Adjunctive Treatment with Low Dose Intraarterial Integrilin and Intravenous Aspirin During Carotid stenting – Case Series

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**Abstract**

According to most guidelines,medical protocol used for carotid stenting includes Oral Aspirin and Clopidogrel administered at least four days before the procedure, with intra-procedural Intra-venous Heparin.

Some publications are showing safty of adding Glycoprotein 2b/3a inhibitors to the protocolduring carotid stenting.

In this retrospective study, we aimed to evaluate the safety of a new medication protocol that includes an addition of Intravenous ASPIRIN and Intra-arterial Integrilin during the procedure.

Methods: All patients who underwent carotid stenting in Soroka University Medical Center (emergent cases were excluded) from January 2015 to May 2020 were included. We divided the patients into two groups: 1. Patients treated under the standard protocol 2. Patients treated according to the new protocol in which in addition to the standard protocol regimen, patients received just immediately before stenting Intravenous Asprin 150 mg, and immediately post stenting 2-3 mg of intra-arterial slow injection of Integrilin(Glycoprotein 2b/3a antagonist).

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

Conclusions: In this study, we would like to share the safety and possibly the efficacy of this specific protocol that includes an addition of intravenous Aspirin and a small dose of Integrilin Intra-arterial immediately post stenting. Further studies are needed to prove the safety and efficacy of a specific drug regimen that will decrease further the complication rate of carotid stenting.

**Introduction**:ron

During the last decade, carotid stenting has become widely used for secondary stroke prevention in selected patients(1)(5). Early ischemic complications during carotid stenting occur in 3-13% of the 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 placed in the vessel are contributing to the development of the ischemic events(1).

Embolic protection devices are used to prevent stroke by the first mechanism, and antiplatelet medications are given to help dealing with the second one(1–5).

Current medical menegment according to most guidlinesfor carotid stenting includes Oral Aspirin and Clopidogrel administered at least four days before the procedure, with intraprocedural Intra-venous (IV)Heparin with a goal of 250-300 seconds ACT( activated clotting time)(6). Clopidogrel resistance is found 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).There are some point of care tests to asses platelets inhibition under Clopidogrel effects but theyre positive predictive value is still low.(20)

Some publications are dealing with adding different doses of Glycoprotein 2b/3a inhibitors to the protocol in order to reduce the rate of ischemic events. Most of them showed safety, and some showed efficacy as well, but no large multicenter trials were published yet to confirm the usage of a specific protocol(2,7–9).

Usage of (IV)Aspirin during endovascular procedures, including during emergant stenting, is considered safe and effective(10,18). According to our knowledge, no available publications are dealing with its specific use as a routine,during non –emergant carotid stenting..

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When IV Aspirin became available in our country, we decided in our center to add a low dose of IV Aspirin (150mg) just before stenting as a preventive measure in order to boost the effect of Aspirin taking under consideration the high rate of clopidogrel resistance. Even after adding IV Aspirin to the protocol, we noticed, in some cases, minimal stent protrusions that responded well to a low dose of Intra-arterial (IA) Integrilin (Glycoprotein 2b/3a Inhibitor). Stent protrusions are known to be predictors of ischemic events post stenting (12), but sometimes it is visually unclear if there are micro protrusions seen post stenting. In order to prevent possible micro protrusions, we started to add a low dose of Intra-arterial Integrilin in all patients post stenting routinely and follow them for ten more minutes radiologically and clinically before ending the case.

In this retrospective study, we aimed to evaluate the safety and outcomes after changing the medication regimen during the procedure, compared to the standard protocol we used before.

**Methods:**

In this retrospective analysis, we analyzed the outcome of ICA stenting before and after a change in the prevention protocol.

Study population: All patients who underwent elective or urgent carotid stenting in Soroka University Medical Center (emergent cases were excluded) from January 2015 to May 2020. We divided the patients into two groups: 1. Patients treated before May 2018 according to the standard protocol: oral Aspirin 100 mg+ oral Plavix 75 mg at least four days before the procedure, and at least six weeks post-procedure, IV Heparin during the procedure with keeping the ACT between 250-300 seconds 2. Patients treated after May 2018according to the new protocol in which in addition to the standard protocol regimen, patients received just immediately before stenting Intravenous Asprin 150 mg, and immediately post stenting 2-3 mg of IA slow injection of Integrilin(adjusted to body weight). All the patients treated, did not have ASPECT score <8. We compared the demographic characteristics, medical history, procedural details, medications, indications for the procedure, and complications between groups. The institutional ethics committee approved the study protocol.

