Original Article

A Safety Study of The Thai Red Cross Society Intravenous Immunoglobulin in Various Diseases

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Objective: Intravenous immunoglobulin (IVIG) is an effective treatment in several diseases with few adverse effects. The authors studied the safety of locally manufactured IVIG by the Thai Red Cross Society (TRCS).

Materials and Methods: The present report was a prospective descriptive study to collect the safety data of TRCS-IVIG in various diseases. Patients indicated for IVIG treatment at Siriraj Hospital were enrolled between September 2016 and August 2017. The authors collected demographic data of the patients and side effects at each cycle of IVIG administration and compared with other commercial IVIG.

Results: Forty-three patients including 18 children and 25 adults, with 100 cumulative IVIG infusions, were included in this study. Indications for treatment were immune thrombocytopenic purpura (ITP) (13 patients), chronic inflammatory demyelinating polyneuropathy (11 patients), autoimmune encephalitis (7 patients), myasthenia gravis (5 patients), inflammatory myopathy (4 patients), and primary immunodeficiency (3 patients). There was no transfusion-related infection or life-threatening side effect. One pediatric chronic ITP patient died from a condition unrelated to the treatment. Minor side effects such as electrolyte imbalance, anemia, renal impairment, and transaminitis were found in less than 10% of the patients. Allergic rash was reported in 3% of the patients.

Conclusion: The authors found no serious adverse event and only some minor side effects from the TRCS-IVIG. When compared to safety profiles data of conventional IVIG from previous study at Siriraj Hospital, the TRCS-IVIG appeared to have comparable safety profiles. TRCS-IVIG, as a locally manufactured product, can be safely used in various conditions.

Keywords: Intravenous immunoglobulin, IVIG, Thai Red Cross Society, Safety

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Intravenous immunoglobulin (IVIG) is derived from a plasma pool of several thousand donors. It contains immune antibodies and physiologic autoantibodies and provides powerful immunomodulatory and anti-inflammatory effects in different diseases based on multiple mechanisms of action, which are modulation of complement activation, suppression of idiotypic antibodies, modulation of expression and function of Fc receptors on macrophages, and effect on the activation and effector functions of T and B cells and suppression of various inflammatory mediators, including cytokines, chemokines, and metalloproteinases[1-3].

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IVIG is effective for various autoimmune and infectious diseases, such as Guillain-Barre syndrome (GBS), myasthenia gravis (MG) crisis, chronic immune demyelinating polyneuropathy (CIDP), immune thrombocytopenic purpura (ITP), primary immunodeficiency (PID), inflammatory myopathy, and autoimmune encephalitis. IVIG is considered to be a safe treatment with less than 5% of serious side effects[4-6]. Post-transfusion adverse symptoms include headache, flushing, chills, myalgia, wheezing, tachycardia, low back pain, nausea, and hypotension. Transaminitis and minor electrolyte abnormalities can also occur. Anaphylaxis is found occasionally, particularly in patients with IgA deficiency[7]. Other uncommon but more serious complications include thromboembolic events[8] such as stroke, myocardial infarction, deep venous thrombosis, hemolysis, aseptic meningitis, and acute kidney injury[9,10].

With the collaboration and technology transfer from the South Korea-based Green Cross Corporation, Thai Red Cross Society (TRCS) recently established a plasma fractionation center to manufacture plasma-derived products, of which IVIG is one of them.

In the present study, the primary goal was to prospectively collect the safety data of IVIG locally manufactured from TRCS. The secondary goal was to compare the safety data of TRCS-IVIG with the previously reported side effect profiles of conventional IVIG from a prior study at Siriraj Hospital.

Materials and Methods

The present report was a prospective study performed at Siriraj Hospital, Bangkok, Thailand between September 2016 and August 2017, and aimed to collect the safety data of the IVIG from Thai Red Cross Society (TRCS-IVIG). Patients aged more than three months and less than 70 years who fulfilled indications for IVIG treatment were enrolled. Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection, history of IVIG allergy, significantly impaired renal function (defined as estimated glomerular filtration rate (eGFR) less than 40 mL/minute), significant transaminitis (defined as aspartate aminotransferase (AST) and alanine transferase (ALT), more than three times of the upper limit), recent thromboembolic events, or had terminal illness were excluded from the study. The product preparation is 5% immunoglobulin with 10% maltose as stabilizer. Dosage and number of infusions for each patient varied upon the indications. The infusion rate was started at 0.01 mL/Kg/minute, and stepped up twice as much every 30 minutes to a maximum of 0.08 mL/Kg/minute.

The authors collected demographic data of the patients and side effects in each cycle of TRCS-IVIG administration.

Immediate post-transfusion side effects, such as hypotension, anaphylaxis and rash were monitored during and after TRCS-IVIG administration. Blood tests including complete blood count, serum creatinine, sodium, potassium, calcium, AST, ALT, were checked pretreatment and at day 3 and 7 after each treatment. Anti-HIV, HBsAg, and anti-HCV were screened before treatment and at day 60.

