTT and AbESTT II [8]. This dose was adapted from that reported by Cheung and Ho (2000) and Lee et al (2001) [21, 22]. Two subjects requested that a lower dose of abciximab be used and the treatment team complied (0.185 mg/kg). Aspirin was permitted and often prescribed at the time of initial diagnosis. Baseline demographic data such as NIHSS, age, pretreatment glucose and time to treatment were tabulated. Ninety-day functional outcomes in terms of modified Rankin score (mRS), mortality and hemorrhage rate were collected. A neurologist (RHF) reviewed the results after each five patients for safety concerns. One protocol change implemented through the course of the study was to reduce the time window for enrollment for posterior circulation stroke from 24 to 12 h. To assess for early signals of efficacy or

Table 1 Study inclusion/exclusion criteria

Inclusion criteria
Patients are 18 years of age or older
Suffer from an ischemic stroke within the last 6 h for anterior circulation stroke and within 12 h for posterior circulation strokes
Suspicion for large vessel or cardioembolic stroke based on clinical judgment supplemented by laboratory studies
Ineligible for treatment with intravenous t-PA
Exclusion criteria
Initial CT of the head suggests stroke like symptoms are not due to an ischemic stroke but as a result of hemorrhage or tumor or other cause
Platelet count below 100,000
PTT greater than 75
International Normalized Ratio (INR) greater than 2.5
ACT >250 if measured
Have clinical signs and symptoms of liver failure or elevations in AST, and ALT to 3 times the normal values
Creatinine greater than 2
Treatment team considers the patient to be at increased risk of intracerebral hemorrhages or systemic bleeding
Pre-morbid modified Rankin Score >2 suggesting a functionally dependant patient
Suspected lacunar stroke

increased mortality, outcomes of the abciximab-treated group were periodically checked against a model of stroke outcomes derived from a pooled sample based on the control arm of randomized stroke clinical trials (pPREDICTS ©; ref 4), and no signal of increased mortality was seen through the course of the study while outcomes were consistently better than predicted. Note that total subjects presented here include those presented previously at earlier stages [8, 23, 24].

Platelet Function Testing with Verify Now™

A point-of-care testing device used extensively in the setting of percutaneous coronary interventions from Accumetrics Inc. which displays platelet aggregation units (PAU) was utilized [25–27]. Platelets in a whole blood sample are maximally stimulated to aggregate by means of thrombin-receptor-agonist peptide. PAU was obtained before treatment and 10–20 min after bolus dose of abciximab. Platelet function inhibition is determined by

$$(\mathrm{PAU}_{\text{at baseline}} - \mathrm{PAU}_{\text{after treatment}})/\mathrm{PAU}_{\text{at baseline}}$$

The platelet function inhibition as measured by the GP IIb/IIIa assay is not thought to be affected by heparin or aspirin treatment [27].

Group data of platelet function inhibition was expressed as mean and standard deviation (SD) and compared by means of Student's *t* test against a large prospective multi-center PCI trial (n=394), in which platelet inhibition was obtained at a comparable time following the abciximab bolus (10 min) [26].

Matching Methodology

The goal of the method is to generate a matched sample from two different databases, in this case between subjects in the abciximab/heparin group and from the control arm of the NINDS rt-PA trial [28]. The matching of subjects was performed in terms of weighted distance [20, 29].

Matched pairs with distances greater than a threshold

$$\text{Threshold} = \mathrm{Q75} + 1.5(\mathrm{IQR})$$

that depends on the 75th percentile (Q75) and the interquartile range (IQR) were considered outliers[30], and eliminated from further consideration.

Choice of Comparison Group

We selected the NINDS rt-PA database for the comparison sample [31]. We previously established that this sample is representative of other randomized stroke clinical trials including those published up to 2008 using our pPREDICTS© method (see Fig. 2a in Ref. [4]), in which an outcome function is developed from pooled data from randomized trials. Placebo arms of recent large trials such as SAINT 1 and 2 also yield comparable results relative to their baseline NIHSS and age (see Fig. 2b in Ref. [4]), indicating little drift of outcomes in the placebo arms over the recent years; although there may have been overall improvement in outcomes drift from the earlier decade [28, 32, 33]. Note also that a public database such as VISTA [34] could theoretically be used for this purpose.

