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Determination of pain and response to methylprednisolone in Guillain-Barré syndrome

Received: 22 October 2006
Received in revised form: 29 November 2006
Accepted: 3 December 2006
Published online: 11 April 2007

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■ **Abstract** Pain can be a serious problem in patients with Guillain-Barré syndrome (GBS). Different pain symptoms and the effect of methylprednisolone on pain are evaluated. *Methods* GBS patients were recruited from a randomized placebo-controlled study comparing intravenous immunoglobulin (IVIg) + methylprednisolone (500 mg for 5 days) versus IVIg + placebo. Presence and severity of pain were prospectively scored at randomization and after 4 weeks. Efficacy of methylprednisolone was evaluated using endpoints: percentage of patients with pain and percentage of patients improving in pain-severity level. Medical records of the subgroup of patients treated in the Erasmus MC were screened retrospectively for different pain symptoms and course. Pain was scored at different time intervals: within 4 weeks before randomization and 0–2, 2–4, 4–24, 24–52 weeks after randomization.

Results 123 (55%) of 223 patients had pain at randomization. In 70%, pain already started before onset of weakness. Methylprednisolone did

not show a positive effect on the presence and reduction of pain. In the subgroup of 39 patients, backache (33%), interscapular (28%), muscle (24%), radicular pain (18%) and painful par-/dysaesthesiae (18%) were most frequently present within the period of 4 weeks before randomization. Twenty-six percent had extreme pain 0–2 weeks after randomization. Most symptoms of pain decreased after this period, but painful par-/dysaesthesiae and muscle pain often remained present during at least 6 months. *Conclusions* Pain frequently occurs, often starts before onset of weakness and may cause severe complaints. Especially painful par-/dysaesthesiae and muscle pain may persist for months. Methylprednisolone seems to have no significant effect on the presence and intensity of pain.

■ **Key words** Guillain-Barré syndrome · pain symptoms, course · methylprednisolone

Introduction

The most striking and alarming feature in patients with Guillain-Barré Syndrome (GBS) is progressive

paralysis. Generally, less attention has been paid to pain, which may be a common and severe symptom in patients with GBS. Recognition of pain is very important, especially in patients unable to commu-

nicate due to intubation, because treatment against pain can be offered. Pain as a presenting symptom of GBS before the onset of weakness may be misleading in making the diagnosis of GBS and therefore can cause a delay in starting treatment for GBS.

Pain has been described in 3–89% of patients with GBS [1, 6, 9, 14]. Different symptoms of pain associated with GBS have been distinguished: par-/dysaesthesiae, backache / root pain, meningism, muscle pain, joint pain, visceral pain and other types [12]. One larger study in 55 GBS patients subdivided the different symptoms of pain as reported on admission into the following: low back pain with radiation (67.3%), dysaesthetic extremity pain (20%) and myalgic-rheumatic extremity pain (9.1%) [9]. During the further non subdivided period of six months, low back pain with radiation (61.8%), dysaesthetic extremity pain (49.1%) and myalgic-rheumatic extremity pain (34.5%) were noted [9]. As far as we know, there are no publications on the more detailed course and level of severity of the different pain symptoms during the first year after onset of GBS.

Pain in GBS can be very severe, and treatment is often far from successful. In some cases however a positive effect of treatment of pain in the acute phase has been described using corticosteroids [8, 16]. The pathophysiology of pain is likely multifactorial. Increased endoneurial fluid pressure in nerve trunks possessing the epi- and perineurium may play a role [2]. A possible cause of a salutary effect of corticosteroids could be a reduction of the perineurial and endoneurial inflammatory reaction in GBS.

Most reports on the effect of medication to relieve pain in GBS are based on limited numbers of patients. When measuring a treatment effect, often all types of pain are lumped together [4, 8, 10, 11, 15–17]. Because it is likely that different pathophysiological mechanisms are related to these symptoms, a more detailed classification of different pain symptoms associated with GBS can be of help to study the effect of drugs.

