INTRAVENOUS IMMUNOGLOBULIN USAGE AMONG PATIENTS IN HOSPITAL KUALA LUMPUR

BY

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DISCLAIMER

I hereby declare that this research has been sent to Universiti Sains Malaysia for the degree of Master of Medicine in Transfusion Medicine. It is not to be sent to any other universities. With that, this research might be used for consultation and can be photocopied as a reference.

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LIST OF ABBREVIATIONS

CFR	Case fatality rate
CIDP	Chronic inflammatory demyelinating polyneuropathy
CNS	Central nervous system
CRC	Clinical Research Centre
EFNS	European Academy of Neurology/Peripheral Nerve Society
ESBL	Extended spectrum beta-lactamase
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GVHD	Graft versus host disease
HIV	Human Immunodeficiency virus
HKL	Hospital Kuala Lumpur
HREC	Human Research Ethics Committee
HUKM	Hospital Universiti Kebangsaan Malaysia
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ITP	Immune thrombocytopenic purpura
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
MMN	Multifocal motor neuropathy
MG	Myasthenia gravis
MRSA	Methicillin-resistant *Staphylococcus aureus*

NHS	National Health Service
NMRR	National Medical Research Register
PDMP	Plasma-derived medicinal products
PE	Plasma exchange
PID	Primary immunodeficiency disease
WHO	World Health Organization

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ABSTRAK

Pengenalan: Imunoglobulin intravena (IVIG) telah digunakan secara meluas. Kajian ini memfokuskan kepada ciri-ciri penggunaan IVIG dan faktor-faktor yang berkaitan dengan status kekerapan penggunaan IVIG dalam kalangan pesakit dewasa dan kanak-kanak di Hospital Kuala Lumpur.

Kaedah: Kajian keratan rentas retrospektif telah dijalankan ke atas 482 pesakit yang menerima IVIG di Hospital Kuala Lumpur. Data diekstrak daripada borang permintaan IVIG yang direkodkan di Jabatan Farmasi. Analisis *Chi-square* dan *T-test* digunakan untuk analisis statistik, dan nilai $p < 0.05$ dianggap signifikan

Keputusan: Seramai 482 pesakit telah menerima IVIG di Hospital Kuala Lumpur dari Januari 2018 hingga Disember 2019. Terdapat 243 (50.4%) pesakit perempuan dan 228 (47.3%) pesakit lelaki. Umur median pesakit adalah 27 tahun. Indikasi tertinggi IVIG di kalangan pesakit adalah *hypogammaglobulinemia and other deficiency state*, 127 pesakit (26.3%). Indikasi yang paling kerap bagi sekali rawatan IVIG untuk pesakit dewasa ialah *hypogammaglobulinemia and other deficiency state*, 72 pesakit (35.0%), manakala untuk pesakit kanak-kanak adalah penyakit Kawasaki, 28 pesakit (20.3%). Penggunaan tertinggi bagi rawatan biasa di kalangan pesakit dewasa ialah *chronic inflammatory demyelinating polyneuropathy*, 18 pesakit (23.4%); manakala pesakit kanak-kanak ialah sepsis, 19 pesakit (31.1%). Kategori klinikal berkaitan dengan status kekerapan penggunaan IVIG dalam kedua-dua kohort dewasa dan kanak-kanak adalah signifikan dengan $p = 0.004$ dan $p = 0.017$ masing-masing.

Kesimpulan: Terdapat perbezaan yang ketara antara rawatan sekali sahaja dan terapi biasa di kalangan pesakit dewasa dan kanak-kanak. Garis panduan kebangsaan yang dikemas kini mengenai preskripsi IVIG berasaskan bukti perubatan untuk pesakit diperlukan untuk membantu doktor dalam preskripsi IVIG dengan sewajarnya.

Kata kunci: intravena immunoglobulin, indikasi luar label, *hypogammaglobulinemia, chronic inflammatory demyelinating polyneuropathy,* dewasa, kanak-kanak

ABSTRACT

Introduction: In the last decade, intravenous immunoglobulin (IVIG) has become widely used. This study focused on the characteristic of IVIG usage and associated factors towards the frequency status of IVIG among patients in Hospital Kuala Lumpur.

Methods: A retrospective cross-sectional study was performed on 482 patients who received IVIG in Hospital Kuala Lumpur. Data were extracted from request form for IVIG recorded in the Pharmacy Department. Chi-square and T-test analysis were used for statistical analysis, a p-value of < 0.05 was considered significant.

