PHARMACEUTICAL SERVICES PROGRAMME
MINISTRY OF HEALTH MALAYSIA

PHARMACY RESEARCH REPORTS

• VOLUME 2 • 2019 •

PHARMACY RESEARCH REPORTS

• VOLUME 2 • 2019 •

The Pharmacy Research Reports is published by the Pharmaceutical Services Programme, Ministry of Health Malaysia (MOH). This is an International Standard Serial Number (ISSN) registered publication with the National Bibliography Centre, National Library of Malaysia. This document contains compilation of peer-reviewed research articles of pharmacy related researches conducted in the MOH by the MOH pharmacists and other professionals. All researches included in this report were registered with the National Medical Research Register (NMRR) and ethics approvals had been obtained from the Medical Research and Ethics Committee (MREC) if required. The opinions expressed in all articles are the authors' own and do not necessarily reflect the view of the Pharmaceutical Services Programme, Ministry of Health Malaysia.

December 2019

Editorial Address:

Editor in Chief
Pharmacy Research Reports
Pharmacy Policy and Strategic Planning Division
Pharmaceutical Services Programme
Ministry of Health Malaysia
Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor, Malaysia
Tel. : (603) 7841 3200
Fax : (603) 7968 2222
Website : https://www.pharmacy.gov.my

PHARMACY RESEARCH REPORTS

• VOLUME 2 • 2019 •

EDITORIAL BOARD

MEMBERS OF THE MOH PHARMACY RESEARCH AND DEVELOPMENT (R&D) COMMITTEE 2018-2019

Chairperson

Dr. Hasenah Ali
Director of Pharmacy Policy and Strategic Planning Division

Secretary

Dr. Azuana Ramli
Deputy Director, Pharmacy Policy and Strategic Planning Division

Committee Members

Manzatul Azrul Azrie Sulaiman
Pharmacy Enforcement Division

Ida Syazrina Ibrahim
National Pharmaceutical Regulatory Agency

Datcayani Ramadoo
Pharmacy Board Malaysia

Norazila Abd. Ghani
Hospital Sultanah Bahiyah, Kedah

Saidatul Raihan Ibrahim
Hospital Melaka

Sharifah Nor Sazlin Syed Zainuddin
Hospital Sultan Haji Ahmad Shah, Pahang

Dr. Abdul Haniff Mohd Yahaya
Hospital Teluk Intan, Perak

Norharlina Sulaiman
Klang District Health Office, Selangor

Jerry Liew Ee Siung
Hospital Queen Elizabeth, Sabah

Soo Bee Kuan
Labuan State Health Department

Siti Shahida Md Sharifudin
Hospital Kuala Lumpur

Dr. Rosliana Rosli
Pharmacy Practice and Development Division

Fayizatul Akmar Rahman
Pharmacy Policy and Strategic Planning Division

Zahrina Abdul Kadir
Johor State Health Department

Nazmi Liana Azmi
Hospital Raja Perempuan Zainab II, Kelantan

Mohd Farizh Che Pa
Hospital Tuanku Ja'afar, Negeri Sembilan

Teoh Chee Jia
Hospital Seberang Jaya, Penang

Hazlin Syafinar Hussein
Perlis State Health Department

Mazlina Mukhtar
Kuala Terengganu District Health Office, Terengganu

Kamaruddin Ahmad
Hospital Miri, Sarawak

Yuzlina Mohd Yahaya
Hospital Rehabilitasi Cheras, Kuala Lumpur

Azmi Nor Mohd Farez Ahmat
National Cancer Institute

Secretariat

Chan Pui Lim
Pharmacy Policy and Strategic Planning Division

Ho See Wan
Pharmacy Policy and Strategic Planning Division

Dr. Nor Ilham Ainaa Muhsin
Pharmacy Policy and Strategic Planning Division

Dr. Noraini Nordin
Pharmacy Policy and Strategic Planning Division

Mary Chok Chiew Fong
Pharmacy Policy and Strategic Planning Division

Tineshwaran Velvanathan
Pharmacy Policy and Strategic Planning Division

Azzy Iyzati binti Ahmad Shanizza
Pharmacy Policy and Strategic Planning Division

ACKNOWLEDGEMENTS

The Editorial Board of the Pharmacy Research Reports wishes to express our deepest appreciation to all the reviewers for their valuable time and efforts in reviewing the manuscripts.

List of Reviewers

Dr. Azuana Ramli

Azzy Iyzati Ahmad Shanizza

Chan Lai Yue

Chan Pui Lim

Gopi Muniandy

Ho See Wan

Mary Chok Chiew Fong

Dr. Noraini Nordin

Dr. Nor Ilham Ainaa Muhsin

Teoh Chee Jia

Tineshwaran Velvanathan

Wong Shui Ling

Yong Yee Vern

CONTENTS

		page
1.	Review on the Usage of Oral Medications for Spasticity in a Rehabilitation Hospital in Kuala Lumpur *Wong Shieh Teng, Lee Lin Jia, Yuzlina Muhamad Yunus*	1
2.	Cost Analysis of Snakebite Management in a Malaysian Tertiary Care Hospital *Norazila Abdul Ghani, Chew Beng Hong, Nadia Abdul Shukur, Shahrul Adham Abd Rahman Dairi, Ahmad Zulqarnain Ahmad Rahim, Amir Asyraf Zakiudin Nizam Akhbar, Ibtisam Ismail, Noor Syahireen @ Siti Rahmah Mohammed*	7
3.	Comparing the Cost of Standardised and Individualised Parenteral Nutrition in Clinically Stable Infants in a Malaysian Public Hospital *Leao Xin Yi, Chan Huan Keat, Hasif A Rusli, Tan Hooi Kuan, Lim Li Xin*	14
4.	Carbapenem and Cephalosporin Antibiotics Usage in Cheras Rehabilitation Hospital *Syazzana Dzulkifli, Noor Hafizah Tajuddin, Wong Shieh Teng, Dashini Jaganathan, Yuzlina Muhamad Yunus*	21
5.	Comparative Evaluation of International Normalized Ratio (INR) Monitoring Between Point-Of-Care (POC) and Laboratory-Based Testing Methods in Patients Receiving Warfarin Therapy in Sultanah Nur Zahirah Hospital *Nurul Najmi Muhammad, Rafidah Abd Razak, Fong Chui Wei, Siti Rahayu Othman, Mahfuzah Ishak, Mohd Amirul Arif Yaakub, Norsima Nazifah Sidek, Liyana Ahamad Fouzi*	27
6.	Comparing the Clinical Effectiveness of Levothyroxine Intake before Breakfast versus at Bedtime in Patients with Hypothyroidism *Mohd Farizh Che Pa, Saodah Yaacob, Simrenjit Kaur Gurnam Singh, Noor Lita Adam*	33
7.	Appropriateness of Intravenous Proton Pump Inhibitor Use in Labuan Hospital, Federal Territory of Labuan *Siu Loe Ching, Latha Devi Sukumaran*	40

Review on the Usage of Oral Medications for Spasticity in a Rehabilitation Hospital in Kuala Lumpur

Wong Shieh Teng[1], Lee Lin Jia[1], Yuzlina binti Muhamad Yunus[1]

[1] Cheras Rehabilitation Hospital, Federal Territory of Kuala Lumpur & Putrajaya, Ministry of Health Malaysia

Abstract

Introduction: Spasticity is a major problem affecting patient's mobility, function and activities of daily living during rehabilitation therapy.

Objective: This study aimed to examine the prescribing pattern of oral medication used for the treatment of spasticity in the Cheras Rehabilitation Hospital.

Methods: All inpatients prescribed with at least one oral drug indicated for spasticity from 1 January 2017 to 30 June 2017 were included in the study. Prescriptions with incomplete data or clinical notes were excluded from the study.

Results: A total of 99 patients who were prescribed with oral spasticity medications were included in this study. Baclofen was the most prescribed oral spasticity drug (81%) followed by Clonazepam (22%) and Eperisone (13%). There were 14 patients who received combination treatment of which 10 patients received Baclofen with Clonazepam combination. Baclofen was the preferred choice of treatment for all the cause of spasticity in HRC. Spinal cord injury recorded the highest usage of Baclofen (35%) and Clonazepam (60%). The diagnosis with the highest mean daily dose (MDD) for Baclofen were cerebral palsy and hypoxic ischemic encephalopathy among adults (60mg/day), and traumatic brain injury among paediatric patients (27.5mg/day). For Clonazepam, spinal cord injury patients had the highest MDD in both adult (1.27mg/day) and paediatrics (0.5mg/day). The MDD of Eperisone was highest among the adult spinal cord injury and cerebral palsy patients (150mg/day). The MDD of oral spasticity medications were lower in patients who received adjunct treatment with *Clostridium Botulinum* Toxin injections for both adult and paediatric patients. Percentage of discontinuation was 14.7% in Baclofen and 33.3% in both Clonazepam and Eperisone.

Conclusion: Patients with spasticity received either single or combination of oral spasticity medications in Cheras Rehabilitation Hospital. Further study is prompted to evaluate the effectiveness and safety of spasticity treatment in this hospital.

Keywords: spasticity, medication, baclofen, clonazepam, eperisone, mean daily dose

NMRR ID: NMRR-17-1391-36617

Corresponding Author: Wong Shieh Teng
Department of Pharmacy, Hospital Rehabilitasi Cheras, Jalan Yaakob Latif, 56000 Kuala Lumpur
Email: wongshiehteng@moh.gov.my

Introduction

Spasticity is defined as disordered sensorimotor control resulting from an upper motor neuron (UMN) lesion, presenting as intermittent or sustained involuntary activation of muscles. It commonly affects people with chronic neurological disorders such as stroke, spinal cord injury, traumatic brain injury, cerebral palsy and multiple sclerosis (1). It greatly affects patient's mobility, function and activities of daily living.

Baclofen is the most widely used oral antispasmodic drug. It is a gamma-aminobutyric acid (GABA) receptor B agonist. It works by reducing calcium influx and suppresses release of excitatory neurotransmitters and thus down-regulates activity of 1a sensory afferents, spinal interneurons and motor neurons (2). It is the most commonly used medication to control spasticity in spinal cord injury (3). The other group of widely used medicines for spasticity is Benzodiazepines, which work via the GABA mediated pathways as well. They increase the affinity of GABA at the GABA receptors and causes presynaptic inhibition and thus a decrease in mono and polysynaptic reflexes. Diazepam and Clonazepam are the oldest and most frequently used Benzodiazepines to treat spasticity (2). On the other hand, the use of Eperisone to treat spasticity has not

been recommended in most of the management guidelines and the number of studies investigating its clinical efficacy is still scarce (3).

Based on the data of Cheras Rehabilitation Hospital (HRC) Pharmacy Census of 2016, Baclofen is among the top twenty most commonly used drugs in the hospital and has been the main choice of treatment for spasticity followed by Clonazepam (4). Eperisone is another newer drug of choice in the treatment of spasticity in HRC. Although all three oral medications have demonstrated efficacy in clinical trials, Clonazepam and Eperisone are not listed for the treatment of spasticity in the Ministry of Health Medicines Formulary, Malaysia (5). This study was carried out to examine the prescribing pattern of oral medications used for the treatment of spasticity in HRC. We wished to understand whether the choice of oral spasticity medications were specific to any specific diagnoses, the common dosages used among patients with spasticity and the trend of drug changes among the patients.

Methods

This is a retrospective cross-sectional study which was conducted using a universal sampling method. All inpatients of HRC diagnosed with spasticity and who were prescribed with at least one oral spasticity medication for the indication of spasticity during their stay in the ward from 1 January 2017 to 30 June 2017 were included from the study. Prescriptions with incomplete data or patients with incomplete clinical notes were excluded.

Demographic data such as age, race and gender were obtained from the Pharmacy Information System (PhIS). Information on patient's disease and medication therapy was obtained from the Pharmacist Clinical Notes (forms CP1 and CP2). Disease data collected were the cause of spasticity or diagnosis, factors that could affect the dose of spasticity treatment such as the presence of side effects, and the date of event or illness to estimate the length of disease or illness. Patient's medication therapy was recorded at two points, which were the first and last prescriptions within the period of 1 January 2017 to 30 June 2017. Medication information collected were dosage and frequency of oral medication for spasticity treatment, other drugs that may affect the dosage of oral antispasmodic prescribed, the date the drug was started and stopped, and the reason for stopping if available. Data was collected with a Data Collection Form.

The data were collected and analysed descriptively using the Microsoft Excel Spreadsheet Software version 2010. Discrete data were presented as frequency (n) and percentage while continuous data were expressed as mean (standard deviation (SD)).

Results

A total of 106 patients with at least one of the study medications indicated for the treatment of spasticity were identified but 7 patients were excluded due to incomplete data. The final number of patients included in the study was 99 patients. The majority of patients were male (n= 67, 68%) with the mean age of 35 (SD 20) years old and were of the Malay ethnic (n=68, 69%) (Table 1). Traumatic brain injury and spinal cord injury were the most common causes of spasticity among the study population, both with 31 (31%) patients. Majority of the patients were newly diagnosed or had recent events of spasticity with the length of illness between zero to twelve months (n=33, 44%).

Table 2 compared the utilisation of each drug in the first and the final prescriptions within the six-month study period. There were 74 (75%) patients that received at least one oral spasticity medication during the initial stage of study while the final stage of study recorded a total of 92 (93%) patients prescribed with oral spasticity medications. Findings showed that 25 (25%) of the patients were newly prescribed with oral spasticity medication. Majority of patients received spasticity monotherapy (n=78, 85%) and Baclofen was the most prescribed oral spasticity medication (n= 75, 82%).

Table 3 showed the use of oral spasticity medication by diagnoses. Baclofen was the preferred choice of treatment for all causes of spasticity in HRC. Table 4 tabulated the mean daily dose (MDD) of Baclofen, Clonazepam and Eperisone by the causes of spasticity. The MDD of Baclofen was the highest for cerebral palsy and hypoxic ischemic encephalopathy in adults (60mg/day). Among the paediatric patients, traumatic brain injury group had the highest MDD of Baclofen (25.5mg/day). Eperisone was not used in paediatric patients in HRC. The MDD of Eperisone was the highest among the adult spinal cord injury and cerebral palsy groups with 150mg/day.

The percentage of discontinuation was 14.7% in Baclofen and 33.3% in both Clonazepam and Eperisone when compared to the initial stage of the study. As shown in Figure 1, Baclofen had the highest number of drug discontinuation, dose increment and dose reduction among the three oral spasticity medications. It was stopped in one case due to allergic reaction and in one paediatric patient due to change of treatment to intrathecal Baclofen. Clonazepam was stopped in one case due to dizziness. The reason for Eperisone discontinuation was not documented. There were five cases of switching antispasmodic therapy whereby three patients switched from Baclofen to Eperisone, one with combination Baclofen and Clonazepam switched to Eperisone and one with Baclofen switched to Clonazepam.

Table 5 showed the effect of adjunct medications on the MDD of oral spasticity medications. The MDD of both Baclofen and Clonazepam was lower in adult patients receiving oral adjunct treatment with Gabapentin (32.2mg/day and 0.8mg/day respectively). The MDD of all three oral spasticity medications were lower in both adult and paediatric patients who received adjunct treatment with *Clostridium Botulinum* Toxin injections.

Table 1: Demographic and baseline characteristics of patients included in the study (N=99)

Characteristics	n (%) / mean (SD)
Age, year, mean (SD)	35 (20)
Age, n (%)	
< 18	21 (21)
18 – 64	69 (70)
≥ 65	9 (9)
Gender, n (%)	
Male	67 (68)
Female	32 (32)
Ethnicity, n (%)	
Malay	68 (69)
Chinese	21 (21)
Indian	10 (10)
Diagnosis, n (%)	
Traumatic brain injury	31 (31)
Spinal cord injury	31 (31)
Stroke	19 (19)
Cerebral palsy	12 (12)
Hypoxic ischemic encephalopathy	3 (3)
Others	3 (3)
Length of illness (months)*, n (%)	
0 – 12	33 (44)
13 – 60	27 (36)
61 – 120	9 (12)
> 120	6 (8)

* The sample size for length of illness was only 75 patients (N=75) due to incomplete data.
Abbreviation: SD – standard deviation

Table 2: Utilisation of oral spasticity medications at the initial and final stage of the study

Utilisation	Initial Stage, n (%)	Final Stage, n (%)
Therapy		
Monotherapy	60 (81)	78 (85)
Combination therapy	14 (19)	14 (15)
Medication		
Baclofen	68 (92*)	75 (82*)
Clonazepam	15 (20*)	20 (22*)
Eperisone	6 (8*)	12 (13*)

* The percentage did not total up to 100% as some patients received two or more medications

Table 3: Patients on oral spasticity medication in accordance to diagnoses or illness

Cause of Spasticity	Baclofen, n (%)	Clonazepam, n (%)	Eperisone, n (%)
Traumatic brain injury	24 (32)	0	6 (50)
Spinal cord injury	26 (35)	12 (60)	3 (25)
Stroke	8 (11)	6 (30)	2 (17)
Cerebral palsy	12 (16)	1 (5)	1 (8)
Hypoxic ischemic encephalopathy	2 (3)	0	0
Others*	3 (4)	1 (5)	0
Total	75	20	12

* congenital rubella syndrome, congenital toxoplasmosis, neurodegenerative brain disorder

Table 4: Mean daily dose of Baclofen, Clonazepam and Eperisone according to the causes of spasticity

Cause of Spasticity	Mean Daily Dose (SD), mg/day					
	Baclofen		Clonazepam		Eperisone	
	Adult	Paediatric	Adult	Paediatric	Adult	Paediatric
TBI	28 (13.5)	25.5 (11.1)	-	-	117 (25.8)	-
SCI	37 (18.0)	-	1.3 (0.98)	0.5	150	-
Stroke	38 (19.2)	-	0.7 (0.6)	-	100	-
CP	60	22 (12.4)	2	-	150	-
HIE	60	15	-	-	-	-
Others*	60	19 (12.8)	0.5	-	-	-

*congenital rubella syndrome, congenital toxoplasmosis, neurodegenerative brain disorder

Abbreviation: SD – standard deviation; TBI - traumatic brain injury; SCI - spinal cord injury; CP - cerebral palsy; HIE - hypoxic ischemic encephalopathy

Figure 1: Treatment modification within the six-month study period

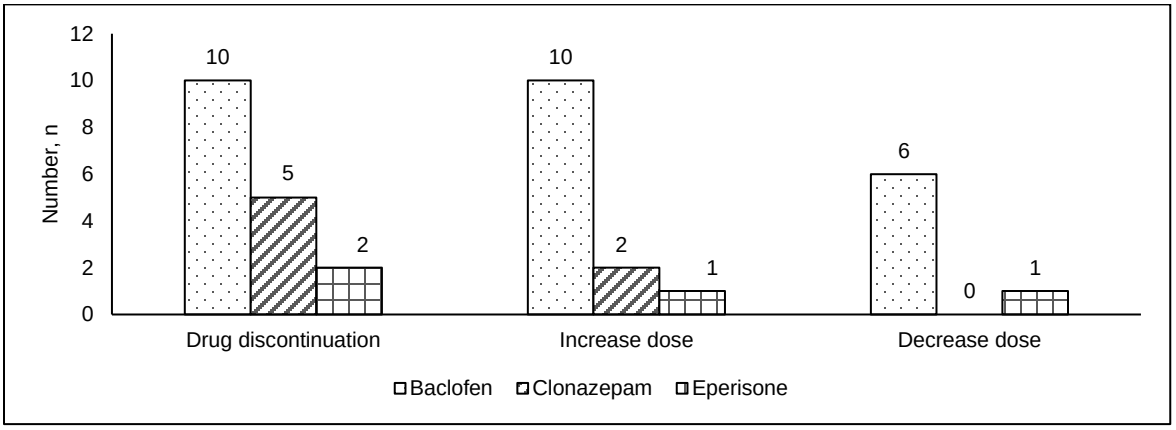


Table 5: MDD of Baclofen, Clonazepam and Eperisone when used concurrently with medicines that may affect spasticity treatment

Concurrent medications	Mean Daily Dose (SD), mg/day			
	Baclofen		Clonazepam	Eperisone
	Adult	Paediatric	Adult	Adult
Gabapentin	32.2 (11.6)	-	0.8 (0.3)	133.3 (28.9)
Pregabalin	43.0 (11.0)	-	1.3 (0.4)	150.0
Clostridium Botulinum toxin type A	24.4 (15.4)	15.0 (5.3)	0.5 (0.5)	100.0
None	34.4 (18.2)	22.8 (12.7)	1.2 (0.7)	116.7 (25.8)

Discussion

From the HRC Pharmacy Census of 2016 (4), Baclofen was among the top 20 most commonly used drugs in HRC. It is one of the oldest drugs used to treat spasticity. Although Baclofen still remains the main drug of choice for the treatment of spasticity, there was indeed a slight shift in the choice of antispasmodic agent in HRC over the six-month study period. The percentage of Baclofen usage had decreased a little and there had been a small increase in the usage of Clonazepam and Eperisone for the treatment of spasticity.