Patient Matching

Since only subjects with suspected large vessel occlusion were treated with abciximab and heparin, subjects in the NINDS database classified as suffering from 'Large vessel' or 'Cardioembolic' stroke were considered for matching. We matched patients based on gender and three baseline parameters simultaneously: NIHSS, age and blood glucose, all factors associated with outcomes [35–38]. For each case subject, Delaunay triangulation [39] was used to identify the nearest same gender neighbor from the control population in three-dimensional space of baseline NIHSS, age and pretreatment glucose [20]. Since the three factors varied over different absolute ranges and so as not to have any single factor unduly influence the matching, NIHSS, age and pretreatment glucose were multiplied by weighting factors 10.0, 2.27, and 1 for male patients and 8.41, 2.28, and 1 for

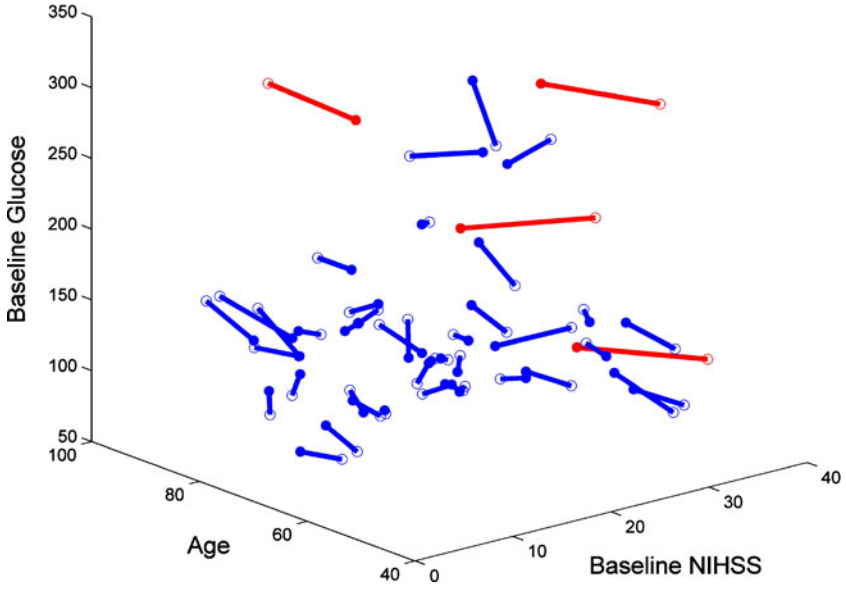

Fig. 1 Matching between abciximab-treated patients and subjects from the NINDS rt-PA study placebo arm. The distance between matched subjects in three-dimensional space based on baseline NIHSS (*x* axis), age (*y* axis) and glucose (*z* axis). *Open circles* represent abciximab-treated patients and *closed circles* represent controls from the NINDS rt-PA study placebo arm. The *lines* between *dots* indicate the nearness of the matched pair. Overall, closely matched subjects in the three-dimensional space were identified by the method. The *lines in red* indicate those subjects who were considered "outliers". Matching results can be seen in Table 2. Outcome analysis assessed with and without the outliers and did not differ substantially (Table 2 and Fig. 2)

females, which represented the means of the three factors. Hence the term "weighted" Euclidean distances [20].

For each case subject in the abciximab-heparin database, a nearest neighbor from the control NINDS rt-PA study placebo arm was identified. Baseline and 90-day outcomes for the matched pairs were stored.

Other Statistical Tests Used

Wilcoxon rank-sum test was applied to compare distributions in terms of median NIHSS. Student's *t* test was used to compare distributions in terms of mean and standard deviation and Fisher's test to compare proportions. For matched groups the paired proportions of mRS 0–2, mRS 0–1 and mortality were tested using the McNemar's test with continuity correction.

Results

Demographics

Forty-four patients (37 male and 7 female) were treated with our low-dose abciximab and heparin protocol. The

Table 2 Baseline demographics and outcome results for the abciximab-treated patients compared with gender-matched subjects from the NINDS rt-PA database

	Abciximab + heparin + outliers (n=44)	NINDS placebo + outliers (n=44)	p Value	Abciximab + heparin − outliers (n=40)	NINDS placebo − outliers (n=40)	p Value
Median NIHSS	17.5	16	0.90	16.5	15.5	0.92
NIHSS (mean + SD)	17.2±9.1	16.6±8.1	0.74	16.3±8.2	16.0±8.0	0.86
Age (mean + SD)	66.6±12.7	67.2±9.9	0.81	67.2±12.8	67.1±10.2	0.97
Glucose (mean + SD)	149±58.5	150±59	0.98	141±47.8	142±49.5	0.92
Male/Female	37/7	37/7		33/7	33/7	
Proportion mRS0-2	0.57	0.37	0.04	0.63	0.38	0.02
Proportion mRS0-1	0.43	0.25	0.03	0.48	0.28	0.03
Mortality	25%	27%	1.0	23%	23%	1.0

p Value for comparison of median NIHSS was obtained from Wilcoxon rank-sum test. p Values comparing means of NIHSS, age and glucose were obtained by applying Student's t test. p Values for matched subjects were obtained by McNemar's test of discordant pairs

median NIHSS of 44 patients was 17.5, mean age 66.6 years, baseline glucose 149 mg/dl. Time to treatment was 317±266 min. Twenty-seven subjects suffered an anterior circulation stroke and were treated at 244± 67 min, and 17 subjects with posterior circulation strokes were treated at 582±326 min.

