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Webinar EVER Pharma

New international Guidelines in stroke and subacute rehabilitation

March 23, 2021

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Webinar EVER Pharma (March 23, 2021)

New international Guidelines in stroke and subacute rehabilitation

Participants

Andreas Winkler

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Moderator

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Topic: The CARS trial - Pharmacological multimodal support in acute and early subacute stroke neurorehabilitation

Thomas Platz

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Topic: Movement and Rehabilitation – linking concepts and evidence in arm motor rehabilitation

Steven Zeiler

Associate Professor of Neurology Johns Hopkins Hospital

Topic: Can we enrich stroke rehabilitation? Medical and Technological Enrichment

Order of the webinar

Introduction

A. Winkler

Dr. Winkler opened the webinar and greeted the audience from around the world joining the first in a series of EVER Pharma-sponsored scientific and medical events planned for 2021. He encouraged the audience for active participation and initiated this interaction by collecting feedback on a question regarding the clinical value of available means for supporting motor rehabilitation after stroke. More than 50% of participants indicated a pharmacological intervention, about 20% suggested a non-invasive brain stimulation and robotics while the remaining 10% supported virtual reality as a preferred tool in augmenting motor recovery. This exercise set the tone for the program designed to cover the various aspects of clinical practice of early stroke rehabilitation.

The CARS trial - Pharmacological multimodal support in acute and early subacute stroke neurorehabilitation

D. Muresanu

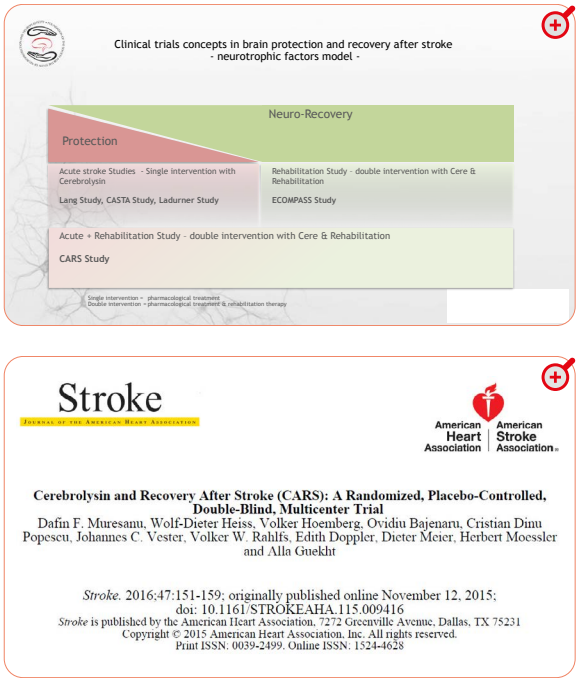
The field of neurorehabilitation in the past three decades has been marred by the failure of clinical trials in neuroprotection to deliver on their promise to bring in new effective and safe therapies. The gap between the evidence-based medicine approach to clinical research and the reality of clinical practice contributed to this problem. Today, we are still in the process of finding our way out of this impasse. Addressing the scientific prerequisites of the clinical trial's design is one necessary step in this way. The results of basic research continuously increase our knowledge of the pathophysiology of stroke. This knowledge has to be matched with the choice of an adequate treatment protocol. Finally, the clinical protocol has to be tailored specifically to the mode of action (or the therapeutic potential) of any given intervention of interest. In his lecture, Dr. Muresanu overviewed this development in the field of neurorehabilitation, with a focus on motor rehabilitation.

The scientific evidence indicates that after the brain injury, a continuous brain defense response is activated consisting of two anti-correlated sequences of events: neuroprotection and neuroregeneration. The processes of neuroprotection are immediate and aim at reducing the brain damage that leads to the clinical picture of impairment. They are followed by the mechanisms of neuroregeneration that underly the repair of the damaged brain tissue and decrease the related disability. Neuroprotection and neuroregeneration appear to be in balance after stroke and phase out each other during the recovery period. When applied for a therapeutic strategy, this concept entails for example blocking the glutamate pathway (aimed at reducing excitotoxicity) at an early stage, for neuroprotection. However, activation of the same glutamate pathway is subsequently needed for stimulating the endogenous processes of brain repair (e.g. neuroplasticity, neurogenesis).

The hyperacute (<24 h), acute (1 to 7 days), and early subacute (1 week to 3 months) phases of stroke are of special interest for developing the motor rehabilitation strategies, as they offer the time windows for both neuroprotective and neuroregenerative interventions. Nevertheless, the timing and the intensity of early rehabilitation are the subjects of continuous discussions. Early mobilization after stroke is recommended in many clinical practice guidelines, but the findings of the AVERT trial suggest that high dose, very early mobilization within 24 hours of stroke onset can reduce the odds of a favorable outcome at 3 months.[1] It seems that after stroke, the timing of intervention must reflect the patient's readiness for a clinically meaningful response to happen. It was shown, that the time window of spontaneous recovery is limited to the initial 11 weeks after stroke onset.[2] The use of biomarkers specific for the targeted neurorehabilitation domain (e.g. motor, somatosensory, cognitive, language) could help to define the biological reserve of each patient during this higher sensitivity period. For example, the Predict Recovery Potential algorithm is used to predict upper-limb functional outcomes and uses the cluster analysis based on the Actions Research Arm Test (ARAT) score at 3 months to guide early rehabilitation strategies. Unfortunately, the efforts to develop effective and safe early subacute motor rehabilitation strategies, especially for the upper limb, were inadequate or sub-optimally designed. Until 2013, out of 532 clinical trials in neurorehabilitation, only 12 met the criteria of early (within 30 days of stroke onset) intervention while investigating the pharmacological support of neurorehabilitation.[3] Additionally, a mismatch between the mechanism of action