There has not been much research investigating the effectiveness of combination therapy using multiple medications (6). However, spasticity treatment combining Baclofen and Clonazepam, being the most common combination, has been utilised in HRC with 90% for spinal cord injury patients. A study conducted by Chendrowski on the efficacy of Clonazepam and Baclofen found that both drugs were significantly more effective than placebo. There was no significant difference in terms of efficacy between Baclofen and Clonazepam. (7) Although combination therapy was not investigated, the study concluded that there was a possibility that the combination of Baclofen and Clonazepam may be more effective than either drug alone (7). Nonetheless, there seemed to be a decrease in the use of combination therapies over the six-month period in HRC. There were five cases of switching from combination to monotherapy and only one case of switching from mono to combination therapy.

Open-label studies have shown that oral Baclofen improved spasticity in 70% to 87% of patients whereas 75% to 96% of patients had improvement in spasms. Some of the major side effects of Baclofen are sedation, weakness, vertigo and psychological disturbances (8,9). In a double-blinded cross-over study to investigate the effects of low dose Benzodiazepine to manage spasticity among children with cerebral palsy, Clonazepam significantly reduced spastic restraint compared to placebo (10).

Overall, there was lack in high-quality evidence supporting the use of oral spasticity medications to treat specific diagnosis and to help guide the choice of one medication over the other (11). According to a review by Rabchevsky *et al.*, Baclofen is currently the pharmacologic agent of choice for the treatment of spinal cord injury-induced spasticity (12). This was reflected in this study as the use of Baclofen was used most in the spinal cord injury group. The MDD of Baclofen used in HRC ranged from 28mg/day to 60mg/day. This was supported by a risk-benefit assessment by Dario *et al*. which showed that the effective and well tolerated dose of Baclofen ranged from 30mg/day to 80mg/day (8).

In a review by Chang *et al*., it was demonstrated that Benzodiazepines had the tendency to act primarily on flexor reflexes. Benzodiazepines were better suited to treat spasticity of spinal origin than cerebral origin spasticity because spinal origin spasticity had an inclination to affect flexor reflexes (6). This explained the findings that Clonazepam was most highly used in spinal cord injury patients in this study and was least prescribed for patients with spasticity of cerebral origin.

Eperisone was mostly used for treatment of spasticity among traumatic brain injury patients in HRC with relatively low MDD of 117mg/day. In a cross-over, placebo-controlled trial conducted by Bresolin *et al*., they discovered a significant reduction in muscle tone compared to baseline measures among patients with spastic palsy. The ability to walk was also seen to have improved significantly with patients on 300mg/day of Eperisone. The incidence of adverse effects in this study was few and was deemed to be mild or moderate and thus suggested a positive tolerability profile (13). When compared to Baclofen, both drugs significantly improved functionality of lower limbs but only Eperisone improved this parameter in the upper limbs. Although both drugs decreased muscle hypertonia, only Eperisone improved joint range of motion in week two of the study. These recent findings could mean that Eperisone is a potential alternative treatment for spasticity. Nonetheless, further clinical investigations need to be carried out to ensure its safety and efficacy (14).

An analysis was carried out to determine the effect of certain concurrent medication such as Gabapentin, Pregabalin and Botulinum Toxin injection on the MDD of oral Baclofen, Clonazepam and Eperisone. The MDD of both Baclofen and Clonazepam was lower in patients with adjunct Gabapentin treatment. Similarly, a study by Chang *et al*. showed that the use of Gabapentin alone demonstrated a reduction in the Ashworth scale compared to placebo. However, it is rarely used as monotherapy (6). On the contrary, Pregabalin which is considered to be the next generation of Gabapentin did not show reduction in MDD for all treatment groups in this study. However, there was a retrospective case study which concluded that Pregabalin may be effective in reducing spasticity in a portion of patients with spinal cord injury (12). The findings in this study could not conclude whether the adjunct treatments would affect the MDD of spasticity

medications, but it could be seen that the MDD of oral treatments were generally lower in patients who received Botulinum toxin injections. The reason for this could be that these patients only experienced focal spasticity and thus a higher dose of systemic agents were not needed.

There were several limitations to this study, such as, dependency on the accuracy of written records, incomplete clinical data (especially the reason for discontinuation of treatment), and difficult to control bias and confounders. The recommendation would be to conduct a prospective observational study for the next stage of this research.

Conclusion

HRC utilises a variety of combination and monotherapy in the treatment of spasticity. The exact choice of treatment for spasticity of varying origin remains unclear. Further study is needed to evaluate the safety and efficacy of spasticity treatment.

Acknowledgement

We would like to thank the Director General of Health Malaysia for his permission to publish this article. We would like to thank the Deputy Director of Health (Pharmacy) in Kuala Lumpur & Putrajaya, the Director of HRC, Clinical Research Centre of HRC and those who have helped provide us with the information and data needed to complete this study.

Conflict of Interest Statement

The author declared no conflict of interest

References

1. Sheean G. The pathophysiology of spasticity. *European Journal of Neurology.* 2002; 9(1):3-9.
2. Kheder A, Padmakumari K. Spasticity: Pathophysiology, Evaluation and Management. *Practical Neurology.* 2012; 12:289–298
3. Krach LE, Pharmacotherapy of Spasticity: Oral Medications and Intrathecal Baclofen. *J Child Neuro*. 2001 16(1):31-36
4. Cheras Rehabilitation Hospital. 2016. *Cheras Rehabilitation Hospital Pharmacy Census of 2016*. (*unpublished*)
5. Pharmaceutical Services Programme, Ministry of Health Malaysia. 2017. *Ministry of Health Malaysia Drug Formulary*. Available at: https://www.pharmacy.gov.my/v2/en/apps/fukkm
6. Chang, E, Ghosh, N, Yanni, D, et al. A review of spasticity treatments: Pharmacological and interventional approaches. *Crit Rev Phys Rehabil Med.* 2013; 25(1-2): 11-22.
7. Cendrowski W, Sobczyk W. Clonazepam, Baclofen and Placebo in the Treatment of Spasticity. Eur Neurol. 1977; 16: 257-262
8. Dario A, Tomei G. A Benefit-Risk Assessment of Baclofen in Severe Spinal Spasticity. Drug Safety 2004; 27(11): 799-818
9. Scheinberg A, Hall K, Lam LT, O'Flaherty S. Oral baclofen in children with cerebral palsy: A double-blind cross-over pilot study. Journal of Paediatrics and Child Health. 2006; 42: 715-720
10. Dahlin M, Knutsson E, Nergardh A. Treatment of Spasticity in Children with Low Dose Benzodiazepine. Journal of the Neurological Sciences. 1993; 117: 54-60
11. Watanabe, T. Role of oral medication in spasticity management. *American Academy of Physical Medication and Rehabilitation*. 2009; 1: 839-841.
12. Rabchevsky, A, Kitzman, P. Latest approaches for the treatment of spasticity and autonomic dysreflexia in chronic spinal cord injury. Neurotherapeutics. 2011; 8(2): 274-282.
13. Bresolin N, Zucca C, Precori A. Efficacy and tolerability of eperisone in patients with spastic palsy: a cross-over, placebo-controlled dose-ranging trial. Eur Rev Med Pharmacol Sci. 2009; 13(5): 365-370.
14. Bresolin N, Zucca C, Precori A. Efficacy and Tolerability of Eperisone and Baclofen in Spastic Palsy: a Double-Blind Randomized Trial. Adv Ther. 2009; 26(5): 563-573.

Cost Analysis of Snakebite Management in a Malaysian Tertiary Care Hospital

Norazila Abdul Ghani[1], Chew Beng Hong[1], Nadia Abdul Shukur[1], Shahrul Adham Abd Rahman Dairi[2], Ahmad Zulqarnain Ahmad Rahim[3], Amir Asyraf Zakiudin Nizam Akhbar[4], Ibtisam Ismail[5], Noor Syahireen @ Siti Rahmah Mohammed[5]

[1] Hospital Sultanah Bahiyah, Kedah, Ministry of Health Malaysia, [2] Kaki Bukit Health Clinic, Perlis, Ministry of Health Malaysia, [3] Hospital Selama, Perak, Ministry of Health Malaysia, [4] Hospital Kulim, Kedah, Ministry of Health Malaysia, [5] Clinical Research Centre, Hospital Sultanah Bahiyah, Kedah, Ministry of Health Malaysia

Abstract

Introduction: Snakebite is a common cause of morbidity and mortality worldwide. From 2010 to 2014, a total of 15,798 snakebite cases were reported in the country. However, the actual cost of managing snakebite is currently unknown.

Objective: This study aimed to estimate the cost of the management of snakebites in a tertiary care hospital in Kedah, Malaysia.

Methods: The cost analysis was conducted from the healthcare provider's perspective. An activity-based costing approach was used. Healthcare resources utilisation for managing patients with snake bites were obtained from the patients' medical record at Sultanah Bahiyah Hospital, Kedah in 2015. The costs were expressed in 2017 Malaysian Ringgit (RM).

Results: In 2015, 184 patients presented to the emergency department of HSB with snakebites. Of that, 131 patients were admitted for further treatment. Among the admitted patients, 50 patients received monovalent antivenom and 21 patients received polyvalent antivenom. The total cost involved in the management of snakebites was RM351,560.56 and the average cost of managing a snakebite patient in HSB was RM1,910.66. Medications made up the largest portion of the cost (36.25%). In the emergency department, the average cost for snakebite management was RM744.01 per patient while in the wards, the average cost was RM1,638.65. Among the patients who received antivenoms, the average treatment cost in patients who received polyvalent antivenoms (RM3,608.44) was 5.85% higher than the average treatment cost in patients who received monovalent antivenoms (RM3,408.88).

Conclusion: Our results highlighted considerable economic impact of snakebites management in the hospital. Further analysis on the outcome of the management with polyvalent and monovalent antivenom should be conducted to ensure the best management of snakebite envenoming.

Keywords: snakebite, antivenom, antivenin, cost analysis, economic

NMRR ID: NMRR-16-2244-33131

Corresponding author: Norazila Abdul Ghani
Pharmacy Department, Hospital Sultanah Bahiyah, KM6, Jalan Langgar, 05460 Alor Setar, Kedah.
Email: azilaghani@moh.gov.my

Introduction

Snakebite is a serious medical problem in Malaysia. According to the Ministry of Health Malaysia (MOH) Health Informatics Centre, the number of snakebites from year 2010 to 2014 was 15,798 cases. The number of deaths due to snakebites over the same period totalled to 16, averaging from three to four deaths per year. In addition, some venom has local necrotic effects that may cause prolonged morbidity or crippling deformity. In 2011, the state of Kedah recorded the highest incidents with 836 cases, and the state of Perak recorded the second highest with 576 cases (1), presumably associated with agricultural activities (2). Besides, a large proportion of their populations are living near snake habitat area such as villages near the forests.

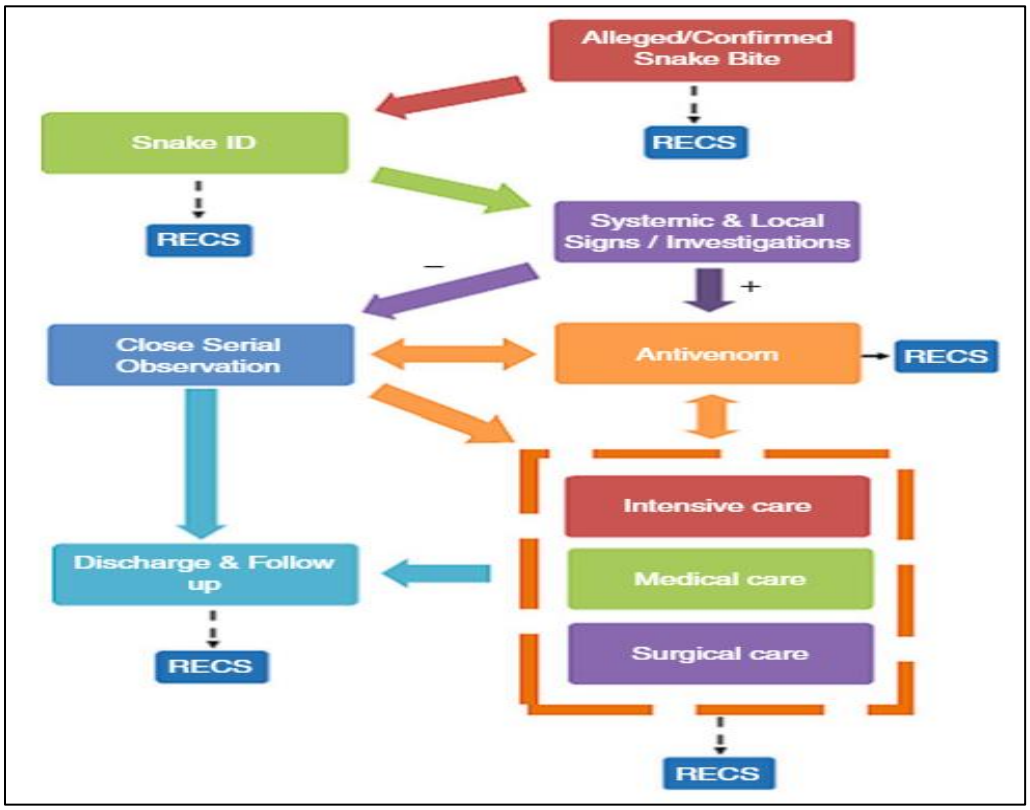
Snakebite management workflow was summarised in Figure 1. Snakebite patient who arrives at a medical centre will be reviewed in the critical zone of the emergency department. It is generally divided into general examination, wound examination, and examination for specific signs of envenoming. Therefore, all

unidentified snakebite patients, especially those without symptoms, must be admitted for serial monitoring and observation for at least 24hours. Management of snakebite is standardised for all healthcare facilities in Malaysia. In situations where expert consultation is required, the Remote Envenomation Consultation Services (RECS) is available. RECS was established in 2012 to provide 24-hour “on-call” consultation service for Malaysian healthcare providers (1).

The management of snakebite envenomation may range from outpatient treatment for mild cases to hospitalisation and treatment with antivenom for more severe cases. Antivenoms are effective in reducing mortality and remain as the mainstay of therapy in snakebites (3). There are specific systemic and local indications and strict protocol for antivenom administration (4,5). Antivenom administration should be based on the clinical and laboratory evidence and the severity of systemic and local envenomation. The choice of antivenom will depend on the snake identity. If the snake species can be positively identified, monovalent antivenom is preferable, and if the snake species could not be identified, polyvalent antivenom is recommended (1). Antivenoms are very expensive and their administration requires close patient monitoring. Few safety issues need to be considered when antivenom is used. There is a need for anaphylaxis protocol to be in place prior to the provision of antivenom and ventilation support should be made available (1).

In Sultanah Bahiyah Hospital, they are five types of antivenom for snakebite envenoming which are, antivenom polyvalent, hemato polyvalent, neuro polyvalent antivenom, cobra monovalent and Malayan pit viper monovalent. In the MOH healthcare facilities, the treatment costs are highly subsidised. To date, no study has addressed the treatment burden associated with snakebites and the cost of snakebite management. Given the potential financial implications associated with snakebite management, this study sought to examine the resource utilisation in the management of the snake bites from the perspective of MOH hospitals in Malaysia. Our objective was to estimate the cost of the management of the snakebites in a tertiary care hospital in Kedah, Malaysia. This information was hoped to draw policy maker’s attention to the financial burden of snakebite management and thus allocating more budget towards improving the care and management of snakebite victims.

Figure 1: The workflow of snakebite management



Source: Ismail 2015 (pp.81) (1)

Abbreviation: RCS - Remote Envenomation Consultation Services; ID – identity

Methods

Sultanah Bahiyah Hospital (HSB) is a tertiary care hospital located in the state of Kedah, one of the states with the highest number of snakebite cases in Malaysia. Most of the snakebites in the state will be referred to HSB due to its expertise. This study included all patients who visited the emergency department of HSB due to snakebites injuries in 2015 regardless of the ability to identify the identity of snake types and whether antivenoms were received.

The cost analysis was conducted from the MOH healthcare provider's perspective. Activity-based costing method was used. Activities of the snakebite management starting from the point patients presented at the emergency department until discharge were recorded. The activities and healthcare resource utilisations in the snakebite management activities were identified retrospectively from the patient medical records and Electronic Hospital Information System (e-HIS). The resources consumed to manage antivenom-associated adverse drug reactions (ADR) were also included and costed. A data collection form was used to collect information about the main activities and resources consumption in snakebite management of every patient such as laboratory test, diagnostic test, consumables, fluid management, medication, length of hospitalisation, and other related activities. The data collection form was divided into three sections: Section A: Socio-demographic characteristics, Section B: Data for observation / emergency department management, and Section C: Data for inpatient management. The collected data was then cross-checked among data collectors to ensure the accuracy and completeness of the data.

