HEALTH-RELATED QUALITY OF LIFE AMONG HAEMOPHILIA CHILDREN IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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LIST OF ABBREVIATION

PedsQL ™: Pediatric quality of life inventory TM

HRQOL: Health-related quality of life

QOL: Quality of life

Hospital USM: Hospital Universiti Sains Malaysia

MOH : Ministry of Health

CDC: Centre of Disease control and prevention

DEFINITIONS

Health-Related Quality of Life (HRQOL):

Individual's perception of their position of life in the context of the culture and value system in which they live and in relation to their goals, expectations and concerns (World Health Organization, 1993).

Quality of life (QOL)

Individual's subjective well-being which generally measures how satisfied they are with their life as a whole which include about marriage, housing and employment (Patrick D.L. et al., 1993).

On demand therapy

A replacement therapy that was given as needed only to stop bleeding when the bleeding could not be stopped by compression only (Pipe S.W. et al., 2013).

Prophylaxis therapy

A replacement therapy that was given to haemophilia patients a few times in a week to prevent bleeding (Pipe S.W. et al., 2013).

ABSTRAK

Latar belakang

Hemofilia adalah salah satu penyakit genetik yang paling kerap di dunia. Ia disebabkan oleh kekurangan faktor pembekuan darah VIII dalam hemofilia A dan kekurangan faktor pembekuan IX dalam hemofilia B. Kedua-dua faktor ini, penting dalam sistem koagulasi badan manusia. Pesakit hemofilia terdedah kepada risiko pendarahan yang berlebihan selepas sebarang kecederaan yang berlaku sama ada secara spontan ataupun trauma. Oleh itu, mereka memerlukan bantuan faktor pembekuan secara berkala atau bila perlu bagi mengurangkan risiko pendarahan, sekaligus mengelakkan komplikasi pendarahan yang teruk seperti kecacatan selepas pendarahan otak, kecacatan sendi, penyakit jangkitan yang disebabkan transfusi darah seperti hepatitis B, C atau HIV dan juga kematian. Seperti penyakit-penyakit kronik yang lain, penyakit hemofilia bukan sahaja memberi implikasi secara fizikal kepada pesakit tetapi juga pada emosi, psikososial dan persekolahan pesakit. Penyelidikan ini bertujuan untuk menilai kualiti kehidupan kesihatan kanak-kanak yang menghidap penyakit hemofilia dengan menggunakan borang soal selidik yang telah diterjemah dan disahkan, PedsQL^{TM} 4.0 Teras Generik Skala versi Bahasa Melayu.

Objektif

Untuk mengkaji kualiti hidup pesakit hemofilia yang menerima rawatan di Hospital Universiti Sains Malaysia.

Kaedah

Kajian melibatkan 12 pesakit hemofilia yang masih menerima rawatan sama ada yang menghadiri Klinik Pakar Pediatrik atau pernah dimasukkan ke wad Hemato-onkologi di Hospital USM sehingga April 2017. Borang kaji selidik PedsQL^{TM} 4.0 Teras Generik Skala bagi laporan kanak-kanak dan laporan ibubapa. Wilcoxon signed-rank test telah digunakan untuk membandingkan tahap kualiti hidup dari perspektif pesakit sendiri dan ibu bapa atau penjaga mereka.

Keputusan

Kesemua 12 pesakit hemofilia A di Hospital USM adalah lelaki dan median umur mereka adalah 16 tahun. Secara keseluruhan, kajian inventori kualiti hidup kanak-kanak hemofilia adalah bagus terutama dalam domain fizikal iaitu 90 (83,99) dan domain sosial iaitu 90 (80,99). Manakala markah yang paling rendah adalah pada domain sekolah iaitu 68 (60,75). Median purata markah untuk jumlah keseluruhan kualiti hidup yang dilaporkan oleh ibubapa adalah rendah berbanding pesakit dengan nilai [81 (75,89), 75 (73,83), z score -2.09, p value 0.037]. Laporan ibubapa lebih rendah terutama pada domain emosi [85 (76,94), 75 (58,85) z score -2.12, p value 0.034] dan sosial [90 (80,94), 80 (71,89) z score -1.98, p value 0.047].

Kesimpulan

Kualiti hidup pesakit hemofilia yang menerima rawatan di Hospital USM adalah baik. Ibubapa dan pesakit bersetuju bahawa fungsi domain sekolah terganggu oleh kehadiran ke hospital kerana sakit atau kerana rawatan susulan. Ibubapa mempunyai perspektif yang berlainan pada tahap kualiti hidup anak mereka terutama pada fungsi domain emosi dan sosial.

