Systematic Review

Endovascular management for tandem occlusions of anterior cerebral circulation

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ABSTRACT

الأهداف: لمقارنة بين طرق العلاج المختلفة من ناحية القسطرة العصبية لعلاج انغلاق الشريان السباتي المتزامن.

الطريقة: تمت مراجعة الأبحاث المنشورة في طرق علاج انغلاق الشريان السباتي المتزامن من خلال استخدام القسطرة العصبية.

النتائج: وجد الباحثون 106 حالات (متوسط العمر كان 64 عاما،من 18-90 عاما)، وكان معدل الإعاقة حسب NIHSS 16.5. وكان متوسط الوقت ما بين بداية الأعراض إلى بداية القسطرة 396.85 دقيقة، و 80.3 دقيقة ما بين بداية القسطرة إلى فتح الشريان. كان متوسط التحسن mRS 2.31، حيث أن 61.3% لديهم mRS 2 فأقل. بالإضافة إلى ذلك، فإن 80% من المرضى الذين تم فتح الشريان لديهم في أقل من 60 دقيقة من بداية القسطرة، كان معدل mRS 2 فأقل ، مقارنة ب 51.5% فقط في المرضى الذين احتاجوا زمنا أطول لفتح الشريان. على الرغم من أن 11.3% فقط خضعوا لعلاج القسطرة بالطريقة العكسية لفتح الشريان، إلا أن 81.8% منهم كان معدل mRS لديهم 2 فأقل، مقارنة ب 60.8% فقط ممن خضعوا للعلاج بالطريقة التقدمية. وجد أن إعطاء العلاج المذيب tPA يعطي نتائج إيجابية من ناحية درجة فتح الشريان.

الخاتمة: وجد أنه إذا كان الوقت من بداية القسطرة إلى حين فتح الشريان 60 دقيقة فأقل وأن استخدام الطريقة العكسية لفتح الشريان، كلاهما، يعطي نتائج إيجابية عل مقياس mRS. كما وجد أن استخدام العلاج المذيب الوريدي كان مصحوباً بمعدل أعلى في فتح الشرايين دون أن يكون لذلك أثر من الناحية السريرية.

Objectives: To compare the endovascular approaches and techniques used to treat tandem occlusions of anterior cerebral circulation.

Methods: A literature review was carried out using PubMed to review the studies that described endovascular therapies for patients with tandem cerebral occlusions.

Results: A total of 106 patients (median age: 64 years; range: 18-90 years) were identified. The median National Institutes of Health Stroke scale score at the time of admission for 104 patients was 16.5 (standard deviation [SD] ±5.7). The mean times and ranges from symptom onset to recanalization were 396.85 minutes (range: 120-1,574 minutes) and from groin puncture to recanalization were 80.3 minutes (range: 14-180 minutes). The mean outcome modified Rankin scale (mRS) score was 2.31 (SD ±2.2), and 61.3% of patients had an outcome mRS score ≤2. Moreover, 80% of patients with a groin puncture-to-recanalization time of ≤60 minutes had a mRS score ≤2 compared to 51.5% of patients with longer times (p=0.02). Despite that only 11.3% of patients underwent a retrograde approach, 81.8% of them had an outcome mRS score ≤2 compared to 60.8% of patients with an anterograde approach (p=0.023).

Conclusion: A groin puncture-to-recanalization time of <60 minutes and a retrograde approach were shown to be favorable prognostic factors in terms of mRS score. The use of intravenous tissue plasminogen activator was associated with higher Thrombolysis In Cerebral Infarction scores, but not superior prognosis based on mRS.

