Intra-arterial treatment in acute ischemic stroke

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General Discussion

This thesis describes the evolution of intra-arterial stroke treatment in the Netherlands. It captures the period before publication of the large randomized controlled trials that would eventually lead to implementation of intra-arterial treatment as standard treatment for patients with acute ischemic stroke caused by large cerebral artery occlusion.

Evolution of intra-arterial treatment

In the Netherlands intra-arterial treatment was first applied at the beginning of this century. Initially, intra-arterial treatment consisted of administration of thrombolytics at the site of the occlusion. Later this evolved to the use of clot-retrieval devices. While the first intra-arterial treatments were done in patients suffering from posterior circulation stroke, nowadays intra-arterial treatment merely focusses on treatment of anterior circulation stroke. In chapter 1 we describe the early developments in a large Dutch teaching hospital and in chapter 2 we broaden this to a nationwide database of intra-arterial treated patients treated in the period before start of the MR CLEAN trial.[1] We studied the shift from intra-arterial therapy with local application of thrombolytics to the clot towards the use of mechanical clot retrieval devices. First, thrombectomy was performed with the Merci device, later with stent-retrievers. During the observation period, time to treatment was reduced and intra-arterial treatment was more often combined with intravenous therapy. This led to higher rates of successful recanalisation and favourable outcome.

The usefulness of stent-retrievers in reaching recanalization and hence higher rates of favourable outcome is also reflected in several large trials. At first, trials such as IMS III and MR RESCUE in which stent-retrievers were infrequently used, did not show a favourable effect of intra-arterial treatment.[2,3] In IMS III only a small minority of patients was treated with a stent-retriever and MR RESCUE merely used first generation embolectomy devices, not including stent-retrievers.[2,3] Second, three out of the five subsequent large clinical trials that evidently showed more favourable outcomes in patients treated with intra-arterial therapy, used stent-retrievers exclusively in their intervention arm (EXTEND IA, SWIFT PRIME and REVASCAT).[4,5,6] In addition, in the other two, the MR CLEAN and ESCAPE trials, stent-retrievers were used in over 80% in the intervention arm.[1,7]

A recent development in intra-arterial treatment is the so called ADAPT technique. ADAPT stands for A Direct Aspiration first Pass Technique and involves placement of the catheter in the proximal part of the clot followed by forceful suction. As the catheter does not have to travel through the whole clot, as is the case with the use of a stent-retriever, recanalisation may be accomplished faster. In addition,

because the clot is invaded only proximally, there may be less clot disruption and lower risk of distal emboli during the procedure. Several cohort studies report high recanalisation rates and shorter times to recanalisation with the ADAPT technique compared with the use of the stent-retrievers.[8,9] One would expect that these shorter times to recanalisation and high recanalisation rates result in higher rates of favourable clinical outcome. However, ASTER, until now the only randomized trial that compared the ADAPT technique with the use of stent-retrievers, failed to show a significant difference between the two techniques. Successful recanalisation was achieved in 85.4% in the aspiration group versus 83.1% in the stent-retriever group. Also, functional outcome did not differ between these two groups.[10] In addition, analysis of treatment techniques used in the MR CLEAN Registry also showed no difference in functional outcome nor recanalisation in patients treated with direct aspiration versus patients treated by a stent-retriever.[11]

In the aforementioned studies[8,9], the stent-retriever technique was often applied as escape therapy if ADAPT fails. It would be interesting to investigate whether primarily applying a combined stent-aspiration technique results in higher recanalisation rates, less distal emboli and hence higher rates of favourable clinical outcome. So far, only small cohort studies have reported on the use of this combination technique.[12,13,14]

The combination of thrombectomy techniques can be broadened even further. The PROTECT (PRoximal balloon Occlusion TogEther with direCt Thrombus aspiration during stent retriever thrombectomy) technique encompasses the use of a balloon guided catheter in addition to the aspiration and stent-retriever technique. The balloon guided catheter is used as an aid in achieving proximal flow arrest and hence results in less fragmentation and distal emboli during thrombectomy.[15] Moreover, a recent paper reported on the use of the combination of the PROTECT technique with the SAVE (stent-retriever-assisted vacuum-locked extraction) technique; the so called PROTECT^{PLUS}. PROTECT^{PLUS} resulted in higher rates of first pass complete recanalisation and a trend towards better clinical results and lower rate of embolization to new, previously unaffected vascular territories compared with PROTECT.[16] In the coming years, it may be expected that other techniques will appear to further improve intra-arterial treatment.