Platelet Function Inhibition

Platelet function inhibition was measured in 21 subjects. Mean platelet inhibition was 92.1±6.7 (Range, 75 to 100; one subject at each extreme). In the two subjects that requested a lower dose of abciximab be used, both subjects achieved platelet inhibition >95 and had good clinical outcomes. While trending lower, the platelet function inhibition achieved with the low-dose abciximab compared with that reported with the higher dose in the setting of PCI was not significantly different (vs 96±10,n=394 p=0.08 Steinhubl et al. 2001)[26].

Matching

Since matching was limited to "Large vessel" and "Cardioembolic" subtypes in the NINDS placebo group, the target group size was reduced to 272 subjects from the original 312. Of the 272 there were 157 male subjects and 115 female. The graphical results of matching between the abciximab patients and the NINDS placebo group are shown in Fig. 1 which demonstrates the close match between the majority of the treated sample and the NINDS placebo subjects. Subjects in RED are the subjects identified as outliers. Matching and outcome results are provided for the samples with and without the outliers eliminated in Table 2. Matching generally was good especially when the four outliers were eliminated.

Outcomes Compared With Matched Sample

In the full sample of abciximab and heparin-treated group 57% achieved an mRS of 0–2 compared with 37% of the matched NINDS placebo group (p=0.04; Fig. 2a). The proportion of patients who achieved an mRS 0–1 was also significantly improved (p=0.03). Eliminating outliers based on a distance threshold yielded similar results (right three columns of Table 2 and Fig. 2b).

Mortality of the abciximab group was 25% compared to 27% for the matched NINDS placebo group; p=1.0 which was similar after outlier exclusion (23% vs 23%). There was one symptomatic hemorrhage in a patient treated for basilar artery thrombosis at 23.5 h, yielding a symptomatic hemorrhage rate of 2% compared with 0% in the matched NINDS placebo group (p=1.0). Note that we modified inclusion criteria to limit to 12 h for posterior circulation stroke after this event and there were no further symptomatic hemorrhages in the next 13 patients.

