



Characteristics of Guillain-Barre Syndrome Patient Underwent Hyperbaric Oxygen Therapy at Lakesla 2016–2019

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Abstract

BACKGROUND: Guillain-Barre syndrome (GBS) is considered an acute immune-mediated monophasic illness. Standard therapy includes intravenous immunoglobulin (IVIg) and/or plasmapheresis. Yet, long-standing disability remains a problem. In Indonesia, the availability and cost of these therapies are constraints.

AIM: To show the capability of hyperbaric oxygen (HBO2) therapy in GBS patients who did not undergo standard therapy. HBO2 also provides healing in patients who experience delays in therapy.

METHODS: Data included identity, demographic, social history, current disease history, disease progression and therapies used. Data were displayed in the form of tables and graphs.

RESULTS: Twenty-five GBS patients underwent HBO2 from 2016 to 2019. The majority of patients were males aged 20-30 years, triggered by preceding diarrhea. After approximately three to ten days following HBO2, they felt their first positive changes. They walked with assistance after two to three weeks receiving HBO2 and without assistance after four to 12 weeks receiving HBO2.

CONCLUSION: HBO2 administration show clinical improvement in GBS patients. HBO2 is expected to become an adjunctive therapy for GBS patients in Indonesia.

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Introduction

Guillain-Barre syndrome (GBS) is a group of clinical syndromes with acute onset of polyradiculoneuropathy – axonal or demyelinating – after an autoimmune-mediated process. GBS is characterized by weakness of the locomotor system and loss of tendon reflexes [1], [2]. It is suggested that the pathophysiology of GBS involves a cross-reaction between autoimmune antibodies and inflammatory cells with epitopes on peripheral nerves, roots, or plexuses, leading to demyelination, axonal damage, or both [3]. The immune response is thought to be triggered by various antigenic stimuli 1–3 weeks before neuropathic symptoms, particularly respiratory and gastrointestinal infections in approximately two-thirds of people with GBS. *Campylobacter jejuni*, an important cause of diarrheal disease, is said to be the most common and is associated with slower recovery and severe residual disability due to predominant axonal degeneration [4], [5], [6]. Other pathogens identified included cytomegalovirus, Epstein-Barr virus, mycoplasma pneumonia, and

Haemophilus influenzae [7], [8], [9]. GBS was also observed after vaccination for rabies and swine influenza [10], and potentially associated with Zika virus infection [11], [12], [13].

The estimated incidence rate of GBS in Europe and North America has been estimated 0.8–1.9 cases per 100,000 people [14]. The estimate GBS annual incidence rate has increased by 20% for every 10-year increase in age [14]. It was reported that GBS incidence rate was 0.6/100,000 per year in children and 2.7/100,000 in elderly people aged 80 and over; GBS is slightly more frequent in males than in females [15]. The incidence rate of GBS in Indonesia is not known. In Lakesla, Indonesia, there were 48 cases of GBS from various types between 2010 and 2011, which showed an increase of 10% compared to the previous year [16].

Age, preceding infections, clinical features, syndromes and signs during hospitalization, as well as early recognition and treatment were found to be very important in the long-term prognosis of GBS [17], [18]. Intravenous immunoglobulin (IVIg) and plasma exchange (PE) have been used to hasten

recovery [19], [20], and yet the reported mortality rate ranging between 1% and 18% [21], [22].

At our institution, we have used hyperbaric oxygen therapy (HBO2) as adjuvant therapy for GBS. HBO2 is defined as a treatment in which a patient intermittently breathes 100% oxygen while the treatment chamber is pressurized to a pressure greater than sea level (1.0 atmosphere absolute, ATA) [23]. Acute GBS is one of the non-emergency indications for HBO2 [23]. HBO2 seems to give promising results for GBS. The purpose of writing this article is to present the characteristics of GBS patients undergoing HBO2 at Lakesla, Surabaya, Indonesia.

Materials and Methods

This study took the entire reachable population of GBS patients undergoing HBO2 therapy from 2016 to 2019. We studied all patients with a primary discharge diagnosis of GBS (ICD-10 code G61.0) [24] and diagnosis of rehabilitation (ICD-10 code Z50.X) [24] between 2016 and 2019. The patients were identified from the Lakesla registration center. All patients underwent neurological clinical examinations, including motor, sensory, physiological reflexes, and pathological reflexes. However, cerebrospinal fluid, immunoglobulin, and electromyographic examinations were incomplete due to limited funds. Advances in neurological clinical improvement were evaluated after the patients received 10 treatments of HBO2 (referred to as one package). The ethical clearance of this study was obtained from Lakesla.