ABSTRACT

Background

Haemophilia is one of the most common genetic disorders in the world. It is caused by factor VIII deficiency in haemophilia A and factor IX deficiency in haemophilia B. These factors are important in human body coagulation system. Patients with these disorders are exposed to the risk of excessive bleeding that occur either spontaneous or trauma. Thus, they would need factor replacement therapy either as prophylactic therapy or on-demand need to reduce the risk of any bleeding complication such as neurological abnormality post intracranial bleeding, joint deformity, transfusion transmitted infection such as hepatitis B, C or HIV and even death. As any other chronic illnesses, haemophilia does not only affect patient's physical function but also their emotional, psychosocial and school function. This research is aimed on evaluating health-related quality of life among paediatric patients with haemophilia using translated and validated questionnaire PedsQL™ 4.0 Generic Core Scale.

Objective

To study the health-related quality of life (HRQOL) among children with haemophilia who received treatment in Hospital Universiti Sains Malaysia.

Methodology

This study involved all 12 haemophilia patients who received treatment or came for follow up at Paediatric Clinic Hospital USM, Haemato-oncology ward Hospital USM until April 2017. PedsQL ™ 4.0 Generic Core Scale self-report and parents' reports were used. Wilcoxon

signed-rank test was used to compare the level of each patient HRQOL from patient's own perspective and the caregiver's perspective.

Results:

All twelve Haemophilia A patients in Hospital USM were male with median age of 16 years old. Overall health-related quality of life of the haemophilia patient was good especially in physical domain with score of 90 (83,99) and social domain with score of 90 (80,99). Meanwhile, the lowest score was in school function domain with score of 68 (60,75) especially in item of missed school during unwell and for hospital visit. Total median scored for health-related quality of life reported by parents was lower compared with child self-report with score of [81 (75,89), 75 (73,83), z score -2.09, p value 0.037]. Parents-proxy reported lower score especially in emotional function domain [85 (76,94), 75 (58,85) z score -2.12, p value 0.034] and social function domain [90 (80,94), 80 (71,89)) z score -1.98, p value 0.047].

Conclusion:

Health-related quality of life (HRQOL) among children with haemophilia that received treatment in Hospital Universiti Sains Malaysia was good. Parents and child both agreed that school function domain was affected due to missed school during unwell and for hospital visit. Parents perceived differently on their child HRQOL especially in social and emotional function.

CHAPTER 1

INTRODUCTION

Haemophilia is one of the most common X-linked inherited bleeding disorders. It is a lifelong disease of blood coagulopathy that is characterised by bleeding, which can occur due to or without trauma, and requires replacement of the deficient factor as its main treatment. Based on latest statistics from Centre for Disease Control and Prevention (CDC) in United States, haemophilia A occurs in 1 in 5,000 live male births and is about four times as common as haemophilia B (Data and statistic, CDC, 1998). The prevalence of haemophilia A in Malaysia was 6.6 in 100,000 males whereas haemophilia B was 1 per 100,000 males (Malaysia World Federation of Haemophilia, 2012).

There are two types of haemophilia which is haemophilia A, which result from deficiency of Factor VIII (FVIII) and haemophilia B resulting from Factor IX (FIX) deficiency. Patients are almost always male because of the inheritance pattern and female can be a disease carrier. It can be divided into mild, moderate and severe form of haemophilia based on the level of these factors. Mild disease has more than 5% factor activity level, moderate disease with a factor activity level of 1% to 5% and severe disease with a factor activity level of less than 1%.

Neither Factor VIII nor Factor IX crosses the placenta, hence bleeding symptoms may be present by birth or may occur in the foetus. Obvious symptoms such as easy bruising, intramuscular hematomas, and haemarthroses begin when the child begins to cruise. Haemophilia has high rate of spontaneous mutation, thus, in the absence of a positive family

history, haemophilia may go undiagnosed in the new-born. Eventually, they may present with prolonged bleeding after some small cuts or even after tooth extraction or circumcision.

Haemophilia patients are at high risk of bleeding which can occur spontaneously or secondary to trauma involving any part of the body. Hence, they are subsequently exposed to multiple types of complications which include development of inhibitor, intracranial bleeding, bleeding during surgical procedure or even joint and muscle contracture due to recurrent bleeding. They are also at high risk to get blood transfusion related infections such as hepatitis B or C if they come with severe bleeding.