The unit cost of the resource items were collected from the respective departments in HSB (Table 1). The costs were inflated to 2017 Malaysian Ringgit (RM) using gross domestic product (GDP) deflator. Data collected were analysed using Microsoft Excel.

Table 1: Resources consumed in snakebite management the sources of their unit costs

Category	Resource items	Source of unit cost data
Laboratory [a]	Vital signs 20-minute whole blood clotting factor Full blood count (FBC) Blood urea serum electrolytes (BUSE) Liver function test Coagulation profile (APTT/PT)	Pathology Department
	Computerised tomography (CT) Scan X-ray Magnetic resonance imaging (MRI)	Radiology Department
Consumable Item [a]	Branula Nasal prong Bladder irrigation Oxygen face mask Ice pack Needle Dextrose strip	Pharmacy Department
Medication [a]	Analgesic Antivenom Antibiotic Other medications	Pharmacy Department
Fluid Management [a]	IV Normal saline (NS) IV Dextrose (D5%) IV 1/2NS D5% IV 1g potassium chloride (KCl)	Pharmacy Department
Hospitalisation [b]	Ward charges (depends on the class of ward)	Finance Department
Other Interventions [c]	Intervention charges (price stated by HSB)	Finance Department

[a] Cost = number of items consumed x unit cost; [b] Cost = cost per day x duration of stay; [c] Cost = cost per session x total number of sessions

Abbreviation: IV - intravenous

Results

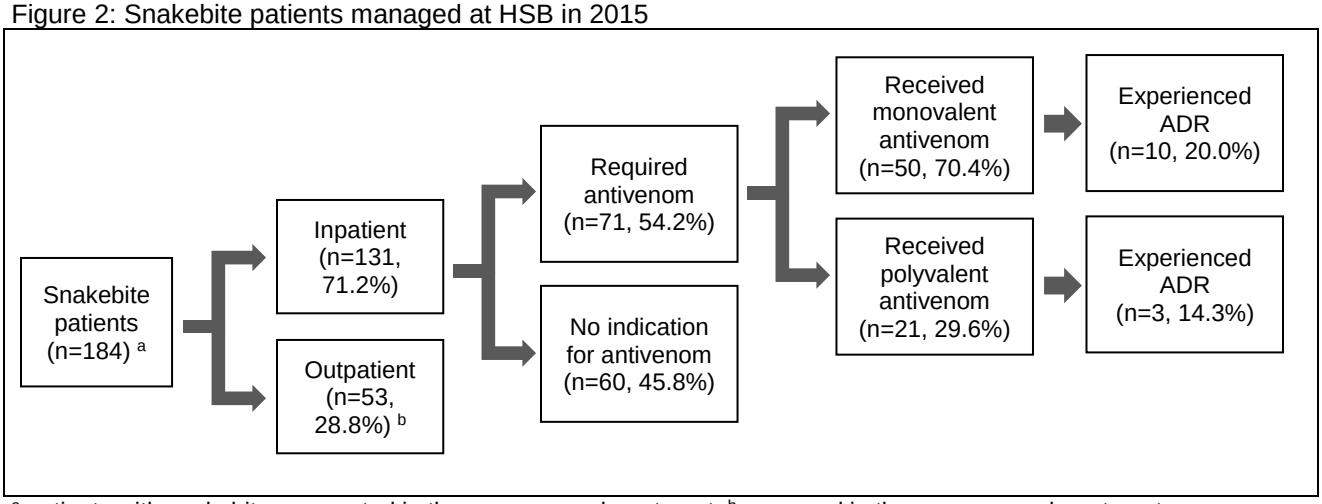
Patient Demography

In 2015, a total of 184 patients presented to the emergency department of HSB with a primary diagnosis of snakebites. The mean age of the patients was 39.35 years old (standard deviation (SD) 24.43 years, ranged from one to 86 years of age). The demographic characteristics of included patients were presented in Table 2. Most of them were Malay and lived in rural area. Slightly more than half of the patients (55.43%) were bitten by vipers and 16.85% were bitten by cobras. It was unable to identify the types of snake in 29.9% of the patients. The average duration of hospitalisation was one day (SD 0.29 days) in the emergency department and three days (SD 3.07 days) in the ward.

Table 2: Demographic data of snakebite patients (N = 184)

Variable	n (%)	Variable	n (%)
Gender		Marital status	
Male	121 (65.76)	Single	75 (40.76)
Female	63 (34.24)	Married	103 (55.98)
Ethnicity		Divorced / widowed	6 (3.26)
Malay	166 (90.22)	Type of snake	
Chinese	3 (1.63)	Viper	102 (55.43)
Indian	1 (0.54)	Cobra	31 (16.85)
Others	14 (7.61)	Unknown	55 (29.89)
Location		Bitten area	
Rural	152 (82.61)	Leg	100 (54.35)
Urban	32 (17.39)	Hand	76 (41.30)
Educational level		Abdomen	1 (0.54)
Primary	49 (26.63)	Head	1 (0.54)
Secondary	75 (40.76)	Wrist	1 (0.54)
No formal education	43 (23.37)	Buttock	1 (0.54)
College	13 (7.07)	Not available	4 (2.17)
Not available	4 (2.17)		

Figure 2: Snakebite patients managed at HSB in 2015



[a] patients with snakebites presented in the emergency department, [b] managed in the emergency department
Abbreviation: ADR - adverse drug reaction

Antivenom for Snakebite Envenoming

Of the 184 patients with snakebite, 131 patients were admitted to the hospital for further treatment and observation, while the other 53 patients were managed in the emergency department as outpatient (Figure 2). Among the admitted patients, 71 of them received antivenom after confirming the specific systemic and local symptoms and fulfilled the protocol for antivenom administration. Another 60 patients were admitted for observation and monitoring as there was no indication for antivenom. 50 patients received monovalent antivenom and 21 patients received polyvalent antivenom. Polyvalent antivenoms were given to the patients when it was unable to identify the types of snakebite based on the haematological or neurological symptoms.

Among these patients, ADRs occurred in 20.0% and 14.3% in the patients who received monovalent antivenom and polyvalent antivenom respectively. The cost of managing the adverse effects of antivenom was also included in the cost analysis.

Cost Analysis

The total cost involved in the management of snakebites in HSB in 2015 was RM351,560.56 (2017 RM) and the average cost of managing a snakebite patient in HSB was RM1,910.66 (Table 3). Medications (36.25%) made up the largest portion of the cost, followed by hospital stay cost (29.33%) and laboratory cost (25.59%). When the costs were broken down, it was found that the cost incurred in the inpatient was more than two folds compared to the emergency department. In the emergency department, the average cost was RM744.01 per patient while in the wards, the average cost was RM1,638.65 per patient. Among the patients who received antivenoms, the average treatment cost in patients who received polyvalent antivenoms was 5.85% higher than the average treatment cost in patients who received monovalent antivenoms (Table 4).

Table 3: Estimation of cost of snakebite management in HSB

Category	Emergency department (RM) (n=184)	Inpatient (RM) (n=131)	Average cost per patient (RM) (n=184)	Percentage (%)
Laboratory	47,481.00	42,500.00	489.03	25.59
Consumable item	9,870.34	4,479.30	77.99	4.08
Medication	79,337.76	48,095.99	692.57	36.25
Fluid management	208.97	291.20	2.72	0.14
Hospitalisation	0	10,3100.00	560.33	29.33
Other interventions	0	16,196.00	88.02	4.61
Total cost	136,898.07	214,662.49		
Average cost	744.01	1,638.65	1,910.66	

Table 4: Cost of snakebite management in patients who received antivenoms

Category	Monovalent antivenom (RM) (n=50)	Polyvalent antivenom (RM) (n=21)
Laboratory	582.54	649.76
Consumable item	108.00	110.00
Medication	1,805.26	1,803.83
Fluid management	5.40	4.85
Hospitalisation	808.00	788.57
Other interventions	99.68	251.43
Total cost	3,408.88	3,608.44

Discussion

Snakebite is not a notifiable disease in Malaysia. Therefore, the reported data about snakebites may not be accurate and it should not be assumed that snakebite is uncommon or treated as an unimportant medical issue in Malaysia. Existing literature and our study highlighted the significant burden of snakebites and envenomation (1). In this study, we found 184 cases of snakebite injuries within one year in Sultanah Bahiyah Hospital. Of these, more than half of the cases involved venomous species and were indicated for antivenoms. This finding was higher compared to previous study. It has been reported that less than 50% of cases were venomous snakebites which resulted in envenoming (12,13). However, one study conducted in India found 67% of the bites were suspected to be caused by venomous snakes and were treated with polyvalent or monovalent antivenoms (13). This may be due to the expertise of the healthcare facility itself. The higher incidence of snake envenoming in HSB could be due to its expertise in identifying the signs and symptoms of envenomation and most of the cases involved with snakebite in the state of Kedah were referred to HSB.

Snakebite antivenom, with their expensive price tags, could affect the overall cost of the treatment in the hospital setting. The findings of this study showed that medications, at RM692.57 per patient, made up the largest portion of the cost of managing snakebites in a tertiary care hospital, followed by hospitalisation cost and cost of laboratory tests. The cost for antivenom for one patient was between RM360– RM5,390. Previous

studies reported the cost of antivenom for one patient varies widely, between RM18 and RM517 (3,13). Our finding is considered high as the antivenoms available in Malaysia were imported mainly from Thailand.

The average cost of treatment in patients treated with polyvalent antivenom was 5.85% higher than the treatment cost in patients who received monovalent antivenom. This was mainly due to the higher costs in hospital stay and other interventions among patients treated with polyvalent anti-venom. Even though the cost per patient for those received monovalent antivenom is lower compared to those received polyvalent antivenom, the incident of ADR in monovalent group was higher (Figure 2). ADR related to antivenom is a common issue. It can happen immediately, for example anaphylactic reaction, or late, which are usually mild, after the administration of antivenom. Previous study reported incidence of ADRs associated with antivenom varied widely, between 3% and 54% (12,13). In our study, 18.3% of the patients who received antivenom developed an ADR. Of these, two cases developed anaphylactic reaction and the others experienced skin reactions such as urticaria rash and itchiness, and epigastric pain. Our observed ADR rate among patients treated with polyvalent antivenom was 14.3% and this was lower than previously published rates (8-10).

The management of patients with snakebite involved both the emergency department and inpatient wards. Inpatients admission rate in this study was 71.2% and this was higher compared to the data from the National Electronic Injury Surveillance System – All Injury Program (NEISS-AIP) in the United States which identified that 1.8% of the patients were admitted as inpatients whereas National Emergency Department Sample (NEDS) data from 2006 to 2008 reported an inpatient admission rate of 4.4% (10). This might be due to severity of the case that needs multiple interventions in the management of snakebite in our study population. Based on our results, treatment cost in the inpatient was more expensive compared to the emergency department. Nevertheless, since antivenoms were mainly administered in the emergency department, the total cost of antivenom was higher in the emergency department. However, because of the factor of the length of hospital stay and the use of other drugs and laboratory testing, the inpatient average cost was higher compared to the emergency department.

The cost of managing snakebite cases may be minimised by getting the correct information when the patient arrives at the emergency department. Critical information, such as body area bitten, the time of incident and the activity at the time of the incident, the geographical location of the snakebite, the identity or description of the snake, intervention done after the bite, eyewitness to the incident, and any signs and symptoms felt by the patient since the incident, are important for the diagnosis and correct treatment of snakebites. History of previous contact with the snakes (nonvenomous and venomous), previous bite and envenoming incident, and the history of allergy and comorbidities may also be helpful in choosing the correct management especially to choose between monovalent or polyvalent antivenom (1).

The main limitation of this study was that cost estimation was based on healthcare provider's perspective. Therefore, patients' perspective such as their loss in their daily income during their stay in the hospital was not taken into account. Besides, this study was conducted retrospectively, hence it had the potential of missing or conflicting data and some needed variables were not in the records, thus may affect the results.

Conclusion

In Sultanah Bahiyah Hospital, there were 184 cases of snakebites in year 2015. More than one third of the cases involved venomous species and required antivenom treatment. The cost analysis showed that the estimated average cost of the snake bite management per patient was RM1,910.66 and the cost of medication constitutes the highest portion of the costs, followed by the cost of hospital stay and laboratory tests. It was more expensive to manage patients in the hospital inpatient setting compared to the management in the emergency department. The average cost for patients treated with monovalent antivenom was slightly lower compared to patients who received polyvalent antivenom. Critical information of the snakebite such as type of snake or location of the snakebite may help to decide the correct snakebite management thus minimising the cost of snakebite management.

Our results reported the considerable economic impact of snakebites management. This may help to draw the policy maker's attention to improve the budget allocation towards improving the patient care and management of snakebite envenomation. We recommend that antivenom should be given only under close medical supervision with full resuscitation facilities readily available, and that reassessment of the indications for antivenom use is warranted. Further analysis on outcome of the management with polyvalent and monovalent antivenom should be conducted to ensure the best management of snakebite envenoming.

Acknowledgment
The authors would like to express their gratitude to the Director General of Health for his permission to publish this article. Special thanks to all individuals who have contributed to this study.

Conflict of Interest Statement
No external funding was received and the authors declared no conflict of interest.

References
1. Ismail, Ahmad Khaldun. (2015). Snakebite and Envenomation Management in Malaysia. In: P. Gopalakrishnakone et al. (eds.), Clinical Toxinology in Asia Pacific and Africa, Toxinology. Springer Netherlands. pp.71-102.
2. Guideline: Management of Snakebite, 2017. Ministry of Health Malaysia, Putrajaya, Malaysia.
3. Habib AG, Lamorde M, Dalhat MM, Habib ZG, Kuznik A. Cost-effectiveness of antivenoms for snakebite envenoming in Nigeria. PLoS neglected tropical diseases. 2015 Jan 8;9(1):e3381.
4. WHO Expert Committee on Biological Standardization. WHO guidelines for the production, control and regulation of snake antivenom immunoglobulins. WHO Technical Report Series. Geneva, Switzerland: WHO. 2010:1-34.
5. World Health Organization. Guidelines for the clinical management of snake bite in the South East Asia region. New Delhi WHO South East Asia Regional Office; 2010.
6. Snow RW, Bronzan R, Roques T, Nyamawi C, Murphy S, Marsh K. The prevalence and morbidity of snake bite and treatment-seeking behaviour among a rural Kenyan population. Annals of Tropical Medicine & Parasitology. 1994 Jan 1;88(6):665-71.
7. Thachil RT, Tony JC, Jude E, Ross C, Vincent NJ, Sridhar CB. Antisnakevenom: an overused medication. Tropical doctor. 1992 Jul;22(3):113-5.
8. Moran NF, Newman WJ, Theakston RD, Warrell DA, Wilkinson D. High incidence of early anaphylactoid reaction to SAIMR polyvalent snake antivenom. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1998 Jan 1;92(1):69-70.
9. Wilkinson D. Retrospective analysis of snakebite at a rural hospital in Zululand. South African Medical Journal. 1994;84(12):844-.
10. Langley R, Mack K, Haileyesus T, Proescholdbell S, Annest JL. National estimates of noncanine bite and sting injuries treated in US hospital emergency departments, 2001–2010. Wilderness & environmental medicine. 2014 Mar 1;25(1):14-23.

Comparing the Cost of Standardised and Individualised Parenteral Nutrition in Clinically Stable Infants in a Malaysian Public Hospital

Leao Xin Yi[1], Chan Huan Keat[2], Hasif A Rusli[3], Tan Hooi Kuan[3], Lim Li Xin[4]

[1] Hospital Sultanah Bahiyah, Kedah, Ministry of Health Malaysia, [2] Clinical Research Centre, Hospital Sultanah Bahiyah, Kedah, Ministry of Health Malaysia, [3] Pharmaceutical Services Division, Kedah State Health Department, Ministry of Health Malaysia, [4] Hospital Langkawi, Kedah, Ministry of Health Malaysia

Abstract

Introduction: In Malaysia, some public hospitals are using individualised parenteral nutrition (IPN) in paediatric patients although standardised parenteral nutrition (SPN) is recommended by more recent guidelines.

Objective: This study aimed to compare the costs of SPN and IPN, and to estimate the potential cost saving when SPN is used in place of IPN for clinically stable paediatric patients receiving treatment in a public tertiary hospital in Malaysia.

Methods: A costing study was undertaken in Sultanah Bahiyah Hospital, Alor Setar, between February and April 2017. All IPN preparations compounded at the pharmacy department during the three-month study period were included in the cost analysis. A bottom-up costing approach was used to compute the cost of IPN based on the consumption of resources including ingredients, disposables, personnel and equipment. The cost of SPN was estimated according to the existing literature. The total cost difference between IPN and SPN was estimated based on a hypothetical model, in which SPN will be given to patients who were clinically stable in place of IPN.

Results: The unit costs of IPN and SPN preparations were RM259.52 and RM156.82 respectively, and SPN was cheaper than IPN by 39%. During the three-month study period, 232 IPN preparations were compounded for 35 patients. Based on the hypothetical model, 140 of the IPN preparations were judged to be replaceable by SPN. Therefore, it was estimated that a total RM14,378.00 could be saved (7.5% cost reduction) if SPN instead of IPN was compounded for the clinically stable paediatric patients. The projected annual savings in Sultanah Bahiyah Hospital could be as high as RM60,000.00.

Conclusion: This study suggested that cost saving is achievable if SPN is used in place of IPN in clinically stable paediatric patients. The findings could help healthcare providers to optimise resource utilisation.

Keywords: infant, child, parenteral nutrition, pharmacy, public hospitals

NMRR ID: NMRR-17-207-34280

Corresponding author: Leao Xin Yi
Pharmacy Department, Hospital Sultanah Bahiyah, KM 6, Jalan Langgar, 05460 Alor Setar, Kedah.
Email: xy819_kitty@hotmail.com

Introduction

Parenteral nutrition (PN) refers to the supply of nutrition by the intravenous route instead of through the alimentary canal. A complete PN preparation consists of fluid, carbohydrate, protein, lipids, electrolytes, vitamins and trace elements. PN is given to adult patients whose nutrition needs are not fully met by oral or enteral tube feeding (1-3). In premature neonates, PN is typically initiated early to promote growth and prevent neurological disorders (4-6). PN is generally safe and tolerable, even if it is used in newborns on their first day of life.

As the metabolic pathways are not fully developed in newborns, PN is normally titrated slowly in the first and second weeks of their life. Most of the time, PN is continued until they achieve an ideal body weight and are able to tolerate enteral feeding (7). However, due to the interpersonal variability in nutrition needs and physical conditions of infants, PNs are extemporaneously prepared in most hospitals (6,8). PN that is adjusted daily according to the laboratory readings of patients is termed as individualised parenteral nutrition (IPN) and

it has long been used worldwide (9). Nevertheless, following the recommendations made by more recent international guidelines, standardised parenteral nutrition (SPN) is becoming more common. Different from IPN, SPN is prepared based on a fixed formula tailored to an age- or weight-based category, mainly used in clinically stable infants despite minor changes in the laboratory findings. The existing literature suggests that IPN and SPN do not differ in safety, efficacy and product stability (13-17).