Results

There were 25 GBS patients underwent HBO2 from 2016 to 2019. Table 1 shows that the majority of GBS patients were male (72%). The majority of male patients were between 20 and 30 years old (27.78%), whereas the majority of female patients were between 30 and 40 (42.86%).

Table 1: Demographic characteristics of study subjects

Characteristics	Males		Females		Total	
	Freq.	%	Freq.	%	Freq.	%
Age (years)						
0–10	1	5.56	1	14.29	2	8.00
10–20	2	11.11	0	0	2	8.00
20–30	5	27.78	0	0	5	20.00
30–40	4	22.22	3	42.86	7	28.00
40–50	1	5.56	0	0	1	4.00
50–60	4	22.22	2	28.57	6	24.00
60–70	0	0	1	14.29	1	4.00
>70	1	5.56	0	0	1	4.00
Total	18	100.00	7	100.00	25	100.00
Occupation and social status						
TNI	10	55.56	0	0	10	40.00
Core family of TNI	2	11.11	2	28.57	4	16.00

Civil service of KEMHAN	0	0	2	28.57	2	8.00
Private	6	33.33	3	42.86	9	36.00
Total	18	100.00	7	100.00	25	100.00

We classified the patients into four categories based on the patients' occupation and social status: The Indonesian national soldier (TNI); the core family of TNI; the civil service of the Ministry of Defense (KEMHAN), excluding the three statuses mentioned earlier; and private patients. The majority of GBS patients were TNI (40%), particularly the navy; followed by private (36%); core family of TNI (16%); and civil service of KEMHAN (8%).

Most GBS patients came to the emergency department due to progressive weakness in the form of difficulty swallowing and breathing that led to death. Around 55% of GBS patients underwent HBO2 at Lakesla were previously hospitalized at Dr. Ramelan Navy Hospital. A small percentage of GBS patients were a referral from other hospitals in Surabaya (in-town); outside Surabaya but in East Java Province.

Between 2016 and 2019 (Table 2), around 44% of all patients were admitted in 2018. Approximately 48% of GBS patients were admitted at Lakesla from January to March, and the majority of them were admitted in February. The time interval from the onset of GBS to receiving HBO2 mostly was 1–7 days (32%). GBS patients who did not receive IVIG or plasmapheresis therapy generally came to Lakesla on the 3rd day. However, patients who had received IVIG and/or plasmapheresis therapy on the first 5 days still sought HBO2 on the 10th day. Four patients came after 28 days from onset of GBS since they were unaware of the advantage of HBO2 and they were not referred to Lakesla by their clinicians.

Table 2: Patients' hometown, frequent hospital admission and month, and the time interval between onset of GBS and receiving HBO2

Characteristics	Surabaya		Outside Surabaya		Total	
	Freq.	%	Freq.	%	Freq.	%
Frequent hospital admission and month						
2016						
October	1	6.67	1	10.00	2	8.00
Total in 2016	1	6.67	1	10.00	2	8.00
2017						
January	0	0	1	10.00	1	4.00
April	1	6.67	0	0	1	4.00
July	1	6.67	1	10.00	2	8.00
August	0	0	1	10.00	1	4.00
November	1	6.67	1	10.00	2	8.00
December	1	6.67	0	0	1	4.00
Total in 2017	4	26.67	4	40.00	8	32.00
2018						
January	0	0	1	10.00	1	4.00
February	5	33.33	2	20.00	7	28.00
March	0	0	1	10.00	1	4.00
July	1	6.67	0	0	1	4.00
Forgot	1	6.67	0	0	1	4.00
Total in 2018	7	46.67	4	40.00	11	44.00
2019						
January	1	6.67	0	0	1	4.00
February	0	0	1	10.00	1	4.00
May	2	13.33	0	0	2	8.00
Total in 2019	3	20.00	1	10.00	4	16.00
Total in 2016–2019	15	100.00	10	100.00	25	100.00
Time interval from onset of GBS to receiving HBO2 (days)						
1–7	3	25.00	5	38.46	8	32.00
8–14	4	33.33	1	7.69	5	20.00
15–21	3	25.00	4	30.77	7	28.00
22–28	0	0	1	7.69	1	4.00
>28	2	16.67	2	15.38	4	16.00
Total	12	100.00	13	100.00	25	100.00