This study focuses on the frequency, characteristics, severity and course of various symptoms of pain during the course of GBS and on the effect of methylprednisolone as was administered in a large placebo-controlled study.

Methods

■ Prospective study

All GBS patients were recruited from a double-blind, randomized placebo-controlled, multicentre study comparing IVIg + methylprednisolone (500 mg for five days) versus IVIg + placebo [18]. A patient was eligible for this trial when the onset of weakness was within 2 weeks before the date of randomization and the patient was unable to walk 10 meters across an open space without assis-

tance (GBS disability score ≥ 3). Presence and severity of pain were collected prospectively at randomization and after 4 weeks. Pain severity was judged as: none, mild (pain but no real complaints), moderate (complaints, but no analgesics necessary) or severe (analgesics necessary).

■ Retrospective study

Medical records of the subgroup of GBS patients who entered the trial and were admitted to the Erasmus MC (the coordinating center) were retrospectively screened for different pain symptoms. These symptoms were divided in nine different pain symptoms as described before [12]. In this subgroup of patients, severity of pain was judged as: none, severe (analgesics necessary in a way the complaints were acceptable) or extreme (severe complaints despite analgesics; defined as feeling uncomfortable due to pain, not well sleeping due to pain). In the Erasmus MC, treatment of pain in the acute phase of GBS is standardized following the WHO's pain ladder. When a GBS patient after a few weeks suffers from pain resembling neuropathic pain, we generally start amitriptyline followed by anti-convulsants. The different pain syndromes and their severity were scored at different time-intervals: within 4 weeks before randomization and 0–2, 2–4, 4–24, 24–52 weeks after randomization. The time points 0 and 4 weeks were fixed visits, during the other intervals we asked the patient at least once for pain at that moment and pain since the last visit. Three patients had to be excluded from the analysis for the time-interval 24–52 weeks after randomization because of lost to follow-up after 24 weeks.

■ Statistics

Percentage of patients with pain and percentage of patients improving in level of pain-severity in independent groups were compared by the χ^2 test. All calculations were performed using Stata/SE 8.2 for Windows 2000 (Stata Statistical Software, College Station, TX 77845, USA). A p-value < 0.05 was considered to be significant.

Results

■ Prospective study

225 GBS patients were included in the prospective study, 2 patients were excluded due to missing data on the presence of pain. Base-line characteristics, including the presence of pain at randomization between the two treatment groups, was not significantly different (Table 1). Pain was reported by 123 (55%) of the 223 patients at randomization, 48 (22%) of these patients had severe pain. Of the 123 patients with pain, 86 (70%) indicated that the pain preceded the onset of weakness (median 3 days, range 1 – 36 days). In 84% of the patients starting with pain, weakness started within one week after the onset of pain (Figure 1).

4 weeks after randomization, 58 patients (57%) in the IVIg/placebo group and 51 (49%) in the IVIg/methylprednisolone group reported pain (no significant difference). In individual patients with pain, there also was no significant difference between the

Table 1 Baseline characteristics of treatment groups at randomization

	IVIg/Placebo group (n = 112)	IVIg/MP group (n = 111)
Sex distribution (n, (%))		
Male	56 (50)	73 (66)
Age (median), years	50	51
F-score (n, (%))		
3	32 (29)	26 (23)
4	80 (71)	76 (68)
5	0 (0)	9 (8)
Pain (n, (%))		
No	45 (40)	55 (50)
Yes	67 (60)	56 (50)
Mild	24 (21)	17 (15)
Moderate	17 (15)	17 (15)
Severe	26 (23)	22 (20)

MP = methylprednisolone

IVIg/methylprednisolone and IVIg/placebo group in decrease or increase of pain severity 4 weeks after randomization (Table 2).

■ Retrospective study

Of the 39 retrospectively analyzed patients, 26 patients (67%) described one or more symptoms of pain within the 4 weeks before randomization (Figure 2). 0–2 weeks after randomization, the prevalence rate increased to 79%, where after it decreased. Within the first 2 weeks after randomization, 26% had extreme pain.