SPN is believed to have a cost-saving potential, mainly through lowering the preparation time and cost (9-13). Waste minimisation is also possible, as the preparations made for a cancelled order could be used for another patient with similar age and weight. Additionally, resource utilisation is likely to be optimised as PN preparations can be produced in batches. The cost incurred by the management of medication errors could also be reduced due to the use of a standardised PN formula (10).

In accordance with the recommendations of local and international guidelines for nutrition care (19-21), some hospitals in Malaysia have started using SPN in infants. However, the cost implication in Malaysia is yet to be determined. This study was carried out to compare the costs of SPN and IPN, and to estimate the potential cost saving when SPN is used in place of IPN in clinically stable patients receiving treatment in a Malaysian public tertiary hospital.

Methods

Study Setting

We performed a three-month study on PN orders received between February and April 2017 from the three paediatric wards at the Sultanah Bahiyah Hospital, Alor Setar. All the PN preparations were made in a cleanroom located at the Pharmacy Department, which was equipped with a Grade A laminar flow cabinet. PN orders will be screened and authorised by the pharmacists before the PN preparations are being compounded by the pharmacy technicians. Each preparation was contained in a TPN compounding bag, consisting of carbohydrate, protein, electrolytes and trace elements. To ensure product stability, lipid emulsion and fat-soluble vitamins were packed separately in a capped syringe.

All PN preparations made for premature infants with body weight less than 1.5kg during the three-month study period were included for the cost analysis. Preparations that failed the quality control process or that were made for infants undergoing surgery were excluded.

Cost Calculation

A bottom-up costing approach was used to compute the cost of IPN based on the observed consumption of resources. The costs of ingredients, disposables, equipment and personnel were included in the cost calculation (22). The summary of these cost elements were presented in Table 1.

Table 1: Summary of cost elements

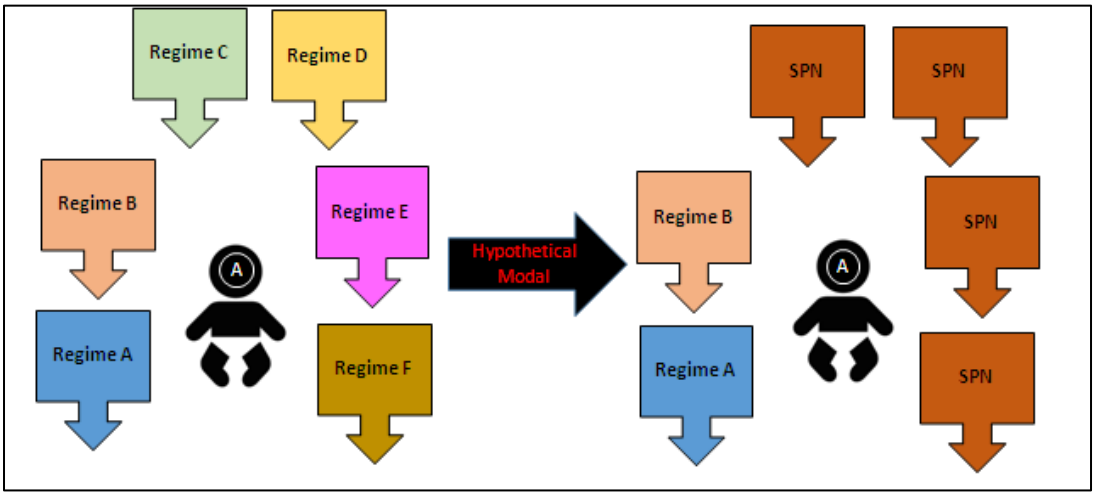
Ingredients	The total costs of ingredients were estimated based on the quantity consumed and their acquisition costs (current market prices).
Disposables	The total costs of disposables were estimated based on the quantity consumed and their acquisition costs (current market prices).
Equipment	Current market prices were used for equipment costs. Depreciation was calculated linearly over a 5-year period for installation and devices (laminar flow hood / bench, compounder, infusion pump, isolator). Information about the price and yearly maintenance costs for the equipment was derived from the recruited sites, which took the information from hospital records.
Personnel	The PN activities of physicians, pharmacist and nurse were systematically timed by the investigators. Time spent by each category of personnel to produce the parenteral nutrition regime (prescription, preparation for compounding, installation / connection of equipment, compounding, supplementation, monitoring, compounder disconnection, stock management / requisition, quality control and training time) were recorded. These timings were combined with the average wage per category of the personnel involved in the activities. The corresponding salary information was obtained from hospital administration data.

Cost Saving Estimation

Renal and liver functions in the premature neonates continue to develop after birth. The fluid and electrolyte balance is affected by extra-renal systems, illness, medications and interventions. Hence, the fixed electrolyte contents of SPN may not be tolerated well by the sick premature neonates. However, Devlieger et al. proposed that the premature neonates are capable, within certain limits, of appropriate homeostasis as early as the first week of life and hence may be managed with few combinations of standard PN formulations and they found that SPN formulations were sufficient to manage most of the very low birth weight (VLBW) neonates without significant electrolyte disturbances (9,23).

Hence, a hypothetical model was applied to estimate the total cost if SPN was used in place of IPN for clinically stable patients (Figure 1). Clinically stable patient refers to those neonates who had no kidney or liver dysfunctions or significant electrolytes disturbances that need daily blood monitoring and adjustments.

Figure 1: A hypothetical model for replacing IPN with SPN in clinically stable patients



Ethic Approval and NMRR

This study was registered with the National Medical Research Register (NMRR) and approved by the Ministry of Health Medical Research and Ethics Committee (MREC). It was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline.

Results

The unit costs of ingredients and disposables used in the compounding of IPN were presented in Table 2 while the workflow of prescribing and preparing PN preparations and the hourly wage of personnel involved were presented in Figure 2 and Table 3.

A total of 232 bags of IPN and 476 syringes of lipid emulsion were compounded for 35 patients during the three-month study period. The overall cost for preparing these PN preparations during the study period was RM190,530.87. The average costs per bag of IPN and SPN preparations were RM259.52 and RM156.82 respectively.

Based on the hypothetical model, 140 of the 232 IPN preparations were judged to be replaceable by SPN when patients were clinically stable, and 92 bags should be remained as IPN for the clinically unstable period. There were no changes in the use of lipid emulsions in the hypothetical model. When the hypothetical model was applied, the total cost of PN preparations over the three-month period became RM176,152.87. Therefore, it was estimated that a total RM14,378.00 could be saved, which was equivalent to 7.5% cost saving, if SPN instead of IPN was compounded for the clinically stable paediatric patients (Figure 3 and Table 4). When this amount was extrapolated, the projected annual savings in Sultanah Bahiyah Hospital could reach around RM60,000.00.

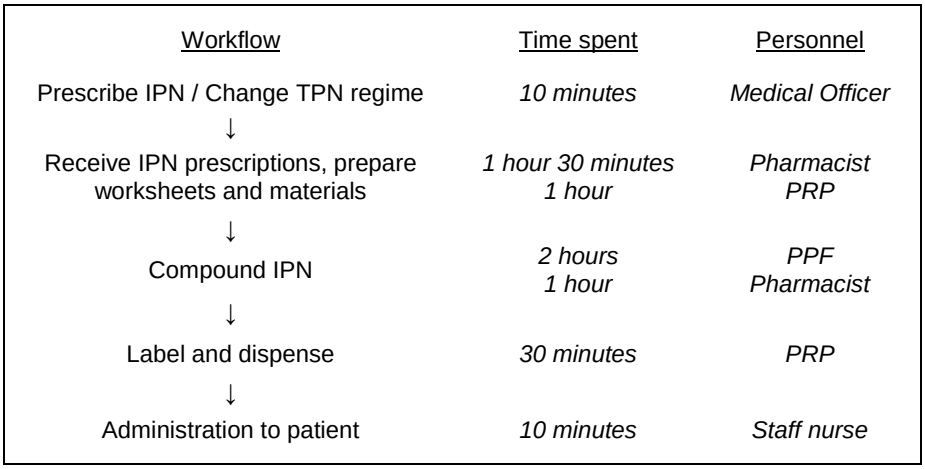
Table 2: Unit costs of ingredients and disposables used in the compounding of IPN

Ingredient	Unit Cost (RM)	Disposable	Unit Cost (RM)
Water for Injection 500ml	2.27	Nutrimix Bag 200ml	21.00
Glucose 50% 500ml	8.00	Nutrimix Bag 500ml	31.00
Aminoven INFANT 10% 250ml	118.75	Sterifix Injection Filter 0.2µm (UFO)	6.20
Peditrace 10ml	35.73	Sterifix IV Filter 0.2µm	15.50
Sodium Acetate 2mmol/ml 20ml	23.99	Mini Spike Blue	4.00
Sodium Chloride 20% 10ml Inj	1.70	Needle 19G	0.07
Potassium Acetate 2mmol/ml 20ml	29.30	Syringe 1ml (luer slip)	0.28
Potassium Chloride 10% 10ml Inj	0.63	Syringe 3ml (luer slip)	0.25
Calcium Gluconate 10% 10ml Inj	4.50	Syringe 5ml (luer slip)	0.30
Magnesium Sulphate 2mmol/ml 5ml Inj	14.17	Syringe 10ml (luer slip)	0.40
Glycophos 20ml	14.00	Syringe 20ml (luer slip)	0.77
Smoflipid 20% 100ml [a]	48.70	Syringe 50ml (luer slip)	2.24
Vitalipid N-Infant 10ml [a]	34.70	Alcohol Swab Sterile	0.04
Soluvit N 10ml [a]	34.70	Nursing Csp	7.20
		Face Mask 3ply	0.38
		Nitrile Gloves (pair)	0.40
		Sterile Gloves (pair)	3.00
		Antiseptics Klercide 1000ml	103.80
		Tyvex Jumpsuit	36.50
		Shoe Cover	17.51
		Sterifix Filter Straw 5µm [b]	4.30
		Intrapur IV Filter Adult 1.2µm [b]	15.50
		Sterifix Filter 5µm [b]	2.60
		Combi Red Stopper [b]	0.50
		Syringe 20ml (luer lock) [b]	1.82
		Syringe 30ml (luer lock) [b]	3.01
		Syringe 50ml (luer lock) [b]	5.30
		Sterilised paper bag (lipid) [b]	0.35

Source: Pharmacy Department, Sultanah Bahiyah Hospital

[a] Ingredients for lipids; [b] Disposables for the compounding of lipids

Figure 2: Standard workflow of prescribing and preparing IPN preparations



Abbreviations: IPN – individualised parenteral nutrition; PRP – provisionally registered pharmacist; PPF – pharmacist assistant

Table 3: Cost of personnel

Personnel	Hourly wage (RM)
Medical Officer	25.00
Pharmacist	25.00
Provisionally registered pharmacist (PRP)	19.00
Pharmacist assistant (PPF)	14.00
Staff nurse	17.00

Source: hospital administration data (Sultanah Bahiyah Hospital)

Figure 3: Illustration of cost saving using the hypothetical model

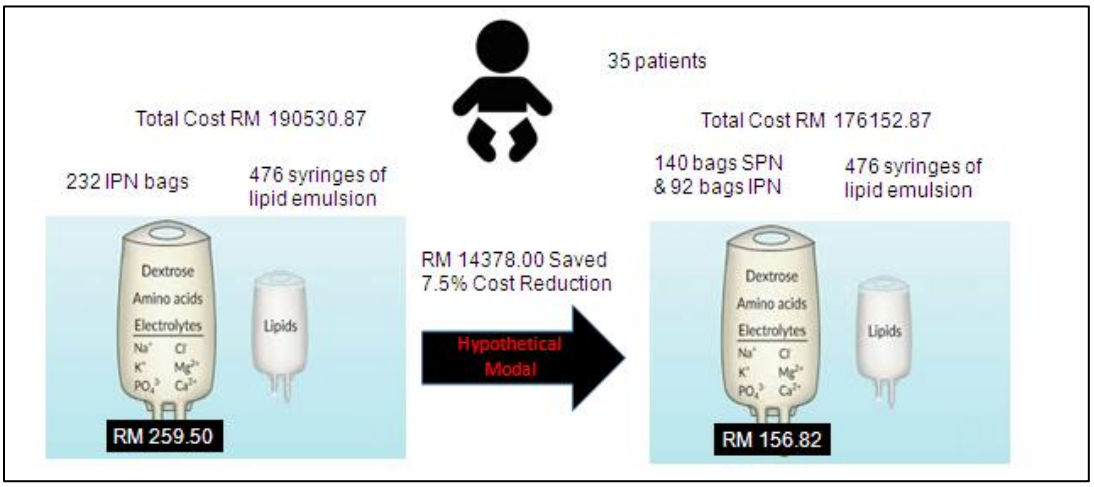


Table 4: Estimated cost saving of the hypothetical model

	Study Data	Hypothetical Model
Quantity of bags compounded	232 IPN	140 SPN + 92 IPN
Quantity of lipids compounded	476	476
Ingredients and disposables cost (bags)	RM60,208.45	RM45,830.64
Ingredients and disposables cost (lipids)	RM27,946.23	RM27,946.23
Equipment Cost	RM75,000.00	RM75,000.00
Personnel cost	RM27,376.00	RM27,376.00
Total	RM190,530.87	RM176,152.87

Discussion

Cost analysis studies are increasingly important in order to support and justify medical procedures and operation expenses. The aim of this study was to compare the cost if standardised instead of individualised parenteral nutrition is compounded for clinically stable paediatric patients by constructing a hypothetical model. To the best of our knowledge, it is the first hypothetical model study done in Malaysia and one of the very few studies that estimate the costs for non-drugs. This study may give policy makers a brief overview about the costs of PN compounding in Malaysian public hospitals and hence may help to develop better policy for supplying PN at lower cost with equivalent effectiveness. Hence, the overall healthcare cost may be saved.

The use of SPN solutions has been reported to be feasible in several observational studies and appears to benefit in some but not all clinical settings. Some reported the use of SPN increased energy and amino acid intake, calcium and phosphate intake, prevent early weight loss, and reduced costs (18-21). The ANZNN consensus Group agreed that SPN offers advantages over routine IPN in terms of providing adequate nutrition without significant alteration in biochemical responses, and with the potential for reduced cost and prescription error. The consensus group agreed on three types of SPN solutions which were starter PN, standard normal sodium PN and high sodium PN for preterm infants (19).

In this study, we demonstrated that the cost of SPN was lower than the cost of IPN. In our calculation, the cost difference between an IPN and SPN was due to the cost of ingredients and disposables. As SPN can be compounded in bulk at one time and it is stable to be stored at 2°C - 8°C up to 7 days, there were savings in the quantity of ingredients and disposables. On the other hand, for compounding of IPN, the amount of ingredients and disposables used were more because new ingredients and disposables items were used on daily basis or according to prescription. In addition, cost of personnel could have been saved for SPN because the workloads may be less especially in terms of weekend on-calls. Nevertheless, we did not attempt to calculate the savings in the personnel cost and just assumed that the personnel costs were the same for the preparation of both IPN and SPN. On the other hand, it is undeniable that wastage may occur if the

compounded SPNs expired before consumption as it may be difficult to estimate the exact usage all time. For neonatal PN compounding, lipid emulsion is prepared separately and it is not mixed into the PN bag because it will affect the stability. In this study, we did not extrapolate the hypothetical model for the lipid emulsion and all patients were given 1 syringe of lipid emulsion per day together with to the PN bags regardless of SPN or IPN.

In some studies, SPN regime was also found to be cost saving due to the proposed prolonged infusion time over 48 hours compared to IPN which is infused over 24 hours. However, there were concerns over the higher potential of bacterial or fungal colonisation if the PN infusion time were longer. In a randomised trial, there was no significant difference in bacterial or fungal colonisation of parenteral or neonatal sepsis in infants receiving 24 or 48 hour infusions of PN solution. The study reported extending PN solution hang time from 24 to 48 hours did not increase the risk for central line associated blood stream infection and in fact it reduced PN related cost and nursing workload (18-21).

The findings on cost comparison between IPN and SPN were consistent with data from the literatures that the cost for SPN was lower than the cost for IPN (19-20). However, this study has a major limitation that it was based on a hypothetical model and we did not do head to head comparison between SPN and IPN. There could be bias if the observations were incomplete or incorrect. The study might have underestimated or overestimated the overall cost saving. Therefore, we recommend conducting a head to head comparison study on SPN versus IPN, so that we could get deeper picture on the pharmacoeconomics of local PN compounding. The other limitation of this study was that it was a single centre study. The study was only reflecting the cost incurred in HSB and cannot represent the other government hospitals settings as the other hospitals might have different practices on IPN and SPN and different brands of products could be used. For example, up to the date of this manuscript preparation, the Kuala Lumpur Hospital has adopted the SPN formulations published by the Ministry of Health Malaysia while Sungai Buloh Hospital has its own SPN formulations. This study also did not consider about the different brands of PN ingredients that may be different in IPN and SPN formulations. As there are a few local and international manufacturers that manufacture PN ingredients of different prices, the cost incurred may differ among hospitals.

Conclusion

This study compared the total costs of IPN versus SPN based on a hypothetical model by considering all cost elements involved in the process. This study suggested that the total cost of SPN was lower than that of IPN in clinically stable paediatric patients receiving treatment in a public tertiary hospital. While financial constraints remain a challenge for the public healthcare system, the findings could help pharmacists to optimise resource utilisation. While more detailed studies should be carried out to gather more information, this information will be helpful in determining the cost of PN therapy and help the healthcare providers and policy makers to formulate healthcare policies.

Acknowledgement

We would like to thank the Director General of Health Malaysia for his permission to publish this article. We thank our colleagues from Sultanah Bahiyah Hospital who provided insights and expertise that greatly assisted the research.

Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

References

1. Boullata JI. Overview of the parenteral nutrition use process. JPEN J Parenter Enteral Nutr. 2012; 36:10S-13S.
2. ISMP's List of High-Alert Medications. Horsham, PA: Institute for Safe Medication Practices; 2012.
3. Andris DA, Mirtallo JM, Guenter P, eds. ASPEN parenteral nutrition safety summit. JPEN J Parenter Enteral Nutr. 2012;36(2 Suppl 2):1S-62S.
4. Moyses HE, Johnson MJ, Leaf AA, Cornelius VR. Early parenteral nutrition and growth outcomes in preterm infants: a systematic review and meta-analysis. Am J ClinNutr; 2013; 97(4):816-26.