Procedural management: After arterial femoral access was established, a 50-Units/KG bolus of intravenous Heparin was administrated to achieve an activated coagulation time between 250-300 seconds. A 8FR guiding catheter (Neuronmax, Penumbra) was navigated to the common carotid. Over 014 microwire, embolic protection device was(SPIDER 5, Medtronic)was navigated and deployed in the petrous carotid. Stenting with Cguard (Inspire-MD)/Xact(Abbott)/Percise (Cordis)/Wall stent(Boston Scientific)was performed based on the operator's decision, followed by balloon angioplasty (Viatrac, Abbott). Patients from group 2,were treated additionally with IV Asprin 150 mg just before stenting and with a slow Intraarterial injection of 2-3 MG Integrilin from the guiding catheter post stenting. After the procedure, all patients were admitted to the Neuro ICU unit with strict blood pressure control and frequent neurological status evaluations for at least one night, followed by at least two nights of ward admission. All patients were treated with Aspirin and Plavix for six weeks. Six weeks later, a Doppler was performed, and if the the follow-up Doppler showed normal flow within the stent, Plavix was stopped, and the patient continued treatment with Aspirin only.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables 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 of carotid stent and those treated with the common one. *t*-test or one-way ANOVA for continuous variables with normal distribution, Mann Whitney U Test (Wilcoxon Rank Sum Test) or Kruskal-Wallis (one-way ANOVA on ranks) for continuous variables with non-normal distribution and Chi-square or Fisher exact test for categorical variables. Statistical significance was defined as a p-value < 0.05.

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

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

**Results:**

Between January 2015 to May 2020, 85 patients underwent a non-emergent carotid stenting in our institution. Forty-five of the patients were treated according to the standard protocol (group 1), and forty-two patients were treated according to the augmented protocol (group 2). Table 1 presents the patient characteristics in both groups. More patients on group 2 had a history of Ischemic heart disease (p=0.031); otherwise, there was were no significant differences in the demographic details and the relevant medical history between groups (Table 1).

Symptomatic carotid stenosis (TIA or stroke) was the indication for stenting in 80% of the patients In group 1 and in 69% of the patients in group 2 (p=0.240). The rest of the patients went through the stenting with the indication of a-symptomatic carotid stenosis of over 80%. The two groups had comparable degree of pre-stenting mean stenosis (85.47±11.44 in group 1 and 84.11±11.17

 in group 2) per CT Angiography (p=0.390) (table 2).All patients received at least four days of Aspirin and Clopidogrel before procedure. Over 50% of the patients received Aspirin and Clopidogrel more than a week before the procedure without any significant difference between groups (p=0.835, P=0.311)(table 2).

In group 1,seven patients had any kind of complications(16.3%)%), three minor (one transient contrast nephropathy and two groin hematoma), and four major complications (three ischemic events: one of them due to stent reocclusion, and one hyperperfusion syndrome with intracerebral hemorrhage). In group 2, no complications from any kind were noted (p=0.012)(table 3).No major or minor beeding was noticed in the second group.

It is also worth mentioning that complications occurred only in symptomatic patients.

Thirty-one patients from group 1 (68.9%) and twenty-four patients from group 2, attended a follow-up visit 8-10 weeks after discharge (p=0.054). None of the patients from both groups complained of new neurologic symptoms. Three of the patients from group 1 (6.7%), and none of the patients from group 2 had over 50% stenosis within the stent on follow up Doppler (table 3).

**Discussion:**

In this retrospective case series, we evaluated the safety and the outcomes of a new medication regimen used during carotid stenting. The new regimen included the addition of intra-venous Aspirin during the procedure before stenting and a low dose of intra-arterial Integrilin immediately post stenting. We compared the complications between groups before and after the protocol has changed and showed a significant reduction in the number of complications.

Qureshi et al.(2)showed the feasibility of combined treatment with high dose Integrin (during and 24 hours post-procedure), Aspirin, Clopidogrel, and low dose Heparin during carotid stenting. Also, Kapadia et al(9). showed safety and even a significant reduction in Ischemic complications after adding Glycoprotein 2b/3a to the treatment protocol.