Factors influencing outcome after intra-arterial treatment

Though the use of stent-retrievers increased over time and recanalisation rates improved with the use of these devices, recanalisation does not automatically lead to better clinical outcome. The percentages of good clinical outcome (mRS

£ 2) found in the two cohorts described in chapters 2 and 3 were similar to that observed in the MR CLEAN trial[1], though recanalisation rates were lower. It is likely that other characteristics, apart from recanalisation, influence outcome. In chapter 7, we describe the influence of circle of Willis anatomy and carotid artery contribution on good clinical outcome after intra-arterial treatment. We hypothesized that good collateral circulation through the circle of Willis results in a higher chance of favourable clinical outcome. Contrary to our expectation, circle of Willis anatomy as such did not influence outcome. The contribution of carotid arteries to the cerebral circulation, however, did influence outcome. Completeness of the circle of Willis contributed to the influence of the carotids: only with two fully developed A1 segments and anterior communicating artery, contralateral carotid contribution can compensate for the burden of acute ipsilateral carotid or M1 occlusion.

As stated above, recanalisation and contribution of the carotid arteries to the cerebral circulation are not the only characteristics that influence outcome after intra-arterial treatment. Thrombectomy devices fragment clots and hence may create distal emboli. In the MR CLEAN trial embolization of clot fragments into new territories was seen in 8.6%.[1] Due to these distal emboli, collateral circulation becomes disrupted, influencing outcome negatively.[17] In addition, complete recanalisation does not always lead to complete (microvascular) reperfusion.[18] Incomplete microvascular reperfusion might explain for these patients with fast and complete recanalisation that they do no reach functional independence.[19] MR CLEAN MED, a trial in which heparine or acetylsalicylic acid is administered during intra-arterial treatment, aims at better reperfusion of the microcirculation.[20]

The combination of all the aforementioned characteristics in interaction with for instance, presence of leptomeningeal collaterals, clot length and time elapsed from onset of complaints probably reflect the extent of infarct core and penumbra and as a result determine good clinical outcome after intra-arterial treatment. With CT perfusion and MRI DWI/FLAIR it is possible to calculate the size of infarct core and penumbra.[21,22,23] Patients suffering from acute ischemic stroke can undergo CT-perfusion or MRI to establish if they have a favourable penumbra/infarct core ratio. In such patients, acute stroke treatment has proven to result in better clinical outcomes compared with standard treatment even after > 4.5 hours (wake-up strokes treated with intravenous thrombolysis)[21] or after >6 hours of "last seen well" (intra-arterial treatment).[22,23]

In addition to selection of suitable patients for late intra-arterial interventions, one could also hypothesize that certain patient groups with unfavourable scan profiles should be excluded from intra-arterial treatment. This results in a shift in patient

selection from a "time based" principle to a "tissue based" principle. Previous studies showed that patients with unfavourable scan profiles with large infarct cores and small penumbra, treated with intravenous thrombolysis, have a lower chance of good clinical outcome and higher chance of developing intracerebral hemorrhage.[24,25] However, the large individual patient data meta-analysis of the HERMES collaboration pooled patient data showed that ischemic core volume did not influence treatment benefit of intra-arterial treatment applied within 6 hours of stroke onset. [26,27] In other words: even in patients with large infarct cores a positive treatment effect of intra-arterial therapy is seen if treatment starts within 6 hours. Using imaging solely as predictor of good clinical outcome thus seems unwise. Future studies should combine both clinical and imaging characteristics in order to define favourable and unfavourable patient profiles resulting in better selection of patients for treatment with intra-arterial treatment.

Observational research

In addition to differences in patient characteristics that might lead to different outcomes, study design might also influence the study results. Observational studies are considered to be prone to bias due to incomparability of treatment groups and misjudgement of the treatment effect.[28] In chapter 4 we describe the effect of age on functional outcome after intra-arterial treatment in an observational cohort study. Age was found to be inversely associated with good functional outcome after intra-arterial treatment. Pooled patient analysis from MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND-IA also showed lower percentages of favourable clinical outcome after 3 months in older patients treated with intra-arterial treatment versus younger patients treated with intra-arterial treatment. However, if intervention was compared with no intervention (control), a trend favouring intervention over control was seen for patients over 80 years of age compared with younger patients.[29]

Our study did not include a control group and hence the fact that elderly suffer from higher rates of mortality and morbidity after stroke was not accounted for.