5. Usmani SS, Cavaliere T, Casatelli J, Harper RG. Plasma ammonia levels in very low birth weight preterm infants. The Journal of pediatrics; 1993; 123:797-800.
6. Guidelines on pediatric parenteral nutrition of the European society of pediatric gastroenterology, hepatology and nutrition (ESPGHAN). J PediatrGastroenterolNutr; 2005; 41(2):81-84.
7. Hussain Imam, Peadiatric Protocols for Malaysian Hospitals, 3rd Edition, Ministry of Health Malaysia. 2012 Chapter 12: Total Parenteral Nutrition for Neonates, page 71.
8. Vaidya UV, Hegde VM, Bhave SA, Pandit AN. Reduction in parenteral nutrition related complications in the newborn. Indian Pediatr. 1991;28(5):477-84.
9. Karen Simmer, Abhijeet Rakshasbhuvankar, Girish Deshpande. Standardized Parenteral Nutrition. Nutrients; 2013 Apr; 5(4): 1058-1070.
10. Srinivas Bolisetty, David Osborn, John Sinn, Kei Lui and the Australasian Neonatal Parenteral Nutrition Consensus Group. Standardized neonatal parenteral nutrition formulations–an Australasian group consensus 2012. Bolisetty et al. BMC Pediatrics 2014, 14:48.
11. Lucie Bouchoud, How are standardized pediatric parenteral nutrition formulations in Europe? EJHP Science 2010 Volume 16• Issue 1 • P. 1-4.
12. Evelyn Walter, Cost analysis of neonatal and pediatric parenteral nutrition in Europe – a multi-country study. European Journal of Clinical Nutrition volume 66, 2012, pages 639–644.
13. Yeong MY, Evaluation of Standardized versus Individualized total parenteral regime for neonates less than 33 weeks of gestation. J Pediatr Child Health. 2003 Nov; 39(8):613-7.
14. Beecroft C, Martin H, Puntis JW: How often do parenteral nutrition prescriptions for the newborn need to be individualized? Clin Nutr 1999, 18:83–85.
15. Iacobelli S, Bonsante F, Vintejoux A, Gouyon JB: Standardized parenteral nutrition in preterm infants: early impact on fluid and electrolyte balance. Neonatol 2010, 98:84–90.
16. Lenclen R, Crauste-Manciet S, Narcy P, Boukhouna S, Geffray A, Guerrault MN, Bordet F, Brossard D: Assessment of implementation of a standardized parenteral formulation for early nutritional support of very preterm infants. Eur J Pediatr 2006, 165:512–518.
17. Smolkin T, Diab G, Shohat I, Jubran H, Blazer S, Rozen GS, Makhoul IR: Standardized versus individualized parenteral nutrition in very low birth weight infants: a comparative study. Neonatology 2010, 98:170–178.
18. PN Standard Solution (Malaysia Neonatal Parenteral Nutrition Consensus Group Formulations) KKM-55/BPF/104/012/01/Jld17(20)
19. Balegar VK, Azeem MI, Spence K, Badawi N: Extending total parenteral nutrition hang time in the neonatal intensive care unit: is it safe and cost effective? J Paediatr Child Health 2013, 49: E57–E61.
20. Matlow AG, Kitai I, Kirpalani H, Chapman NH, Corey M, Perlman M, Pencharz P, Jewell S, Phillips-Gordon C, Summerbell R, Ford-Jones EL: A randomized trial of 72- versus 24-hour intravenous tubing set changes in newborns receiving lipid therapy. Infect Control Hosp Epidemiol 1999, 20:487–493.
21. Gamsjager T, Brenner L, Schaden E, Sitzwohl C, Weinstabl C. Cost analysis of two approaches to parenteral nutrition in critically ill children. Pediatr Crit Care Med 2009; 10: 163-165.
22. Petrelli MD, Nicolai E, Tucci A, Giambenedetti M, Taus M, Busni D *et al*. Total parenteral nutrition: economic investigations comparing hospital prepared nutritional bags versus similar bags prepared by the pharmaceutical industry. *Riv Ital Nut Par Ent* 2004; 22, 186–192.
23. Devlieger, H.; de Pourco, L.; Casneuf, A.; Vanhole, C.; de Zegher, F.; Jaeken, J.; Eggermont, E. Standard two-compartment formulation for total parenteral nutrition in the neonatal intensive care unit: A fluid tolerance based system. Clin. Nutr. 1993, 12, 282–286.

Carbapenem and Cephalosporin Antibiotics Usage in Cheras Rehabilitation Hospital

Syazzana Dzulkifli[1], Noor Hafizah Tajuddin[1], Wong Shieh Teng[1], Dashini Jaganathan[1], Yuzlina Muhamad Yunus[1]

[1] Cheras Rehabilitation Hospital, Federal Territory of Kuala Lumpur and Putrajaya, Ministry of Health Malaysia

Abstract

Introduction: Antibiotic resistance is a critical problem faced worldwide. The development of bacterial resistance was often linked to the irrational use of antibiotics.

Objective: This study aimed to describe the prescribing pattern and antibiotics resistance pattern of carbapenems and cephalosporins in Cheras Rehabilitation Hospital (HRC), and to evaluate whether carbapenems and cephalosporins were used in concordance to the National Antibiotic Guideline (NAG) 2008 and 2014.

Methods: This was a retrospective observational study. All adult inpatients treated with carbapenems or cephalosporins from June 2014 to June 2016 were included and the relevant data was extracted from the patients' medical records. The antibiotic prescribing information was compared against the NAG to determine the concordance to the guideline.

Results: There were 64 cases of which carbapenem and cephalosporin antibiotics were prescribed. Majority of the patients (52%) were male with mean age of 46 (standard deviation 18) years old. Ceftazidime was the most prescribed antibiotics (46.9%) followed by Meropenem (17.2%), Cefuroxime (15.6%) and Ceftriaxone (15.6%). The antibiotics were mostly prescribed as definitive treatment (45.3%) while 35.3% and 17.2% of the antibiotics were given as prophylaxis and empirical treatment respectively. Meropenem was the most preferred carbapenems for extended-spectrum β-lactamase (ESBL) infections (35%). ESBL infections were highly sensitive towards carbapenem antibiotics in which the sensitivity rate was 100%. Overall, more than half of the antibiotics (59.4%) were prescribed in concordance to the NAG. Inappropriate indication was the highest non-concordance to NAG found in this study. Eighty percent of Ceftazidime was given as prophylaxis for urodynamic studies (UDS) which was not recommended by the NAG.

Conclusion: This study found that the concordance to the NAG in HRC was satisfactory. Nevertheless, the adherence to the antibiotic prescribing guidelines should be further improved to reduce the emergence of antibiotic resistance.

Keywords: antibiotic usage, carbapenem, cephalosporin

NMRR ID: NMRR-16-1317-31340

Corresponding author: Syazzana bt Dzulkifli
Department of Pharmacy, Hospital Rehabilitasi Cheras, Jalan Yaacob Latiff, Bandar Tun Razak, Cheras, 56000 Kuala Lumpur.
Email: syazzanadzul@gmail.com

Introduction

Antibiotics are one of the most common medications prescribed in the hospital. About one-third of hospitalised patients receive antimicrobial therapy (1). It has been shown that beta-lactam antibiotics such as penicillins, cephalosporins, monobactams and carbapenems ranked the highest in antibiotics usage worldwide (2). It also has been reported that a large number of patients receiving antibiotics may be due to inappropriate prescribing behaviour (3).

A study in Ghana reported that antibiotics were the second most commonly prescribed medicines (19.1%) after analgesics (27.1%) (4). Another survey on the utilisation pattern of antibiotics showed that the commonly used classes of antibiotics were Cephalosporins, followed by Fluoroquinolones and Azoles. Although there are standard guidelines on the use of the antibiotics, the differences between the prescribing patterns of antibiotics and the guidelines were still being observed (5).

In Malaysia, only 20% of the antibiotics prescriptions were based on the microbiological test results (6). In the Cheras Rehabilitation Hospital (HRC), Kuala Lumpur, intravenous Cefuroxime and Meropenem were the most prescribed type of antibiotic, by define daily dose (DDD), based on the HRC antibiotic audit done in 2015 (7). The DDD for every 100 admission for these two antibiotics were 15.22 and 22.18 respectively, while DDD for every 1000 patient days was 7.78 and 11.35 respectively. The usage of these antibiotics was higher as compared to other antibiotics that were used in HRC during the period of the study. High antibiotics use may contribute to antibiotic resistance if they are used inappropriately (8). It was proven that bacterial resistance is linked to the bacterial species and the type of antibiotics used (9). Therefore, knowledge about the local antimicrobial resistance patterns of bacteria is a valuable guide to empirical antimicrobial therapy and the formulation of antibiotic guidelines. Ultimately, it is also important for the control of the emergence of antimicrobial resistance in hospitals (10).

This study evaluated the rationale use of carbapenem and cephalosporin antibiotics in HRC. The specific aims of the study were to describe the prescribing pattern and antibiotics resistance pattern of carbapenems and cephalosporins, as well as to evaluate whether carbapenem and cephalosporin antibiotics were used in concordance to the National Antibiotic Guideline (NAG).

Methods

This study was conducted using a retrospective, observational study design with universal sampling method. All adult patients from the adult wards in HRC who was treated with carbapenem or cephalosporin antibiotics during their hospitalisation from June 2014 to June 2016 were included. Patients with incomplete medical records, incomplete of antibiotics course and patients who had started the study antibiotics from other hospital were excluded from the study.

The National Antibiotic Guidelines (NAG) were published to assist prescribers in Malaysia in making decision about the choice of antibiotic treatment (11,12). As NAG 2014 was officially published in December 2014, the antibiotic prescribing information in year 2014 were compared against NAG 2008 and the data in year 2015 and 2016 were compared against NAG 2014.

This study was registered with the National Medical Research Registry (NMRR) and approved by the Medical Research Ethics Committee (MREC) before data collection process was started. The data collection was carried out between October 2016 and February 2017 at the Records Department, HRC. A data collection form was used to record all the relevant data extracted from the patients' medical records. Descriptive analysis which consists of mean, standard deviation and percentage was used to analyse the collected data.

Results

Overall, the mean age of patients in this study was 46 years old (standard deviation 18 years) with a majority of them were males (52%). There were 64 cases of which carbapenem and cephalosporin antibiotics were prescribed. Ceftazidime was the most prescribed cephalosporin antibiotics (46.9%) in the wards followed by Meropenem, Cefuroxime and Ceftriaxone (Table 1).

Urinary tract infection (UTI) was the most common infection (n=31, 48.4%), followed by antimicrobial prophylaxis for urodynamic studies (UDS) (n=24, 37.5%) and pneumonia (n=4, 6.4%). The antibiotics were mostly prescribed as definitive treatment (45.3%) and only 17.2% of the antibiotics were given as empirical treatment (Table 2). Meropenem was the most preferred carbapenem antibiotic for treatment of extended-spectrum β-lactamase (ESBL) infection (n=12, 35.3%) cases detected in the ward.

ESBL infections were highly sensitive towards carbapenem antibiotics in which the sensitivity rate was 100%. For non-ESBL infection, the sensitivity rate towards antibiotic was above 50% except for cefotaxime. Table 3 showed the sensitivity pattern of antibiotics on ESBL and non-ESBL infection detected in HRC.

Table 4 showed the concordance of cephalosporin and carbapenem prescribing to the National Antibiotic Guidelines (NAG) 2008 / 2014. Overall, more than half of the antibiotics (59.4%) were prescribed in concordance to the NAG. Inappropriate indication was the highest non-concordance to NAG found in this study compared to dose, frequency and duration of antibiotic use. Ceftazidime, which was the most prescribed cephalosporin antibiotics, was prescribed for the recommended indication in only 20% of the

prescriptions. Eighty percent of Ceftazidime was given as prophylaxis for UDS which was not recommended by the NAG.

Table 1: Cephalosporin and carbapenem usage in HRC (N=64)

Antibiotic	n (%)
Cephalosporin	
Ceftazidime	30 (46.9)
Cefuroxime	10 (15.6)
Ceftriaxone	10 (15.6)
Cefepime	2 (3.1)
Carbapenem	
Meropenem	11 (17.2)
Imipenem + Cilastatin	1 (1.6)

Table 2: Indications of antibiotic usage

Indication	n (%)
Definitive treatment	29 (45.3)
Empirical treatment	11 (17.2)
Prophylaxis	24 (37.5)

Table 3: Sensitivity pattern of antibiotics on ESBL and non-ESBL infection

Antibiotic	Non-ESBL		ESBL	
	Sensitive, n (%)	Resistant, n (%)	Sensitive, n (%)	Resistant, n (%)
Ceftazidime	7 (77.8)	2 (22.2)	0 (0.0)	8 (100.0)
Cefoperazone	10 (90.9)	1 (9.1)	0 (0.0)	11 (100.0)
Cefotaxime	0 (0.0)	1 (100.0)	0 (0.0)	10 (100.0)
Cefuroxime	12 (80.0)	3 (20.0)	0 (0.0)	11 (100.0)
Cefepime	6 (85.7)	1 (14.3)	0 (0.0)	8 (100.0)
Ceftriaxone	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Imipenem + Cilastatin	1 (50.0)	1 (50.0)	12 (100.0)	0 (0.0)
Ertapenem	1 (100.0)	0 (0.0)	11 (100.0)	0 (0.0)
Meropenem	1 (100.0)	0 (0.0)	11 (100.0)	0 (0.0)

Abbreviation: ESBL - extended-spectrum β-lactamase

Table 4: Concordance of antibiotic prescribing to the NAG 2008 / 2014 *

Category	NAG concordant prescribing, n (%)	NAG discordant prescribing, n (%)
Prescribing information		
Indication (n=64)	38 (59.4)	26 (40.6)
Dose (n=64)	64 (100.0)	0
Frequency (n=64)	61 (95.2)	3 (4.8)
Duration (n=64)	61 (95.2)	3 (4.8)
Antibiotic		
Ceftazidime (n=30)	6 (20)	24 (80)
Cefuroxime (n=10)	10 (100)	0
Ceftriaxone (n=10)	8 (80)	2 (20)
Cefepime (n=2)	2 (100)	0
Meropenem (n=11)	11 (100)	0
Imipenem + Cilastatin (n=1)	1 (100)	0

* Data in year 2014 were compared against NAG 2008 and data in year 2015 and 2016 were compared against NAG 2014. Abbreviation: NAG - National Antibiotic Guidelines

Discussion

This was a retrospective study on the use of carbapenem and cephalosporin antibiotics from June 2014 to June 2016 in HRC. The result of this study describes the prescribing and resistance patterns of carbapenems and cephalosporins in HRC, and examined whether these antibiotics were used in concordance to the NAC.

During the study period, Ceftazidime was found to be the most prescribed cephalosporin antibiotics. According to NAG 2014, there was an increment in the use of cephalosporins from 2009 to 2013 in all hospitals in Malaysia where it showed increment of 13.25% (12). Malpani *et al*. in her study investigated the utilisation of antibiotics in the hospital and found that cephalosporins were the most commonly used class of antibiotic (5). This showed that broad spectrum antibacterials were more likely to be chosen as the preferred antibiotic among the prescribers. Other considerations that should be acknowledged in antibiotic selections are clinical skills and local sensitivity pattern, adequate knowledge of the pharmacokinetic properties of the antibiotics and factors such as age, allergies and others (13).

Urinary tract infection (UTI) was the most common infection that has been treated with antibiotics in this study, followed by antimicrobial prophylaxis for urodynamic studies (UDS) and pneumonia. This was an opposite trend compared to other studies. For example, a survey by Ali MH *et al*. showed that 41.4% and 28.3% of patients in Newcastle and Edinburgh respectively, were admitted to the ward due to UTI and 78.9% and 48.4% of patients, were admitted due to community acquired pneumonia (14).

ESBL-producing pathogens, particularly *Klebsiella* pneumonia were highly sensitive towards carbapenems in which the sensitivity rate was 100%. However the pathogens were resistant towards all cephalosporins. NAG 2014 showed that a six-year trend (2008 – 2013) of antimicrobial resistant for *Klebsiella pneumoniae* against selective antibiotics in all hospitals in Malaysia was increasing towards the preference of using carbapenem group of antibiotics (12). A clinical update from Paterson and Bonomo stated that carbapenems should be the drug of choice for ESBL-producing organisms as many clinical experienced has been reported before. Some of the published papers showed great use of imipenem compare to meropenem, despite having slightly lower minimum inhibitory concentrations (MICs) as compared to meropenem (15). For non-ESBL infection, except for cefotaxime, the sensitivity rate of carbapenem and cephalosporin antibiotics in HRC was above 50% in our study.

When compared against the NAG, majority of the antibiotics in this study were prescribed according to the guideline. However, Ceftazidime, which was the most prescribed cephalosporin antibiotics, was given as an antimicrobial prophylaxis for UDS in 80% of the cases which was not in concordance to the NAG. There were no new antibiotic recommendations in NAG 2014 as compared to NAG 2008 for UDS (11,12). Although the antibiotic selection for UDS was not in concordance to NAG, these antibiotics had been used in other studies. When using antibiotic prophylaxis in UDS, consideration has to be made whether it benefits the patients in decreasing the post-intervention bacteriuria and other bacterial related complications. A systematic review by Bootsma *et al*. revealed that there was not enough evidence to support the systematic use of antibiotic prophylaxis to prevent UTI in other procedures except for transurethral resection of prostate (TURP) and prostate biopsy (16).

While NAG suggested that antibiotic prophylaxis for urodynamic study is not recommended except in high risk cases, Ceftazidime has been used widely in HRC for UDS. The use of this antibiotic was mainly due to the preference of the clinicians to give antibiotic prophylaxis as negative urinalysis does not eliminate the possibility of post-procedure UTI. Grab M mentioned in his study that for UDS, the antibiotic of choice were fluoroquinolones and trimethoprim-sulphamethoxazole (TMP-SMX) while aminoglycosides, ampicillin and first generation or second generation cephalosporins were the alternatives (17). Another study by Kartal *et al*. showed that the incidence of UTI after UDS was decreased from 14% to 1% when the patients were given prophylaxis dose of ciprofloxacin. There was significant rate of bacteriuria seen after UDS in patients without prophylaxis of ciprofloxacin and the risk factors were identified to be not giving prophylaxis antibiotic before UDS, antibiotic use previously and the presence of pyuria before UDS (18).

Conclusion

This study evaluated the use of carbapenem and cephalosporin antibiotics in HRC. In conclusion, ceftazidime was the most prescribed cephalosporin group of antibiotics in the ward followed by meropenem in carbapenem group. As just slightly more than half of the antibiotics were prescribed in concordance to the NAG, It is recommended to improve physicians' adherence to the national guidelines to reduce the emergence of antibiotic resistance. Collaboration among the doctors, pharmacists, and supporting staffs in programmes such as the Antibiotic Stewardship Program is needed to optimise the use of antibiotics, reduce antibiotic resistance and improve patient outcomes.