Results: A total of 482 patients received IVIG in Hospital Kuala Lumpur from January 2018 until December 2019. There were 243 (50.4%) female and 228 (47.3%) males. The median age of the patients was 27 years old. The commonest indications for IVIG among all patients were hypogammaglobulinemia and other deficiency state, 127 patients (26.3%). Most common indication for one-off treatment in adult was hypogammaglobulinemia and other deficiency state, 72 patients (35.0%), whereas in paediatric was Kawasaki disease, 28 patients (20.3%). The commonest indication for regular therapy among adult patient was chronic inflammatory demyelinating polyneuropathy, 18 patients (23.4%) while in paediatric was sepsis, 19 patients (31.1%). Clinical category was associated with frequency status of IVIG usage in both adult and paediatric cohort with $p = 0.004$ and $p = 0.017$, respectively.

Conclusion: There were significant differences between the indication for one-off treatment and regular therapy among adult and paediatric patients. Updated national guideline on the prescription of IVIG following evidenced based medicine for patients is needed to help clinicians in prescribing IVIG appropriately.

Keywords: intravenous immunoglobulin, off-labelled indication, *hypogammaglobulinemia, chronic inflammatory demyelinating polyneuropathy,* adult, paediatric

CHAPTER ONE:

INTRODUCTION

CHAPTER ONE

INTRODUCTION

1.1 Overview

This chapter covers the outline of the study on intravenous immunoglobulin usage among patients in Hospital Kuala Lumpur. This chapter also highlights the research justifications and research questions.

1.2 Background of study

Intravenous immunoglobulin (IVIG) is a medicinal formulation of pooled poly-clonal immunoglobulin G (IgG) derived from the plasma of a thousand or more healthy individuals (1–3). IVIG is sterile, which include of intact IgG molecules with a distribution of IgG subclasses (IgG3 and/or IgG4) comparable to that of normal serum. IVIG also contains small amount of other proteins and products such as albumin, IgM, IgA, IgE, salts, sugar, trace amount of solvents, detergents and buffers which may cause to tolerability difficulties (1,3). After infusion, IVIG has a half-life about 2 to 3 weeks. This, however, can vary based on the immune status of the patient (1).

Von Behring et al had previously published their work on diphtheria and tetanus serum administration in 1890 (1). They were the first to detect antibody molecules in the serum of animals that had been given vaccinations and show that these molecules could neutralize diphteria and tetanus toxins (4). Several scientific discoveries and events have occurred since then leading to the discovery and mass production of IVIG. During the World War II, Cohn and colleagues discovered procedures for large-scale immunoglobulin extraction based on cold ethanol fractionation from human plasma (known as Cohn fraction II). Since then, several clinical applications for human immunoglobulins have emerged (1,5,6)

IVIG is one of the plasma-derived medicinal products (PDMP) under fractionation programme (7). According World Health Organization (WHO), only 55 out of 171 reporting countries use PDMP through the fractionation of plasma collected in each reporting country (8). Approximately 25.6 million litres of plasma from 39 reporting countries were fractionated for the production of PDMP including 47% of the plasma recovered from a whole blood donation (8). Malaysia started contract the fractionation with Australia since 1990. National Blood Centre Malaysia collects and supply plasma for the fractionation programme. Factor VIII concentrate, factor IX concentrate, IVIG, and albumin were among the fractionated products returned back to Malaysia. Malaysia has been unable to produce domestic fractionation because the amount of plasma available here is insufficient (9).

IVIG formulas have improved over time, in addition to production techniques. Initially most commercial IVIGs were prepared at pH 6.4–7.2 with a concentration of 50 mg/mL. These products are often freeze-dried in the presence of a stabilizer as IgG solutions at neutral pH are unstable and develop precipitates during storage. In view of better stability of IgG solutions at low pH, current IVIG products are now available as liquid (6).

Administration of IVIG has become an essential therapeutic management in clinical medicine for more than 60 years. In 1952, Bruton used the first immunoglobulin products derived from human plasma to treat primary immunodeficiency (PID) (1,10). The original use of IVIG were as antibody replacement treatment. However, numerous other clinical advantages of IVIG therapy such as immunomodulator have been observed in neurology, dermatology, haematology and infectious disease specialties (11). IVIG has multiple activities as an immunomodulating agent including saturation of Fc receptors on macrophages, modulation of complement activation, reduction of idiotypic antibodies, and suppression of numerous inflammatory mediators such as cytokines, chemokines, and metalloproteinases (1).

