A Brief History of Steroid Therapy for Guillain-Barré Syndrome

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ABSTRACT
Steroids have been used for the treatment of Guillain-Barré Syndrome (GBS) since the 1950s, while their clinical efficacy remains poorly defined. Most randomized controlled trials after the 1970s yielded no clues for significant differences between steroid therapy and symptomatic supportive therapy, while after adjusting the factors that affected the biases, the reanalysis of the two trials with the largest number of samples among them showed that intravenous methylprednisolone was superior to symptomatic supportive therapy, or its combination with intravenous immunoglobulin exhibited superior effects. To date, there is still no strong evidence proving or denying the efficacy of high-dose methylprednisolone, and further studies are still merited for issues regarding steroids for GBS.

Key Words: GBS; steroid; plasma exchange; immunoglobulin

Introduction
Guillain-Barré Syndrome (GBS) is a clinically common autoimmune-mediated peripheral neuropathy found more than 100 years ago, while no satisfactory treatment has been available to date. Plasma exchange (PE) and intravenous immunoglobulin (IVIG) are effective in only 60% to 70% of patients, while controversy over steroid therapy since its inception persists until today.

Prior to the 1950s, many people, including Guillain, thought that GBS was caused by viruses, just like poliomyelitis, while no evidence could substantiate it (Hughes et al., 1981; Asbury et al., 1990). Bannwarth and Furtado proposed in 1943 and 1950 respectively that the GBS is an immune response mainly on the grounds that GBS often occurred secondary to infectious diseases, and that protein cell separation also occurred in the cerebrospinal fluid of patients with some allergic diseases (GRAVESON et al., 1961). Steroids can inhibit immunity, which should be a good therapeutic agent if this hypothesis holds water. In 1949, Hamaker reported his pathologic study on 50 GBS decedents during World War II, and it was found that initial nerve root edema was the only pathological change. Scheinker argued that compressed edematous nerve roots resulted in paralysis (GRAVESON et al., 1961; VERNON, 1954). No matter whether nerve root edema is caused by immune responses or viruses, steroids can attenuate edema. Therefore, they should be reasonable drugs. Based on such a theory, steroids began to be used for the treatment of GBS, while the efficacy observed was inconsistent after their application.
Graveson et al., (1961) believed that Shy et al. began to use steroids for GBS for the first time; in 1951, SHY et al., reported that 3 patients with peripheral neuritis failed to respond to treatment with ACTH. The patients described in the article were symmetrically paralyzed in limbs and sensorily disturbed to varying degrees, and biopsy revealed muscle atrophy; however, disease records were not detailed. Some scholars (VERNON, 1954; JACKSON et al., 1957) believed that the credit should be given to Stillman, who reported in 1952 that ACTH and cortisone yielded significant effects on one patient with GBS. Subsequently, many people reported satisfactory effects using steroid therapy (VERNON, 1954; HELLER and Dejong, 1963; BLOOD et al., 1953).

Also, many people questioned or opposed it (JACKSON et al., 1957; JOHN, 1963; Goodall et al., 1974), and steroid therapy has become the hot spot of research on GBS. At that time, the most commonly used agent was intramuscular ACTH or oral cortisone. Some people thought that the early onset of GBS was manifested as nerve root edema and but not axonal injury, and steroids could reduce the edema and improve symptoms; if the axons were also damaged, steroids would not work. Therefore, steroids should be applied as soon as possible (VERNON, 1954; FAZLULLAH, 1956). In 1957, JACKSON et al. summed up the previous reports covering a total of 68 patients in 34 articles, of which varying degrees of efficacy was shown in 50 patients and inefficacy in 18 patients; they thought that the papers tent to report cases therein efficacy was shown, and that no controls were set. Therefore, the efficacy of steroids could not be defined.

