Intraarterial treatment for acute ischemic stroke

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General discussion

The primary aim of this thesis was to prove the effectiveness and safety of intra-arterial treatment (IAT) in patients with acute ischemic stroke caused by a large vessel occlusion of the anterior circulation. Secondary aims included determination of treatment effect modification by several neuro-imaging and clinical parameters.

Part I: Main Results

After presentation of MR CLEAN results (Chapter 2), which showed a clear benefit towards better outcome on the mRS in favor of intervention (aOR 1.67 [95%CI 1.21 to 2.30]), several ongoing trials were halted. Some met predefined stopping criteria, others were stopped due to loss of equipoise. All studies showed a clear benefit for IAT on the primary outcome, and across all predefined subgroups. A recent individual patient meta-analysis of the recently concluded trials confirmed these results, making IAT standard of care in patients with acute ischemic stroke due to large intracranial vessel occlusion around the world (Class 1 Level A evidence).

Part II: Treatment Effect Modification by Imaging Parameters

Over the last decade, numerous studies have been published about patient selection with the use of advanced neuroimaging. Most of these studies were conducted without data from randomized trials, and therefore lacked information about treatment effect modification of the baseline neuroimaging parameter at question. Unlike most of the other RCTs, MR CLEAN did not use neuroimaging to select patients for trial participation, expect for the presence of a proximal large vessel occlusion of the anterior circulation. As a direct consequence we were able to assess the treatment modifying effect of these neuroimaging parameters.

Non Contrast Computer Tomography

The prognostic value of ASPECTS is well known, with higher scores resulting in better outcomes, in both intravenous and intra-arterial treated patient cohorts. In a post hoc analysis of the PROACT-II trial, ASPECTS dichotomized ≤7 vs. >7, was a significant effect modifier (P=0.021) in adjusted model with dichotomized mRS (0-2 vs. 3-6) as outcome. Patients presenting with baseline ASPECTS of ≤7 had no effect of intra-arterial Pro-Urokinase (RR 1.0 [95%CI 0.6-1.9]), compared to group ASPECTS >7 (RR 5.0 [95%CI 1.3 – 19.2]). For that reason patients presenting with ASPECTS ≤7 were not treated with IAT in clinical practice. Furthermore, ASPECTS has been used to select patients for trial
participation, thereby creating ‘ideal’ patient cohort. A post hoc analysis from IMS-III could not establish a treatment modifying effect of ASPECTS, which might have been related to the overall neutral results of the trial. In addition, NCCTs were made in early time windows, which could have impaired the reliability of infarct assessment. We could not find evidence for excluding patients based on baseline ASPECTS in MR CLEAN (Chapter 3). Moreover, ASPECTS did not affect the safety of IAT. Our analysis suggests that patients with ASPECTS 5-7 should not be excluded from IAT, as investigators of other studies have proposed. Further data are needed to better estimate IAT effect in patients with ASPECTS 0-4.

Computed Tomography Angiography

A major contributor to the positive results of the recent published studies, apart from the usage of retrievable stents, has been the use of vessel imaging to confirm a proximal intracranial vessel occlusion. Unlike the IMS-III and SYNTHESIS Expansion trials, MR CLEAN and others required a radiological proven vessel occlusion for study eligibility. When the IMS-III was designed, the availability of CTA was still limited, and the presence of a proximal arterial occlusion was uncertain in 47% of the patients. Data from post hoc analysis of IMS-III in patients with proven occlusion on CTA showed a shift on the mRS in favor of intervention (P=0.011). An additional advantage of pretreatment vessel imaging is the possibility to study quality of the vasculature. Vascular pathology of the extracranial ICA, such as atherosclerotic stenoses, occlusions, floating thrombi and dissections are known before groin puncture. The selection of guiding and access catheters can be made before entering the angiosuite, potentially saving time, costs and lower complication rate. Co-existing extracranial carotid lesions are associated with less favorable clinical outcome following IAT. However, in a pre-specified subgroup analysis of MR CLEAN, extracranial carotid lesions did not modify the treatment effect (Chapter 4). We found no arguments for withholding IAT in this complex subgroup. Further research is needed to determine the optimal treatment of patients with extracranial carotid disease during IAT of AIS. Treatment options include balloon angioplasty, acute or delayed stent placement or delayed carotid endarterectomy.