Backache, radicular, interscapular painful par-/dysaesthesiae and muscle pain most frequently occurred in the beginning of the disease (Table 3). Most pain symptoms decreased within 2 weeks. However, painful par-/dysaesthesiae and muscle pain remained rather constantly present during at least 6 months.

Discussion

In this study, we prospectively investigated the frequency of pain and the effect of methylprednisolone on pain in a large group of GBS patients included in a randomized controlled trial. Retrospectively we investigated the frequency and course of the different symptoms of pain in more detail in a subgroup admitted to the coordinating center.

Pain appeared to be highly prevalent in this large, well documented group of GBS patients. 55% of these patients had pain at randomization. In other studies, the incidence of pain during the acute phase varies between 3% and 86% (median value 50%) [1, 5–7, 9, 13, 14, 19, 20]. This variation mainly seems to be caused by the rather limited number of patients included in most studies.

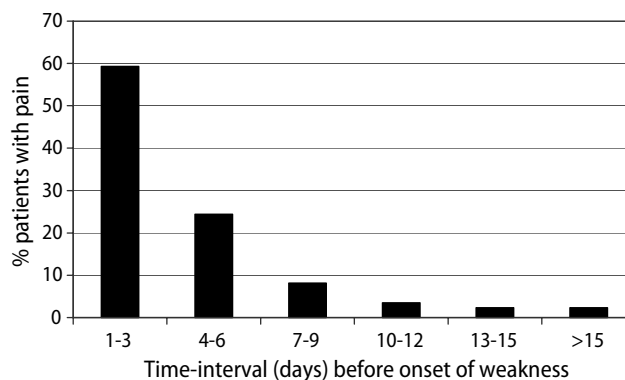


Fig. 1 Occurrence of pain before onset of weakness in 86 GBS patients. Pain = one or more pain symptoms, 86/223 GBS patients started with pain before onset of weakness

It is remarkable that 70% of the patients reporting pain at randomization already had this pain prior to the onset of weakness. Pain as presenting symptom can lead to diagnostic difficulties [3]. When pain initially is the only symptom, considering GBS as a possible diagnosis is not always so likely. So pain in the early phase can be confusing and later on may cause a delay in diagnosing and starting specific treatment for GBS. This is important to realize, because a delay in diagnosing GBS is potentially life threatening and may hamper recovery.

In the subgroup of patients that we investigated retrospectively in more detail, a somewhat higher percentage of patients (79%) reported pain in the acute phase compared to the whole group (55%). This is most likely due to the use of a time-interval of 2 weeks after randomization in stead of the fixed point in time at randomization.

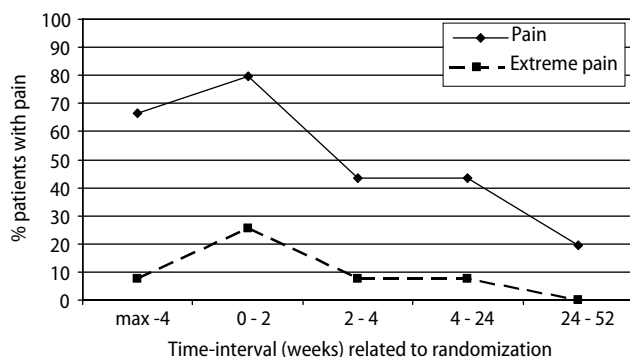
In the randomized controlled trial, methylprednisolone was primarily evaluated in relation to the effect on disability of GBS [18]. We did not use a clinimetrically validated scale to assess the level of severity of pain. Therefore the results of the effect of methylprednisolone on pain have to be interpreted with some caution. In the retrospective part of the study, we were able to assess the level of pain in more detail. We did this in relation to the use of analgesics. Because both treatment of GBS patients and treatment of pain is standardized in our center, it is likely that the prescription of analgesics is rather uniform and reported in a standardized way. This makes it rather well possible to judge about pain severity at a very global level in a retrospective way. It appeared that approximately a quarter of the GBS patients in this study reported extreme pain in the acute phase indicating that pain is not only a common but also a severe symptom.