of investigated agents and the chosen clinical trial protocol designs led to overall poor and unreliable results. What we have learned from these efforts is that even the well-developed (pre-clinically) intervention will fail if a patient's physiopathological status is not recognized and appropriately addressed by a timely administration within a tailored clinical protocol.

The main paradigm of brain protection and recovery assumes that the successful intervention must reflect both the timing and sequence of the endogenous brain processes triggered by a stroke. There are three major categories of pharmacological agents investigated in the context of neurorehabilitation. Monomodal, neuroprotective, suppressive drugs with a single or pleiotropic mechanism of action (all failed in past clinical trials); monomodal pleiotropic drugs stimulating neuroplasticity (e.g. fluoxetine); and multimodal drugs with immediate pleiotropic neuroprotective effect, but supporting also the long-term recovery process through stimulation of neuroregeneration (e.g. cerebrolysin).[4] Cerebrolysin is currently the only agent in clinical use that exhibits neurotrophic factor-like properties. The initial efforts to establish Cerebrolysin in the treatment of stroke brought mixed results due to the aforementioned issues related to the choice of the clinical trial design. The short-term, neuroprotection-centered model of intervention was later replaced by the more comprehensive approach which more closely reflected the therapeutic potential of this multimodal agent (**Fig. 1**).



Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial

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Stroke. 2016;47:151-159; originally published online November 12, 2015;
doi: 10.1161/STROKEAHA.115.009416

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Fig. 1. The clinical development program of Cerebrolysin and the CARS trial

The CARS trial represented the breakthrough concept in the clinical development program of Cerebrolysin, in which the yet untapped therapeutic potential of this drug was investigated in the context of the upper-limb motor rehabilitation.[5] Cerebrolysin was administered within 24-72 hours after stroke onset as an add-on to a standardized upper-limb motor rehabilitation program initiated within 48-72 hours post-stroke. Both interventions were administered for 21 days and the control group received the motor rehabilitation only. The primary endpoint of the study (ARAT score at day 90) showed statistically significant improvement in the double intervention group (median change from baseline = 32) in comparison with the rehabilitation-only group (median change from baseline = 11). The clinically meaningful and statistically significant change was registered already after 14 days of the double intervention. The secondary endpoints included mRS score which also showed a statistically significant shift toward no symptoms/no significant disability category in the double intervention group in comparison with the control group (42.3% vs 14.9% of patients respectively). The multivariate analysis of all 12 endpoints (ARAT plus 11 secondary endpoint parameters) also confirmed the overall superiority of the double intervention over the rehabilitation-only approach (**Fig. 2**).

The CARS design was later explored for investigating the therapeutic effects of Cerebrolysin in a milder stroke population (CARS 2 trial) and the results of the two trials were combined in a dedicated meta-analysis.[6] It confirmed overall positive results of the combined pharmacological treatment and motor rehabilitation reported in CARS. For example, the early clinical benefit measured with NIHSS at 14 and 21 days was apparent in both studies, irrespective of stroke severity, and was further confirmed in the meta-analysis.

