IVIG Shown to Relieve Complex Regional Pain Syndrome

But Study Has Limitations, Experts Say

BY TOM VALEO

ARTICLE IN BRIEF

A small study found IVIG effective for alleviating chronic regional pain syndrome, providing evidence that modulating the immune system could help with managing pain.

A small but intriguing study found that intravenous immunoglobulin (IVIG) can provide relief for people suffering from complex regional pain syndrome, or CRPS, which causes chronic and often intractable pain, usually in an arm or leg, long after recovery from an illness or injury.

While pain management experts not involved with the paper said the trial had several limitations — including the small number of patients and the high cost of the therapy — they said it was valuable in offering evidence that modulating the immune system could help in pain management.

DR. ROBERT SCHWARTZMAN: In the pain business you've got to beat 30 percent relief of pain – that's the placebo effect. Also, IVIG is very hard to blind because people who receive it get a very bad headache. I've always used IVIG with steroids because when I didn't, at least 50 percent of people got a very bad headache."

In the Feb. 2 paper in the *Annals of Internal Medicine*, researchers at the Pain Research Institute at the University of Liverpool in England reported that they administered a half-gram of IVIG per kilogram of body weight to 13 people who had been suffering from CRPS between six and 30 months. All had failed to achieve significant relief from conventional treatments including acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, antidepressants, gabapentin or pregabalin, and physical therapy.

The Liverpool researchers got the idea for the IVIG treatment several years ago when they gave the drug to a patient with primary hypo-gammaglobulinemia, a blood disorder that leaves people unusually susceptible to infections such as pneumonia and influenza. The patient suffered from widespread pain of unknown cause (not CRPS) that was relieved temporarily after IVIG was administered. Repeating the treatment alleviated the pain. The researchers then administered IVIG to other pain patients, who experienced some relief.

Only subjects who reported pain intensity of at least five on an 11-point scale for seven consecutive days were included in the study. One subject dropped out after becoming pregnant. Of the remaining 12, half the subjects received IVIG and half received a saline placebo. Then, after ending treatment and waiting several weeks for responses to diminish, the treatment was reversed, with the IVIG subjects receiving saline, and the saline subjects receiving IVIG.

Beginning six days after infusion, when discomfort from the injection and transient side-effects had subsided, subjects were asked to rate their pain every day for two weeks. Five of the 12 subjects reported median pain scores at least 2 points lower with IVIG than with the saline placebo, and three of the five reported pain scores at least 50 percent lower. (One patient reported a 2-point drop in pain after receiving saline.) The average drop in pain after receiving IVIG was 1.55 points.

"To our knowledge, we have shown for the first time that low-dose IVIG reduces pain in patients with longstanding, refractory CRPS, with few adverse reactions," the study authors, led by Andreas Goebel, MD, PhD, of the University of Liverpool Pain Research Institute in the UK, wrote. "Intravenous immunoglobulin may emerge as an effective and safe novel clinical treatment option for otherwise refractory disease, but confirmatory trials are required."

STUDY LIMITATIONS

But an editorial in the same issue by pain researchers Frank Birklein, MD, PhD, of the Department of Neurology at the University of Mainz in Germany, and Claudia Sommer, MD, PhD, of the University of Wurzburg, asserted that even if the results of this small study are replicated by larger and more rigorous research, the high cost of IVIG — currently $75-$124 per gram in the US — would make it impractical as a long-term treatment, especially when less costly alternatives such as ketamine, magnesium, and tadalafil (Cialis) have shown similar efficacy. (At $100 per gram, one dose for a 200-pound man in the study would cost about $4,500.)

"We remain skeptical that those who make payment decisions will cover IVIG in CRPS … without much more convincing evidence that IVIG is more effective than other therapies," the authors stated.

Another pain researcher, however, pointed out that other treatments for CRPS can be very expensive too. "Compared to prolonged IV ketamine, IVIG is cheap," said Michael C. Rowbotham, MD, professor of clinical neurology and anesthesia at University of California-San Francisco Pain Clinical Research Center. "Ketamine itself is cheap, but the administration protocol is expensive. Putting people into a ketamine coma for days at a time requires intensive nursing support. Nerve blocks frequently employed for treating CRPS also are very expensive. CRPS is a pain problem where the cost of treatment can very rapidly reach many thousands of dollars."

Still, the study by the Liverpool group has other imitations, according to Robert J. Schwartzman, MD, professor and chair of the Department of Neurology at Drexel University College of Medicine in Philadelphia. "Only 13 patients received the therapy, and they had minimal response," he said. "Only three patients got 50 percent relief, and they only studid the patients for three weeks."

Dr. Schwartzman, like the authors of the accompanying editorial, was concerned about the blinding of the study. The study failed to show a placebo response, "which raises doubts about the adequacy of the blinding," the editorial authors wrote. "The observed response to IVIG (20-30 percent pain reduction from baseline) is in the range that one would expect for the placebo response."

Dr. Schwartzman agreed that the weak response to IVIG that most patients displayed is hard to distinguish from a placebo effect. "In the pain business you've got to beat 30 percent relief

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DR. ANNE LOUISE OAKLANDER: "This builds on several other areas of research showing the importance of immune interactions. These include epidemiological research showing that patients with CRPS more likely to have asthma, and evidence of cytokines and other pro-inflammatory markers in tissue fluids and cerebrospinal fluids from these patients. Data from three rat models of CRPS also highlights the importance of the immune and inflammatory response to nerve injury."