Sample size calculation

According to the previous study at Siriraj Hospital on the effects of conventional IVIG[11], the adverse events rate was 10%. With 95% confidential interval (CI) and allowable error of 0.06, the appropriate sample size was about 100 IVIG administrations.

Statistical analysis

Results were expressed as incidence of each parameter and compared to historical data using z-test. The statistics were expressed as difference of proportion, 95% CI and p-values. All analyses were performed using SPSS statistics version 18.0. A p-value of less than 0.05 was considered statistically significant.

Ethical approval

The Siriraj Institutional Review Board (SIRB) approved the present study [Protocol 236/2559 (EC4)]. All participants or their legal guardians gave informed consents for each treatment.

Results

Forty-three patients, 18 children and 25 adults, were enrolled and received a total of 100 doses of TRCS-IVIG. Their basic characteristics are shown in Table 1.

Pediatric patients

Twenty-four TRCS-IVIG infusions were given to 18 children. Their ages ranged from 15 months to 17 years. Female was predominated (11 in 18 patients, 61.1%). No comorbid disease was found, excepted in one patient with ITP having hypertension. There were 13 patients with ITP (17 infusions), one patient with PID (one infusion), two patients with autoimmune encephalitis (two infusions), and two patients with inflammatory myopathy (four infusions) (Table 1).

Table 1. Demographic data of 43 patients, 100 treatments

	Pediatrics n (%)		Adults n (%)		Total
Sex					
Male	7 (38.9)		12 (48.0)		19
Female	11 (61.1)		13 (52.0)		24
Total	18 (100)		25 (100.0)		43
Age (years), Median (minimum, maximum)	7 (1.25, 17)		52 (22, 69)		
Comorbidity					
Diabetes mellitus	0 (0.0)		6 (24.0)		6
Hypertension	1 (5.6)		8 (32.0)		9
Dyslipidemia	0 (0.0)		6 (24.0)		6
Coronary artery disease	0 (0.0)		0 (0.0)		0
Other vascular disease	0 (0.0)		0 (0.0)		0
Chronic kidney disease	0 (0.0)		1 (4.0)		1
Indications for IVIG	Number	Treatment	Number	Treatment	Total treatment
Chronic demyelinating polyneuropathy	0	0	11	43	43
Myasthenia gravis	0	0	5	6	6
Immune thrombocytopenic purpura	13	17	0	0	17
Primary immunodeficiency	1	1	2	20	21
Autoimmune encephalitis	2	2	5	5	7
Inflammatory myopathy	2	4	2	2	6
Total		24		76	100

IVIG=intravenous immunoglobulin

Adult patients

There were 25 patients with 76 TRCS-IVIG cumulative treatments. The age ranged from 22 to 69 years. Female and male sex were almost equal, 13 (52%) and 12 (48%), respectively. Essential hypertension, type 2 diabetes mellitus, and dyslipidemia were comorbidities found in 32%, 24%, and 24%, respectively. One patient (4%) had chronic kidney disease, with eGFR 62 mL/minute. Indications for IVIG were CIDP (11 patients, 43 treatments), MG crisis (five patients, six treatments), PID (two patients, 20 cycles), autoimmune encephalitis (five patients, five treatments), and inflammatory myopathy (two patients, two treatments (Table 1).

Side effects

There was no life-threatening post transfusion reaction, such as anaphylaxis and hypotension. Minor skin rash was found in a 9-year-old ITP patient at each of her three infusions (3%). This was easily relieved by oral antihistamine. Thromboembolic vascular events, such as acute coronary syndrome, ischemic stroke, and venous thrombosis, were not observed. None of patient developed congestive heart failure, aseptic meningitis, or hemolysis. Acute kidney injury (AKI) occurred in one CIDP patient who has chronic kidney disease stage 3. His serum creatinine transiently increased in two of six treatments (from creatinine 1.7 mg/dL to 1.79 mg/dL after the fourth treatment, and from 1.56 mg/dL to 1.57 mg/dL after the sixth treatment) but returned to the baseline level of 1.55 mg/dL after adequate hydration. Transient transaminitis was detected in three patients (3.1%). The highest levels of serum glutamic oxaloacetic transaminase (SGOT) was 58 IU/L and serum glutamate pyruvate transaminase (SGPT) was 88 IU/L (about twice the upper normal limits) and returned to baseline spontaneously.

Temporary drop in hemoglobin was seen in six infusions (6%), ranging from 0.5 to 3.2 g/dL. A decrease in hemoglobin was seen in one patient without evidence of hemolysis. Asymptomatic hypocalcemia, hyponatremia and hypokalemia