Chapter 5 reports the results of a post hoc analysis of the treatment modifying effect of baseline CTA collaterals. In MR CLEAN, collaterals status modified treatment effect, and benefit could not be established in patients presenting with absent or poor collaterals. Data from IMS-III showed no significant interaction by collaterals. As mentioned above, effect modification analyses of neutral trials should be interpreted with caution. An limitation was the use of single phase CTA imaging, which lacks adequate temporal information, thereby increasing the chance of mislabeling patients in the lower collateral categories. Although we found a significant treatment effect modification, we believe that exclusion based on collaterals is not yet justified, because results were
based on a post hoc analysis and the subgroups with poor and moderate collaterals were small.

Part III: Treatment Effect Modification by Clinical Parameters

Time
In MR CLEAN, the absolute risk difference for a good outcome was reduced by 6% for every additional hour until reperfusion was reached (Chapter 6). Data from the SWIFT PRIME only looked at the stent-retriever arm of the study, and estimated 91% probability of functional independence if reperfusion was reached within 150 minutes after symptom onset. The next hour, a 10% decrease of functional independence outcome was estimated, increasing to a 20% decrease for every subsequent hour of delay.24 Both ESCAPE and SWIFT PRIME placed strong emphasis on reducing the delay between onset and groin puncture. Centers were selected based on fast workflow management and proven experience with IAT. Time metrics were kept, and centers received feedback during the trial in order to improve their workflow. The ESCAPE investigators analyzed these time-intervals and showed that for every 30-minute increase in CT-to-reperfusion time the probability of achieving a functionally independent outcome was reduced with 8.3%.25 In MR CLEAN, the inter-hospital transfer increased the total time to reperfusion with 65 minutes. Benchmark times for CTA to groin puncture and reperfusion from ESPACE were only reached in 11%, and 2% of all treated patients respectively. If delivery of IAT was given within these benchmarks, an estimated increase of probability of achieving a favorable functional outcome would have been 6.1% (95% CI: -1.8 to 15.8) and 10.6% (95% CI: -3.2 to 26.7) respectively. Although the inverse relationship between time and good outcome was strong in the average MR CLEAN cohort, there was no reason to withhold treatment within the 6-hour time-window. Even though patients with absent collaterals showed no benefit in MR CLEAN, we cannot exclude the possibility these patients benefit from treatment in the ultra early time windows. Based on our results, supported by data from ESCAPE, it is expected that patients with moderate-to-excellent collaterals will benefit from intra-arterial therapy beyond the 6-hour time window.

Anesthetic Management
The anesthetic approach is most often based on the preference of the interventionist or custom of the center. In a recent survey of neurointerventional practitioners, 49% of respondents reported using general anesthesia primarily.13 A systematic review and meta-analysis on case-series showed benefit for treatment without general anesthesia.26 Before the start of the MR CLEAN trial, a prospective
registry was kept of intra-arterially treated patients in the intervention centers. The registry started in October 2002, and continued until a center started participation in the trial. Data from this MR CLEAN Pre-trial Registry suggested that patients who were treated without general anesthesia had a higher probability of good clinical outcome. In MR CLEAN, we assessed the effect of anesthetic management and observed that only treatment without general anesthesia was associated with a significant benefit (Chapter 7). Most MR CLEAN intervention centers used one approach exclusively, thereby lowering chance of selection bias based on clinical presentation, an often-heard explanation for poor outcome in the general anesthesia group. Taken together, avoidance of treatment under general anesthesia, when possible, is preferred. Clearly, our results need to be confirmed in randomized clinical trial, before solid conclusions can be drawn. Currently three trials are randomizing patients with acute ischemic stroke treated with IAT between general anesthesia and local anesthesia/conscious sedation.

Implications

In less than one year, IAT has been incorporated in guidelines across the world, changing hospital and healthcare policies. It is rare for an intervention to have such impact on health care systems, and more importantly on patient’s health. With these results, new challenges become apparent. One of these is to make the treatment available to all eligible patients, and to triage patients in fast and effective ways. Another is to make sure the treatment effect from the randomized trials is replicated in everyday clinical practice. RCT’s are often conducted in highly specialized centers and in selected patients. Trial results will serve as a benchmark for clinical practice. After conclusion of MR CLEAN, a post-trial registry was developed, in order to study this implementation, monitor outcomes, and adverse events (more information: www.mrclean-trial.org).