Acknowledgement

We would like to thank the Director General of Health, Ministry of Health Malaysia for his approval to publish this article. We would also like to thank the Deputy Director of Health (Pharmacy) JKWPKL&P and the Director of Hospital Rehabilitasi Cheras for approving and supporting us to conduct and publish this research. Last but not least, we would like to thank the head of Records Department, and the staff who have been supportive during our data collection period that had taken place in their unit.

Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

References

1. Erbay A, Bodur H, Akinci E, Colpan A. Evaluation of antibiotic use in intensive care units of a tertiary care hospital in Turkey. J Hosp Infect. 2005,59:53–61.
2. Meletis G. Carbapenem resistance: Overview of the problem and future prespectives. Therapeutic Advances in Infectious Disease. 2016, 3(1):15-21.
3. Bajis S, Van der Bergh R, De Bruycker M, Mahama G, Van Overloop C, Satyanarayana S, Bernardo RS, Esmati S, Reid AJ. Antibiotic use in a district hospital in Kabul, Afghanistan: are we overprescribing? Public Health Action 2014, 4(4): 259–264.4.
4. Ahiabu MA, Tersbol BP, Biritwum R, Bybjerg IC, Magnussen P. A retrospective audit of antibiotic prescriptions in primary health-care facilities in Eastern Region, Ghana. Health Policy and Planning, 2016, 31:250–258.
5. Malpani AK, John NN, Srividya VL, Santoshi Y and Paul S: A broad survey and comprehensive study on utilization pattern of Antibiotics in Tertiary Care Teaching Hospital in North Karnataka. *Int J Pharm Sci Res* 2013; 4(2); 628-632.
6. Lim VKE, Cheong YM, Suleiman AB. Patterns of antibiotic usage in hospitals in Malaysia. Singapore Med J 1993, 34: 525-528.
7. Cheras Rehabilitation Hospital, Federal Territory of Kuala Lumpur and Putrajaya, Ministry of Health Malaysia. *Cheras Rehabilitation Hospital Antibiotic Audit 2015*. Unpublished. 2015.
8. Adnan A., Overcoming antibiotic resistance in the hospital: A never ending battle, Med & Health Rev 2008,1:29-44.
9. Russell AD, Tattawasart U, Maillard JY, Furr JR. Possible link between bacterial resistance and use of antibiotics and biocides. Antimicrobial Agents and Chemotherapy. 1998, 42:2151.
10. Cheong Y.M, Lim V.K.E, Jegathesan M, Suleiman A.B, Antimicrobial Resistance in 6 Malaysian General Hospitals, Med J Malaysia 1994, 49: 4.
11. Ministry of Health Malaysia. *National Antibiotic Guideline 2008*. 2008.
12. Ministry of Health Malaysia. *National Antibiotic Guideline 2014*. 2014.
13. Lim VKE. The rational use of antibiotics. Med J Malaysia 1998, 53 (2).
14. Ali MH, Kalima P and Maxwell SRJ. Failure to implement hospital antimicrobial prescribing guidelines: a comparison of two UK academic centres. Journal of Antimicrobial Chemotherapy. 2006, 57:959–962.
15. Paterson DL and Bonomo RA. Extended-Spectrum B-lactamases: a clinical update. Clin Mircrobiology Review. 2006. 18(4):667-686.

16. Bootsma AM, Laguna Pes M., Geerlings, SE and Goossens, A. Antibiotic Prophylaxis in Urologic Procedures: A Systematic Review. EurUrol 2008; 54(6): 1270-86.
17. Grab, M. Antibiotic prophylaxis in urological surgery, a European viewpoint. International Journal of Antimicrobial Agents. 2011.
18. Kartal ED et al. Effectiveness of ciprofloxacin prophylaxis in preventing bacteriuria caused by urodynamic study: A blind, randomized study of 192 patients. Urology. 2006. 67(6):1149-1153.

Comparative Evaluation of International Normalized Ratio (INR) Monitoring Between Point-Of-Care (POC) and Laboratory-Based Testing Methods in Patients Receiving Warfarin Therapy in Sultanah Nur Zahirah Hospital

Nurul Najmi Muhammad[1], Rafidah Abd Razak[1], Fong Chui Wei[1], Siti Rahayu Othman[1], Mahfuzah Ishak[1], Mohd Amirul Arif Yaakub[1], Norsima Nazifah Sidek[2], Liyana Ahamad Fouzi[2]

[1] Hospital Sultanah Nur Zahirah, Terengganu, Ministry of Health Malaysia, [2] Clinical Research Centre, Hospital Sultanah Nur Zahirah, Terengganu, Ministry of Health Malaysia

Abstract

Introduction: Monitoring of patients receiving warfarin therapy is done by monitoring their International Normalised Ratio (INR) value, either by using the point-of-care testing (POC-T) or laboratory method. However, there are greater variations at higher INR value as claimed by POC-T device provider.

Objective: The study aimed to compare the INR results obtained using POC-T and laboratory based method and to determine the cut-off point for high INR values generated by POC-T device that should mandate confirmatory testing with the laboratory method.

Methods: This retrospective cross-sectional study involved patients attending the INR clinic from 1 June 2016 to 30 May 2017 who had their INR values tested by both the POC-T method and laboratory-based method on the same day. Data was analysed using SPSS version 20 with $p<0.05$ was considered statistically significant. The INR results were compared using correlation analysis and Bland-Altman plot.

Results: A total of 118 patients were included in the study with 236 INR values analysed. There was a statistically significant difference between the INR values obtained by the POC-T (3.87, standard deviation (SD) 1.71) and laboratory-based method (2.88, SD 1.11) ($p < 0.05$). The INR values by POC-T method were significantly correlated to the laboratory method ($r = 0.875$, $p<0.01$). The INR values measured by POC-T exhibited positive bias as the INR values increased, particularly when INR readings were higher than 4.0.

Conclusion: Our findings suggested that POC device is a reliable tool for INR monitoring when the INR value is below 4.0. As the INR values generated by the POC-T device exhibited bias at higher INR values, a repeat test using laboratory method must be considered when the INR is 4.0 or higher.

Keyword: warfarin, INR, POC-T

NMRR ID: NMRR-17-1158-34535

Corresponding author: Nurul Najmi Binti Muhammad
Department of Pharmacy, Hospital Sultanah Nur Zahirah, Jalan Sultan Mahmud, 20400 Kuala Terengganu, Terengganu
Email: nurulnjm@gmail.com

Introduction

Warfarin is one of the oral anticoagulation drugs most commonly prescribed for atrial fibrillation, heart valve replacement or venous thromboembolism (1). Meticulous monitoring of patients receiving warfarin therapy is important due to the drug's narrow therapeutic range, which is typically measured by the International Normalised Ratio (INR). Sub therapeutic anticoagulation can increase the risk of clot formation, thus increasing the chance of stroke or venous thromboembolism, while supra therapeutic anticoagulation increases the risk of bleeding.

The standard method for INR monitoring is laboratory testing of blood obtained by venipuncture. The blood samples are collected into citrate tubes, centrifuged and plasma is loaded on to coagulation analyser. The time taken from the time patient walks in to the laboratory to reporting is approximately 40 – 60 minutes. Alternatively, there is an easier method to monitor INR value which is using the point-of-care (POC) device. POC testing (POC-T) for INR involves putting a sample of whole blood, usually capillary blood from a finger

prick, onto a test strip. The INR result will be produced within two minutes and this is much faster as compared to the laboratory-based method. The immediate results obtained using POC-T will allow rapid adjustment of warfarin dose as compared with more complex laboratory-based method (2-4). This will increase patient convenience, improve the clinical outcomes, reducing patients' waiting time in clinic and reduce health care resources use. However, there have been several documented limitations regarding the accuracy and precision of POC devices. Previous studies (5,6) found that INR measurements generated by POC device exhibit positive bias when compared with the laboratory-based method as INR values increased. Having a predetermined INR cut-off value for mandatory venipuncture and laboratory-based method in INR determination may potentially decrease the frequency of avoidable thromboembolic events and improve patient safety.

In Sultanah Nur Zahirah Hospital (HSNZ), Kuala Terengganu, patients that receive warfarin therapy will be referred to the INR clinic for their follow up visits. The INR clinic is currently managed by a pharmacist, which is also called as a Medication Therapy Adherence Clinic (MTAC), and supervised by the Medical Officer of Medical Department HSNZ. During the clinic visits, the pharmacist manages the appointments, interviews and counsels the patient, performs finger prick tests to measure patient's INR on a POC device, adjusts warfarin dose based on the INR values, refers patients to doctors if indicated, and completes all appropriate documentations.

There are two types of INR testing used in HSNZ which are clinic-based POC testing and laboratory-based testing. In the clinic-based testing, finger prick will be done by the clinic pharmacist to obtain a drop of blood to be put onto the POC device (Coaguchek XS Pro ®, Roche Diagnostics, Indianapolis, Indiana) and the INR result will be obtained within 2 minutes. The INR result will be recorded in the patient's Electronic Medical Record (EMR) in Hospital Information System and Patient's Attendance Book (*Buku Kehadiran Pesakit*). In the laboratory-based testing, venous blood sample will be taken by venipuncture and sent to the laboratory to be analysed using the STAGO STA Compact ® (Diagnostica STAGO Inc, Parsippany, New Jersey). INR result with laboratory method will be obtained within an hour and reported in the patient's EMR. As a routine procedure of INR clinic, POC and laboratory INR will be done for an average of five patients on the same day of every month to monitor the performance of the POC device. As part of the INR clinic's procedure, any patient whose POC-measured INR exceeded 4.0 will have a venipuncture sample sent to the laboratory to double confirm the INR value. In this case, INR measured by laboratory method will be used to guide warfarin dose adjustment.

The data from our routine monitoring of the POC device in the INR clinic from September 2016 to December 2016 highlighted that out of 127 patients whose POC-measured INR were higher than 4.0, the confirmatory INR results using the laboratory method showed that 31.5% of the patients have the INR value within therapeutic range. Because of that, the patient safety might be compromised since clinicians might reduce the warfarin dose if the confirmatory test with laboratory method was not done leading to increased risk of thromboembolic events. Thus, this study aimed to compare the INR results obtained by the POC-T with laboratory based method and to determine the cut-off point for INR values generated by the POC-T device that should mandate confirmatory testing with the laboratory method.

Methods

Study Design and Population

This cross-sectional study was conducted at HSNZ, Kuala Terengganu. Data of patients were reviewed retrospectively. This study included patients who attended the INR clinic of HSNZ between 1 June 2016 and 30 May 2017. The inclusion criteria were patients aged at least 18 years old, who had their INR values tested by both the POC-T method and laboratory-based method on the day which the routine procedure was conducted every month to monitor the POC device. The exclusion criteria were pregnancy and POC INR result higher than 8.0 at the time of assessment since the POC device cannot measure INR more than 8.0.

The POC device used in the INR clinic of HSNZ was Coaguchek XS Pro ® (Roche Diagnostics, Indianapolis, Indiana) while the standard laboratory analyser in the HSNZ laboratory was STAGO STA Compact ® (Diagnostica STAGO Inc, Parsippany, New Jersey).

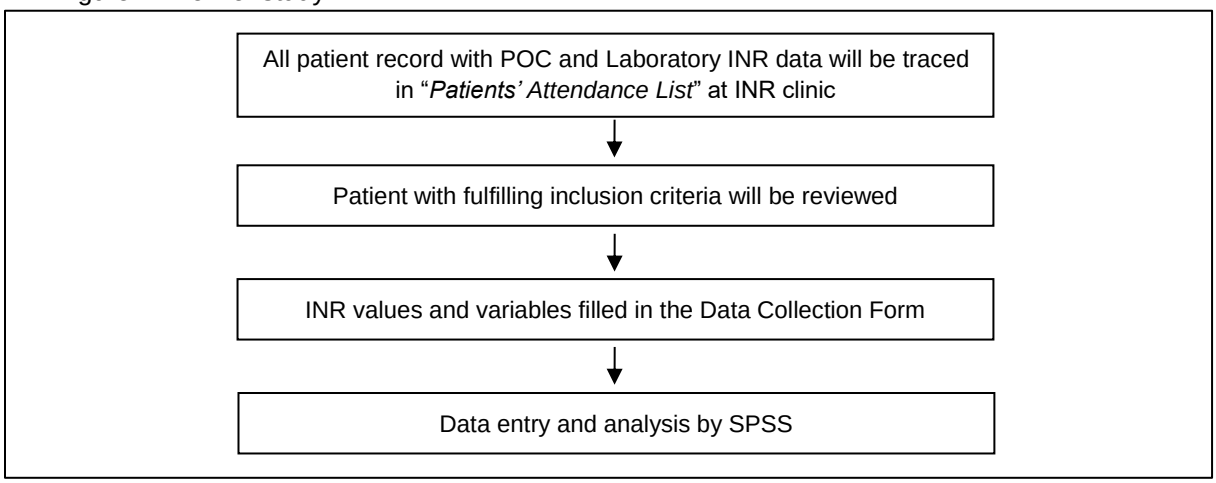
Data Collection and Analysis

Data collection was carried out over 2 months from 15 July 2017 to 15 September 2017. The "*Patients' Attendance List*" maintained at the INR clinic was checked to identify all patients with both POC and laboratory INR data between 1 June 2016 and 30 May 2017. Patients fulfilling the study criteria were included as the subjects for this study.

A specified data collection form was used for data collection. The required information were collected from the patients' EMR in the HIS system. The variables collected for this study were age, gender, race, indication of Warfarin, INR target range and both POC and Laboratory INR values. The INR values that were obtained using the POC device in the INR clinics were collected from the clinic's "*Patients' Attendance List*" while the INR value obtained using the laboratory-based method were traced electronically from the patients' EMR in the HIS system.

The INR results were compared using Pearson correlation and Bland-Altman plot. Data was analysed using SPSS v.20 with $p<0.05$ was considered statistically significant. The flow of the study was summarised in Figure 1.

Figure 1: Flow of study



Results

The data of 118 subjects were collected and 236 or 118 pairs of INR readings were analysed. The mean age of the included patients was 60.7 years old (standard deviation (SD) 14.8). The demographics of the populations evaluated were listed in Table 1. The mean INR values of the POC-T method and laboratory method were listed in Table 2. There was a statistically significant difference between the INR values obtained by the POC-T (3.87, standard deviation (SD) 1.71) and laboratory-based method (2.88, SD 1.11) ($p < 0.05$).

Figure 2 showed the correlation between INR values obtained with POC-T and laboratory method. The INR values of the POC-T were significantly correlated with the laboratory INR values ($r = 0.875$, $p < 0.01$). Even though good correlation was obtained, the use of the correlation coefficient may be misleading in comparing the agreement between the two methods of INR analysis. Therefore, the Bland-Altman plot was used to compare the INR results obtained by these two methods.

The Bland-Altman plot showed that POC-T tended to overestimate the INR compared to the laboratory-based method and the degree of overestimation increased as the INR value increased. The two methods had better agreement (less scattered) when the INR values were less than 3.0. The plots were more scattered and there were more outliers, which meant that the two measurements were less comparable, when the INR values were higher than 4.0. The mean differences calculated showed agreement with the rough variations formula given by the POC device provider (7) (Table 3).

Table 1: Patient demography (N=118)

Parameter	Frequency
Age, years, mean (SD)	60.7 (14.8)
Gender, n (%)	
Female	64 (54.2)
Male	54 (45.8)
Race, n (%)	
Malay	112 (94.9)
Chinese	6 (5.1)
INR Target, n (%)	
2.0 – 3.0	100 (84.7)
2.5 – 3.5	17 (14.4)
3.0 – 4.0	1 (0.8)
Indication, n (%)	
Atrial fibrillation	83 (70.3)
Heart valve replacement	17 (14.4)
Deep vein thrombosis	7 (5.9)
Pulmonary embolism	2 (1.7)
Left ventricular clot	5 (4.2)
Antiphospholipid syndrome	3 (2.5)
Occlusion of Fontan	1 (0.8)

Abbreviation: INR – International Normalised Ratio; SD – standard deviation

Table 2: INR values by POC-T and laboratory method

Parameter	POC-T	Laboratory	p value
INR, mean (SD)	3.87 (1.71)	2.88 (1.11)	$p < 0.05$ [b]
Difference, mean (SD) [a]	0.98 (0.91)		

[a] t-test, [b] statistically significant

Abbreviation: INR – International Normalised Ratio; POC-T – point-of-care testing

Figure 2: Pearson correlation between INR values obtained with POC-T and laboratory-based method

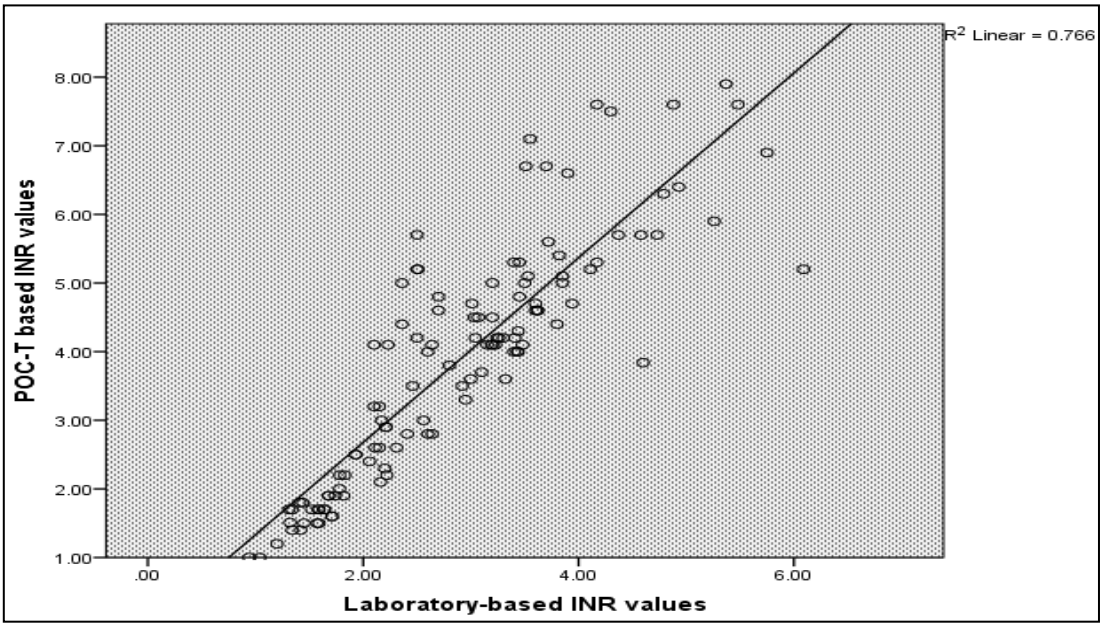


Figure 3: The Bland-Altman plot comparing the INR values measured by POC-T and laboratory-based method