Introduction of factor replacement therapy with plasma derived clotting factors has reduced bleeding episodes among haemophilia patient especially those with severe haemophilia, and thus improves their quality of life. Choices of factors given will be based on type of haemophilia. Factor VIII is for haemophilia A patient and factor IX is for haemophilia B patient. Octaplex is a new Prothrombin Complex Concentrate (PCC) contains factor II, VII, IX and X. It was used in haemophilia A and B patient with inhibitor as an alternative for Novoseven. Factor replacement therapy can either be treated based as on-demand need or as prophylaxis therapy. Factor replacement will only be given if there is bleeding episode for on-demand basis group. Prophylactic therapy is when the clotting factor is given on regular basis either on alternate day or 3 times for week. Prophylaxis therapy helps to prevent recurrent bleeding and risk of developing inhibitor (Gouw S.C. et al., 2007).

The nature of the disease, treatment and complications of the disease itself may inflict psychosocial issue for patients and family members. Parents usually take extra precaution to avoid risk of bleeding. They may prevent their child from involving in any physical activity or

even may impose wearing safety pad on some parts of their body for the whole day. Moreover, child with haemophilia need to go to hospital regularly for treatment or follow-up treatment especially for severe haemophilia patient with prophylaxis therapy. Haemophilia patients may also need prolonged hospital stay if massive bleeding occur, tooth extraction or even for any surgery required. Consequently, parents need to accompany their child for most of the time. Thus, these will subsequently affect quality of life not only patients themselves but also their parents, other family members, their work or even their social life.

Literatures available have focused on assessing health-related quality of life in children with haemophilia. However, those findings of studies were conducted elsewhere might not be the true reflection of haemophilia patient in Malaysia due to different ethnicity, religion and socioeconomic background of the family. Therefore, this study was conducted to look at the impact of haemophilia on health-related quality of life of children with haemophilia within local environment.

CHAPTER 2

LITERATURE REVIEW

Haemophilia is an X-linked recessive bleeding disorder that is caused by deficiency or absence of Factor VIII for haemophilia A and deficiency or absence of Factor IX for haemophilia B. Both factors are important in our body as they have an important function in our coagulation cascade to prevent and to stop bleeding. Thus, the haemophiliacs are at risk of spontaneous or traumatic type of bleeding. The most common presentation of haemophilia was bleeding and most of them had positive family history of haemophilia (Gouw S.C. et al., 2007). They usually would have developed first episode of bleeding by 11 months old and by 25 months of age, they already have first episode of joint bleeding (Gringeri A. et al., 2004).

Subsequently, they are exposed to multiple complications which include functional joint impairments that are significantly increased in the older age group (Gringeri A. et al., 2004). According to Buzzard B.M. et al (2002), the haemophiliacs can develop pain, severe joint damage, disability that later lead to a dramatic impairment of their health-related quality of life.

Development of inhibitor is one of the serious complications in haemophilia patient. Inhibitor is an alloantibody that was formed towards factor replaced. Inhibitors interfere with the infused factor concentrate which lead to ineffective and necessitating use of more costly and less effective alternative haemostatic agents (Gringeri A. et al., 2003). A positive inhibitor titre was defined according to the cut off level of the inhibitor assay used in the laboratory at each centre. Studies showed that patient who had certain genetic mutation (eg intron 22), family history with inhibitor, intense exposure to factors at first presentation and had underwent major

surgery within 50 days of exposure had higher risk to develop inhibitor (Witmer C. et al., 2013 and Gouw S.C. et al., 2007).

Major complications of haemophilia disease are joint disease (haemophilic arthropathy), inhibitor development, transfusion transmitted infection or other related infection and intracranial bleeding. A study done by Brown et al (2006) showed that haemophilia patient with inhibitor had a higher risk of severe bleeding, progression of joint disease which would lead to deterioration of health-related quality of life. Tremendous improvement of haemophilia management especially usage of factor replacement therapy has improved life expectancy of patient with haemophilia to approach normal life expectancy including patient with severe haemophilia (Darby S.C. et al., 2007).

Venous access was one of the major problems for patient to be compliance to prophylaxis therapy and was the second most frequently cited reason for respondents choosing not to administer prophylactic treatment (Gerathy S. et al., 2006). Inserting a central line for haemophilia patient may put them at high risk of catheter related infection (Gringeri A. et al., 2011). However, they would be more compliance to the treatment if they had a good venous access and it will help them to reduced bleeding episode and reduced the risk for inhibitor to develop.