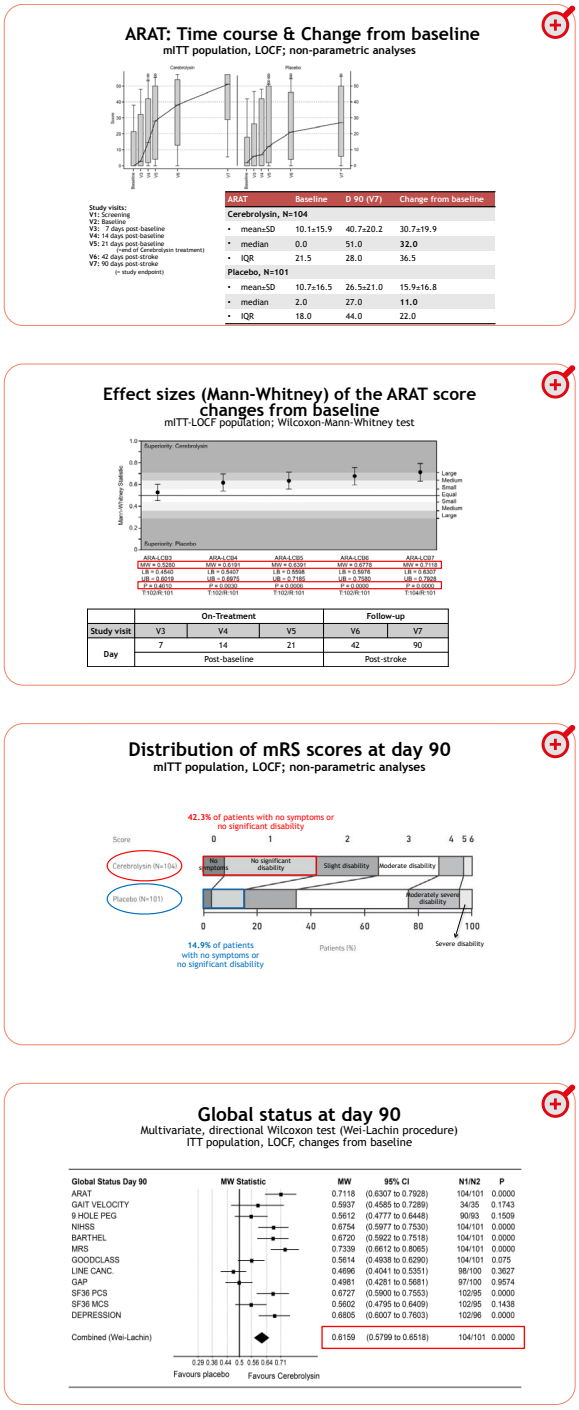

Fig. 2. The results of the CARS trial

The efficacy and safety profile of Cerebrolysin based on stroke interventions were also analyzed in the separate meta-analysis combining 9 major RCTs.[7] The primary endpoint used for this work was NIHSS and the results showed statistically significant improvement in the Cerebrolysin group with the number needed to treat (NNT) for the clinical benefit calculated at 7.7. Also, the mRS score at day 90 (in the subgroup of baseline stroke severity >12 NIHSS) showed statistically significant improvement in the treatment group in comparison with the control group. The safety profile of Cerebrolysin was favorable and similar to that of placebo.

Finally, the mechanism of action of the double intervention - motor rehabilitation plus Cerebrolysin treatment - was explored in the ECOMPASS study.[8] Here, the treatment was initiated in the second week after stroke onset. The double intervention improved, among other measured parameters, the symmetric functional connectivity (measured with rsfMRI) suggesting that Cerebrolysin acts through stimulation of the motor cortical function (**Fig. 3**).

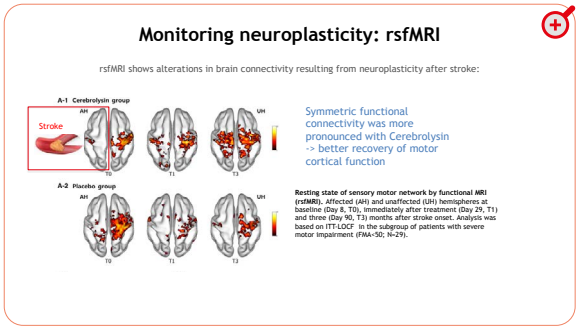

Fig. 3. The results of the ECOMPASS study: Cerebrolysin stimulates neuroplasticity

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Movement and Rehabilitation – linking concepts and evidence in arm motor rehabilitation

T. Platz

When approaching rehabilitation after stroke, we have to realize that arm rehabilitation is beneficial when arm motor function and/or arm activities are improved by the selected intervention(s). However, we have to keep in mind that all these interventions are changing the brain, not the arm. The sensorimotor control of the brain can be studied and is elucidated in neuroscientific research but is difficult to observe and to control in clinical practice. It is, therefore, the role of the clinical practice guidelines to collate the concepts and hypotheses arising from basic research and to test them using data from clinical trials (RCT's). This is how we can try to indirectly reason about the impact of the rehabilitation interventions on the brain's motor control mechanisms. Such recommendations regarding the arm rehabilitation post-stroke are based on solid clinical experimental data (systematic search and appraisal for randomized controlled trials, and systematic reviews) and are the subject of this overview. The Clinical Pathways of Stroke Rehabilitation, Evidence-based Clinical Practice Recommendations, is a collaborative work released under the auspices of the World Federation of Neurological Sciences. In its scope, 411 recombinant clinical trials (RCTs) and 114 systematic reviews were analyzed to form recommendations for arm rehabilitation alone.

The first concept/hypothesis reviewed by Dr. Platz states that motor learning and recovery of arm motor function post-stroke requires specific repetitive prolonged training schedules. The recommendations for the clinical practice confirm this thinking and state that two hours of training per week (Sehatzadeh et al., 2015) or a total of more than 15 hours of training seem to be necessary to achieve measurable effects on arm motor recovery (Pollock et al., 2014). Additionally, increasing therapy time up to two or three hours per day was shown to generate an extra benefit in the subacute phase post-stroke (Han et al., 2013).

Another important question pertains to the functional organization of the brain hemispheres. The science indicates that sensorimotor networks are organized separately in either hemisphere for the contralateral limb. Although they act independently, they can be functionally coupled. This organization suggests better success in the case of unilateral in comparison with bilateral interventions. The evidence concurs with this concept. When comparing unilateral and bilateral training approaches, activities and the actual amount of arm usage were better promoted with unilateral training (Pollock et al., 2014) among mildly affected chronic stroke survivors. At the same time, equivocal or inferior benefits after bilateral training were reported.

