Repurposing a Drug to Answer the Golden Question in Severe Limb Trauma

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SUMMARY STATEMENT

Repurposing a commonly used drug for neurodegenerative disease, 4-aminopyridine (4AP), to temporarily awaken intact but paralyzed nerves.

DISEASE/CONDITION

If a limb injury is severe enough to cause paralysis, then no test can tell if the nerves were cut or not. If the nerve was severed, then urgent surgery is likely the only way to ensure that the limb is usable. If the nerve was not severed, then it is best to monitor the injury and wait for nerve recovery.

Without a usable test of the status of the nerve, surgeons guess at the answer to this critical question. In the most severely injured patients with paralyzed limbs, we cannot know what the best treatment is until long after the window for the best treatment is passed.

The unmet medical need is a method to tell the difference between the two cardinal types of nerve injuries that cause paralysis: Was the nerve cut or not?

CURRENT TREATMENT

We are often forced to simply speculate on the state of nerve continuity based on the appearance of the mangled limb.

If the nerve is believed to be cut, we perform urgent surgical exploration. If, at surgery, we find the nerve intact, then the surgery was unnecessary and harmful.

If we do not explore the nerve and later find that it was severed, the limb may be forever useless. This is the state of the art in current nerve injury diagnosis.

PROPOSED TREATMENT

Repurpose an approved drug used in multiple sclerosis patients, 4-aminopyridine (4AP), in paralyzed limbs to wake up nerves and temporarily return function in non-severed nerves.

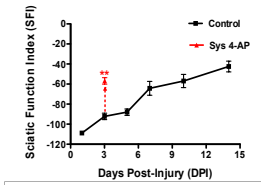


Figure: Transient effect of 4-aminopyridine on nerve function after injury showing transient functional improvement after single dose administration.

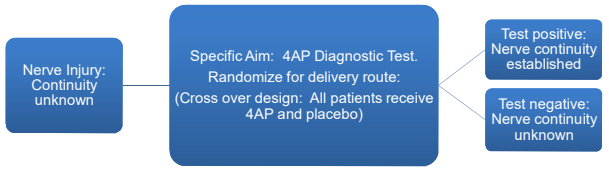
Nerves control everything in a limb, and without nerve input, a paralyzed limb is useless. We have no relevant tests that can even tell us if a nerve is severed or not. Severed nerves require urgent surgery whereas non-severed nerves are best left to recover without surgery – and no test can distinguish these injuries.

We discovered that a commonly used drug for neurodegenerative disease, 4-aminopyridine (4AP) has the property of awakening intact but paralyzed nerves. No currently available test or treatment can do this. If 4AP can return function in patients with non-severed nerves, then we should use the response to 4AP as a treatment relevant diagnostic. Since a single dose of 4AP was enough for us to differentiate severed nerves from non-severed nerves in animals, we propose trying 4AP in humans with the same diagnostic dilemma. In humans, we could benefit from a trial where subjects report return of function - something that animals cannot do. Therefore the proposed treatment is more of a diagnostic challenge - reminiscent of similar types of trials performed in the setting of cancer and other diseases. One key distinction is that 4AP is very fast in its action. We could therefore try both 4AP and a placebo in patients in one day. Taken together, we intend to provide critical pilot data on the use of 4AP as a valid challenge test for nerve continuity.

PROJECT

A single-agent, blinded trial of 4AP in paralyzed limb trauma cases with ambiguous nerve continuity to determine if urgent limb-saving surgery is warranted.

We found a commonly-used drug, 4AP, has the previously unknown effect of waking up nerves if they have not been severed. We propose a small, 5 patient proof-of-concept clinical trial to see if this drug can be repurposed as a single-dose test for severed nerves in our trauma patients.



The potential for translation to routine human use is great because this drug is already used in frail patients today.

This pilot trial in a few selected patients allows testing of a desperately needed, single dose diagnostic drug for nerve continuity that can be used in everyone right away if shown effective. Data gained will build the foundation for a larger, confirmatory trial.

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