Factor replacement therapy in haemophilia can be given either on-demand therapy or prophylaxis therapy. Prophylaxis therapy is the administration of clotting factors concentrate on regular basis at least 1 to 3 times per week regardless of presence of any bleeding episode or not. Otherwise, on demand therapy is clotting factor concentrate given only when there is acute bleeds. Prophylaxis treatment should be started at an early age to prevent recurrent

episode of bleeding, target joint damage and to prevent development of inhibitor (World Federation of Haemophilia, 2014). Manco-Johnson M.J. et al (2007) showed that high percentage of boys in America that were given prophylaxis therapy before the age of 30 months, had their normal joint on magnetic resonance imaging compared to boys that received episodic therapy. A randomized study done by Gringeri A. et al (2011) among Italian children with severe haemophilia A showed that after a median of 82.5 months of therapy, children with prophylaxis therapy had shown significantly fewer haemarthroses and radiological abnormalities in plain radiograph compared to on-demand therapy. Meanwhile, several studies had shown that there was decreased risk of developing inhibitor if the prophylaxis therapy was started in the first 20 days of exposures to the factor compared to on demand treatment (Gouw S.C. et al., 2007 and Morado M. et al., 2005). There were also studies that showed patient who had genetic mutation (eg intron 22), family history with inhibitor, intense exposure towards factors at first presentation and underwent major surgery within 50 days of exposure had a higher risk to develop an inhibitor (Witmer C. et al., 2013 and Gouw S.C. et al, 2007). This showed that prophylaxis therapy was better than on-demand therapy.

However, the need of prophylaxis therapy and the regime should be individualized according to patient's risk, benefit and cost effectiveness of the treatment itself. This type of treatment would also depend on economic resources of the centre and venous access, the number of bleed especially joint bleeds, risk of subclinical microbleeds and risk of recurrent intracranial bleed. Prophylaxis therapy can either be given as primary or secondary prophylaxis. Primary prophylaxis is factor infusions that were given to prevent bleeding and its consequences. It should be given in the first or second year of life, but is usually given after the first bleeding episode. Secondary prophylaxis is a factor infusion that is given in order to prevent recurrent bleeding, at the beginning after target joint bleeding had developed, or after three joints or significant soft tissue bleeding had occurred and given regularly prior to activities. It is

important to prevent joint contracture or deformity by preventing development of target joint or recurrent bleed. Target joint is defined as three or more bleeds into the same joint in a consecutive three month period.

In Malaysia, there was still no study that looked deeply into the effectiveness of prophylaxis therapy versus on demand therapy in preventing bleeding, target joint, inhibitor and cost effective of this treatment. There was also no study done to look into the effectiveness of current haemophilia treatment with health-related quality of life among our haemophilia children.

Quality of life (QOL) and health-related quality of life (HRQOL) are used interchangeably. However, quality of life usually covers all aspects in life but health-related quality of life focuses on the effect of illness and specifically looking on the impact of treatment to the illness. Quality of life (QOL) is a concept which refers to the conceptions of the goodness of life (Zautra A. et al., 1979). It covers broadly all the aspects of human experience about the necessities of life, characterized individual's subjective well-being by generally measures how satisfied they are with their life as a whole which include about marriage, housing and employment (Patrick D.L. et al., 1993).

Health-related quality of life is a subjective and multidimensional, encompassing physical, occupational function, psychological state, social interaction and somatic sensation (Guyyat G.H. et al., 2004). It is a dynamic concept resulting from past experience, present circumstances and their future expectation (Bowling A. et al., 2001). Health-related quality of life is also influenced by patients' injury, illness, complication that had and treatment that they received before. HRQOL can be rated either by proxy's or by patients themselves based on the time availability, patient's health condition or subject difficulty to understand the questions

because of the age or terminal illnesses. The variable answers from proxy will depends on the patient and proxy relationship because a study done by Samsa G. et al in 1999 showed that there was a high correlation in physical function between self and proxy report.

According to World Health Organization (WHO), health-related quality of life helps to determine those aspects of overall quality of life. Analysing HRQOL can help to guide us to improve patient's problems and avert their serious consequences. Furthermore, HRQOL tool assessment addresses patient's perception of the impact of their illness and its treatment which are within the scope of healthcare services and products (WHO, 1984). HRQOL measures also help to clarify the threads off between treatment and intervention with major benefits and health related outcome cost (Guyyat G.H. et al., 2007). Subsequently, HRQOL measures can help in clinical decision making if our primary goal of treatment is to improve the way patient feeling (Guyyat G.H. et al., 2007) and to choose optimal treatment for patient and family themselves (Roila F. et al., 2001).

There are increased developments and utilization of HRQOL measures since the last decade. In children with chronic illnesses, the goal of health care is to provide the best health as possible by improving symptoms management, treatment compliant and their ability to cope with the diseases. This measure shall subsequently, improves patient's health status and determines the value of health services for them (Varni J.W. et al., 1999).