Backache, interscapular and radicular pain were most frequently present in the acute phase. How-

Table 2 Presence and severity of pain at randomization and 4 weeks later

	IVIg/Placebo group (n = 112)	IVIg/MP group (n = 111)
Patients with pain (n, (%))		
Randomization	67 (60)	56 (50)
4 weeks after randomization	58 (57)	51 (49)
Patients with a decrease in pain severity (n, (%))		
4 weeks after randomization	34 (34)	32 (31)
Patients with an increase in pain severity (n, (%))		
4 weeks after randomization	26 (26)	22 (21)

MP = methylprednisolone

**Fig. 2** Prevalence rate of pain over time in 39 patients with GBS. Pain = one or more pain symptoms. Extreme pain = severe complaints due to one or more pain symptoms despite analgesics; defined as feeling uncomfortable due to pain, not well sleeping due to pain. Time-interval 24–52: n = 36 patients

ever, painful par-/dysaesthesiae remained rather constantly present during at least one year (Table 3). This trend is comparable to findings in another larger study in which the different pain symptoms were noted on admission and during one further non subdivided period of 24 weeks [9]. The pathophysiological explanation of pain in GBS is diverse. It seems that pain in the acute phase is predominantly nociceptive pain, due to inflammation of the nerve roots and peripheral nerves which may activate nociceptors. Later on, many GBS patients have neuropathic pain. This neuropathic pain is a non-nociceptive pain that doesn't arise from pain receptors but results from degeneration and perhaps even regeneration of nerves and is often encountered in patients with chronic neuropathies. The persistence of muscle pain on the other hand may be related to more mechanical factors due to limitation of physical activities.

Previous case-reports suggest that corticosteroids might be an effective treatment for pain, possibly due to its anti-inflammatory effect [8, 16]. This is the first study that evaluated the effect of methylprednisolone on pain in a placebo-controlled way.

Table 3 Prevalence of pain symptoms during course of GBS in 39 patients

Pain symptoms [12]	Number of weeks related to randomization				
	Before		After		
	(-4-0) n (%)	0-2 n (%)	2-4 n (%)	4-24 n (%)	24-52* n (%)
Backache	13 (33)	11 (28)	1 (3)	2 (5)	0 (0)
Interscapular pain	11 (28)	5 (13)	0 (0)	0 (0)	0 (0)
Muscle pain / cramps	9 (24)	6 (15)	6 (15)	6 (15)	1 (3)
Painful par-/dysaesthesiae	7 (18)	7 (18)	8 (21)	11 (28)	5 (14)
Radicular pain	7 (18)	8 (21)	1 (3)	2 (5)	1 (3)
Others	6 (15)	12 (31)	7 (18)	3 (8)	0 (0)
Joint pain	2 (5)	2 (5)	2 (5)	5 (13)	0 (0)
Visceral pain	2 (5)	4 (10)	4 (10)	3 (8)	0 (0)
Meningism	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)

* n = 36 patients

We did not find a significant decrease in the presence and severity of pain in the methylprednisolone treated group. This indicates that methylprednisolone for pain in general does not seem to have a positive effect. However, there are many symptoms of pain. In previous case reports, corticosteroids were reported to have a positive effect on radicular pain. In our series 10 out of 39 patients had radicular pain. All 5 patients treated with methylprednisolone, but also 4 out of 5 patients treated with placebo, had a decrease in severity of radicular pain after 4 weeks. The number of patients with radicular pain is too small to conclude about a possible favourable effect of methylprednisolone on this type of pain in GBS.

In conclusion, pain frequently occurs and may cause severe complaints in patients with GBS. It often starts before onset of weakness and therefore can lead to diagnostic difficulties. Most pain symptoms decrease within 2 weeks, but painful par-/dysaesthesiae and muscle pain may persist for months. Methylprednisolone seems to have no positive effect on the development and reduction of pain during the acute phase of GBS.

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