The Cost-effectiveness and Long Term follow-up in patients randomized in MR CLEAN (CLOT-MR CLEAN) was recently concluded and results are awaited eagerly. Patients included in CLOT-MR CLEAN have an extended follow-up period from 90 days up to 2 years after stroke onset. Every 6-months the mRS, Barthel Index and health questionnaires concerning quality of life were collected. During this period, data on healthcare costs was also collected. Data on cost-effectiveness will be essential for future reimbursement of IAT in the Netherlands.

Future research

Despite, the strong shift on the mRS in favor of IAT, poor outcome remains in 67% of the patients in MR CLEAN. Future research should aim to increase the number of patients treated, to guarantee intra-arterial treatment of all eligible patients in a safe and effective manner, to better identify patients that will not benefit, and to increase
the effect of intra-arterial therapy itself. The final outcome is related to a complex interplay of events from symptom onset to reperfusion and beyond. All steps of this chain (from stroke onset to admission, patient selection, and treatment) should be optimized to further increase the outcome of patients with AIS.

Stroke onset to admission

In order the increase the number of eligible patients presenting within the time-window for intravenous and intra-arterial therapy, we need to improve public awareness. Secondly, we need to triage patients with high likelihood of a large vessel occlusion to the nearest intervention center, bypassing the community hospital. Third, we need to assess effect of neuroprotective agents in patients presenting with large vessel occlusion.

The first goal is to create effective awareness, in order to fetch the number real stroke cases, without increasing the number of false-positive emergency department presentations. The Dutch national emergency number already triages incoming calls by assessing symptoms, and time of onset, during the telephone interview. In addition, multiple studies developed and validated paramedic stroke scales in acute setting.²¹⁻³³ Two acute stroke trials randomized patients screened by paramedics, and they only enrolled a small proportion of stroke mimics (4-12%).³⁴,³⁵ Taken together, we are able to train personnel to effectively triage stroke patients, and we need to focus on awareness itself. Public education through schools, social media and mobile apps is necessary but difficult in time of information overload.³⁶,³⁷ A TV commercial is currently being broadcasted on Dutch television sponsored by the Dutch Heart Foundation. Telemedicine, e-health-care, and telemonitoring will play major role in our lives, and will have immense effect on everyday clinical practice. Technologically advances enable secure live connection, and neurological assessment can be viewed in real-time or recorded to be assessed by neurologist or trained personnel, while patient is being transferred. These options are currently investigated in European funded project called MEDUSA (http://medusa.wptem.tsp.eu).

A second goal should be to optimize patient triage by paramedics. We need to find out what the optimal triage route is for patients with suspected large vessel occlusion. In ideal world you would have a CT scanner in every ambulance with capability to first differentiate between ischemic or hemorrhage stroke, and to assess vessel patency with CTA. There have been studies with ambulance equipped with CT-scanners,³⁸ but since the Netherlands has a very good infrastructure, and short driving distances, this option seems waste of valuable resources at this moment in time. When large vessel occlusion is suspected we need to know if we should first transport the patient to nearest hospital to receive IV treatment, or if we need to bypass the community hospital and drive to nearest intervention center. We need to assess this based on prediction model, including time of onset and additional inter-hospital transfer time. In MR CLEAN, patients transferred from a community hospital had an average increase of
110 minutes in onset to door time compared to patients who presented directly. With an average decline of 6% for chance of good functional out for every hour patient is treated later (Chapter 6), we can easily increase the effectiveness of our treatment. In addition, we need to assess how many intervention centers we need in our country, based on regional information, and total population serving the intervention centers. Similar research in intravenous alteplase treatment has been conducted in the northern part of the Netherlands.\textsuperscript{39} Centralizing this 24/7 care, making sure that all eligible patients receive IAT, in the most cost-effective manner will be necessary.