Studies in the 1950s mainly focused on individual case reports and case analysis, and control groups were set in quite a proportion of studies in 1960s. In 1968, Chhuttani et al. statistically analyzed patients who received steroids therapy and supportive therapy, respectively, and found that the efficacy was not different; more studies (MARSHALL, 1963; McFarland, 1960; Löffel et al., 1977) were in favor of steroid therapy in terms of data, while no statistical analysis was available. In 1969, Asbury et al., reported the pathological findings of 19 GBS patients, which showed that all patients had inflammatory cell infiltration and that one patient died only 30h after the onset of GBS. Such a finding served as a testament to the immune responses to GBS and the mechanisms underlying its pathogenesis, and also supported the theoretical basis of steroid therapy. However, more people questioned the efficacy of steroids after a long-term clinical observation. The number of samples was significantly increased in studies in the 1970s, statistical analyses were applied in more studies, and randomized controlled trials were conducted. In 1977, Löffel et al., reported his findings on 123 GBS patients, pointing out that there was no difference in the cure rate between patients who received steroid therapy and other treatments. In 1974, Goodall et al. reported that steroid therapy even prolonged the recovery time and the length of hospital stay. The best modality to confirm whether steroids are efficacious is to conduct randomized controlled trials. In 1976, Swick et al. reported the first steroid therapy randomized controlled trial with a sample size of 38 patients (Hughes et al., 2016). During the trial, patients in the treatment group and the control group were injected with 100 units of ACTH or placebo for 10 days. The average duration from the onset of GBS to complete recovery was 4.4 months and 9 months in the treatment group and the control group, respectively (P=0.05). In the 8 steroid therapy randomized controlled trials summarized by Hughes et al., (2006, 2010 and 2016), only Swick's trial proved that the steroid was effective.

In 1978, Hughes published a multi-centre randomized controlled trial on oral prednisolone versus supportive therapy. The 21 patients in the treatment group were treated with prednisolone in a tapering manner (initial dose at 60mg/day), and the 19 patients in the control group were given the supportive therapy alone. The degree of recovery of patients in the treatment group at 1, 3 and 12 months after treatment was worse compared to the control group.

After 30 years of clinical observation, the efficacy of steroids cannot be defined clearly, and the first two clinical randomized controlled trials have also yielded contradictory conclusions. After the 1980s, PE and IVIG were proved successively to show significant effects, enabling them to be the new hot spots of studies on GBS. Many articles (Moore and James, 1981; Pollard, 1987) have clearly proposed that steroid therapy is inefficacious or groundless, and therefore, it is not recommended for use. However, due to the unavailability of theoretically reasonable explanations, further studies on steroids are still merited.

In 1981, Hughes et al. published a rat experiment regarding steroid therapy for the treatment of experimental allergic neuritis (EAN). A high dose of prednisolone (10mg/kg/day) was administered in the treatment group, which
resulted in shortened disease course, reduced degree of disability at the peak of the disease and decreased mortality. Subsequently, similar results were obtained in the animal experiments by King et al., (1985) and Watts et al., (1989). The success of steroid therapy for EAN and its clinical efficacy were vastly different. Hughes and van der Meché (2000) argued in his analysis that perhaps the pathogenesis of EAN and GBS was different in that the autoimmune response was still only a hypothesis after all; or perhaps the clinical efficacy of steroids was offset by some cause which was still poorly defined. For example, clinical medication could not be performed as timely as that in animal experiments, and a high dose of steroid is not used as frequently in clinical practice as in animal experiments. Subsequently, In 1980s and 1990s, high-dose steroid therapy became one of the focuses of GBS research.

In 1986, Steiner et al. reported GBS in three patients undergoing steroid therapy. They thought that different doses of steroids showed different effects: a small dose of hydrocortisone and azathioprine could aggravate experimental myasthenia gravis, while a large dose of them did have definite effects. Recurrence of systemic lupus erythematosus patients is very common in the process of steroid reduction. In 1988, Haass et al. reported a total of 11 GBS patients on methylprednisolone therapy (1000 or 500 mg/day), including inefficacy in 3 patients and fast improvement in 8 patients after administration. 2 of them showed aggravated conditions soon after dose reduction, while the rest 6 patients had no recurrence after slow dose reduction. Haass’s report was consistent with the results of animal experiments, proving the efficacy of high-dose steroids. He believed that early use of high-dose steroids and slow reduction were the key for successful treatment.