GBS: Guillain-Barre syndrome, HBO2: Hyperbaric oxygen therapy

GBS is usually preceded by infection and a greater number of GBS patients who underwent HBO2 reported that they had a history of diarrhea (44%) and common colds (28%) as a precursor (Figure 1). The main types of GBS patients underwent HBO2 were motor impairment (72%), whereas 20% of GBS patients came with motor and sensory impairment. The classification was based only on neurological physical examinations with hammers, cotton, needles, and hot-cold sensations. Only 2 patients (8%) showed Miller Fisher syndrome (MFS), with double vision as the chief complaint on their initial visit. Approximately 36% of GBS patients who underwent HBO2 had received IVIG therapy, no patient received plasmapheresis, and 4% of the patients received corticosteroid therapy.

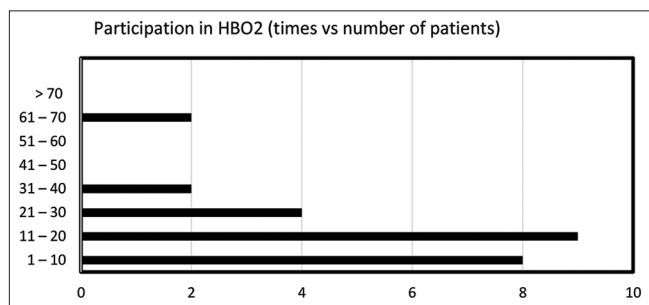


Figure 1: Chart type showing participation in hyperbaric oxygen therapy

At Lakesla, one package of HBO2 consists of 10 exposures to HBO2, given once daily, and the package is completed in 10 days. Figure 1 shows that the majority of GBS patients (36%) received 11–20 HBO2 treatments, 32% received 1–10 HBO2 treatments, 16% received 21–30 HBO2 treatments, and the remainder received more than 30 HBO2 treatments. Two of the GBS patients received 61–70 HBO2 treatments (six–seven packages) solely because they were members (one navy, one army) and received HBO2 for free; they were free from duty due to their illness (Figure 1).

Around 60% of GBS patients felt their first positive changes after less than a week of receiving HBO2. Approximately 16% of GBS patients reported their first positive changes after 1–2 weeks of HBO2 and the remainder after more than 2 weeks of HBO2. However, we had two patients who did not feel positive changes: One died on the 4th day; the other because there was no one takes the patient to hospital.

One indicator of clinical improvement after receiving HBO2 was the patient’s ability to walk with or without assistance. Figure 2 shows that a large proportion of GBS patients (44%) could walk with assistance after 2–3 weeks of receiving HBO2, and 32% of patients could walk without assistance after 4–12 weeks of receiving HBO2. Around 12% of GBS patients could walk without assistance in 1–2 weeks after receiving HBO2. However, two patients did not show any improvement and died on the 4th day of treatment.

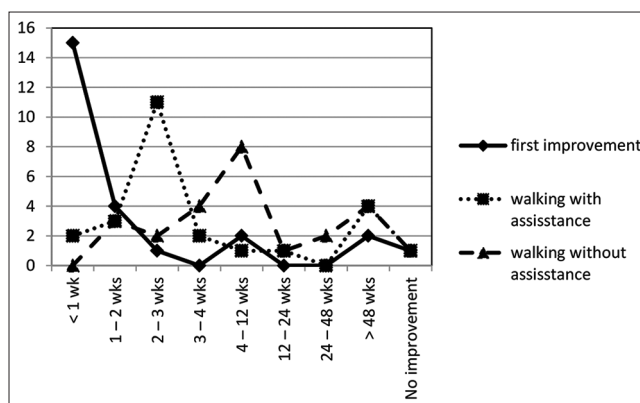


Figure 2: Line chart showing gradual improvement from the first improvement, walking with assistance until without assistance