The hypothesis of cerebral sensorimotor networks having a diverse organization with different network constellations in cases of basic motor competencies (like selective movement in individual joints) and various advanced sensorimotor capacities (like fast finger movements, grip formation/manipulating objects, steadiness, aimed movements, visuomotor tracking) was then discussed. Dr. Platz indicated that one single center (n=60) and two multi-center RCTs (n=60 and n=148, resp.) demonstrated a superior effect of the impairment-oriented arm training, i.e. the arm basis training (ABT) for severe arm paresis and the arm ability training (AAT) for mild arm paresis. The ABT enhances selective motion capacities by systematic repetitive training of individual joint motions without gravity influence to start with, with gravity influence next, and finally multi-joint movements in a progressive training scheme. The ABT had a bigger effect on selec-

tive motion capacity (FM Arm) with incomplete severe arm paresis compared to therapeutic time equivalent control therapies, i.e. Bobath therapy or "best conventional" therapy (Platz et al., 2005; Platz et al., 2009). The AAT specifically trains speed and accuracy of abilities such as fast finger movements, aiming, visuomotor tracking, steadiness, and dexterity as well as endurance. The AAT improved sensorimotor efficiency with arm activities (TEMPA; Desrosiers et al., 1993) with a long-term effect (Platz et al., 2001) and superiority compared to therapeutic time equivalent "best conventional" therapy (Platz et al., 2009) (**Fig. 1**).

A similar conclusion can be drawn regarding the use of robots for precision motor control training. The evidence unequivocally supports robot-assisted arm training. Patients who received electromechanical and robot-assisted arm and/or hand training during the acute/subacute phase after stroke improve their activities of daily living, arm, and hand function, and muscle strength. However, these effects were uncertain in the chronic phase of stroke.

The fourth concept/hypothesis discussed by Dr. Platz concerned the division of the cerebral networks into dorsal (sensorimotor control) and ventral (conceptual knowledge, semantics/object recognition) streams. The dorsal stream has been further divided into a dorsodorsal and a ventrodorsal stream. The dorsodorsal stream is proposed to subserve online sensorimotor control of actions. The ventrodorsal stream is regarded as functionally linked to object awareness for action recognition/organization. This concept appears to be relevant for the task-specific training where the movement of the arm is contextualized within the activities of everyday life. The evidence sug-

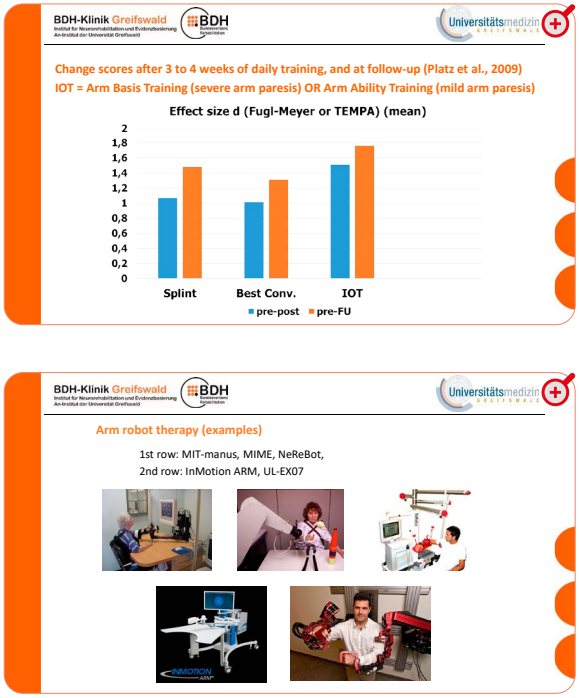

Fig. 1. The superiority of severity-adjusted motor control-focused rehabilitation (including arm robot therapy) in comparison with the splint or best conventional individualized rehabilitation practices

gests that the task-specific training does improve the outcomes, albeit the observed improvements were not big. They seemed dependent on the careful impairment assessment of the leading clinician that allows for the precise adjustment of the training regimen.

If the concept/hypothesis stipulating that cerebral networks for contralateral sensorimotor control can be activated by movement execution, movement observation (including a mirror image), and mental practice is clinically valid, then such non-physical methods could also be practiced (**Fig. 2**).

A Cochrane review (Thieme et al., 2018) included 62 studies (ten studies addressing the lower limb) with a total of 1982 participants that compared mirror therapy with other interventions. When compared with all other interventions, mirror therapy for the arm had a significant effect on motor function (activity level) (post-intervention data: SMD 0.46, 95% CI 0.23 to 0.69; 31 studies, 1048 participants). Also, mirror therapy improved the capability for selective movements (post-intervention data: FM, arm motor score MD 4.32, 95% CI 2.46 to 6.19; 28 studies, 898 participants). Similarly, according to two Cochrane reviews, Mental Practice in combination with other treatment appeared more effective in improving upper extremity (impairment and) activity than the other treatment alone (5 studies, 105 participants; SMD 1.37, 95% CI 0.60 to 2.15; Barclay-Goddard et al., 2011; 7 studies, 197 participants; SMD 0.62, 95% CI 0.05 to 1.19; Pollock et al., 2014b).