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Tandem cerebral occlusion is defined as stenosis or occlusion of the cervical segment of the internal carotid artery (ICA), which is associated with thromboembolism to one or more sites along the anterior cerebral circulation. Although intravenous (IV) tissue plasminogen activator (t-PA) is the standard of care for stroke patients, only 31% of patients achieve successful recanalization.[1] This poor outcome is attributed to the limited delivery of thrombolytic medications to the distal ICA thrombus due to proximal ICA occlusion/stenosis. Recently, endovascular management of this challenging condition was shown to have promising results; however, controversies still exist as to whether an endovascular approach is associated with better prognosis and whether or not thrombolytic or antiplatelet medications should be used.[2] Our study was conducted to review the previously published endovascular therapies in the literature and to compare approaches, primarily anterograde and retrograde techniques, as well as to determine the most appropriate timing of procedures and the use of medications based on outcome-related prognostic scales.

Methods. A literature review was carried out using PubMed; studies that described the endovascular management of tandem occlusions related to the anterior cerebral circulation were searched. We used the following search terms: "tandem", "occlusion", and "cerebral". Our inclusion criteria were defined as follows: patients who were ≥18 years at the time of diagnosis of an ischemic stroke at one or more sites of the anterior cerebral circulation with concomitant extracranial ICA stenosis/occlusion; and those who were treated through endovascular stentriever techniques. Endovascular therapy included thrombectomy for the intracranial thrombus, as well as angioplasty or stenting of the extracranial ICA stenosis/occlusion. The endovascular approaches were classified, both in the literature and in our study, as either anterograde or retrograde based on the sequence in which the 2 lesions were addressed. In the anterograde approach, extracranial revascularization was performed first via angioplasty or stenting followed by removal of the thrombus at the distal intracranial site. The retrograde approach was represented by the opposite order, where a thrombectomy was carried out first before going back to manage the proximal ICA stenosis/occlusion. For the identified patients, we reviewed their demographics, presenting and follow-up National Institutes of Health Stroke Scale (NIHSS) scores, lesion sites, endovascular approach used, timing from the onset of symptoms to revascularization, timing from groin puncture to revascularization, the use of antiplatelet or thrombolytic therapy, modified Rankin scale (mRS) scores, Thrombolysis In Cerebral Infarction (TICI) scale scores, and associated complications. Although some of the research included studies that missed some variables, the studies that did not mention most variables – especially variables related to approach and prognosis, or those that indiscriminately mentioned the variables for all patients – were excluded. Review articles and published abstracts were also excluded.

As publications of positive stentreiver studies started to emerge in 2013, we limited our study to the period spanning 2013–2015 (**Figure 1**). Data were collected and then analyzed using IBM SPSS Statistics for Windows version 21 (IBMCorp, Armonk, NY, USA). Pearson's chi-squared test was used to determine statistical significance.

Results. After the literature review was performed, we identified 12 studies that met our inclusion criteria.[2-13] After applying our exclusion criteria to the included articles and their data, we ended up with 10 studies that included 106 adult patients. All patients presented with acute ischemic strokes and had concomitant ICA stenosis or occlusion and were managed via endovascular measures. **Table 1** presents the included articles, their year of publication, the number of patients in each study, and the endovascular approach used.

Of the included studies, 5 were from the United States, 2 were from South Korea, one was from Germany, one was from the United Kingdom, and one was from Jerusalem. In these studies, 32 patients were male (30.3%), 10 were female (9.4%) and, interestingly, gender was not mentioned for 64 patients (60.4%). The median age at the time of presentation for 65 patients was 64 years (range: 18–90 years).

The median (standard deviation) NIHSS score for 104 patients at the time of presentation was 16.5±5.7. The mean mRS score for 40 patients was 1.93±2.28. All patients had associated extracranial ICA stenosis or occlusion. Further, 29 (27.4%) patients had their stenosis/occlusion at the right ICA compared to 23 (21.7%) patients who had theirs at the left side. The remaining 54 patients had stenosis/occlusion of unidentified lateralization. The intracranial occlusion site was described for all patients. The most common intracranial occlusion site was found in the middle cerebral artery (MCA) in 69 patients (65.1%), which was followed by the occlusion of intracranial segments of the ICA in 30 patients (28.3%) and the anterior cerebral artery (ACA) in 7 patients (6.6%). Six patients (5.7%) experienced more than one intracranial occlusion along the anterior cerebral circulation.