Immunoglobulin (Ig) demand continues to rise at a regular annual pace of roughly 10% to 12% in Australia and around the world (12). The factors that influence annual consumption growth are complex, including increased usage in secondary immunodeficiency diseases (SID), neurological diseases, and improved diagnosis for PID especially in the developed countries (7).

Covid-19 pandemic has continue to challenge the world in relation to the critical work required to ensure safety and affordable supply of blood, blood product and services. The most significant challenges are caused by high demand for IVIG and intermittent reduction in blood donation. In 2020-21, Australia had issued 7.53 million grams of Ig at a cost of $742 million (including the cost for plasma fractionation). Of this amount, Australia had produced 53.2% of the Ig, while 46.8% was imported (12). In Malaysia, a total of MYR 3.7 million (885,220 USD) was spent in two government tertiary care hospitals for IVIG used for treating various conditions (13).

Till date so far, there is limited data collected for patients who received IVIG in Malaysia. The absence of national registry for IVIG usage further compounded this issue. As a result, the lack of data on actual IVIG usage among Malaysian patients, necessitating for this study.

1.3 Literature review

Immunoglobulin is becoming a well recognised therapy for a multitude of medical illnesses, not only because of its potential to combat infection by replacement treatment, but also because of its anti-inflammatory and immunomodulatory effects (4,12). In 1986, Malaysian hospitals began administering IVIG to patients with primary immunodeficiency (13). Since then, the demand has grown as a result of its use as a primary or adjunct treatment for a variety of illnesses (13).

The products of IVIG are produced from plasma pools collected from large numbers of healthy individual donor (1,6,7). Under the terms of the national fractionation contract,

Malaysia sends about 80,000 packs of blood to the Commonwealth Serum Laboratory (CSL) in Australia for fractionation (13). However, there is insufficient immunoglobulin G collected, thus the majority of IVIG products must be purchased on the international commercial market (13). The two IgG formulations that Malaysia has authorised for use are intravenous immunoglobulin (IVIG) and subcutaneous immunoglobulin (SCIG) (13).

IVIG was approved by the Food and Drug Administration (FDA) for eight indications; i. therapy of primary immunodeficiency ii. prevention of bacterial infections in patients with hypogammaglobulinemia and recurrent infection caused by B-cell chronic lymphocytic leukaemia iii. prevention of coronary artery aneurysms in Kawasaki disease iv. prevention of infections, pneumonia, and acute graft versus host disease (GVHD) after bone marrow transplantation v. suppression of serious bacterial infection in children with HIV vi. increase of platelet count in idiopathic thrombocytopenic purpura (ITP) to prevent or control bleeding vii. chronic inflammatory demyelinating polyneuropathy (CIDP) viii. multifocal motor neuropathy (MMN) (2,11,14).

Despite the FDA's approval of eight indications for IVIG, it is also widely used for other diseases in medicine, neurology, and dermatology as off-labelled indications. For the supply of IVIG, nations like Australia, Canada, and the United Kingdom have clear prescribing standards and priority protocols. However, the majority of hospitals in Malaysia lack explicit instructions for using IVIG. The Malaysian Ministry of Health's Medicines Formulary provides a quick list of the approved indications and doses. Consequently, it's possible that IVIG is overused for off-labelled indications (13).

Many studies were conducted in other countries to compare labelled versus off-labelled IVIG indications among their patients. In USA the mean rate of off-labelled IVIG admissions has climbed by 6.3% whereas the mean rate of IVIG admissions for FDA-approved indications by 4.4% from 2007 to 2014 (15). Around 14% of IVIG treatment was administered for off-label indications, according to a survey from Spain on IVIG usage from 2000 to 2004 that included 273 individuals (16). Another study conducted in Singapore and Saudi Arabia reported that IVIG has been used for off-labelled indications for 9.5% and 31.8% (2,17). In Iran, 22 (18.5%) cases of IVIG were administered based on FDA approval, while the remaining patients, 97 (81.5%), were administered off-labelled (18). While in Malaysia, a study conducted in HUKM reported from 115 IVIG cases administered, 61 cases (53.0%) were utilised for FDA approved indications and 54 cases (47.0%) were utilised for off-labelled indications (16).

