Adjunctive Treatment with Low Dose Intra-arterial Integrilin and Intravenous Aspirin During Carotid stenting – Case Series

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**Abstract**

Introduction: According to most medical guidelines, the standard protocol for carotid stenting includes the administration of oral aspirin and clopidogrel at least four days before the procedure, with intraprocedural intravenous (IV) heparin. Some publications have also reported the safety of adding glycoprotein 2b/3a inhibitors to the protocol. In this retrospective study, we evaluated the safety of a new medication protocol that includes IV aspirin and intra-arterial Integrilin during carotid stenting.

Methods: All patients who underwent carotid stenting at Soroka University Medical Center from January 2015 to May 2020 were included (emergent cases were excluded). We divided patients into two groups: 1. patients treated under the standard protocol; and 2. patients treated under the new protocol, in which patients received both the standard protocol regimen, as well as 150 mg IV aspirin immediately before stenting, and a slow intra-arterial injection of 2–3 mg Integrilin (glycoprotein 2b/3a antagonist) immediately after stenting.

Results: Forty-four patients were treated according to the standard protocol (group 1), and 41 patients were treated according to the new protocol (group 2). In group 1, six patients had complications, while in group 2, no complications of any kind were noted (p = 0.027).

Conclusions: The safety and possible efficacy of this novel protocol was preliminarily demonstrated in the present study. Further studies are needed to prove the safety and efficacy of a specific drug regimen that will further reduce the complication rates of carotid stenting.

**INTRODUCTION**

During the last decade, carotid stenting has been widely applied for the prevention of secondary stroke in selected patients.[1, 5] Early ischemic complications during carotid stenting occur in 3%–13% of all patients.[1] The mechanisms involved are not fully understood, yet it is presumed that both distal embolization caused by ruptured plaque and platelet activation secondary to intimal injury (or a foreign body within the vessel) contribute to the development of ischemic events.[1] Embolic protection devices are used to prevent strokes caused by the first mechanism, and antiplatelet medications are administered to address the second mechanism.[1-5]

Current medical management, according to most guidelines for carotid stenting, includes the administration of oral aspirin and clopidogrel at least four days before the procedure, with intraprocedural intravenous (IV) heparin, with the goal of achieving an activated clotting time (ACT) of 250–300 s.[6] Clopidogrel resistance occurs in up to 52% of the population.[11, 19] Ischemic events related to carotid stenting are significantly more common in patients with clopidogrel resistance.[19] Some point of care tests are available, which can assess platelet inhibition under the effects of clopidogrel, but their positive predictive value is low.[20]

Some publications have been focused on adding different doses of glycoprotein 2b/3a inhibitors to the protocol, to reduce the rate of ischemic events. Most of those studies have reported safety, and some have also shown efficacy, but no large multicenter trial has yet confirmed the application of a specific protocol.[2, 7-9] Furthermore, the administration of IV aspirin during endovascular procedures, including emergent stenting, is considered both safe and effective.[10, 18] To our knowledge, no available publications have investigated its specific routine use during non-emergent carotid stenting.

When IV aspirin became available locally, at our center, we decided to add a low dose of IV aspirin (150 mg) just before stenting as a preventive measure, considering the high rate of clopidogrel resistance. Even after adding IV aspirin to the protocol, we noticed minimal stent protrusions in some cases that responded well to a low dose of intra-arterial Integrilin (glycoprotein 2b/3a Inhibitor). Stent protrusions are known to be predictors of ischemic events after stenting.[12] However, micro protrusions are sometimes visually unclear after stenting. In order to prevent possible micro protrusions, we also started to routinely administer a low dose of intra-arterial Integrilin to all patients after stenting, and monitored them both radiologically and clinically for a further 10 min before discharge.

In this retrospective study, compared with the standard protocol, we aimed to evaluate the safety and outcomes of a modified medication regimen administered during carotid stenting.

**METHODS**

In this retrospective analysis, we analyzed the outcome of internal carotid artery stenting, before and after a modification to the medication protocol.