Table 2. Complications of TRCS-IVIG treatments compared to conventional IVIG

Complications	TRCS-IVIG (n=100) n (%)	Conventional IVIG[11] (n=145) n (%)	Difference of proportion (95% CI)	p-value
Hypotension	0 (0.0)	9 (6.2)	6.2 (2.27 to 10.13)	0.011
Anaphylaxis	0 (0.0)	2 (1.4)	1.4 (–0.5 to 3.3)	0.235
Allergic symptoms	3 (3.0)	3 (2.1)	–0.9 (–0.5 to 3.18)	0.655
Hypocalcemia	4 (4.5) (n=88)	3 (2.1)	–2.4 (–1.97 to –6.85)	0.279
Hyponatremia	8 (8.6) (n=93)	52 (35.9)	27.30 (17.63 to 36.97)	<0.001
Hypokalemia	1 (1.1) (n=93)	75 (51.7)	50.6 (38.81 to 62.39)	<0.001
Anemia	6 (6.3) (n=96)	28 (19.3)	13.00 (4.16 to 21.84)	0.004
Congestive heart failure	0 (0.0)	1 (0.7)	0.7 (–0.67 to 2.06)	0.402
Acute coronary syndrome	0 (0.0)	1 (0.7)	0.7 (–0.67, 2.06)	0.402

IVIG=intravenous immunoglobulin; TRCS-IVIG=IVIG from Thai Red Cross Society

Some laboratory results were missing. Percentage calculation based on only available data

developed after four, eight, and one administration with the lowest level of 7.9 mg/dL, 132 mmol/L, and 3.3 mmol/L, respectively. These resolved without any treatment. All patients remained seronegative for HIV, HBV, and HCV after 60 days of treatment.

A 9-year-old girl with chronic ITP died of fatal intracerebral hemorrhage at day 26. She had severe thrombocytopenia with platelet count of 4,000/mm^3. This was considered unrelated to TRCS-IVIG.

When compared to the study by Raden et al[11] at Siriraj Hospital among 145 conventional IVIG recipients, the incidence of anaphylaxis, hypotension, congestive heart failure, and acute coronary syndrome was lower in the TRCS-IVIG study. Only hypotension showed statistical significance with difference of proportion of 6.2 (95% CI 2.27 to 10.13, p=0.011). Incidence of minor allergic symptoms was not significant between the two studies with difference of proportion of –0.9 (95% CI –0.5 to 3.18, p=0.655). Anemia, hyponatremia and hypokalemia also occurred less in the TRCS-IVIG group, with difference of proportion of 13.0, 27.3, 50.6 and p-value of 0.004, <0.001, and <0.001, respectively. Hypocalcemia occurred more often in the TRCS-IVIG group but was not statistically significant, with difference of proportion of –2.4 (95% CI –1.97 to –6.85, p=0.279) (Table 2).

Discussion

IVIG has been widely used across Thailand as a standard treatment for many autoimmune diseases and primary immunodeficiency disorders. The demand has been increasing due to the expanded list of indications. Access to this product is limited[12,13] due to the very high cost as all the supplies have to be imported.

The TRCS receives more than 600,000 units of donated blood from approximately 300,000 healthy volunteers each year[14]. Therefore, the derived plasma products from this enormous pool of healthy donors contain a wide range of antibodies effective for immunomodulation and anti-inflammatory effects. To ensure safety, serology tests for venereal disease research laboratory (VDRL), HIV, HBsAg, and HCV are done in every unit and double checked with nucleic acid amplification test (NAT) to detect the last three organisms[15]. To optimize the use of excess plasma product that must be discarded at the expiry date, TRCS has recently built a plasma product factory with transferred technology from the South Korean Green Cross Corporation. Plasma products are processed with global standards and strict infection screening and disinfection techniques (i.e., cold ethanol fractionation, ion-exchange chromatography, solvent detergent (S/D) treatment, and nanofiltration (20 nm filter)[16]. The present study aimed to collect the safety data of TRCS-produced IVIG.

The authors found no serious side effect, such as anaphylaxis, congestive heart failure, or acute coronary syndrome with the TRCS-IVIG. Although direct comparison with the historical control from a prior study need to be interpreted with caution, the frequency of serious adverse events was less than in patients receiving the imported IVIG in the study by Raden et al[11]. Allergic symptoms were similar. Hypotension, hyponatremia, hypokalemia, and anemia were significantly lower in the TRCS-IVIG recipients.

Renal and liver dysfunctions were asymptomatic and transient. For the matter of transfusion-related infections, none of the present study patients reported seroconversion of HIV, HBV, or HCV after treatment.

The youngest patient recruited in the present study was 15 months old and reported no side effect. From the safety data in the present study, the authors considered that the TRCS-IVIG had only few minor side effects and had comparable safety data profiles comparing to the imported IVIG from the study by Raden, et al[11].

Conclusion

The present study shows that the safety profile of the TRCS-IVIG is comparable to the safety profile of conventional IVIG previously reported by Raden et al[11]. Life-threatening complications were not found, even in young children. Minor side effects such as anemia and electrolyte abnormalities were equal or even lower. Renal and hepatic dysfunction were uncommon and transient. Furthermore, abnormal laboratory results were asymptomatic. Transfusion-related infection was not reported. The authors concluded that the TRCS-IVIG, the first locally manufactured IVIG in Thailand, is safe and can be used in pediatrics and adults with careful patient selection to avoid high-risk cases.

What is already known on this topic?

Imported IVIG is an effective and safe treatment in several diseases.

What this study adds?

The locally manufactured TRCS-IVIG, as compared with imported IVIG, has comparable safety profiles.

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Conflicts of interest

The authors declare no conflict of interest.

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