Above mentioned prehospital directions focus on decreasing the time to treatment, a well-known saying in stroke research ‘time is brain’. Decreasing time to treatment has always been major focus, but numerous studies have shown that treatment beyond commonly used time windows can result in excellent outcomes. Patients presenting with excellent collateral circulation have a higher chance of good functional outcome compared to those with poor collaterals (Chapter 5). A pre-existing carotid lesion could lead to increase of collateral pathways, but development takes times, and adjusting the amount of collaterals seems impossible in acute setting. One interesting approach would be to increase the quality of the existing collateral network in the individual patients, thereby increasing the cerebral perfusion in pre-hospital setting. Improving cerebral perfusion might result in preservation of penumbra, resulting in slower transformation to infarct-core.

Since we are unable to differentiate between acute ischemic stroke and intracranial hemorrhage, we need a drug that is capable of increasing perfusion without harming patients presenting with hemorrhage. Glyceryl trinitrate has a well-established safety profile in acute stroke. This drug showed increased cerebral blood flow and reduced infarct size in meta-analysis of animal studies.\textsuperscript{40} Glyceryl trinitrate has been tested in two acute stroke trials, which both included patients with ischemic stroke, as well as patients with intracerebral hemorrhage.\textsuperscript{34,41} There were no safety concerns in over 4000 randomized patients. Subgroup analysis pointed towards improved outcome in patients treated within 6 hours (OR 0.55 [95%CI 0.36 to 0.84]), and patients presenting with severe strokes (OR 0.84 [95%CI 0.70 to 1.01]).\textsuperscript{41} It would be interesting to assess the effect of transdermal GTN, by randomizing patients between GTN versus no GTN in pre-hospital setting.

Patient selection

Extending the time window in acute ischemic stroke research has been major focus for the last decade. Based on findings of our collaterals post hoc analysis and data from the ESCAPE, it is a logical next step to assess the effect of IAT in the 6-12 hours time window. Selection based on collaterals seems reasonable, but there are some concerns that come to mind. First, we need uniform reporting of collaterals. Reported interobserver rates are often based on expert reads, with sufficient amount of training before assessment, and are reviewed in central-core lab environment, without
experienced microvasculature. The withheld therapy.

This belief might have been harmful in patients with low scores (eq large core-infarct size). Assessment with DWI is highly sensitive and specific, with similar accuracy to $^{11}$C flumazenil PET, and has been recommended as Class I, level A evidence. DWI has a high signal-to-noise ratio, and allows fast and easy volumetric quantification. Due to the high signal-to-noise ratio DWI core-assessment has a strong inter-rater reliability for quantifying lesion extent. A potential limitation is so-called diffusion reversibility, but recent studies have shown that the occurrence is very uncommon, and involves small negligible tissue volumes, that appear of almost no clinical relevance. In an ideal world, infarct-core assessment with DWI would be used for stratification, but in the Netherlands only few hospitals have 24/7 MRI availability.

The effect of pretreatment with intravenous alteplase before intra-arterial therapy is unknown. The update AHA/ASA guideline for early treatment state the following: "Too few data are available from the small number of those who did not receive intravenous r-tPA, either for time-based or non-time-based exclusion criteria, to determine with certainty if there are characteristics that identify those who benefited from endovascular treatment". The individual patient meta-analysis of HERMES study group showed no interaction ($P=0.43$), with almost similar point estimates. In addition, the effect was even significant in the subgroup without intravenous alteplase itself. We believe that there is no reason to assume that the effect of IAT in patients with contra-indication for IVT is different the effect in patients without these contra-indications. This also raised the question if IVT is necessary in patients eligible for endovascular therapy. Some advocate that pretreatment with IVT makes thrombus extraction easier, kind of thrombus precondition. Secondly, clinical improvement before start of intra-arterial therapy was seen in 8 patients in MR CLEAN. And an additional 8 patients experienced ultra-early reperfusion and no target clot was seen on pretreatment DSA. Some studies showed that short thrombi, residual flow, occult antegrade flow, and thrombus permeability are factors of influence. Third, after thrombus extraction, IVT might have residual effect on distal emboli, embolization in new territory, and/or microvasculature. The later might be solved to use alteplase during IAT whenever needed. On the other hand, a feared complication of IVT is risk of intracerebral hemorrhage, and skipping IVT might increase effectiveness of IAT. IVT will cause additional delay to IAT initiation. Furthermore, in patients with cervical ICA pathology that require stenting, immediate antiplatelet therapy is necessary. Early antiplatelet therapy and IVT has increased risk of intracerebral hemorrhage. On the contrary, fourteen MR CLEAN patients were allocated to intervention, but IAT was withheld due to procedure related difficulties. If intracranial access is not possible,
foregoing IVT might have negative effect on functional outcome. The SYNTHESIS Expansion trial assessed the effect of IAT versus intravenous treatment. The trial included patients without the use of vessel imaging, which might have been important reason for trial neutrality. Important point is that patient in the intervention arm received treatment one hour later compared to IVT arm, with similar outcome results. If we want to assess the effect of IV alteplase prior to IAT we need a head-to-head trial randomizing patients between IVT + IAT or IAT alone. The trial should focus fast treatment initiation after randomization.