**Study population**

All patients who underwent elective or urgent carotid stenting at Soroka University Medical Center from January 2015 to May 2020 were included (emergent cases were excluded). We divided the patients into two groups. Group 1 included patients treated before May 2018, according to the standard protocol of 100 mg oral aspirin + 75 mg oral clopidogrel (Plavix), at least four days before the procedure, and continuing for at least six weeks after the procedure; IV heparin during the procedure while keeping the ACT between 250 and 300 s. Group 2 included patients treated after May 2018 according to the new protocol, which included both the standard protocol regimen, as well as the administration of 150 mg IV aspirin immediately before stenting, and 2–3 mg of a slow intra-arterial injection of Integrilin (adjusted to body weight) immediately after stenting.

No patient under evaluation had an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) < 8. We compared the demographic characteristics, medical history, procedural details, medications, indications for the procedure, and complications between groups. The institutional ethics committee of the Soroka University Medical Center approved the study protocol.

**Procedural management**

After arterial femoral access was established, an IV bolus of heparin (50 units/kg) was administered to achieve an ACT between 250 and 300 s. An 8FR guiding catheter (Neuron MAX, Penumbra) was introduced to the common carotid. A 014 microwire, embolic protection device (SPIDER 5, Medtronic) was navigated and deployed in the petrous carotid. Stenting with a Cguard (InspireMD)/Xact (Abbott)/Precise (Cordis)/Wall stent (Boston Scientific) was performed, based on the operator's decision, followed by balloon angioplasty (Viatrac, Abbott).

Patients from group 2 were additionally treated with 150 mg IV aspirin just before stenting, and a slow intra-arterial injection of 2–3 mg Integrilin through the guiding catheter post stenting. After the procedure, all patients were admitted to the Neuro intensive care unit and subjected to strict blood pressure monitoring and control, as well as frequent neurological status evaluations for at least one night, followed by ward admission for at least two nights. All patients were treated with aspirin and clopidogrel for six weeks. After six weeks, a Doppler sonographic examination was performed. If the follow-up Doppler sonogram showed normal flow within the stent, clopidogrel was stopped, and the patient was allowed to continue treatment with aspirin alone.

**Statistical Analysis**

Continuous variables were presented as the mean ± standard deviation (SD), and categorical variables were presented as frequency and percentages.

In the univariate analysis, we compared demographic and clinical values between the two study groups, i.e., patients treated with the new protocol and those treated with the standard protocol. The *t*-test or one-way analysis of variance (ANOVA) was applied for continuous variables with normal distribution, while the Mann–Whitney U Test (Wilcoxon Rank Sum Test) or Kruskal–Wallis test (one-way ANOVA on ranks) was applied for continuous variables with non-normal distribution. The chi-squared or Fisher’s exact test was applied for categorical variables. Statistical significance was set at p < 0.05.

The impact of the new procedure on possible complications was examined by logistic regression, considering complications after the procedure as the main outcome variable and adjusting for the patients’ age (in years). Point estimates of association were presented as odds ratios along with their 95% confidence intervals [OR (95% CI)].

The significance level was set at p < 0.05, based on a two-sided Wald test. No adjustments were made to multiple comparisons, owing to the exploratory nature of our investigation. All statistical analyses were conducted using the SPSS Version 25 software (SPSS Inc., Chicago, IL).

**RESULTS**

Between January 2015 and May 2020, 85 patients underwent non-emergent carotid stenting at our institution. Forty-five patients were treated according to the standard protocol (group 1), and 42 patients were treated according to the modified, augmented protocol (group 2). Table 1 presents the patient characteristics of both groups. A greater number of patients in group 2 had a history of ischemic heart disease (p = 0.031). However, no other significant differences were noted in the demographic details or relevant medical history between the two groups (Table 1).