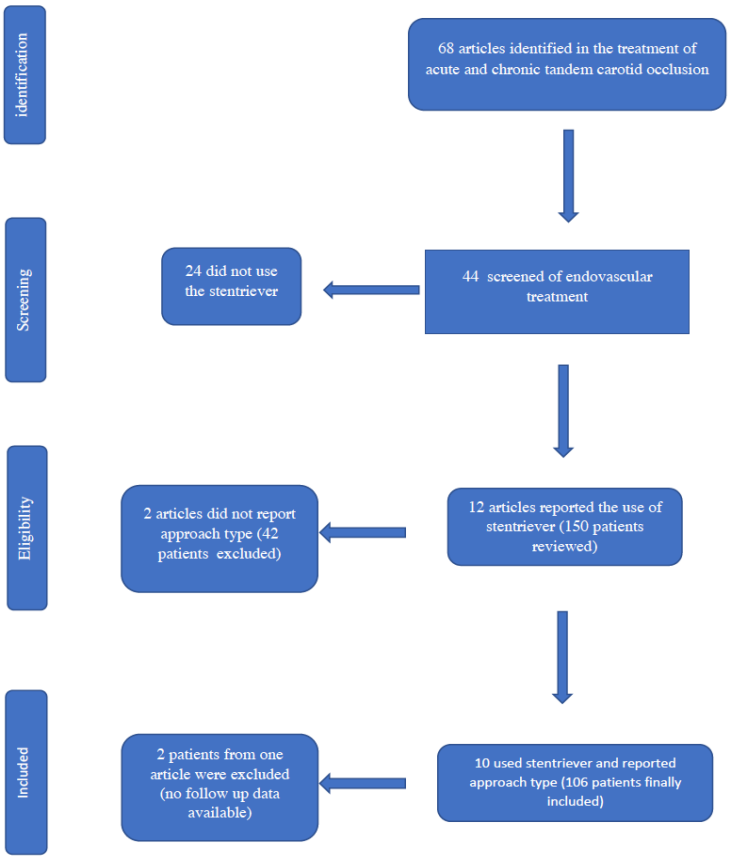

Figure 1 - Flow chart indicating the process of screening papers on tandem carotid occlusions.

All patients underwent endovascular management to address the 2 lesions. Ninety-four patients (88.7%) were treated with an anterograde approach, meaning that the ICA stenosis/occlusion was addressed first, followed by the intracranial thromboembolism. In the remaining 12 patients (11.3%), a retrograde endovascular approach was employed, where an initial mechanical thrombectomy was performed, followed by balloon angioplasty and stenting of the involved ICA in some cases, and by the Dotter technique in others. In 60 patients (56.6%), extracranial carotid stenosis or occlusion was treated using endovascular stenting alone; the combined use of stenting and angioplasty was applied in 35 patients (33%). The Dotter technique was used for 7 patients (6.6%), aiming to recanalize the extracranial segment of the ICA. Conversely, the intracranial occlusions sites were managed by mechanical thrombectomy in 102 patients (96.2%), and spontaneous recanalization following carotid revascularization was noted in the remaining 4 patients (3.8%), who underwent the anterograde approach. The mean and median times from symptom onset to recanalization of the intracranial occlusion (described

Table 1 - Included studies, their years of publications, countries and number of patients.

Study number	Year of publication	Number of patients	Endovascular approach
1[3]	2013	7	Both
2[4]	2013	17	Anterograde
3[5]	2014	11	Anterograde
4[6]	2014	4	Anterograde
5[7]	2015	7	Retrograde
6[2]	2015	16	Anterograde
7[8]	2015	3	Anterograde
8[9]	2015	11	Anterograde
9[10]	2015	23	Anterograde
10[11]	2015	7	Anterograde

Table 2 - Groin to tecanalization yime versus modified rankin scale.