Hugh et al(13) Showed the safety of adding glycoprotein 2b/3a inhibitors to the regimen in emergent carotid stenting, which is considered a procedure with an even higher risk for hemorrhagic transformation to begin with.

 On the other hand, Wholey et al.(7), showed a significantly higher rate of carotid stenting complications when adding a high dose of Glycoprotein 2b/3a inhibitors to Aspirin, Plavix, and Heparin (administrated during the procedure).

Dornbos et al.(14) . reviewed over 20 publications in which Glycoprotein2b/3a inhibitors were added to an Aneurysm coiling medical regimen as a preventive/ salvage treatment. The medication was given IA/IV, in different doses, with/ without 12 hours of infusion post procedures. This review showed a significant reduction in thromboembolic events with a minimal increase in the risk of intracerebral hemorrhage.

It should be mentioned that the use of Glycoprotein2b/3a is indicated formally for coronary thrombosis(15); therefore, the doses and treatment protocol used in most neuroendovascular studies are based on Cardiologic recommendations. Since the brain tissue is known to be the most sensitive tissue in the body for ischemic/reperfusion processes(16), an adjustment of the dosage should be considered.

Based on existing studies(2,7,13,14), adding Glycoprotein2b/3a inhibitors to the treatment protocol seems to be safe and probably effective. Currently, it is unclear which one of the medications from this group is the safest, what is the minimal dose that needs to be given, and if there is a better effect administrating the drug intra-venous or intra-arterial.

Other than our study, we did not find any publications dealing with the combination of Intravenous Aspirin with Intra-arterial low dose of Glycoprotein2b/3a inhibitors post endovascular stenting.

Based on the existing literature, most of the symptomatic thrombotic events post carotid stenting are immediate or within the first 24 hours(17). Therefore, improvement of the anti-platelets treatment during and immediately after carotid stenting may improve the outcomes of carotid stenting.

It is possible that the small Intra-arterial bolus of Integrilin administrated directly to the stented artery ,as presented in our study, is just enough to protect from a possible acute thrombogenic process until the IV Aspirin effect will start and boost the oral antiplatelets given to the patient before the procedure.

We also noticed in our study, that delayed restenosis was found only in patients from group 1. It is theoretically possible, that immediate post stenting aggressive antiplatelet protocol influences late in-stent stenosis.

Besides the size limitation, our study is also limited since it is showing one specific regimen using IV Aspirin with one specific glycoprotein2b/3a antagonist (Integrilin). It is very likely that other combinations can be safe and effective.

In this study, we would like to share the safety and possibly efficacy of this specific protocol. Further studies are needed in order to prove the safety and efficacy of a specific drug regimen that will decrease further the complication rate of carotid stenting in specific, and endovascular procedures in general.

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**Tables:**

Table 1: Patients Demographic and clinical Characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | Old ProtocolN=45 | New ProtocolN=42 | P-value |
| Gender (male) –N (%) | 30 (66.7%) | 33 (78.6%) | 0.214 |
| Age, years –Mean ± SDMedian (IQR) | 65.02±8.4265.0(58.5;71.0) | 66.14±7.9566.0(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 |

Table 2: Pre-procedural indications (clinical and radiological) and medical treatment

|  |  |  |  |
| --- | --- | --- | --- |
|  | Old ProtocolN=45 |  New ProtocolN=42 | P-value |
| Percentage of stenosis per CTAMean ± SDMedian (IQR) | Treated artery | 85.47±11.4490.0(80.0;95.0) | 84.11±11.1790.0(80.0;90.0) | 0.390 |
| Days with Plavix (prior) - N (%) | 4-6 | 13 (48.1%) | 12 (35.3%) | 0.311 |
| 7< | 14 (51.9%) | 22 (64.7%) |
| Days with Aspirin (prior) -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 at admission(yes)- N (%) | 26 (57.8%) | 22 (52.4%) | 0.613 |
| Symptomatic (yes)- N (%) | 36 (80.0%) | 29 (69.0%) | 0.240 |

Table 3: Complications during and after the procedure

|  |  |  |  |
| --- | --- | --- | --- |
|  | Old ProtocolN=45 |  New ProtocolN=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 Complication (yes)- N (%) | 7 (16.3%) | --- | 0.012 |
| Follow-up Visit (yes)- N (%)  | 31 (68.9%) | 24 (57.1%) | 0.054 |
| \*Stent significant Stenosis on follow up visit (yes)- N (%)  | 3 (6.7%) | --- | 0.243 |