Discussion

GBS is considered an acute immune-mediated monophasic illness, with the worst condition occurring 2–4 weeks after the onset of the first symptoms [25], [26]. However, 6–7% of GBS patients reported recurrence [26]. GBS is generally easy to diagnose – generally within a few days – based on the specific neurological clinical manifestations and progressive weakness. Patients usually present with symmetrical ascending muscle weakness along with areflexia. The initial symptoms of motor weakness are sudden, with some patients experiencing neck and back stiffness [27], [28]. Definitive diagnosis is obtained from cerebrospinal fluid testing and electromyography, which is effective after the 1st week. Cerebrospinal fluid testing shows increase protein levels but with normal white blood cells count, whereas the nerve conduction study shows a slowing or blockage of conduction. Patients should be hospitalized and receive standard therapy including emergency treatment and definitive therapy, namely, IVIG and plasmapheresis [29].

HBO2 has been known as a therapy for diving-related diseases. Gradually, this therapy has been recognized as beneficial for wound healing. In the field of neurology, hyperbaric therapy is useful in central nervous system diseases (e.g., stroke) and peripheral nerve diseases (e.g., herniated nucleus pulposus) [23], [30]. GBS is one of the non-emergency indications for HBO2 [23]. Lakesla is an institution under the leadership of the Indonesian navy. At present, Lakesla carries the full costs of HBO2 for patients who come from the Indonesian soldier, the civil service of the Ministry of Defense (KEMHAN) and their core families. Therefore, 64% of GBS patients who underwent HBO2 were from this community. Private patient is the second community to have HBO2 at Lakesla. Despite paying fully out of pocket, private patients chose to have HBO2 because they wanted to hasten the improvement of their condition after receiving primary pharmacotherapy.

Evidence for seasonal variation in GBS incidence has been contradictory [15]. At Lakesla, most GBS patients were admitted in February. Besides, the majority of GBS patients were from Surabaya, where the Lakesla is located, and 10% of patients were from out of town.

It is estimated that 25–40% of GBS patients worldwide have *C. jejuni* infection 1–3 weeks before the illness [31]. Other literature also states that two-thirds of GBS patients have a history of previous viral or bacterial infections and vaccination [2], [9], [11]. At Lakesla, a greater number of GBS triggers were preceding diarrhea 1–2 weeks earlier followed by common colds.

GBS has four subtypes: Acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN), and MFS [32], [33]. AIDP is the most common subtype of these four constituting 85–90% of GBS cases [33]. AMAN and AMSAN are axonal forms of GBS that are most prevalent in Asia, and South and Central America [8].

Almost all GBS patients who came to Lakesla did not undergo electromyography, thus the data only described clinical symptoms. Most patients (72%) clinically showed motor impairment only, which could be either AIDP or AMAN. Around 20% of patients showed motor and sensory impairment types, which could be AMSAN. There were 8% of patients who were diagnosed as having MFS, with symptoms of double vision and unbalanced walking.

In general, GBS patients who come to Lakesla have undergone definitive therapy at other hospitals, but they seek for HBO2 to aid their recovery. Around 36% of patients have received IVIG therapy, 4% received corticosteroids, none received plasmapheresis, and 60% received other therapy.

There are three phases in the course of GBS disease, namely, progressive phase, plateau phase, and healing phase [34]. Few investigators have reported worsening of weakness after the onset of improvement or a plateau phase, called as treatment-related fluctuations, which is different from relapses [35], [36]. Clinical features, early recognition, and treatment contribute in the prognosis of GBS [17], [18]. Neurological symptoms can persist for up to 20% of the patients and half of the patients experience severe disability. More than 80% experience severe fatigue that persists after resolution of other symptoms [29].

At Lakesla, HBO2 was administered as adjunctive therapy for GBS patients. The biomolecular mechanism of HBO2 for GBS patients was not clear, but some experimental studies have demonstrated improvement in the acceleration of cerebral microcirculation and oxygenation, metabolism, angiogenesis, and reduction in inflammation in stroke and non-stroke diseases [37], decreased lipid peroxidation, inhibition of leukocyte activation, and promotion of neuronal survival [38]. From 2016 to 2019,

around 60% of GBS patients at Lakesla felt their first positive changes in less than a week after receiving HBO2, 44% of GBS patients walk with assistance after 2–3 weeks receiving HBO2, and 32% walk without assistance after 4–12 weeks receiving HBO2.

