EDITORIAL

The Time–Reset Effect

Thrombectomy Trials Challenge the Existence of a Time Window

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The concept of a time window suggests that a certain stroke treatment such as intravenous tissue plasminogen activator (IV tPA) or thrombectomy has a clearly defined time window between stroke (symptom) onset and initiation of therapy [1]. Therapy is expected to be futile if a patient is treated at a later time point. Usually, the time window is defined to end when the lower 95% confidence interval (CI) of the estimated treatment effect crosses 1.0 (“line of no effect”) or, simpler, according to the inclusion criteria of the particular trial.

Over the years, the time window became wider, in part, because accumulating data in the meta-analyses minimised the CIs that then crossed the “line of no effect” later. Whereas in an analysis of the NINDS data the “line of no effect” was already reached after 2.5 h [2], later meta-analyses including studies with broader inclusion criteria suggested time windows of 4.5 h in 2010 [3] and of 5.1 h in 2014 [4]. A similar effect can be observed for thrombectomy that seemed to be efficacious until 6.3 h first [5] and later until 7.3 h [6]. It is important to understand that the decreasing therapy benefit (for the patient population within the trials) is inversely related to the *average* increase in infarct volume (and thus shrinking amount of tissue and function that can be saved by the therapy). However, there are considerable interindividual differences in the actual course of ischemic core expansion. This leads to the issue of patient selection and its influence on the observations within the trials.

The REVASCAT authors reported a slightly disturbing observation in patients with small infarcts (ASPECTS

8–10) [7]: the adjusted odds ratio (OR) for a 30-min delay from symptom to imaging was 1.19 (range 0.75–1.88) and from imaging to revascularisation was 0.81 (range 0.50–1.30). If significant, this data would suggest that actually delaying imaging would be beneficial (sic) but then we need to hurry up once imaging is done. Similarly, in the patient-level meta-analysis of the recent thrombectomy trials [6], there was no interaction of the time from symptom onset to the emergency room and therapy effect. In contrast, there was an absolute poor outcome (mRS 3–6) risk increase for every hour delay between emergency room and reperfusion of 13.7% (8.6 to 18.2). Indeed, a hospital seems to be a very dangerous place. Based on the data, one could conclude that the transport duration to the hospital service does not matter but we need to start running as soon as the patient enters the hospital door. The missing time-is-brain effect prior to imaging or hospital admission in REVASCAT alone or in the meta-analysis contradicts everything we know about stroke. How do we explain this?

For the matter of simplicity, let us assume that we talk about the next five patients with proximal occlusion of the middle cerebral artery (MCA) in the catchment area of your hospital (Fig. 1). Let us further assume that there is a 60% chance of good outcome after thrombectomy in a patient with noncomplete infarct in the MCA territory. At 3 h after symptom onset, all five patients have the same 60% chance of good outcome. One hour later, one of the patient’s collaterals broke down because of a hypotensive period resulting in an infarct within the complete MCA territory [8, 9]. Accordingly, only four patients are left, each with 60% chance of good outcome. This results in a 48% chance of good outcome for all five patients, on average. At 5 h, another patient develops an infarct within the complete MCA territory resulting in a 36% chance of good outcome for the entire population of five.

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Fig. 1 The time–reset effect: Influence of patient selection on time dependency of therapy effects

If we now look at the three remaining patients, time does not matter. They still have the same 60% chance of good outcome after 3, 4 or 5 h. Only these patients would have been included into the majority of thrombectomy RCTs. Patients with good prognosis, as defined by small ischemic core in imaging, could be included into the trials at 3 h or at 6 h. They qualified by incomplete infarction, irrespective of time. For them, the time is virtually reset by imaging. For them, the clock again starts ticking within the CT. For the entire unselected patient population, however, time is crucial.

The time–reset effect has not been observed in the IV tPA studies or in the earlier intra-arterial stroke trials, probably because of the more population-based approach with very limited imaging selection criteria and minor influence of imaging-based patient selection. “All 5 patients” would have been included into these studies.

This time–reset effect is also beneficial for designing regional stroke organisation models. Is it better to treat five patients in a less experienced centre with a rate of 40% mRS 0–2 (total $5 \times 40\%$) or risk “losing” one patient on the transport to the more experienced centre $4 \times 60\%$ mRS 0–2 (48%)? Both the rate of “losing patients” and the differences in experience can be modified to define border conditions and other assumptions.

By no means should an earlier arrival time at imaging lead to less effort in patient logistics based on the reasoning that the patient is still within the time window. This is one of the serious practical drawbacks of the time window concept. In fact, it could be quite the opposite. If the same infarct volume (e.g. ASPECTS 6) is observed at 2 h compared

to as late as 5 h, it might indicate a more dynamic lesion expansion leaving even less time to effectively treat. These considerations may lead to the following conclusions:

First, recent data confirm that time is brain. We need to treat as early as possible as we do not know when the patient in front of us will deteriorate. Second, time windows derived from studies are profoundly influenced by patient selection and are not sacrosanct. A treatment effect can be expected even in patients far beyond the time windows as long as there is brain tissue left to rescue. In the age of individualized care and precision medicine, we need to look beyond the time window. Future studies need to define the extent of tissue damage that leaves enough tissue volume and function to save by endovascular therapy [10, 11].

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