Time	Modified rankin scale		Total
	≤2	>2	
≤60 minutes	20	5	25
>60 minutes	17	16	33
Total	37	21	58

$p<0.05$ is statistically significant

Table 3 - The relationship between the administration of IV t-PA and TICI Scale.

IV t-PA	TICI scale		Total
	≥2b	<2b	
Received IV t-PA	23	1	24
Didn't receive IV t-PA	25	8	33
Total	48	9	57

$p<0.064$ is statistically significant, IV t-PA - ntravenous tissue plasminogen activator, TICI - Thrombolysis In Cerebral Infarction

for 54 patients) were 396.85 minutes and 326 minutes, respectively (range: 120–1,574 minutes). However, the mean and median times from groin puncture to recanalization for 61 patients were 80.3 minutes and 71 minutes, respectively (range: 14–180 minutes).

Furthermore, 99 patients (93.4%) received antiplatelet medications as part of their treatment, while 7 patients (6.6%) did not. It is critical to mention that all 7 patients underwent a retrograde approach and Dotter technique in this review. Moreover, 40 (37.7%) patients received IV t-PA and no patients received intra-arterial t-PA. The median outcome NIHSS score (SD) for 57 patients was 5±5.6. The outcome mRS was described for 103 patients with a mean and median of 2.31 and 2, respectively, and a standard deviation of ±2.2. Sixty-five patients (61.3%) had outcome mRS scores ≤2. TICI scale scores were described for 79 patients with a mean of 3.62±1.15. Sixty-two patients (58.5%) had TICI scale scores of 3/2b.

Table 2 shows the correlation between the groin puncture to recanalization time of less and more than 60 minutes and the outcome mRS score. As shown, 80% of patients who had a groin puncture to recanalization time of ≤60 minutes had an mRS score ≤2 compared to 51.5% of patients with longer times who had the same outcomes (p=0.025). Moreover, 73.8% of patients who were recanalized within 90 minutes had an mRS score ≤2 compared with 37.5% of patients with a time >90 minutes (p=0.01).

Furthermore, 81.8% of patients who underwent a retrograde approach had an mRS score ≤2, while 60.8% of patients who were treated through an anterograde technique had similar results (p=0.023). However, it is important to mention that 7 patients in the retrograde group underwent the Dotter technique for extracranial ICA stenosis/occlusion and they did not receive antiplatelet therapy.

Table 3 elaborates on the relationship between the administration of IV t-PA and TICI scale scores; 95.8% of patients who received IV t-PA had a TICI score ≥2b compared to 75.7% of those who did not having the same TICI score (p=0.064). However, 60.5% of patients who received IV t-PA had an mRS score ≤2 compared to 63.3% of patients who did not receive the same type of medication (p=0.14).

The mortality rate in this review was 21.7%. The most commonly noted complication was cerebral hemorrhage in 11 patients (10.4%). Cerebral hemorrhage was significantly associated with mortality in 80% (p=0.05). Three patients (2.8%) had subarachnoid hemorrhage and 2 patients (1.9%) had acute re-occlusion of the ICA. Other complications included MCA perforation, non-flow-limiting dissection, and pneumonia. Finally, 53 patients (50%) had no reported complications.

Discussion. Tandem cerebral occlusion is a rare subtype of acute ischemic stroke, which affects the extracranial segment of the ICA by stenosis/occlusion in conjunction with thromboembolism in one or more sites of the anterior cerebral circulation. This is more critical and challenging to manage, as the delivery of IV t-PA is hindered by the occlusion of the ipsilateral ICA with a low recanalization rate.[1,13,14] Similar to what was reported in the literature,[15] we found that the most common intracranial occlusion site is the MCA (found in 65.1% of patients), followed by the intracranial segments of the ICA (28.3% of patients).