Guillain-Barré Syndrome steroid group (1993) reported a multi-centre randomized controlled trial on intravenous methylprednisolone versus placebo, in which a total of 242 patients were randomized to methylprednisolone (500mg) or placebo for 5 days. The degree of recovery in the steroid group at 4 weeks and 12 weeks was superior to that in the control group, while the difference was not statistically significant. The P value for comparison between the two groups was 0.06, the critical value. In the 1990s, PE had become the gold standard for the treatment of GBS. The number of patients who received PE in the control group of this trial was larger than that in the treatment group, so the conclusion of the trial was not entirely reliable. The Cochrane Systematic Review for GBS did not found any other randomized controlled trials on high-dose steroids versus supportive therapy. That’s to say, there is still no strong evidence to date demonstrating or denying the efficacy of high-dose steroids.

According to the Cochrane systematic review of steroid therapy for GBS published in 2000 (Hughes and van der Meché, 2000), the efficacy and most side effects of steroids was not different from those of symptomatic supportive therapy, and new hypertension cases on steroid therapy were fewer than those on symptomatic supportive therapy. The article clearly stated that steroids should not be used for GBS, and that they were not detrimental for patients who needed to use them due to other circumstances. The guideline on GBS treatment developed by the American Academy of Neurology in 2003 (Hughes et al., 2003) recommended PE and IVIG solely for GBS, but no steroids.

The clinical application of PE and IVIG provides more options to the armamentarium for GBS, and combination treatment may yield better results. In 1989, Levchenko et al., reported combined PE and steroid (methylprednisolone or prednisolone) versus PE alone, and the results were that there were no differences in efficacy between the two groups.

In 1994, the Dutch Guillain-Barre Study Group reported a before-after trial (BAT) on IVIG in combination with methylprednisolone versus IVIG. The control group comprised of 74 patients on IVIG treatment alone in another trial that had been completed, and the results showed that the efficacy using combination therapy for 4 weeks was better than that of IVIG alone. The authors also compared it with the therapeutic results of PE from other trials, and it was found that the combination therapy showed superior effects. The results of this trial suggested that steroids and IVIG might have synergistic effects. In the same year when the paper was published, Dutch researchers immediately initiated a multi-center clinical randomized controlled trial on IVIG in combination with methylprednisolone versus IVIG alone (Van Koningsveld et al., 2004), and ultimately, this trial wavered the idea that steroids should not be used for GBS. The results of the trial were published in 2004. The recovery of patients on combination therapy was quicker than that on IVIG therapy at 4 weeks, but the P value was 0.06. The P value was 0.03 after such factors that could
cause bias as age and severity of the disease had been adjusted.

Van Koningsveld and Van Doorn (2005) argued that the existing treatment options did not further reduce both the mortality and morbidity, so in the absence of contraindications, combination of IVIG and methylprednisolone could serve as an optional method for GBS. In 2006, Hughes et al. analyzed oral and intravenous steroids respectively, and the results were that the efficacy of oral steroids was significantly inferior to that of the supportive care, however, intravenous methylprednisolone was superior to that of the supportive care in terms of data, but no statistical difference was reached. As regards the side effects from treatment, steroid therapy was not associated with increased infection and gastrointestinal bleeding, and the incidence of hypertension in patients administered with intravenous steroid was significantly lower compared to those who received other treatments. The conclusions of the article were that oral steroid slows down recovery from GBS, intravenous methylprednisolone was neither efficacious nor harmful, and combined IVIG and methylprednisolone may be efficacious. The updated Cochrane systematic review for GBS in 2010 and 2016 (Hughes et al., 2010 and 2016) maintained the above view.

Steroids are affordable and user-friendly, making them the theoretically reasonable agents for the treatment of GBS, while they have not produced the anticipated efficacy during their application for nearly 60 years. Continued studies on issues regarding steroid therapy for GBS are still merited, i.e. whether intravenous methylprednisolone is superior to symptomatic supportive therapy; whether intravenous methylprednisolone and IVIG exhibit synergistic effects and what the specific mechanisms of action underlying the effects are; and why the incidence of hypertension in GBS patients on intravenous steroids is lower than that in those on other therapies, etc.

References


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