Although similar-sized adult trials have been conducted, the clinical indications and IVIG dosages for adult cases significantly different from those for children. In Iran, 42.3% IVIG were prescribed for CIDP, 19.6% for ITP, 11.8% for Guillain-Barré syndrome (GBS) and others were less than 10.0% (19). While a study in French found five diseases which represented 50.0% of the total IVIG usage which were 11.0% for multifocal motor neuropathy (MMN), 10.2% for CIDP and dermatomyositis, 9.9% for ITP in adult and 9.1% for immune deficiency conditions (14). These results almost similar with the adults from Australia, the USA, and Japan, which found prominent indications of IVIG usage would include GBS, CIDP, acquired hypogammaglobulinemia secondary to haematological malignancies and primary immunodeficiency disease (PID) (17).

Few studies were done among paediatric patients to look for prevalence and indications of IVIG usage. In Singapore, the commonest indication for IVIG administration was Kawasaki disease, 794 (60.0%) patients (17). Kawasaki disease was used the largest proportion of the total IVIG by 34.0% (17). While in United State of America (USA), paediatric patients with ITP and mucocutaneous lymph node syndrome were the two most common IVIG users (15). Other top-ranked indications were acute infectious polyneuritis and prophylaxis of infections in patients who received antineoplastic chemotherapy (15).

Out of the 115 cases of IVIG administered, sixty-nine percent of IVIG cases were given in a single dose while the remaining 31.0% were given in multiple doses, up to 5 doses, with an interval of 2 to 5 days per case (16). A study was conducted to look for the effect of several doses of IVIG treatment versus single dose IVIG treatment in new born with blood group incompatibility. The results showed that the rate of exchange transfusion in the several doses IVIG group, was lower than single dose IVIG group ($p<0.05$) and the control group ($p< 0.01$) (20).

In few studies, newborns who received high dosage IVIG had less need for exchange transfusions in neonatal jaundice (21,22). IVIG also appears to lower the time in the high risk zone for neurological impairment as well as the risk of complications related to exchange transfusion (22). Another study shown that the administration of IVIG therapy at high doses would change the course of serum bilirubin levels. After receiving high dose IVIG therapy, the majority of the treatment group's children's serum bilirubin levels remained stable for 24 to 48 hours. The subsequent rise in bilirubin levels was usually slow and easily controlled by phototherapy (23).

A study conducted in HUKM Malaysia showed that 53.0% IVIG utilization and FDA approved indications were KD (27.0%) (17). However, this study were only conducted on paediatric patients. In view of the gaps in Malaysian data, this study aims to determine the characteristics of IVIG usage among the adults and paediatric patients.

1.4 Research justification

Products of IVIG is produced externally and very expensive. Inappropriate use of IVIG can result in wastage besides exposing the patient to unwanted adverse effect. The IVIG usage is under-reported in Malaysia. Furthermore, the problems are further complicated by the absence of national patients' registry for IVIG usage. Thus, the true number of IVIG usage remained unknown in Malaysia. Limitation of approval indications and doses of IVIG in The Malaysian Ministry of Health Medicine Formulary also may caused high IVIG usage for off-labelled indications and will lead to an increase in unnecessary healthcare cost to the country. The main gap identified in Malaysia is limited local data available for IVIG usage. Therefore, study on the characteristic of IVIG usage needs to be carried out in Malaysia tertiary hospitals. This study aimed to characterise the IVIG usage among the patients in Hospital Kuala Lumpur and subsequently provides an objective measurement of frequencies of IVIG usage in the area studied. A better understanding of IVIG usage will contribute towards a better clinical management guideline in Malaysia.

1.5 Research questions

1. What are the characteristic of IVIG usage in Hospital Kuala Lumpur?
2. What are the indications of IVIG usage as one-off treatment to adults and paediatric patients in Hospital Kuala Lumpur?
3. What are the indications of IVIG usage for regular therapy among adults and paediatric patients in Hospital Kuala Lumpur?
4. Are there any difference indications of IVIG usage among adult patients compare to paediatric patients?
5. Are there any significant relationship between the demographic (age, gender and ethnic) and indication of IVIG usage with selected factors (one-off treatment and regular therapy)?