Finally, Dr. Platz discussed a concept exploring the notion that motor learning and motor recovery can be modified by increasing the level of excitability of sensorimotor networks performing and learning motor tasks. Repetitive transcranial magnetic stimulation (rTMS) has been applied during the acute, post-acute, and chronic post-stroke phases to improve motor recovery in stroke patients having upper- and/or lower limb paresis. The rationale has been that priming the

Fig. 2. The mirror therapy and the mental practice in arm rehabilitation

arm motor cortex by an excitatory stimulation of the lesioned hemisphere or by an inhibitory stimulation of the non-lesioned hemisphere (that itself might inhibit the ipsilesional motor cortex) can promote arm motor recovery. This hypothesis was corroborated in the analysis of thirty-four studies with 904 participants included in the systematic review by Zhang et al. (2017). Pooled estimates show that rTMS significantly improved short-term (SMD 0.43, 95% CI 0.30 to 0.56) and long-term (SMD 0.49, 95% CI 0.29 to 0.68) manual dexterity. The mean effect size for the acute subgroup was 0.69 (95 % CI 0.41 to 0.97), for subacute stroke 0.43 (95% CI 0.16 to 0.70), and for chronic stroke 0.34 (95% CI 0.00 to 0.69; P = 0.048), respectively.

Summing up his lecture Dr. Platz listed the key elements of arm motor rehabilitation confirmed in the evidence-based analyses. The rehabilitation should involve high-intensity motor control-specific repetitive training schedules. The sensorimotor domains of interest should be addressed specifically depending on the severity of the arm movement impairment. The process of rehabilitation should activate sensorimotor networks by specific tasks at the performance limit of a particular patient. Although active training is still the core of rehabilitation, one should consider an additional activation by mirror therapy or mental practice. Focal excitability modulation by rTMS, if the trained staff is available, is a further clinical option. These and all other recommendations can be found in the newly published guidelines of WFNR, which are freely accessible online (**Fig. 3**).

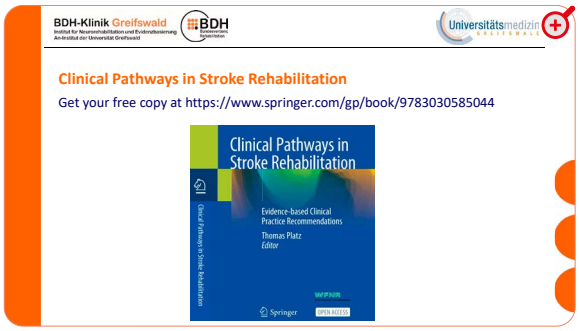

Fig. 3. The Clinical Pathways in Stroke Rehabilitation guidelines (free access)

Literature

1. All references under: Clinical Pathways in Stroke Rehabilitation. Get your free copy at https://www.springer.com/gp/book/9783030585044

Can we enrich stroke rehabilitation? Medical and Technological Enrichment

S. Zeiler

The enrichment of stroke rehabilitation requires enriched environments, which can enhance stimulation of sensory, motor, and cognitive functions. This can be achieved with the help of various means like equipment, stimulation, open spaces, desire to want to engage in restorative interventions, and internal or pharmacological enrichment. In his lecture, Dr. Zeiler focused on motor rehabilitation of the arm and he defined motor recovery as an improved success at a task that was compromised by an ischemic stroke. He also made a clear distinction between the true recovery, which represents a reduction in impairment (or restitution of kinematics) through plasticity processes, and the compensation of the lost function.

The current gold standard in motor rehabilitation remains occupational therapy which, unfortunately, affords us little influence on the restitution of the kinematics and true motor recovery of upper extremities (Cochrane Review, French, et al., 2009). This conclusion was also drawn in a more recent analysis (Veerbeek et al., PLOS one Review 2014) which found a 5% variance (statistical noise) for the clinical outcome of the occupational and physical therapy. Finally, Dr. Zeiler and coworkers (Stinear et al., 2020) analyzed 15 RCTs in the area of motor arm rehabilitation published between 2016 and 2019.[1] All these trials, irrespective of used technology or occupational/physical therapies, gave similar results as the standard of care (control groups) except the CARS trial.

Despite the largely passive character of the standard hospital environment for patient's recovery, we observe that within a specific, discreet timeframe patients do recover to a certain extent (**Fig. 1**).