BOOKSHELF

Why The Truth About The Health of Our Leaders Matters

FDR's Deadly Secret. By Steven Lomazow, MD and Eric Fettmann. 296 Pages. Public Affairs: Perseus Books Group 2010.

BY JAMES F. TOOLE, MD

There is more and more evidence that subterfuge and misinformation have been part and parcel for maintaining the image of leaders of the world who have been impaired, if not totally unable to serve in office due to physical and or mental illness. In many cases ineptitude caused by dementia or paranoia have led to local or regional as well as national and international armed conflict. In the past these conflicts were local, regional, or national but now the risk of intercontinental nuclear missiles makes the danger global.

No nation can protect itself unless the very best brains are in leadership positions! Examples from history with warriors equipped with swords, slings, and arrows abound and they were welcomed home as heroes. Now in war entire cities are targets for intercontinental nuclear-tipped missiles.

A prime example of this is Franklin Delano Roosevelt whose disability from poliomyelitis was kept quiet and whose untreated hypertension with heart failure was ignored by his doctors for fear of retribution if medical management went awry. Near death, he was a nonperformer at the crucial Yalta meeting at the end of WW II. So too was it said that Sir Winston Churchill was demented and unable to perform, leaving Joseph Stalin, the sole person whose paranoid mind controlled the division of major portions of the world into the Soviet or the Western Blocks, including Poland, Vietnam, Korea and others, each of which led to international crises and national disasters, some of which persist to this day.

> 'No nation can protect itself unless the very best brains are in leadership positions!'

Now we have evidence through the sleuthing of the authors of *FDR's Deadly Secret* that FDR had a malignant melanoma above his left eyebrow in his left forehead, which the authors opine may have led to intracranial metastases that further disabled his capacity for mental processing. It seems that Roosevelt did have a melanoma, which was hidden from the public by altering the photographs of

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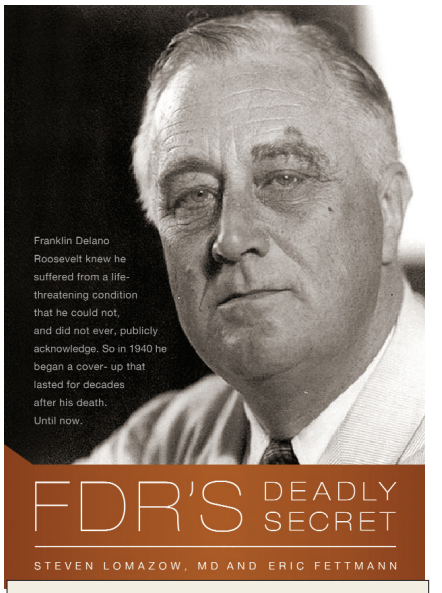

DR. JAMES F. TOOLE WRITES:
"Steven Lomazow and Eric Fettmann have done a service for the nation by publishing this book, which adds fuel to the thought that people with poor prognosis for survival throughout their term in office should not be candidates."

CRPS

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of pain – that's the placebo effect," he said. "Also, IVIG is very hard to blind because people who receive it get a very bad headache. I've always used IVIG with steroids because when I didn't, at least 50 percent of people got a very bad headache.

While the authors of the study did not administer steroids, they placed a cotton bag over the IV apparatus to conceal the bubbles and foam that IVIG produces in the drip chamber during the infusion. And because IVIG is stickier than saline, they primed the infusion line with normal saline to prevent the patient or the physician from identifying the substance by its viscosity if it dripped from the end of the IV line.

ROLE OF IMMUNE SYSTEM: PAIN

The study, while small, adds additional evidence that the immune system plays a key role in generating the chronic and disproportionate pain characteristic of CRPS, said Anne Louise Oaklander, MD, PhD, associate professor of neurology at Harvard Medical School, who was not involved with the study.

> 'We remain skeptical that those who make payment decisions will cover IVIG in CRPS...without much more convincing evidence that IVIG is more effective than other therapies.'

The study authors noted, for example, that other researchers also have found antineuronal autoantibodies in patients with CRPS. "Intravenous immunoglobulin not only potentially interferes with these autoantibodies but also downregulates proinflammatory cytokines, which are important in the mechanisms of CRPS pain and hyperalgesia, in the peripheral and the central nervous systems," they wrote.

"This builds on several other areas of research showing the importance of immune interactions," said Dr. Oaklander. "These include epidemiological research showing that patients with CRPS more likely to have asthma, and evidence of cytokines and other pro-inflammatory markers in tissue fluids and cerebrospinal fluids from these patients. Data from three rat models of CRPS also highlights the importance of the immune and inflammatory response to nerve injury."

These studies may help explain why CRPS develops in just a few of the many patients who sustain injuries, Dr. Oaklander said. "I think this may be similar to peanut allergies," she said. "Some patients are primed to have a disproportionate response to a stimulus that is innocuous or trivial for the vast majority of people."

The immune system is very important in pain, Dr. Schwartzman agreed, adding that this is further evidence that dampening the immune system helps regional pain syndrome and probably other pain syndromes. "We used to think all pain had to do with pain transmission neurons, but a lot of it has to do with turning on microglia and astrocytes that make inflammatory cytokines that stimulate pain processes. So if you can turn off the immune component of this, you really can help dramatically. It's a whole new way of looking at pain." •

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- Birklein F, Somer C. Editorial — Intravenous immunoglobulin to fight complex regional pain syndromes: Hopes and doubts. *Ann Intern Med*2010; 152:188-189.