CHAPTER TWO:

OBJECTIVE

CHAPTER TWO

OBJECTIVE

2.1 General objective

To determine the characteristics of IVIG usage among the adult and paediatric patients in Hospital Kuala Lumpur (HKL)

2.2 Specific objective

1. To describe the indication of one-off treatment of IVIG in adult and paediatric patients in HKL
2. To describe the indication of regular replacement therapy of IVIG in adult and paediatric patients in HKL
3. To compare the indication of IVIG usage between adult and paediatric patients in HKL
4. To determine the association between the patient's demographic (age, gender and ethnic) and indication with one-off treatment and regular replacement therapy of IVIG among patients in HKL

2.3 Alternative Hypotheses

- There is association between patient's demographic (age, gender and ethnic) with selected factors (one-off treatment and regular therapy)

- There is association between indication with selected factors (one-off treatment and regular therapy)

2.4 Null hypothesis

- There is no association between patient's demographic (age, gender and ethnic) with selected factors (one-off treatment and regular therapy)
- There is no association between indication with selected factors (one-off treatment and regular therapy)

CHAPTER THREE:

METHODOLOGY

CHAPTER THREE

METHODOLOGY

3.1 Study background

This study focused on the characteristics of IVIG usage as one-off treatment and regular therapy among adult and paediatric patients in Hospital Kuala Lumpur. This study also explores the association factors between patient's demographic (age, gender and ethnic) and the indication of IVIG usage.

3.2 Study design

This was a retrospective cross-sectional study using original database records from Pharmacy Department in Hospital Kuala Lumpur.

3.3 Study area

This study was conducted at Hospital Kuala Lumpur. Hospital Kuala Lumpur is the largest hospital under the Ministry of Health of Malaysia and is considered to be one of the largest in Asia. It is a government tertiary referral centre, situated on 150 acres of prime land with 83 wards and 2300 beds.

Due to the availability of comprehensive medical facilities and a wide range of subspecialty treatments, a large number of patients with various diseases sought treatment at this hospital. This centre also served as a supra-regional referral centre for various medical sub-specialties cases such as neurology, dermatology, nephrology, urology, genetic, orthopaedic, national transplant resource centre and others. Therefore, HKL is expected to have a different demographic characteristics of patients. This made Hospital Kuala Lumpur an appropriate place for this study to be conducted.

3.4 Study population

All adult and paediatric (age less than 18 years old) patients who had received IVIG from 1st January 2018 until 31st December 2019 were identified. The list of patients was obtained from request form of IVIG recorded in Pharmacy Department Hospital Kuala Lumpur.

3.5 Subject criteria

3.5.1. Inclusion criteria

- All adult and paediatric (age less than 18 years old) patient who had received IVIG

3.5.2. Exclusion criteria

- Incomplete data in the requesting form or incomplete documentation

3.6 Sample size

The sample size was calculated using single proportion and two proportion formula.

Specific objective 1: To determine the indication of one-off treatment of IVIG in adult and paediatric patients in HKL

Single proportion, $n = \left(\frac{z}{\Delta}\right)^2 p(1-p)$

Where, n = sample size

z = the value to estimate the 95% confidence interval (1.96)

p = true population proportion

Δ = precision or detectable difference of expected population proportion and true population proportion

Based on J Wu et al. (2013), the proportion of IVIG usage according to FDA approved indication in Singapore was 75%. This study wished to estimate population proportion in Malaysia within 10% from true proportion with 95% confidence interval. The minimum sample size required with an additional 20% non-response rate is:

$$n = \left(\frac{1.96}{0.1}\right)^2 (0.1(1-0.1))$$

= 72 + 20% non-response rate

= 86

Specific objective 2: To determine the indication of regular replacement therapy of IVIG in adult and paediatric patients in HKL

Single proportion, $n = \left(\frac{z}{\Delta}\right)^2 p(1-p)$

Where, n = sample size

z = the value to estimate the 95% confidence interval (1.96)

p = true population proportion

Δ = precision or detectable difference of expected population proportion and true population proportion

Based on J Wu et al. (2013), the proportion of IVIG usage according to regular replacement therapy for PID in Singapore was 2.4%. This study wished to estimate population proportion in Malaysia within 10% from true proportion with 95% confidence interval. The minimum sample size required with an additional 20% non-response rate is:

$$n = \left(\frac{1.96}{0.1}\right)^2 (0.02(1-0.02))$$

$= 8 + 20\%$

$= 10$

Specific objective 3: To compare the indication of IVIG usage between adult and paediatric patients in HKL

$$\text{Two proportion : } n = \frac{p_1(1-p_1)+p_2(1-p_2)}{(p_1-p_2)^2}(z_\alpha + z_\beta)^2$$

Where, n = sample size

p1 = proportion of the associated factor among higher risk

p2 = proportion of the associated factor among lower risk

$z\alpha = 1.96$ for $\alpha = 0.05$ (two tailed)