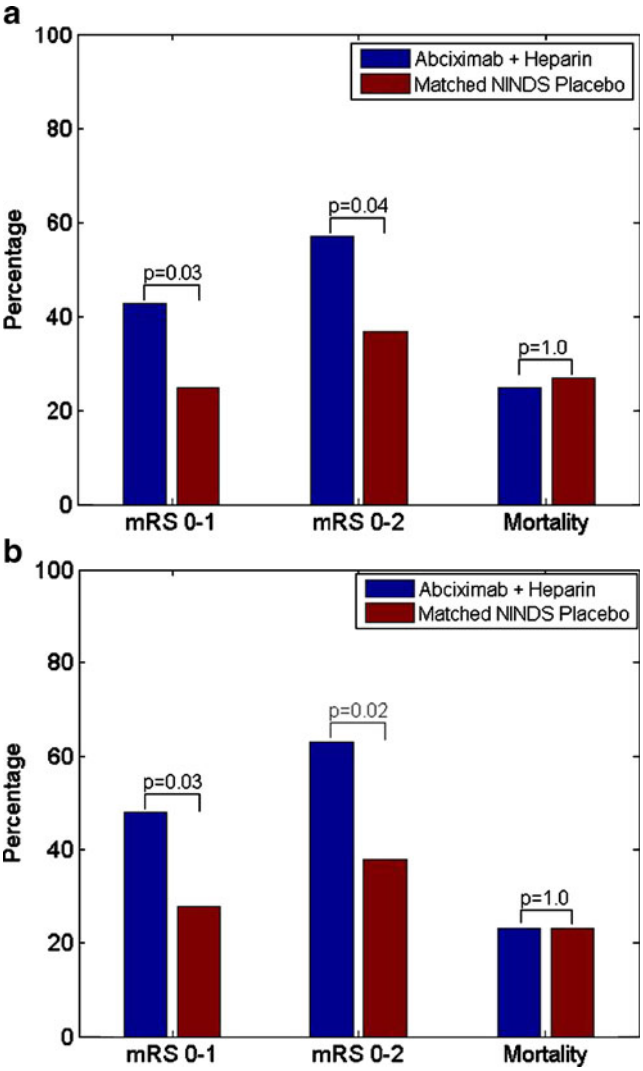

Fig. 2 Outcomes of matched samples. Graphical representation of the outcomes (mRS 0–1; 0–2 and mortality) of the matched abciximab and NINDS rt-PA study placebo subjects. **a** Includes outliers; **b** shows outcomes following outlier elimination. The proportions of patients who achieved an mRS 0–1 and 0–2 were significantly higher in the abciximab-treated group, while mortality did not differ. p Values were obtained with McNemar's test of discordant pairs

Discussion

In this pilot study, a 30% lower total dose of abciximab achieved a platelet inhibition equivalent to that obtained with cardiac dose in the setting of PCI [26] and we found preliminary evidence for efficacy and safety with this lower dose in combination with unfractionated heparin. In the

setting of PCI, up to 9% of patients develop significant bleeding at these doses [40]. The antithrombotic effect of abciximab plateaus at 0.2 mg/kg while the bleeding time continues to prolong up to 0.4 mg/kg [12]. Similarly, with other antiplatelet agents, significant antithrombotic effects can be achieved with only a modest effect on bleeding times [41, 42]. It is therefore possible that the higher doses used in AbESTT contributed to significant bleeding with only a marginal increase in antithrombotic effect. It is reassuring that with the dose of abciximab used in this study none of the subjects were below the 70% inhibition at which there is prevention of thrombus formation in vitro [12]. While these favorable outcome results with our lower dose protocol need to be confirmed with blinded randomized trials, it is possible that stroke patients are more sensitive to abciximab, although this remains to be tested. The contribution of unfractionated heparin also needs to be confirmed with follow-up trials.

While our outcome results are encouraging, randomized and double-blind clinical trials remain the gold standard for determining therapeutic efficacy and safety. However, even if control arm is present and randomization of patients occurs, it does not guarantee that balanced groups will result because of the variability in presentation. This problem is not limited to trials with small number of patients [43, 44], but extends to trials that are considered large [PROACT II (glucose), NINDS (baseline severity) and ECASS-III (NIHSS)] [28, 45, 46]. Mismatched populations in randomized controlled trials have resulted in considerable debate regarding the generalizability of their results, for example, as related to the NINDS rt-PA trial itself [47, 48]. We have contended that mismatches may also have contributed to early positive results that were later proved erroneous in several instances [4].

Gender, baseline NIHSS and age influence outcomes [2, 35–38] as does baseline glucose, particularly when associated with thrombolytic therapy [49, 50]. The high proportion of males in this sample reflects that the bulk of recruitment occurred in a VA setting. While the numbers of females is relatively small, there was no suggestion of differential response in this early sample (data not shown), a finding that will need to be confirmed in a larger sample.

Among these and likely other factors, a mismatch among patient groups in RCTs is accentuated when numbers are small, although larger subject numbers does not insure adequate randomization in a condition as heterogeneous as stroke. We presented here a method to match, in terms of baseline demographic values, individual patients against a larger NINDS database and compare the outcomes of the matched groups. The method used here can potentially be extended to other databases. Our choice of NINDS database as the comparator group can be criticized since the NINDS group had to be randomized to treatment within 180 min and our abciximab and heparin-treated patients were treated at longer time intervals. This is a weakness that comparison to other databases with longer time windows may be able to resolve. It is reassuring though, that the NINDS rt-PA control population is for the most part representative of expected outcomes of placebo populations from a heterogeneous group of stroke trials, as shown earlier by us [4]. While we matched treated to target populations on a 1:1 basis here, the same method can be extended to match on other ratios if there are enough patients in the target group.

GP IIb/IIIa inhibitors have been tested in various protocols for the treatment of acute stroke with varying degrees of success [7, 8, 15, 44, 51–54]. Our results indicate a low rate of complications in patients treated within the protocol described here and a suggestion of benefit when compared to a mathematically derived comparison group from the NINDS database.

Theoretical advantages of using GP IIb/IIIa inhibitors in stroke include the ability to inhibit a final common pathway for platelet aggregation prior to platelet-fibrinogen bridge formation [55]. These effects lead to partial clot recanalization shown in the setting of PCI if combined with aspirin and unfractionated heparin [19], as well as evidence for additional beneficial effects on the distal cerebral microcirculation [11]. Given these interesting actions, it appears reasonable to revisit the use of these agents in ways that may maximize their safety and effectiveness.

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