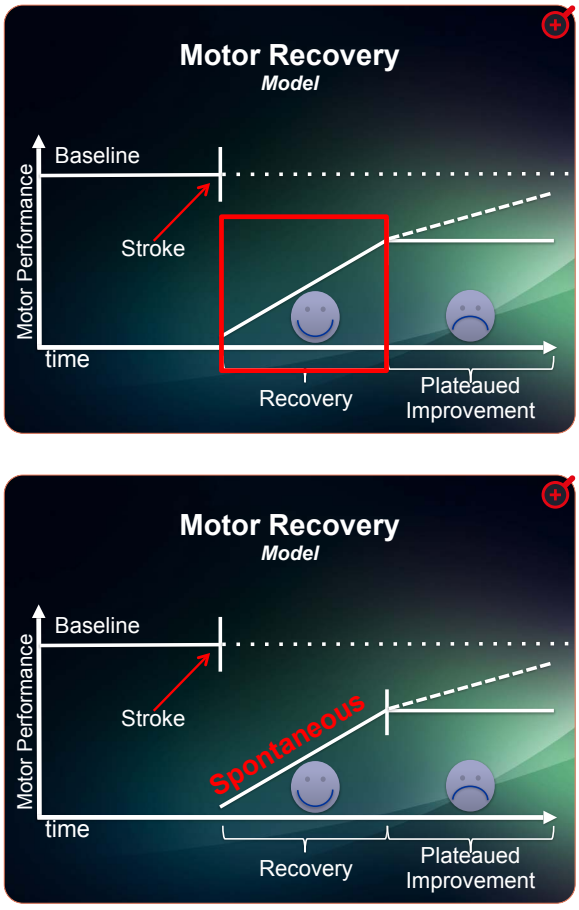

Fig. 1. The spontaneous, time-limited recovery of motor functions (true restitution of kinematics) post-stroke (period depicted by a red frame) in a standard hospital environment

After this sensitive period, the restitution of kinematics is no longer possible. Instead, rehabilitation can still progress through compensation of the lost motor function. It seems that the intact corticospinal tract (meaning, functional communication pathways from the motor cortex) is a prerequisite for spontaneous recovery to occur. This knowledge helped to define the PREP2 algorithm. What it suggests is that our rehabilitation efforts have no impact on the motor recovery of stroke patients. The question arises: can we beat this spontaneous recovery mechanism with some alternative approaches to rehabilitation? We want our patients to recover their overall, very diverse, and complex functions. However, the rehabilitation standards that we currently use offer little diversity as, mostly, they are focused on task-oriented training. We hope that the correlation equals covariation, but there is no data available confirming that the success in task-specific training will generalize or extend to domains beyond that particular task. On the contrary, task-specific training leads to improvement in that particular task, while spontaneous recovery leads to improvement generally.

According to Dr. Zeiler, there are two potential pathways to achieve the important goal of improving spontaneous recovery post-stroke. First entails quilting together multiple tasks. Albeit positive clinical effects of such an approach have been recently reported, it is not the realistic option from both the standpoint of time needed as well as the resources required for building and maintaining such an expanded therapeutic facility. The second pathway relates to the enriched environments. This concept was extensively studied in animal models of stroke. The animals exposed to an enriched environment recovered effectively the tasks on which they were never trained.[2] The question remains, what constitutes the enriched environment in the case of humans and how can we apply it for the clinical practice of rehabilitation? Dr. Krakauer's group from the Johns Hopkins University developed the concept of enriched environment based on the statistical assessment of the scope of normal arm and hand movements and the idea of attractiveness of the movement representation as seen in large viewerships of sports broadcasts and animated movies. This novel neuroanimation technology is currently undergoing clinical evaluation in the SMARTS2 trial (Study to Enhance Motor Acute Recovery With Intensive Training After Stroke). The first results coming from this effort are currently in press (**Fig. 2**).

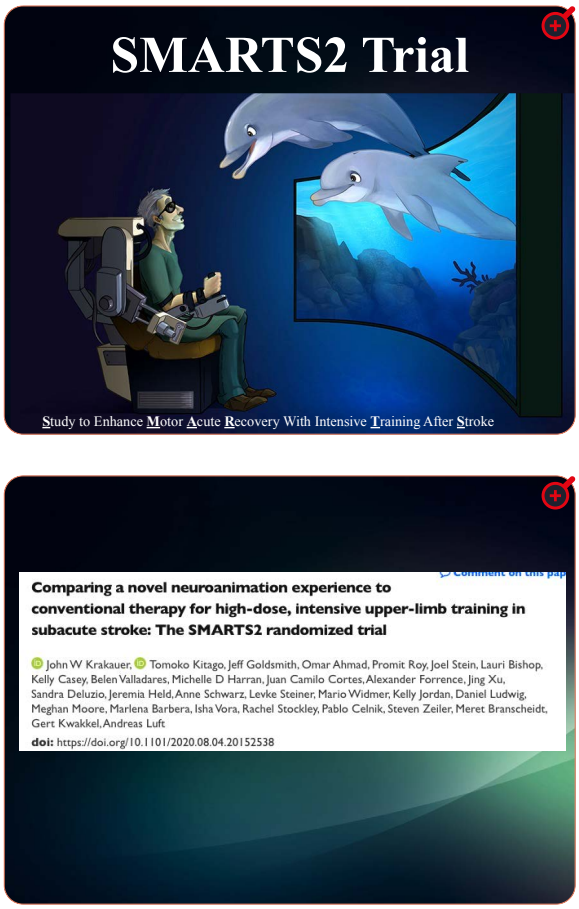

Fig. 2. The SMARTS2 trial assesses the enriched environment for motor rehabilitation after stroke

The included patients experienced the first-ever stroke 4 weeks before the start of the study and were randomized to either the robotic game therapy group or to the time-matched 30 hours of conventional occupational therapy (2 hours/day, 5 days/week, 3 weeks), which is close to an order of magnitude more therapy than currently delivered as a standard. The study tested the idea that this high intensity, high dose upper limb therapy focused on movement quality rather than on the task-oriented and task-specific training will reduce the motor impairment to a greater extent than the standard of care. However, both tested approaches delivered similar changes measured using Fugl-Meyer, ARAT scales, and assessment of enrichment of the kinematics and finger strength (**Fig. 3**).