$z\beta = 0.84$ for 80% power

Based on Kato H et al., (2000) the proportion of IVIG usage for infectious disease among adults in Japan was 73% while the proportion in paediatric was 33%. This study wished to estimate population proportion in Malaysia with level of significance 0.05 and power of 80%. The minimum sample size required with an additional 20% non-response rate is:

$$n = \frac{0.73(1-0.73) + 0.33(1-0.33)}{(0.73-0.33)^2} \times (1.96 + 0.84)^2$$

$n = 20 + 20\%$

$n = 24 \times 2$

$n = 48$

Specific objective 4: To determine the association between the patient's demographic (age, gender, ethnic) and indication with one-off treatment and regular therapy of IVIG among patients in HKL

Two proportion: $n = \frac{p_1(1-p_1)+p_2(1-p_2)}{(p_1-p_2)^2}(z_\alpha + z_\beta)^2$

Where, n = sample size

p1 = proportion of the associated factor among higher risk

p2 = proportion of the associated factor among lower risk

zα = 1.96 for α = 0.05 (two tailed)

zβ = 0.84 for 80% power

Based on (Toh et al., 2018) the proportion of IVIG usage for single dose is 69% while the remaining 31% administered in divided doses. This study wished to estimate population proportion in Malaysia with level of significance 0.05 and power of 80%. The minimum sample size required with an additional 20% non-response rate is:

$$n = \frac{0.69(1-0.69)+0.31(1-0.31)}{(0.69-0.31)^2} \times (1.96+0.84)^2$$

$n = 23 + 20\%$

$n = 27.6$

$n = 28 \times 2$

$n = 56$

Conclusion

Based on the calculation from each objective, the biggest sample size is 86 from first objective. Thus, the final sample size for this study is 86.

3.7 Sampling method and subject recruitment

3.7.1. Sampling method

Universal sampling was used as all patients listed in the request form are recruited as a subject

3.7.2. Subject recruitment

Target population: Patients who received IVIG in Hospital Kuala Lumpur

Sampling frame: Taken from the request form for IVIG record in Pharmacy Department Hospital Kuala Lumpur.

3.8 Research tool

a. Patient's PROFORMA was prepared to ensure data collection was complete and easy to be reviewed (Appendix A). The data included were:

- Patient's identification number
- Age
- Gender
- Ethnic
- Department
- Indication of IVIG
- Dosage of IVIG used

b. Patient's medical record in request form

3.9 Data collection method

Clinical Research Centre (CRC) of Hospital Kuala Lumpur and National Medical Research Register (NMRR) were approached to get approval and written consent to conduct this research in Hospital Kuala Lumpur. Patient's details were identified using the request form from Pharmacy Department in Hospital Kuala Lumpur. All the information and parameters were recorded in the patient's proforma form by the main researcher (registered medical officer).

3.10 Statistical analysis

Data entry and analysis were performed using IBM SPSS version 27 for Window-software. The data were analysed using descriptive and inferential analyses.

Descriptive analysis was done for general objective, specific objective 1 and 2 which were to determine the prevalence and indications of IVIG usage for one-off treatment and regular replacement therapy in Hospital Kuala Lumpur.

Descriptive analysis was done for specific objective 3 which to compare the indication one-off treatment and regular replacement therapy between adults and paediatric patient also descriptive statistic were used.

Chi-square test and independent sample T-test were done for specific objective 4 which to determine the association between demographic data (age, gender and ethnic) and indication with one-off treatment and regular therapy. The level of significance was set at p- value of less than 0.05.

3.11 List of variables

3.11.1 Dependent variables

a. frequency of IVIG treatment

3.11.2 Independent variables

a. age, gender, ethnic, indication of IVIG

3.12 Operational definition

Age

Patient age is defined as years from the birth date as per identification card (I/C)

Gender

Gender of patient (male or female) is determined by their official and valid I/C

Ethnic

Ethnic of patient (Malay, Chinese, Indian, Other) is determined by their official and valid I/C

Frequency IVIG treatment

Frequency is defined as the rate of IVIG usage (one-off or regular) during this study time

Indications

Indications is defined as the diagnosis from the clinical management team judgement to receive IVIG treatment (as stated in the request form to Pharmacy Department, Hospital Kuala Lumpur)

3.13 Ethical issue

Ethical approval (NMRR-19-3835-52071(IIR) and USM/JEPeM/20010011) were obtained from National Medical Research Register (NMRR) and Human Research Ethics Committee (HREC) of Universiti Sains Malaysia.

3.14 Study flowchart