The definitive treatment for such a condition is still controversial.[3,16] Patients who suffer from acute ischemic strokes with tandem occlusions have high risks of morbidity and mortality.[17] Recently, the endovascular treatment of tandem cerebral occlusions has shown encouraging outcomes through stenting or angioplasty of the extracranial lesion and mechanical thrombectomy for the intracranial thrombus.[4,13,18-21] However, the explicit endovascular method remains unclear in terms of the sequence in which the two lesions should be addressed, as well as in terms of the recanalization techniques used.[3]

The anterograde approach aims to address the ICA stenosis/occlusion prior to reanalyzing the distal lesion. Balloon angioplasty, stenting, or both are usually utilized to achieve this goal. The anterograde approach

is currently the most favored approach and has the advantage of enhancing the blood flow distally through collateral circulation, decreasing the risk of subsequent thromboembolism; this approach is technically more convenient, as it enables the easier passage of the guide catheter.[12,22,23] In our review, 2 patients had recanalization of their distal lesions that was achieved just by treating the proximal ICA without the need for mechanical thrombectomy. The theoretical disadvantage of the anterograde approach is that it might delay the recanalization of the distal occlusion, which could lead to a less favorable prognosis.[1]

On the other hand, the retrograde approach is advocated for salvaging as many neurons as possible by crossing the ICA plaque to evacuate the distal thrombus intracranially, which is the direct cause of cerebral ischemia; following this, the ICA stenosis/occlusion can then be addressed. However, this approach is technically more challenging and has a risk of re-occlusion, as the ongoing atherosclerotic plaque might shower more thromboembolic materials.[22,23] Stent-assisted and aspiration devices are the most commonly used measures employed to perform mechanical thrombectomies. A trans-anterior communicating artery (Acom) approach was also described in the literature, where an operator utilizes the contralateral ICA to go through Acom with the aim of accessing the ipsilateral anterior cerebral circulation to perform mechanical thrombectomy before addressing the ICA stenosis/occlusion.[24] The recently described Dotter technique to recanalize the ICA has also shown promising results.[7]

There is no valid consensus on which endovascular approach is best for patients with tandem occlusions.[12] In our review, although only 12 patients were treated with the retrograde approach, they had a statistically significant better prognosis (mRS ≤2) compared to those who underwent the anterograde approach (81.8% versus 60.8%, respectively; p=0.023). However, this could be the result of a confounding bias, as 7 of the patients from the retrograde treatment group were not treated with antiplatelet therapy and they were treated using the Dotter technique to manage the ICA stenosis/occlusion. We do not propose that any approach is better, as there is no clear evidence in support of this to date. Randomized controlled trials are essential to determine the superiority of treatments based on prognosis.

An interesting and significant prognostic factor that we noticed was the groin puncture to recanalization time. Patients who were recanalized within 60 minutes had a statistically significant better prognosis (mRS ≤2) (80%) than those with longer procedural times (51.5%, p=0.025). This was also noted for patients with a groin puncture to recanalization time of <90 minutes. Moreover, 73.8% of patients who were recanalized within 90 minutes had an mRS score ≤2 compared to 37.5% of patients with a delayed procedural time (p=0.01).

We noticed a successful revascularization (TICI ≥2b) rate of 58.5%. Patients who received IV t-PA had a higher rate of TICI scores ≥2b (95.8%) than those who did not receive this treatment option (75.7%). However, this was not statistically significant, and patients who received IV t-PA had a similar mRS score to patients who did not receive the same medication.

The limitation of this review includes the relatively small number of patients, the disproportionate assignment of the various approaches, missing data of interest from published articles, a confounding bias, and the paucity of prospective cohorts and randomized controlled trials in the literature.

In conclusion, from this review, we observed a significantly better prognosis in patients who had a groin puncture to recanalization time between 60 minutes and 90 minutes. The superior prognosis among patients who underwent the retrospective approach was statistically significant, but this could be attributed to a confounding bias. The use of IV t-PA was associated with a non-statistically significant higher rate of TICI scale scores, but these patients did not show a better overall prognosis. We recommend conducting multicenter, prospective, randomized controlled trials to determine the optimal treatment modality (i.e., endovascular versus pharmacological therapies), and the best endovascular approach, techniques, and timing.

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