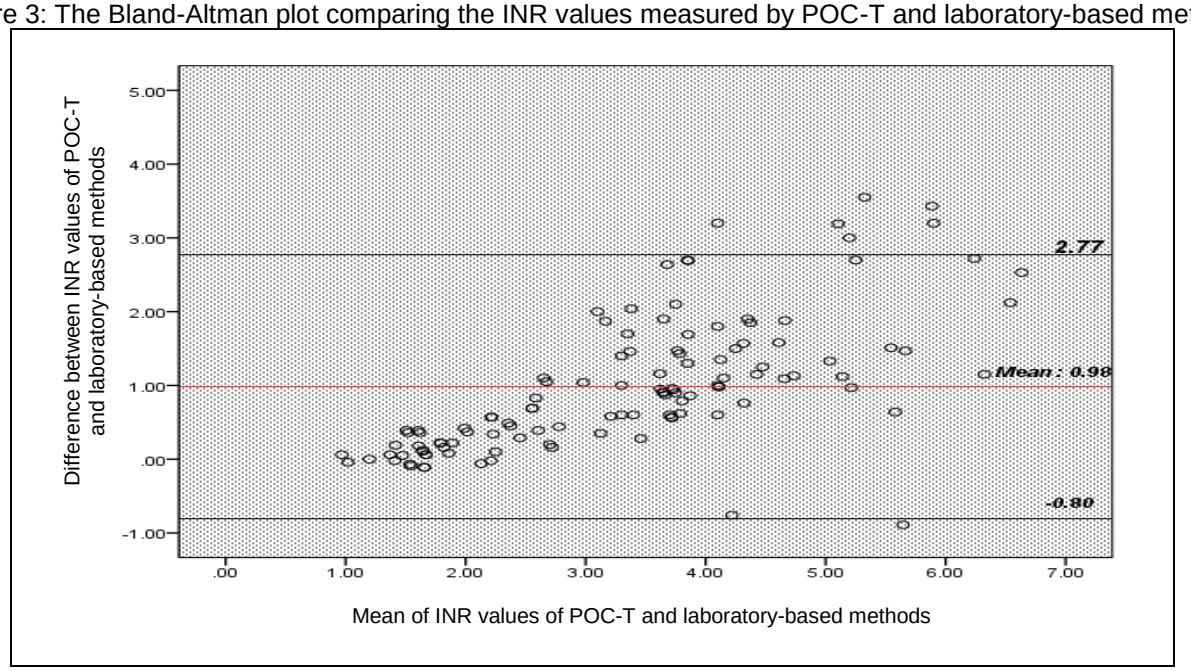


Table 3: Mean differences calculated in INR ranges compared with the rough variation formula

INR	Mean INR		INR Difference	Rough variation [a]
< 2.5	POC LAB	1.71 1.58	0.13	0.1-0.3
2.5 – 4.5	POC LAB	3.67 2.89	0.78	0.5-1.0
> 4.5	POC LAB	5.59 3.77	1.82	1.0-2.0

[a] provided by the POC device provider (7)

Discussion

Donaldson *et al*. reported that the INR values measured by POC-T device correlated well with the laboratory testing, with the correlation coefficient (r) of 0.949 (6). In comparison, we calculated a lower correlation coefficient of 0.845. Our analysis of 118 paired of INR samples included 29 pairs that differed by more than 1.0 unit, thus skewed the overall correlation analysis. Nevertheless, the correlation coefficient of 0.875 has shown that the INR values obtained using POC device and laboratory-based method had strong positive correlation. Even though POC-T and laboratory method has a strong correlation, there was a disagreement between the two methods as shown by the t-test, and the Bland-Altman plot was used to show where the disagreement occurred.

In this study, we found that the INR values measured by POC device exhibited positive bias as the INR values increased, especially when INR values were higher than 4.0. Out of the 65 POC-T measured INR readings that were 4.0 or higher, 41.5% of the repeated assessment with laboratory method had shown that the INR values were actually within the therapeutic range. This observation may have potentially profound clinical implications. Without the awareness of positive bias, clinicians might reduce the dose of warfarin based on POC-T measurement and this could lead to the increased risk of thromboembolic events.

The Bland-Altman plot showed that the POC-T tended to overestimate the INR compared to the laboratory measurement and the degree of overestimation increased as the INR values increased. Our results were consistent with other previous studies which also observed positive bias of INR measurements when comparing the POC-T and laboratory-based method (5-6,8). However, we found more outliers with more scattered Bland-Altman plot when the INR values were greater than 4.0, as compared to other studies. The

factors that influence the INR values includes genetic, diet, concomitant disease and other concurrent medications (9,10).

Despite the positive bias that may happen when the INR is above 4.0, the POC-T is a suitable alternative to the laboratory assessment of INR as they have comparable accuracy and the measured INR values were found to be in agreement with the laboratory-measured INR values when the INRs were below 4.0 (8). POC devices will increase patient convenience and can help to reduce healthcare resources. Based on our study finding that was consistent with the previous study (5), an INR of 4.0 should be recommended as the cut-off point that mandates a repeated INR test using the laboratory method.

Conclusion

The findings of this study suggested that the POC device is a reliable tool for INR measurement when the INR is lower than 4.0. As the INR values generated by POC-T device may exhibit bias at INR more than 4.0, a repeated test using the laboratory method should be made mandatory when INR is above this value.

Acknowledgement

We would like to thank the Director General of Health Malaysia for his permission to publish this article. The authors would also like to acknowledge the Medical Department and Pathology Department of Sultanah Nur Zahirah Hospital for their assistance in this study.

References

1. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 2012; 141:152-184.
2. Zimmerman CR. The role of point-of-care anticoagulant monitoring in arterial and venous thromboembolic disorders. *J Thromb Thrombolysis*. 2000; 9:187-98.
3. Gosselin R, Owings JT, White RH, Hutchinson R, Branch J, Mahackian K, Johnston M, Larkin EC. A comparison of point-of-care instruments designed for monitoring oral anticoagulation with standard laboratory methods. *J ThrombHaemost*. 2000; May; 83(5):698-703.
4. Celenza A, Skinner K. Comparison of emergency department point-of-care international normalized ratio (INR) testing with laboratory-based testing. *J Emerg Med*. 2011; 28:136-140.
5. Dorfman DM, Goonan EM, Boutilier MK, Jarolim P, Tanasijevic M, Goldhaber SZ. Point-of-care (POC) versus central laboratory instrumentation for monitoring oral anticoagulation. *J Vascular Medicine*. 2005; 10:23-27.
6. Donaldson M, Sullivan J, Norbeck A. Comparison of international normalized ratios provided by two point-of-care devices and laboratory-based venipuncture in a pharmacist-managed anticoagulation clinic. *Am J Health Syst Pharm*. 2010 Oct; 1;67(19): 1616-22.
7. Operator Manual, Coaguchek XS Pro, Version 5.0, 2013-12.
8. Havrda DE, Hawk TL, Marvin CM. Accuracy and precision of the coaguchek S versus laboratory INRs in a clinic. *Ann Pharmacother*. 2002; 36:769-775.
9. Jorgensen AL., Al-Zubiedi S, Zhang JE, Keniry A, Hanson A, Hughes DA, Pirmohamed M. Genetic and environmental factors determining clinical outcomes and cost of warfarin therapy: a prospective study. Pharmacogenetics and genomics, 2009; 19(10), 800–812.
10. White PJ. Patient factors that influence warfarin dose response. Journal of Pharmacy Practice, 2010; 23(3):194-204.

Comparing the Clinical Effectiveness of Levothyroxine Intake before Breakfast versus at Bedtime in Patients with Hypothyroidism

Mohd Farizh Che Pa[1], Saodah Yaacob[1], Simrenjit Kaur Gurnam Singh[1], Noor Lita Adam[2]

[1] Pharmacy Department, Hospital Tuanku Ja'afar Seremban, Negeri Sembilan, Ministry of Health Malaysia; [2] Medical Department, Hospital Tuanku Ja'afar Seremban, Negeri Sembilan, Ministry of Health Malaysia

Abstract

Introduction: Levothyroxine is the treatment of choice for hypothyroidism. Several studies have explored Levothyroxine administration at bedtime as an alternative dosing regime to the traditional morning regime and reported improvements in thyroid functions.

Objective: This study aimed to compare the clinical effectiveness of Levothyroxine administration, either in the morning or at bedtime, on the serum thyroid stimulating hormone (TSH) and thyroxine (T4) levels as well as to determine the effect of Levothyroxine administration time on patients' quality of life (QoL).

Method: A quasi interventional study was conducted at the Endocrinology Clinic of Tuanku Ja'afar Seremban Hospital from July to October 2017. Recruited hypothyroid patients were allocated to either before breakfast or at bedtime Levothyroxine regime. The primary outcomes measured were the changes in TSH and T4 levels and the patients' QoL was assessed using the 36-Item Short Form Survey (SF-36) instrument. The outcomes were measured before the beginning of the study and after 12 weeks.

Results: Thirty-five patients completed the 12-week study period. The serum TSH and T4 level showed improvement in the bedtime regime group, in which the mean TSH level reduced from 2.5mIU/L (standard deviation (SD) 1.3mIU/L) to 1.8mIU/L (SD 1.0mIU/L) (p=0.13) while the mean T4 level increased from 15.3pmol/L (SD 2.7pmol/L) to 15.7pmol/L (SD 3.3pmol/L) (p=0.51). However, these differences were not statistically significant when compared with the morning regime group. Patients in both regimes reported statistically significant improvements in three SF-36 QoL parameters after twelve weeks namely role limitations due to physical problems, social functioning and pain. The QoL scores differences between the two groups after twelve weeks, however, were not statistically significant.

Conclusion: Our study showed that administration of Levothyroxine at bedtime could be an alternative dosing regime to the traditional morning regime which could potentially improve patients' thyroid profiles and QoL.

Keywords: Levothyroxine, hypothyroidism, before breakfast, at bedtime

NMRR ID: NMRR-17-1179-36125

Corresponding author: Mohd Farizh Che Pa
Pharmacy Department, Hospital Tuanku Ja'afar, 70300 Rasah, Seremban, Negeri Sembilan
Email: farizh@moh.gov.my

Introduction

Thyroid hormones, iodine-containing thyroxine (T4) and triiodothyroxine (T3) are regulated by the hypothalamic–pituitary–thyroid gland (HPT) axis through a negative feedback mechanism (1,2). Low concentrations of serum T4 and T3 hormones triggers the release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid stimulating hormone (TSH) from the pituitary gland (3). TSH then stimulates the thyroid follicular cells on the thyroid gland to synthesis T4 and T3 and increases their concentration in the bloodstream. An increase in serum concentrations signals the inhibition of TRH and TSH release via the negative feedback mechanism (4).

The predominant hormone produced by the thyroid gland is T4 and only approximately 20% of the hormones produced are T3 which is the hormone required by the body. The production of the T3 hormone by the thyroid gland is insufficient to meet the daily requirements of the body and therefore, the remaining 80% is obtained from the peripheral conversion of T4 to T3 by enzyme deiodinase. The metabolically active T3 hormone has a 10-fold greater affinity for thyroid receptors in the organs and is responsible in mediating the physiological functions of thyroid hormone in the body (5).

Hypothyroidism is a common endocrine disorder in which the body lacks sufficient thyroid hormone. The prevalence of hypothyroidism increases with age, with more than 10% of the women of over 60 years having subclinical hypothyroidism (6). There can be many factors contributing to hypothyroidism namely autoimmune disease such as Hashimoto's thyroiditis, surgical removal of the thyroid, radiation treatment, other medications and either too much or too little iodine which is necessary for the production of thyroid hormone. Regardless of the factors contributing to the condition, Levothyroxine is the first line treatment for hypothyroidism (7).

However, the oral intake of Levothyroxine should follow a few restrictions to ensure the optimal therapeutic efficacy of the drug. Levothyroxine absorption is the lowest when taken with food (8). Therefore, patients are advised to take the drug before breakfast. However, in reality patients wait a varying length of time before eating food and this may have an effect on compliance. Besides that, the consumption of coffee when the day begins may also influence Levothyroxine absorption. Levothyroxine is also known to interact with other medications such as cholestyramine resin, sucralphate, iron sulphate, calcium preparations, aluminium antacids, raloxifene, activated charcoal, various soya products, as well as food and herbal remedies (9).

Several studies have explored Levothyroxine administration at bedtime as an alternative dosing regime to the traditional morning regime and had reported marked improvements in the thyroid functions (10-12). Therefore, the aims of this study were to compare the clinical effectiveness of Levothyroxine administration taken in the morning or at bedtime on the serum TSH and T4 levels, and to determine the effect of different administration time of Levothyroxine on patients' quality of life (QoL).

Method

Study Design and Setting

A quasi, interventional study was conducted in a state hospital, Tuanku Ja'afar Seremban Hospital (HTJS) in Malaysia. This study was conducted in the Endocrinology Clinic from July 2017 to October 2017. The study protocol was reviewed and approved by the Ministry of Health Malaysia Medical Research Ethics Committee (MREC) and was registered in National Medical Research Register (NMRR).

Clinical effectiveness was defined as the improvement in thyroid hormones levels (TSH and T4). Patients were divided into two groups representing the morning and bedtime regime. Patients in the morning regime was required to take their dose of Levothyroxine at 8.30am and patients in the bedtime regime was required to take their dose of Levothyroxine at 10pm. For patients who find it hard to adjust their lifestyle to the suggested timing, they were advised to consume Levothyroxine 30 minutes before breakfast and 1 hour before retiring to bed according to the regime they are assigned too.

The primary outcomes measured were the changes in thyroid hormone levels (TSH and T4) while the secondary outcomes measured were QoL, serum creatinine, liver function, body mass index (BMI), heart rate and blood pressure. Patient's quality of life was assessed using the 36-Item Short Form Survey Instrument (SF-36). Patient's baseline thyroid profiles (TSH and T4 level) and patients' quality of life were taken prior to the start of the study and after 12 weeks. The data collected was analysed using the Statistical Package for the Social Sciences (SPSS). Multiple paired t-test was used to demonstrate the differences between the study groups.

Patient Recruitment

All patients age 18 and above who were diagnosed with primary hypothyroidism of any cause, are consistent with their follow ups at the clinic, able to swallow tablets without any difficulty and consistent on the same dose of Levothyroxine for 6 months before study enrolment were recruited.

Pregnant woman and lactating mother were excluded. Patients who were taking the following drugs concomitantly, such as oestrogen / progesterone replacement therapy, oral contraceptives, testosterone replacement, or tamoxifen within the last 3 months, bile acid sequestrants, aluminium hydroxide antacids, sodium polystyrene sulfonate, cholestyramine, colestipol, raloxifene, high-fibre diets, and diets high in soy were excluded. Patients on medications that may potentially affect the serum TSH concentrations, such as steroids, T3 preparations, dopamine analogues, or somatostatin analogues, and taking medications affecting

thyroid hormone metabolism such as phenytoin, carbamazepine, sertraline, and rifampicin were also excluded.

Patient's Compliance

To ensure the patients' compliance, each patient was supplemented with a copy of patient diary where the patient was required to record the time of Levothyroxine consumptions throughout the study period. This served as a mean to identify whether the patients had consumed their Levothyroxine medication in the correct way. The importance of self-reporting about their adherence was explained to the patients. The recruited patients were also required to bring along their refill prescriptions for Levothyroxine to ensure that they had refilled their prescriptions according to the To Come Again (TCA) appointment note from the pharmacy.

Results

A total of 35 patients fulfilled the inclusion and exclusion criteria in this study and completed the 12-week study period. The gender ratio of male to female was 1:10 in the morning group and 1:1.6 in the bedtime group. The Shapiro-Wilk Test showed that the age of patients was normally distributed (p=0.244). The patients' age had a range of 52 years between 18 and 70 years old in the morning group while the bedtime group had a range of 56 years between 19 and 75 years old. Malay was the most common ethnic group in this study followed by Indian and Chinese. However, there were no Chinese patients in the bedtime group.

Table 1: Demographics and baseline characteristics of the study population (N=35)

Characteristics	Morning Group (n=22)	Bedtime Group (n=13)
Gender, n		
Male	2	5
Female	20	8
Age, mean (SD), year	43.7 (14.2)	49.0 (19.5)
Elderly status, n		
Elderly (> 60)	3	4
Non-elderly (18-60)	19	9
Race, n		
Malay	10	9
Chinese	4	0
Indian	8	4
BMI, kg/m^2, mean (SD)	23.6 (4.2)	26.7 (5.3)
Weight Classification, n		
Underweight	7	2
Normal	1	4
Overweight	5	2
Pre-obese	6	4
Obese	3	1
Cigarette-smoking status, n		
Yes	0	3
No	21	10
Ex-smoker	1	0
Alcohol status, n		
Yes	0	0
No	22	13
Aetiology of hypothyroidism, n		
Hashimoto disease	0	2
Post-radioactive Iodine 131	5	6
Thyroidectomy	10	
Others	7	0
Patients who used other medications		
Yes	15	8
No	7	5
Duration of hypothyroidism, year, median (IQR)	4.5 (5.0)	5.0 (5.0)
Levothyroxine dosage, µg, median (IQR)	75 (56)	75 (50)
TSH level, mIU/L, mean (SD)	1.6 (1.1)	2.5 (1.3)
Free thyroxine, T4 level, pmol/L, mean (SD)	15.8 (3.7)	15.2 (2.6)

Abbreviation: BMI – body mass index; SD – standard deviation; IQR – interquartile range

The mean BMI for morning group was in the overweight category while the bedtime group was in the obese category. Most of the patients in both groups did not smoke and none of them drank alcohol. In the morning group, the mode aetiology of hypothyroidism was thyroidectomy while bedtime group was post-radioactive Iodine 131. Other aetiology includes unspecified hypothyroidism, autoimmune hypothyroidism, congenital hypothyroidism, postpartum hypothyroidism, primary hypothyroidism, subclinical hypothyroidism and thyroid lymphoma. The median duration of hypothyroidism and Levothyroxine dosage were not much different between the two groups. Concurrent medications were taken by 15 patients from the morning group and eight patients from the bedtime group. Among these 23 patients, nine patients took calcium supplement, two patients took iron supplement, 10 patients with vitamins supplement and 18 patients had other medications such as Amlodipine, Simvastatin, Metformin, Cardiprin, Gliclazide, Metoprolol, Bisoprolol, Perindopril, Omeprazole and Magnesium Trisilicate Mixture (MMT). Note that one patient might take more than one concurrent medication. The characteristics of patients at baseline were shown in Table 1.

The results of the primary and secondary outcomes were tabulated in Table 2 and Table 3 while the results on quality of life were summarised in Table 4. It was reported that at the end of 12 weeks, the bedtime regime showed a reduction in mean TSH level from 2.5mIU/L (SD 1.3mIU/L) to 1.8mIU/L (SD 1.0mIU/L) in comparison to the morning regime which showed an increase in TSH level, from 1.6mIU/L (SD 1.1mIU/L) to 2.0mIU/L (SD 1.4mIU/L). However, these changes were not statistically significant. The mean T4 level was reported to have a slight increase in the bedtime group from 15.3pmol/L (SD 2.7pmol/L) to 15.7pmol/L (SD 3.3pmol/L). In contrast, the morning group showed slight reduction from 15.8pmol/L (SD 3.73pmol/L) to 15.6pmol/L (SD 3.0pmol/L). Nevertheless, this was also not statistically significant. When comparing between the morning and bedtime group at the end of 12 weeks, it was found that there was no significant difference in the means of both TSH and T4 levels.