An advantage of observational research is that it is possible to study treatment effects in patients who would otherwise not be included in a randomized controlled trial. In chapter 5 we describe the use of intra-arterial treatment, including intra-arterial thrombolysis, in patients on oral anticoagulants. These patients were historically excluded or only allowed to participate in a trial if they had subtherapeutic INR levels, or if the oral anticoagulant was reversed.[30,31,32] We found that intra-arterial treatment could be safely applied in patients with prolonged INR yielding similar clinical outcomes as those with normal INRs. In the MR

CLEAN, ESCAPE and REVASCAT trials, patients with prolonged INR were no longer excluded from intra-arterial treatment.[1,6,7] The MR CLEAN and REVASCAT trials allowed inclusion of patients with an INR up to 3 and in the ESCAPE trial no upper limit of INR was defined for inclusion.[1,6,7] In addition, in the most recent national protocol on stroke treatment in Netherlands, the use of oral anticoagulants and higher age are no longer mentioned as a contra-indication for the use of intra-arterial treatment.[33]

Diagnostics

CT angiography (CTA) is used as diagnostic technique for detection of arterial occlusion or stenosis in ischemic stroke in most stroke centers over the world. For the acute setting, CTA is the preferred diagnostic technique as it can rapidly establish an acute intracranial large artery occlusion. However, for the diagnosis of high grade carotid artery stenosis, as a cause of stroke, duplex sonography is often used. Vertebral artery stenosis is related to posterior circulation stroke in the same way as carotid artery stenosis is to anterior circulation stroke. In chapter 6 we describe the use of duplex sonography for the detection of extracranial vertebral artery stenosis. We found that although duplex sonography is very capable of detecting a significant stenosis (> 50% stenosis), adequate assessment of the vertebral artery segments is often not possible due to anatomical difficulties. Most stroke patients are elderly and hence are likely to have degenerative changes of the cervical vertebrae which might hinder adequate assessment of the vertebral arteries.

The treatment of high grade, symptomatic, carotid artery stenosis is proven to result in lower risk of recurrent stroke.[34,35] For vertebral artery stenosis this is less clear. Only two trials have been performed, and both trials stopped enrolment prematurely. The first, the Vertebral Artery Stenting Trial (VAST), showed high (5%) periprocedural risk and no reduction in recurrent stroke risk in patients treated with stenting.[36] The second, the Vertebral Artery Ischaemia Stenting Trial (VIST), did report a reduction in risk of recurrent strokes in patients treated with stenting, but without reaching statistical significance.[37] Both trials included mostly proximal, extracranial vertebral artery stenoses. However, intracranial vertebral artery stenosis is considered to have a much higher recurrent stroke risk compared with extracranial vertebral artery stenosis.[38]

In summary, duplex sonography is technically capable of detecting extracranial vertebral artery stenosis, but adequate assessment is often not possible due to anatomical difficulties. In addition, if such stenosis is found, there is no evidence-based treatment, such as stenting, in addition to best medical treatment. Moreover, the extracranial artery stenosis has a lower recurrent stroke risk compared with

intracranial stenosis. Hence, it does not seem reasonable to routinely determine the presence of extracranial vertebral artery stenosis with duplex sonography in patients with vertebrobasilar stroke or TIA.

Final conclusions

In the last decade, there has been a large change in acute treatment of ischemic stroke. In the Netherlands, the first patients were treated with intra-arterial treatment at the beginning of this century and nowadays it is part of standard treatment. During this period, there has been a shift from intra-arterial thrombolysis to mechanical thrombectomy. With the use of stent-retriever devices, recanalisation rates and favourable outcomes have increased.

Selection of the appropriate patient for intra-arterial treatment remains essential. Patients on oral anticoagulants and elderly people should not be withheld such treatment. In addition, identification of predictors of favourable clinical outcome such as contribution of the carotid arteries to the circle of Willis, may help in deciding which patients should be selected for intra-arterial treatment.

Future perspective

Currently, patients are selected to undergo intra-arterial treatment within 6 hours after stroke onset if CT angiography shows a symptomatic, intracranial large vessel occlusion. Recently, for certain patient groups with a favourable penumbra/infarct core ratio, indication for intra-arterial treatment was broadened beyond 6 hours. Though different scan techniques can assist in deciding which patient would benefit from intra-arterial treatment, this should not be the only selection criterion. Future studies should focus on combining hands-on clinical and radiological characteristics that enable the clinician to make adequate treatment decisions quickly.

Besides broadening of indication for intra-arterial treatment, technical and procedural improvements will continue. Nowadays, intra-arterial treatment is mostly performed with a stent-retriever. However, aspiration techniques also seem adequate at reaching successful recanalisation with less periprocedural complications. Currently, the use of heparin during intra-arterial treatment with the aim to reduce distal emboli and restore microcirculation is studied in the MR CLEAN MED.[21] In addition, MR CLEAN No IV studies whether intra-arterial treatment without preceding intravenous thrombolysis might reduce the prevalence of hemorrhage after acute stroke treatment.[39] The results of these and other trials may result in higher recanalisation rates, shorter time to recanalisation, and less peri-procedural complications. In turn, this should result in higher rates of favourable outcomes in stroke patients.

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