Quality of life is a generic measure that allows collection of qualitative and qualitative data (Frish M.B. et al., 1992). Health-related quality of life or quality of life can be assessed either using qualitative or quantitative measure. Quantitative data are measures of values or counts that are expressed as numbers. The answer will usually expressed using numbers of scales

which subsequently transformed to a score according to questionnaire protocol description and later can be analysed. Qualitative data were designed to gain in depth understand of what the concept and further explains of research finding using patient's or client's own words, expression or opinion. Qualitative data makes better understanding why QOL across several domains is impaired. It also yields information that would remain unobserved by quantitative QOL questionnaire (Abbey et al., 2011). Combination of both qualitative and quantitative data yields more complete analysis and they complement each other's (Creswell J.W. et al., 2004). It will also provide more comprehensive picture of health services than either method alone (Wisdom J.P. et al., 2001).

The Paediatric Quality of Life Inventory (PedsQL) was built on a programmatic measurement instrument development effort by Varni and colleagues in paediatric chronic health conditions during the past 15 years. This instrument is designed to measure HRQOL in children and adolescents with chronic diseases using quantitative data and can be implemented in a normal healthy population. Now, this module is accessible and well recognized as an important health outcome in clinical trials and health services. This PedsQL comprised of generic core measurement and disease specific module based on different specific diseases (Varni J.W. 1999; 2001; 2007).

PedsQL™ 4.0 Generic Core Scales questionnaire is a quantitative questionnaire that designed for both patient and healthy population. It can be used in acute ill patient to assess their problem within 7 days or even in chronic ill patient to assess their problem within 4 weeks. The questionnaire will involve both patient self-report and parents as proxy report. They will be asked separately using different questionnaire according to their child age group. Patient self-report is a patient reported outcome that come directly from patient without interpretation by

physician or other person about how he feels about the disease, treatment and complications itself. However, it is also important to capture about how is the patient feeling from his caretaker perspective. This will help to capture the disease and treatment from the patient's perspective and his caretaker's perspective. Thus, this will better assess the value of the treatment received. This will also enable health care provider to recommend strategies to improve care and help the parents or caretaker to tackle their children's feeling and help them improve their child health-related quality of life.

The questionnaire was originally developed by Dr James W. Varni (Varni J.W. et al., 2001) to measure the impact of paediatric chronic health condition on patient's health-related quality of life. This Paediatric Quality of Life Inventory (PedsQL™) questionnaire, version 4.0 with permission was translated and validated in Malay version questionnaire by Dr Nurul and team researcher under Paediatric Department Hospital Universiti Sains Malaysia in 2012 (Zakaria N.H. et al., 2012).

The impact of haemophilia towards patient itself had been shown to be significant by many researchers before. In a study done in Philippines showed that there was a good health-related quality of life among moderate and severe haemophilia patient. Younger age group patient showed most impairment in family subscales as parents turn to be more cautious in handling their children and avoiding them from being involved in most of the children activities (Espaldon A.M.D. et al., 2014). Adolescents with severe haemophilia had a better compliance and cautious than those with mild or moderate disease. As disease severity affects the personality traits and behaviour patterns especially in this age group (Stehl et al., 2009). The severity of haemophilia and how it affects the QOL was consistent with other studies (Mercan A. et al., 2010, Tantawy A.A. et al., 2011 and Bagheri S.H. et al., 2012).

However, there is no local data available and none of the researcher before used PedsQL™ questionnaire specifically to assess haemophilia patient's health-related quality of life from patient's own perspective and caretaker's or parents' own perspective. As haemophilia has significant morbidity towards patient's life, it is important for paediatrician to understand the impact of the illness to the patients. It is equally important to identify the factors that could contribute to poor quality of life.

Thus, the aim of the study is to provide the local data of children with haemophilia in Hospital USM and to identify the health-related quality of life of haemophilia patient to help us to conduct early intervention that can be made to improve their life.

CHAPTER 3

OBJECTIVES

3.1 General Objectives:

To evaluate health-related quality of life (HRQOL) in haemophilia children treated in Hospital Universiti Sains Malaysia.

3.2 Specific Objectives:

1. To describe health-related quality of life among haemophilia children treated in Hospital Universiti Sains Malaysia using child self-report and parents-proxy report.
2. To compare the mean difference of child self-report and parental proxy-report of HRQOL scores using PedsQL™ 4.0 module among haemophilia children treated in Hospital Universiti Sains Malaysia.

3.3 Study Hypothesis:

1. The health-related quality of life among haemophilia children in Hospital USM is impaired.
2. There is a different in total score of health-related quality of life among haemophilia children in Hospital USM between child self-report and parental-proxy report.