The interpretation of this neutral result is that the control group was improving much better than expected and also better in comparison with the historical group. This comparison to the historical group shows that the concept is working versus the currently practiced standard of motor rehabilitation as well as versus the spontaneous recovery alone. Importantly, the gains were also seen in tasks in which participants were never trained, constituting the proof of concept evidence. The new tested intervention must possess an active ingredient that potentially can be further optimized in terms of efficacy, efficiency, cost-effectiveness, and even scalability. This is what Dr. Zeiler's group is working on right now.

Fig. 3. The results of the SMARTS2 trial

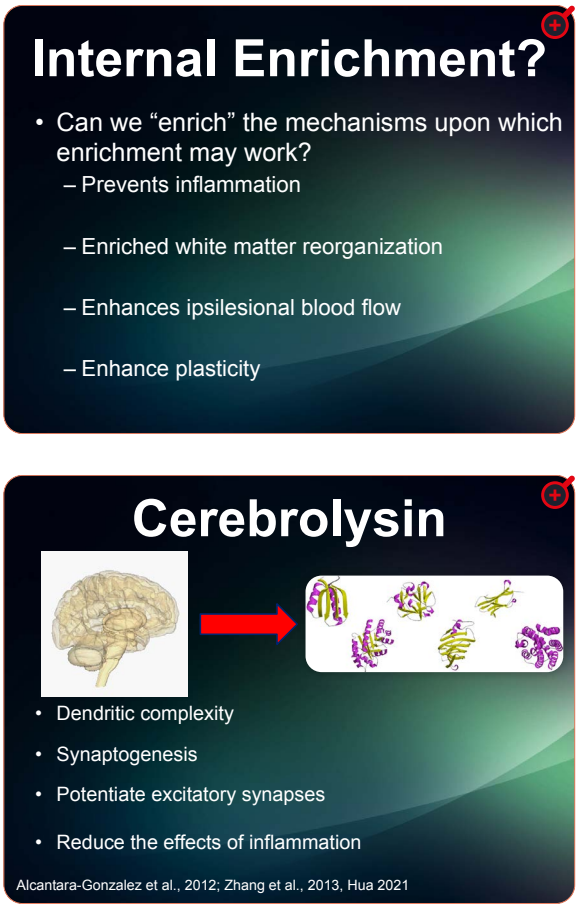

Fig. 4. Cerebrolysin as a candidate agent for the pharmacological/internal enriched environment strategy in motor rehabilitation after stroke

A complementary approach explores the novel area of a pharmacologically enriched environment (internal enrichment strategy). Can we capitalize on the mechanisms underpinning the enriched environments? Several strategies have been proposed, including preventing inflammation, enriched white matter reorganization, enhanced ipsilesional blood flow, and enhanced plasticity. It seems reasonable, that if we can act on these mechanisms using multimodal pharmacological agents we could enhance the endogenous mechanisms of spontaneous recovery leading to improved clinical outcomes. Cerebrolysin appears to be a suitable candidate agent to test this hypothesis. It exhibits neurotrophic-like activity and has been shown to act through many of the aforementioned pathways (**Fig. 4**).

Dr. Zeiler presented new experimental data exploring the use of Cerebrolysin as an internal enrichment agent (in press). The mice were trained to perform the complex prehension task and subsequently underwent experimentally induced ischemic stroke affecting their motor cortex. When left in cages without training they poorly recovered the lost function. When trained for a few days within 24 hours post-stroke, they recovered fully the lost functions. When given Cerebrolysin within 24 hours (or after a few days) of stroke, they recovered even in the absence of motor training. This represents the post-stroke training-independent recovery using the model of a complicated motor task in mice. The use of Cerebrolysin (when given within a few days post-stroke) obviates the need for, normally indispensable for motor recovery, training and exemplifies the pharmacologically enhanced spontaneous recovery post-stroke (**Fig. 5**). The