Treatment

Rigorous registration of all steps during the treatment is necessary to improve workflow. Treatment should be optimized to achieve TICI 2B-3 reperfusion grades in the majority of patients. However even with TICI 2B-3 reperfusion grade 57% of the patients had a poor outcome in MR CLEAN. Besides large infarct core at presentation, and failure to open the occluded vessel, one additional important factor is incomplete microvascular reperfusion. Recanalization is defined as opening of occluded vessel, while reperfusion is defined as adequate perfusion of the brain microcirculatory itself. Incomplete microvascular reperfusion can occur, even if the primary target vessel occlusion is recanalized adequately. This could be caused by distal embolization of microthrombi from the removed clot, or on cellular level. The mechanism behind this so called ‘no-reflow’ status, or ‘impaired microvascular reperfusion’ on cellular level, include luminal narrowing due to capillary constriction and extra-luminal compression by swollen astrocyte endfeet and pericyte contractions. The intra-luminal filling is caused by entrapped erythrocytes, leukocytes and platelets. Oxidative stress causes damage of the vessel endothelial, which results in exposure of extra-cellular matrix to blood flow, thereby triggering the adhesion and activation of platelets. Blood brain barrier permeability actives tissue factors causing fibrin deposition and microvascular occlusion. Future research should increase knowledge about mode of action and potential effect of drugs in clinical practice. From preliminary data from the Erasmus MC CorTAck biobank both presence of retrieved microthrombi and circulating Neutrophil Extracellular Traps (NETs) were associated with incomplete microvascular reperfusion. The effect of NETs is neutralized by the non-anticoagulant fraction of heparin. Unfractionated heparin is commonly used during neuro-interventional procedures for aneurysm coiling, and has historically been applied in acute ischemic stroke treatment. Data from the International Stroke Trial, showed that patients allocated to heparin had significantly fewer recurrent ischemic strokes within 14 days (2.9% vs. 3.8%) but this was offset by a similar-sized increase in hemorrhagic strokes (1.2% vs. 0.4%), so the difference in death or non-fatal recurrent stroke (11.7% vs. 12.0%) was not significant. A post hoc analysis was performed on data from the MERCI trial in patients who received periprocedural heparin with patients who did not receive periprocedural heparin. There was no significant between-group difference in
rates of hemorrhage, procedural complications, or 90-day mortality. In multivariable analysis, a 90-day good outcome (modified Rankin Scale score of 0-2) was associated with periprocedural heparin use (OR 5.89; 95% CI 1.34-25.92; \( P=0.0189 \)).

A recent retrospective study found a non-significantly higher reperfusion rate achieved in heparin-treated patients compared to non heparin-treated patients (63% vs. 50%, \( P=0.35 \)). Interestingly, patients who received heparin had significantly lower rates of hemorrhage (\( P=0.02 \)). Based on these studies, heparin could increase microvasculature reperfusion, and should be further investigated in randomized setting.

**Conclusion**

Intra-arterial treatment is of benefit in most patients presenting with acute ischemic stroke caused by an occlusion of the proximal anterior circulation. All patients presenting within the 6-hour time window should receive intra-arterial therapy, irrespective of clinical or neuro-imaging characteristics. Future research should identify patients in whom intra-arterial therapy is not effective and safe, and further increase the effectiveness and number of eligible patients.
References

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