Table 1: Patient demographic and clinical characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | Old protocol  N = 45 | New protocol  N = 42 | P-value |
| Gender (male) -  N (%) | 30 (66.7) | 33 (78.6) | 0.214 |
| Age, years -  Mean ± SD  Median (IQR) | 65.02 ± 8.42  65.0 (58.5; 71.0) | 66.14 ± 7.95  66.0 (61.7; 73.0) | 0.526 |
| Smoking (yes) - N (%) | 21 (46.7) | 20 (47.6) | 0.929 |
| Diabetes (yes) - N (%) | 20 (44.4) | 19 (45.2) | 0.941 |
| Hypertension (yes) - N (%) | 34 (75.6) | 30 (71.4) | 0.663 |
| Dyslipidemia (yes) - N (%) | 25 (55.6) | 23 (54.8) | 0.941 |
| Malignancy (yes) - N (%) | 6 (13.3) | 2 (4.8) | 0.167 |
| Ischemic heart disease (yes) - N (%) | 7 (15.6) | 15 (35.7) | 0.031 |

Symptomatic carotid stenosis (transient ischemic attack or stroke) was the indication for stenting in 80% of the patients in group 1 and 69% of the patients in group 2 (p = 0.240). The other patients underwent stenting with indications of asymptomatic carotid stenosis > 80%. The two groups showed a comparable degree of mean pre-stenting stenosis (85.47% ± 11.44% in group 1, and 84.11% ± 11.17% in group 2) on computed tomography angiography (p = 0.390) (Table 2). All patients received aspirin and clopidogrel for at least four days before the procedure. Over 50% of the patients received aspirin and clopidogrel for more than a week before the procedure without any significant difference between the groups (p = 0.835, p = 0.311, respectively) (Table 2).

Table 2: Pre-procedural indications (clinical and radiological) and medical treatment of patients scheduled for internal carotid artery stenting

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | Old Protocol  N = 45 | New Protocol  N = 42 | P-value |
| Percentage of stenosis per CTA  Mean ± SD  Median (IQR) | Treated artery | 85.47 ± 11.44  90.0 (80.0; 95.0) | 84.11 ± 11.17  90.0 (80.0; 90.0) | 0.390 |
| Days of clopidogrel (Plavix) administration prior to procedure - N (%) | 4–6 | 13 (48.1) | 12 (35.3) | 0.311 |
| > 7 | 14 (51.9) | 22 (64.7) |
| Days of aspirin administration prior to procedure - N (%) | 4-6 | 8 (23.5) | 10 (25.6) | 0.835 |
| > 7 | (76.5) 26 | 29 (74.4) |
| TIA (yes) - N (%) | | 10 (22.2) | 7 (16.7) | 0.514 |
| Stroke on admission (yes) - N (%) | | 26 (57.8) | 22 (52.4) | 0.613 |
| Symptomatic (yes) - N (%) | | 36 (80.0) | 29 (69.0) | 0.240 |

CTA, computed tomography angiography; TIA, transient ischemic attack.

In group 1, seven patients showed complications (16.3%); three were minor (one transient contrast-induced nephropathy and two groin hematomas), and four were major complications (three ischemic events, one of which was due to stent reocclusion, and one hyperperfusion syndrome with intracerebral hemorrhage). In group 2, no complications of any kind were noted (p = 0.012) (Table 3). No major or minor cases of bleeding were observed in the second group. It is also worth mentioning that complications only occurred in symptomatic patients.

Thirty-one patients from group 1 (68.9%) and 24 patients from group 2 returned for a follow-up visit, 8–10 weeks after discharge (p = 0.054). None of the patients from either group complained of new neurological symptoms. Three of the patients from group 1 (6.7%), and none of the patients from group 2 had > 50% stenosis within the stent on follow-up Doppler sonography (Table 3).