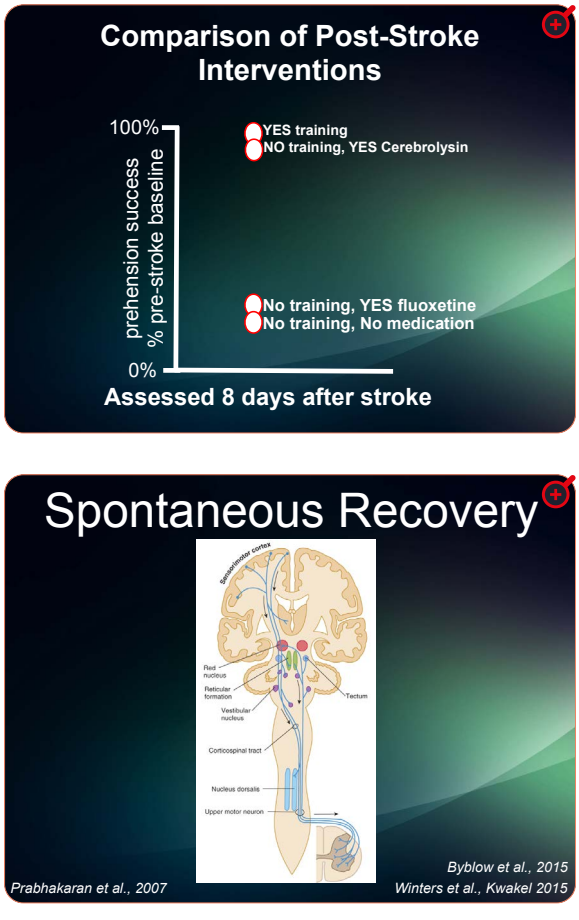

Fig. 5. Cerebrolysin enhances the endogenous spontaneous recovery in the animal stroke model

observed effects were independent of the infarct volume indicating that Cerebrolysin does not act (at least in this case) as a neuroprotective agent.

Dr. Zeiler suggested that Cerebrolysin probably acts as a plethoric agent impacting the motor pathways described earlier as essential for the spontaneous recovery after stroke. This should be a subject for further experimental and clinical research. The work by Chang et al., 2016 indicated already that Cerebrolysin may act on the cortico-spinal tract (see also the lecture of D. Muresanu). According to Dr. Zeiler, these findings can explain the success of the CARS trial discussed earlier during this webinar. The positive experimental and clinical data describing the supporting role of Cerebrolysin during the motor rehabilitation after stroke led to several recommendations in the international stroke guidelines, including the Canadian Evidence-based Review of Stroke Rehabilitation where Cerebrolysin is recommended as class 1a treatment for motor function rehabilitation.[3]

Concluding his lecture, Dr. Zeiler proposed that we should probably use all available means to enrich the stroke rehabilitation environment rather than rely on a single, focused intervention. This also includes pharmacological support as an add-on to the enriched social and therapeutic environment.

Selected literature

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Questions and Answers session, discussion

A. Winkler, D. Muresanu, T. Platz, S. Zeiler

The first question was directed to Dr. Platz and concerned the validity of German guidelines recommendations for use of SSRIs and L-Dopa in rehabilitation despite the recent failed trials. Dr. Platz stated that the general neuroscience reasoning based on the research gathered throughout the years suggests that a properly combined medication and specific training might enhance the effect of that training. For example use of L-dopa in a subgroup of patients with severe arm paresis showed some positive enhancing effects on the rehabilitation. Therefore, we can consider it as an option, but there is no recommendation for using it. We have to observe very specific circumstances of such a treatment concerning a patient's condition, particular intervention or combination thereof, and what kind of outcome is measured. Such medication can be used, but as an option within a very specific clinical situation. Concerning SSRIs, there is currently no recommendation for their use in the enhancement of motor recovery. However, we can still use them to treat post-stroke depression. The major problem of the large RCTs testing such agents was the lack of a specific combination of the studied agent and the training. Hence, the issues with the outcomes. Still, we believe that these drugs could work in a particular properly tested training combination and a specific group of patients by enhancing motor learning and motor recovery.

The second question raised the open discussion what is the right level of impairment in stroke patients to see the clinical benefits of Cerebrolysin treatment? Dr. Muresanu suggested that we need to discuss it from two perspectives. One concerns evidence-based medicine and it indicates that moderate-to-severe stroke patients can benefit more from Cerebrolysin treatment. This is just because it is difficult to measure the treatment effects in a milder stroke population (e.g. avoiding ceiling effect of recovery). Another one concerns his long clinical experience using this agent for a wider group of patients (treating over 30 thousand of them in the last 28 years). All stroke patients can benefit from Cerebrolysin, but we can notice it when some particularly sensitive deficit (e.g. aphasia) is present even in a patient with NIHSS 3 or 4 (mild cases). Evidence-based recommendations are rather formal and we need proper medical judgment and experience to use the medication correctly.

Another question to Dr. Muresanu concerned the optimal dose of Cerebrolysin. Once again, the evidence-based recommendations of 30 ml per day iv with saline (for 3 weeks) can be extended even up to 100 ml per day in very severe cases when extensive clinical experience is brought to the table. For longer-term application (up to 3 months and more), we need to use it within the chronic intermittent treatment regimen (with repetitive cycles of treatment) and a lower dose of 10 ml per day is viable for this purpose.

The final question was directed to Dr. Zeiler and concerned the optimal selection of chronic stroke patients for the treatment with Cerebrolysin. Dr. Zeiler stated that this question cannot be answered at this moment because we do not have clinical data to draw from and create a sound conclusion and recommendation. For designing a trial, he would choose patients with severe disability vs patients with a mild disability to compare the effects in both groups and to draw conclusions. In any case, our current data suggest that we should always combine behavioral training with any other tested intervention plus we should always have the right outcome measure in place (mRS being quite useless in this respect).

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of Cerebrolysin concentrate in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: For treatment of cerebrovascular disorders. Especially in the following indications: Senile dementia of Alzheimer's type. Vascular dementia. Stroke. Craniocerebral trauma (commotio and contusio). Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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CERE/INT/04/2021/11