We observed that a total of eight patients who participated in hyperbaric therapy for less than 1 week also experienced the first changes at less than 1 week. At between 1 and 3 weeks, these patients could walk with support and were able to walk unaided within 1 month. This is quite surprising considering that half of the patients in this group come with the ability to perform only adduction abduction despite receiving IVIG therapy. Another 12 patients (five came in the interval of 8–14 days, seven came in the interval of 15–21 days) showed the first improvement in less than 2 weeks, walking with support in less than 1 month, and without support in less than 3 months. We also found one patient who came with hemiplegia and remained for 1 month without receiving IVIG therapy, experiencing changes in the 1st month, walking with help in the 2nd month, and walking without assistance in the 4th month. Two patients with MFS experienced very good clinical improvement. Even though they had received IVIG therapy for 5 days, they still complained of double vision and ataxia. After 5 days following HBO2 therapy, on the 2nd day, they reported that their double vision was greatly reduced and they were able to use their cellular phones. In less than 2 weeks, they were able to walk without help.

Unfortunately, we observed four patients who showed no improvement more than 21 days after the first symptom of GBS. Two had undergone IVIG therapy, but did not finish the first package of HBO2 therapy (fewer than 10 treatment). In these four patients, we observed their first improvement from 3 weeks to 12 months after treatment. Eighteen months later, they all still walked with assistance.

The use of definitive therapy such as IVIG and plasmapheresis can increase the cost of treatment up to 5–10 times. Therefore, most patients followed all hyperbaric therapy procedures in one to two packages (10–20 times) in an orderly manner. Some patients discontinued hyperbaric therapy because they felt improvement and wanted to have other therapies (physiotherapy and acupuncture) that were closer to their homes.

The GBS mortality rate ranging between 1% and 18% [21], [22] and predominantly occurred in the elderly and severely affected patients, especially during the recovery phase [21]. At Lakesla, 2 patients (8%) died, one due to disease progression in the 4th day of treatment and the other died 3 months later.

There are limitations in this study. This study only presents data with a very small population of GBS patients who come to the hyperbaric installation in Lakesla. This is because the GBS population is small. Of the few, only a few are aware of HBO2 therapy.

According to all neurology's textbook, the main therapy for GBS is not HBO2. Likewise in the hyperbaric consensus, GBS is not included in the indications for therapy. In Indonesia, the majority of hyperbaric chambers are owned by Naval hospitals or hospitals that have underwater workers.

With experience at Lakesla over the past 3 years, it can be observed that HBO2 is beneficial for the clinical improvement of GBS patients. It is tempting to give HBO2 therapy as an adjuvant for GBS, when the patient cannot afford IVIG and the patient has no absolute contraindications to HBO2 therapy. With the hope of high interest in taking HBO2 therapy, of course, more samples can be taken. So that in the future, we can generalize the benefits of HBO2 in GBS cases.

Conclusion

At Lakesla, GBS was more common in males than females; the most common age group was 20–30 years. Clinical manifestations at admission were predominantly motor impairment in the form of muscle weakness in both legs. The prognosis of GBS patients who underwent HBO2 was generally good, even though 8% of patients died due to disease progression. Standard therapy (IVIG and plasmapheresis) has been carried out in the majority of patients, but the patients still did not experience complete motor function. Most GBS patients felt their first positive changes within the 1st week, walked with assistance in 2–3 weeks, and walking without assistance in 4–12 weeks after receiving HBO2. We were not going to say that HBO2 gonna be replacing IVIG and plasmapheresis as standard therapy. Examining the GBS patients based on all the clinical changes, we hope that HBO2 could be an adjunctive therapy for GBS in Indonesia.

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Ethical Statement

The Ethics Committee of Naval Health Institute, Indonesian Navy stated that this study was feasibly approved the study (Animal Ethical Clearance Certificate No.009/AECC/NHI/IX/2019).

Authors' Contributions

1. Ni Komang Sri Dewi Untari: Conceptualization, methodology, formal analysis, investigation, data curation, original draft preparation, review, and editing
2. Kurnia Kusumastuti: Methodology, investigation, and review
3. M. Guritno Suryokusumo: Methodology, investigation, and review
4. I Ketut Suidiana: Methodology, validation, and review.

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