Table 3: Complications during and after internal carotid artery stenting

|  |  |  |  |
| --- | --- | --- | --- |
|  | Old Protocol  N = 45 | New Protocol  N = 42 | P-value |
| Side of stent (right) - N (%) | 25 (55.6%) | 17 (40.5%) | 0.198 |
| Complications during the procedure (yes) - N (%) | 2 (4.7%) | --- | 0.494 |
| Complications after the procedure (yes) - N (%) | 5 (11.1%) | --- | 0.056 |
| Any complications (yes) - N (%) | 7 (16.3%) | --- | 0.012 |
| Follow-up visit (yes) - N (%) | 31 (68.9%) | 24 (57.1%) | 0.054 |
| \*Significant stenosis within stent on follow-up visit (yes) - N (%) | 3 (6.7%) | --- | 0.243 |

**DISCUSSION**

In this retrospective case series, we evaluated the safety and outcomes of a new medication regimen during carotid stenting. The new regimen included the addition of IV aspirin before stenting, and a low dose of intra-arterial Integrilin immediately after stenting. We observed a significant reduction in the number of complications after the protocol was modified.

Qureshi et al.[2] showed the feasibility of combined treatment during carotid stenting, using high-dose integrin (both during and 24 h after the procedure), aspirin, clopidogrel, and low-dose heparin. Kapadia et al.[9] reported the safety and even a significant reduction in ischemic complications, after adding glycoprotein 2b/3a to their treatment protocol.

Hugh et al.[13] reported the safety of adding glycoprotein 2b/3a inhibitors to the standard regimen in emergent carotid stenting, which is considered a procedure with an even higher risk of hemorrhagic transformation. On the other hand, Wholey et al.[7], showed a significantly higher rate of carotid stenting complications after adding a high dose of glycoprotein 2b/3a inhibitors to a protocol comprising aspirin, clopidogrel, and heparin (administered during the procedure).

Dornbos et al.[14] reviewed over 20 publications in which glycoprotein 2b/3a inhibitors were added to a medical regimen for aneurysm coiling as a preventive/salvage treatment. The medication was administered by the IA/IV route, in different doses, either with or without 12 h of infusion after the respective procedures. That review reported a significant reduction in thromboembolic events, with a minimal increase in the risk of intracerebral hemorrhage.

The use of glycoprotein 2b/3a is recommended for coronary thrombosis;[15] therefore, the doses and treatment protocol used in most neuroendovascular studies are based on cardiologic recommendations. As the brain tissue is known to be the most sensitive to ischemic/reperfusion processes,[16] an adjustment in the dosage should be considered.

Based on existing studies,[2, 7, 13, 14] adding glycoprotein 2b/3a inhibitors to the treatment protocol seems to be safe and likely effective. Currently, it is unclear which of the medications from this group is the safest, the specific minimal dose required, or whether there are any advantages to administering the drug by the IV or intra-arterial route. Other than the present study, we found no other publications focused on the combined treatment of IV aspirin with a low dose of intra-arterial glycoprotein 2b/3a inhibitors after endovascular stenting.

Based on the existing literature, most of the symptomatic thrombotic events after carotid stenting are either immediate or within the first 24 h.[17] Therefore, improving the antiplatelet treatment during and immediately after carotid stenting may also improve the outcomes of carotid stenting. The small intra-arterial bolus of Integrilin administered directly to the stented artery, as presented in this study, was possibly just enough to protect against a possible acute thrombogenic process, until the effects of IV aspirin were evident. Aspirin boosts the oral antiplatelet therapy administered to the patient before the procedure.

We also observed delayed restenosis in patients from group 1 alone. It is theoretically possible that immediately after stenting, an aggressive antiplatelet protocol influenced late in-stent stenosis.

Besides a sample size limitation, the present study is also limited by its focus on just one specific regimen, using IV aspirin with a single specific glycoprotein 2b/3a antagonist (Integrilin). It is very likely that other combinations may also be safe and effective.

The safety and possible efficacy of this specific protocol was confirmed in the present study. Further studies are needed to prove the safety and efficacy of a specific drug regimen that could further reduce the complication rates of carotid stenting specifically, and endovascular procedures generally.

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