Secondary outcomes showed significant difference between means of the two groups in serum creatinine level (p=0.02) and BMI (p=0.04). There were no significant differences between the two study groups in term of albumin level, ALP level, ALT level and vital signs.

In referring to Table 4, the QoL assessment using the SF-36 instrument demonstrated an improvement of all parameters in the bedtime regime as compared to baseline except for general health. On the other hand, the morning regime group showed improvements in only a few parameters such as limitations due to physical and emotional problems, energy levels, pain and overall general health as compared to the baseline. There was no statistically significant difference between the two groups in terms of QoL scores.

Table 2: Comparison of biochemical parameters of the morning and bedtime groups at baseline and at the end of 12 weeks (N=35)

Biochemical parameters	Mean (SD)				Mean Difference (95% CI)		p value [a]	
	Morning Group		Bedtime Group		Morning Group	Bedtime Group	Morning Group	Bedtime Group
	Baseline	12 weeks	Baseline	12 weeks				
TSH level, mIU/L	1.6 (1.1)	2.0 (1.4)	2.5 (1.3)	1.8 (1.0)	-0.4 (-1.0, 0.2)	0.7 (-0.2, 1.6)	0.158	0.129
T4 level, pmol/L	15.8 (3.7)	15.6 (3.0)	15.2 (2.6)	15.7 (3.3)	0.2 (-1.5, 1.9)	-0.5 (-2.0, 1.1)	0.817	0.505
Creatinine, µmol/L	77.5 (27.4)	72.2 (16.7)	108.7 (30.5)	98.0 (30.9)	5.3 (-9.4, 20.1)	10.7 (-3.5, 24.9)	0.444	0.114
Albumin	39.2 (3.7)	40.5 (4.8)	37.2 (2.0)	42.5 (2.7)	-1.2 (-4.3, 1.8)	-5.3 (-8.2, -2.5)	0.396	**0.005**
ALP	68.3 (13.5)	67.8 (15.7)	81.3 (15.6)	88.7 (13.0)	0.6 (-5.3, 6.4)	-7.3 (-12.9, -1.8)	0.830	**0.019**
ALT	22.0 (8.9)	22.3 (10.0)	73.8 (69.5)	44.8 (43.1)	-0.3 (-5.0, 4.5)	29 (-1.5, 59.5)	0.909	0.058
BMI, kg/m2	23.6 (4.2)	23.2 (3.8)	26.7 (5.3)	26.6 (5.2)	0.3 (-0.1, 0.8)	0.1 (-0.3, 0.6)	0.155	0.543
Heart rate, beats/min	84.7 (12.3)	85.8 (11.2)	81.0 (18.8)	80.2 (15.5)	-1.0 (-8.8, 6.7)	0.8 (-5.6, 7.1)	0.781	0.796
SBP, mmHg	122.0 (18.0)	126.2 (21.4)	124.9 (21.6)	126.6 (17.1)	-4.3 (10.5, 2.0)	-1.7 (-10.7, 7.4)	0.169	0.691
DBP, mmHg	74.9 (8.5)	77.3 (8.0)	72.0 (8.9)	74.2 (9.0)	-2.5 (-4.8, -0.1)	-2.2 (-5.4, 1.1)	0.042	0.175

[a] Multiple paired t-test

Abbreviation: CI – confidence interval, SD – standard deviation

Table 3: Comparison of biochemical parameters of the morning and bedtime groups at the end of 12 weeks (N=35)

Biochemical Parameters	Mean (SD)		Mean Difference (95% CI)	p value [a]
	Morning Group	Bedtime Group		
TSH level, mIU/L	2.0 (1.4)	1.8 (1.0)	0.2 (-0.7, 1.1)	0.606
T4 level, pmol/L	15.6 (3.0)	15.7 (3.3)	-0.2 (-2.4, 2.0)	0.884
Creatinine, µmol/L	66.0 (17.9)	92.0 (33.2)	-26.0 (-46.5, -5.5)	**0.015**
Albumin	40.7 (4.4)	40.2 (4.8)	0.4 (-3.6, 4.5)	0.826
ALP	72.3 (26.7)	87.3 (12.4)	-15.0 (-37.2, 7.1)	0.172
ALT	21.3 (9.5)	42.6 (40.8)	-21.3 (-58.1, 15.6)	0.210
BMI, kg/m2	23.2 (3.8)	26.6 (5.2)	-3.3 (-6.4, -0.2)	**0.036**
Heart rate, beats/min	85.8 (11.2)	80.2 (15.5)	5.5 (-3.7, 14.8)	0.229
SBP, mmHg	126.2 (21.4)	126.6 (17.1)	-0.4 (-14.6, 13.8)	0.956
DBP, mmHg	77.3 (8.0)	74.2 (9.0)	3.1 (-2.8, 9.1)	0.289

[a] Multiple paired t-test

Abbreviation: CI – confidence interval, SD – standard deviation

Table 4: SF-36 QoL scores, expressed as mean (SD), of the morning and bedtime groups at the end of 12 weeks

SF-36 Item	Morning Group		Bedtime Group		p value [a]
	Baseline	12 weeks	Baseline	12 weeks	
Physical functioning	83.86 (11.54)	82.05 (9.84) (p=0.42)	81.54 (15.33)	85.00 (5.40) (p=0.51)	p=0.33
Role limitations due to physical problems	46.36 (34.58)	66.39 (22.77) **(p=0.04)**	51.92 (27.88)	75.00 (22.82) **(p=0.03)**	p=0.29
Role limitations due to emotional problems	53.25 (45.52)	71.75 (30.37) (p=0.11)	51.27 (35.01)	69.25 (21.36) (p=0.15)	p=0.80
Vitality	64.46 (15.75)	73.18 (8.10) **(p=0.02)**	72.31 (10.33)	73.46 (10.49) (p=0.75)	p=0.93
Mental health	82.00 (7.38)	79.36 (5.29) (p=0.16)	78.15 (5.32)	79.08 (7.15) (p=0.71)	p=0.89
Social functioning	80.68 (11.40)	73.77 (7.78) **(p=0.02)**	69.23 (10.96)	77.89 (12.70) **(p=0.10)**	p=0.24
Pain	68.75 (8.99)	76.82 (9.13) **(p=0.01)**	67.89 (11.13)	78.65 (7.75) **(p=0.01)**	p=0.55
General health	83.09 (10.45)	85.91 (10.76) (p=0.28)	80.15 (12.82)	79.58 (10.33) (p=0.61)	p=0.11

[a] Multiple paired t-test, showing the difference between the morning and bedtime groups at the end of 12 weeks.

Discussion

The findings of our study were consistent with that of Bolk *et al*. (2007) and Bolk *et al*. (2010) which suggested that the bedtime regime is superior at improving thyroid profiles compared to the morning regime, although our results were not statistically significant. A possible explanation for improvement of thyroid profiles in the bedtime group may be due to better absorption of Levothyroxine in the gut in the fasted state. Bolk *et al*. (2010) stated that 30 minutes before breakfast may not be sufficient to promote complete absorption of Levothyroxine in contrast to patient who take their medication 2 hours or later after dinner. A longer fasting state may have increased the bioavailability of the drug. Besides, higher secretion of gut gastric acid at night as opposed to morning may provide a feasible environment for the optimal absorption of Levothyroxine (10,11). Rajput *et al*. also mentioned that slower gastric motility at night contributed to increased bioavailability

of the drug for absorption and a reduction in the activity of deiodinase enzyme might change the pharmacokinetics of the drug (12).

Based on the results of our study, clinicians could inform patients with hypothyroidism that Levothyroxine intake at bedtime is a good alternative to the morning intake, as long as the Levothyroxine is taken on empty stomach. For patients who do not attain normal thyrotropin or free T4 levels with morning Levothyroxine intake, a switch to the bedtime regime can be recommended. Drug information resources and guidelines on the management of hypothyroidism require revisions in this respect (11).

Our study demonstrated that patients in both the morning and bedtime regimes reported statistically significant improvements in some of the SF-36 QoL parameters after twelve weeks of treatment including role limitations due to physical problems, social functioning and pain. The differences between the two groups in terms of QoL scores after twelve weeks, however, were not statistically significant. A similar finding was found by Samuels *et al*. (2018) who reported that changing the doses of Levothyroxine to alter TSH levels to low-normal, high-normal, or mildly elevated range did not affect the QoL of hypothyroid patients. Also, the authors noted that most published studies could not demonstrate significant changes in the QoL of subclinical hypothyroid subjects (13). Similarly, Tan *et al*. (2019) reported that the QoL of patients on Levothyroxine therapy for hypothyroidism was not associated with their clinical parameters and thyroid hormones levels, but poorer QoL was significantly associated with their co-morbidities and symptoms of hypothyroidism (14).

The available literature discussing the change in administration times in comparison to the efficacy of Levothyroxine mostly reported a study period of maximum of 12 weeks, which may not be sufficient to conclude if the change achieved in thyroid profiles is significant. Longer duration of study period should be conducted to identify the long-term effects. The lack of data available regarding the pharmacokinetics, the maximum serum concentration and the area under the concentration curve for thyroid hormones also makes it difficult to conclude if the night regime is an equivalent alternative dosing choice. An hourly serum concentration at time 0, 1, 2, 3, 6, 9, 12, 24 of Levothyroxine ingestion would probably mirror the change in thyroid profiles better rather than a cumulative concentration after 12 weeks (15). The lack of this information in the available literature makes it difficult to determine the exact mechanism of action of nocturnal efficacy of Levothyroxine. However, this process would incur an increase in cost, which may be difficult to fund.

Conclusion

Although not statistically significant, the results of our study showed that the bedtime regime of Levothyroxine is slightly better compared to the morning regime in terms of improving the thyroid profiles as well as in the quality of life of the patients. Future work is necessary to address the shortcomings of our research and to strengthen the findings. Nevertheless, in our opinion, prescribers and pharmacists should inform and educate patients on the availability of this alternative and possibly superior dosing regimen for Levothyroxine in hypothyroidism, particularly for patients whom are not responding well to the morning regime and those that find the bedtime regime a more convenient alternative befitting their daily schedules.

Acknowledgement

We would like to thank the Director General of Health, Ministry of Health of Malaysia for his permission to conduct this study and to publish this article. Besides that, we would also like to acknowledge the Hospital Director for his approval to conduct this study in Tuanku Ja'afar Seremban Hospital. Also, we would like to thank the Head of Pharmacy Department, Madam Basariah Naina, for her support and all the colleagues in both the Pharmacy Department and Medical Department who had helped us in the recruitment of the respondents.

Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

References

1. Haynes R, Thyroid and Antithyroid Drugs. In: Gilman AG, Rall TW, Nies AS, Taylor P (editors). Goodman and Gilman's The Pharmacological Basis of Therapeutics, New York: McGrawHill, Inc., 1993;1361–83.
2. Dong BJ, Thyroid and Parathyroid Disorders. In: Herfindal ET, Gourley DR, Hart LL (editors). Clinical Pharmacy and Therapeutics, Baltimore: Williams & Wilkins, 1992;267–306.
3. Pangaro LN, Physiology of the Thyroid Gland. In: Becker KL (editor). Principles and Practice of Endocrinology and Metabolism, Philadelphia: J.B. Lippincott Company, 1990.
4. Mandel SJ, Brent GA, Larsen PR, Levothyroxine therapy in patients with thyroid disease, Ann Intern Med, 1993;119(6):492–502.
5. Cavalieri RR, Rapoport B, Impaired Peripheral Conversion of Thyroxine to Triiodothyronine, Annu Rev Med, 1977;28:57–65.
6. Hong J. Y. H, Tan A.T.B, Lim P. C, Loh Y. F (2010) Malaysian Statistics on Medicines 2007. Chapter 14. Use of Drugs for Endocrine Disorders. Pharmaceutical Service Division and Clinical Research Centre. Ministry of Health, page 75.
7. W. M. Wiersinga, "Subclinical hypothyroidism and hyper- thyroidism. I. Prevalence and clinical relevance," *Netherlands Journal of Medicine*, vol. 46, no. 4, pp. 197–204, 1995.
8. American Thyroid Association. http://www.thyroid.org/hypothyroidism Accessed 11 April 2017.
9. M.P. Vanderpump, W.M. Turnbridge, J.M. Frenchetal., "The incidence of thyroid disorders in the community: a twenty year follow up of Whickham survey," *Clinical Endocrinology*, vol. 43, pp. 55–68, 1995.
10. Bolk, N. (2007). Effects of evening vs morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients. *Archives of Internal Medicine*, 170(22), 1996. doi 10.1001, archinternmed.2010.436.
11. Bolk, N. (2010). Effects of evening versus morning levothroxine intake. *Archives of Internal Medicine*, 170(22), 1996. doi 10.1001, archinternmed.2010.436.
12. Rajput, R., Chatterjee, S., & Rajput, M. (2011). Can Levothyroxine Be Taken as Evening Dose? Comparative Evaluation of Morning versus Evening Dose of Levothyroxine in Treatment of Hypothyrodism. *Journal of Thyroid Research*, 2011, 1-5. Doi:10.4061/2011/505239.
13. Samuels, MH., Kolobova, I., Niederhausen, M., Janowsky, JS. & Schuff, KG. (2018). Effects of Altering Levothyroxine (L-T4) Doses on Quality of Life, Mood, and Cognition in L-T4 Treated Subjects. *J Clin Endocrinol Metab*, 103(5), 1997-2008.
14. Tan, NC., Chew, RQ., Subramanian, RC., Sankari, U., Koh, YLE. & Cho, LY. (2019). Patients on Levothyroxine replacement in the community: association between hypothyroidism symptoms, co-morbidities and their quality of life. *Family Practice*, 36(3), 269–275.
15. Bach-Huynh, T.-G., Nayak, B., Loh, J., Soldin, S., & Jonklaas, J. (2009). Timing of Levothyroxine administration affects serum Thyrotropin concentration. *The Journal of Clinical Endocrinology & Metabolism*, *94*(10), 3905–3912. doi:10.1210/jc.2009-0860.

Appropriateness of Intravenous Proton Pump Inhibitor Use in Labuan Hospital, Federal Territory of Labuan

Siu Loe Ching[1], Latha Devi Sukumaran[1]

[1] Hospital Labuan, Federal Territory of Labuan, Ministry of Health Malaysia

Abstract

Introduction: There are increasing concerns that intravenous (IV) proton pump inhibitors (PPIs) are being prescribed inappropriately in the hospital settings. Prolonged PPI therapy may cause hypergastrinemia, enterochromaffin-like cell hyperplasia, and parietal cell hypertrophy which may lead to rebound acid hypersecretion.

Objective: This study aimed to determine the appropriateness of IV PPIs use in two non-intensive care unit adult wards of Labuan Hospital.

Methods: All patients admitted to the two non-intensive care unit adult wards of Labuan Hospital who received IV PPIs during the seven-month study period were included in the study. Data collection was performed prospectively using a data collection form to collect data on patient demographics and information related to IV PPI prescription. The indication of IV PPIs recorded was compared against a set of "Appropriate indications for IV PPIs" developed based on the Ministry of Health Drug Formulary, product prescribing information, guidelines and published literature to assess the appropriateness of the indication.

Results: A total of 117 patients received IV PPIs during the study period. The most common indications for prescribing IV PPIs were gastritis (19.7%), prevention of drug-induced ulcer (19.7%) and gastrointestinal symptoms such as abdominal pain, nausea and vomiting (17.9%). Of the 117 patients, only 17 (15%) were prescribed with the appropriate indications. Among the 10 patients whom IV PPIs were indicated for upper gastrointestinal bleeding, all were identified to be appropriately indicated. However, when IV PPIs were prescribed for the prevention of drug-induced ulcer and gastrointestinal symptoms, the use of IV PPI was only considered appropriate in 4.4% and 4.8% of the patients respectively.

Conclusions: This study highlighted the inappropriateness of IV PPI utilisation in non-ICU patients in Labuan Hospital. Restriction of IV PPI use for justified indications and route of administration is recommended.

Keywords: quality use of medicine, Federal Territory of Labuan, proton pump inhibitor, appropriateness

NMRR ID: NMRR-16-1459-31548

Corresponding author: Siu Loe Ching
Department of Pharmacy, Hospital Labuan, Peti Surat 81006, 87020 WP Labuan.
Email: siuloeching@moh.gov.my

Introduction

Proton pump inhibitors (PPIs) are potent gastric acid suppressing agents (1). Currently, intravenous (IV) PPIs are approved for treating patients who are unable to tolerate oral medications due to gastroesophageal reflux disease (GERD) with a history of erosive esophagitis and in patients with pathological hypersecretory states with Zollinger-Ellison syndrome (ZES). They are also approved to reduce the risk of re-bleeding in gastric or duodenal ulcers following therapeutic endoscopy (2,3). In real life practices, the use of IV PPIs is not restricted to regulatory approved indications. They are been used in the treatment of high-risk peptic ulcers, complicated gastroesophageal reflux, stress-induced ulcer prophylaxis, and whenever it is impossible or impractical to give oral therapy (1,4).

There are increasing concerns that IV PPIs are being prescribed inappropriately in the hospital setting (1). Studies have shown that IV PPIs were prescribed inappropriately in 53 – 75% of cases (5-7). Such extensive use of unnecessary PPI therapy has led to the investigation of potential associated adverse effects. Retrospective studies found that the use of PPIs may be associated with adverse effects such as increased risk of enteric infections including *Clostridium difficile*-associated diarrhoea, community-acquired pneumonia, bone fracture, nutritional deficiencies, and interference with the metabolism of antiplatelet agents. Moreover, prolonged PPI therapy may cause hypergastrinaemia, enterochromaffin-like cell hyperplasia, and parietal cell hypertrophy which may lead to rebound acid hypersecretion (8).

With the increasing concerns regarding the adverse effects of PPI usage and the increasing pressure on the healthcare budget, it is important to investigate the indication for PPI treatment and to identify the factors of such extensive use (5,9). Previous review article documented that PPI overutilization in the inpatient setting was often a result of inappropriate stress ulcer prophylaxis (SUP) in non-intensive care unit (non-ICU) patients (10).

Currently, three IV PPIs are available in Labuan Hospital, which are Esomeprazole, Pantoprazole and Omeprazole. The average monthly usage of IV Esomeprazole and IV Pantoprazole were 49 vials and 136 vials respectively with an average cost of RM1,480 per month. IV omeprazole is reserved for paediatric patients and therefore not investigated in this study. As IV PPIs consume a considerable amount of the drug budget, it is important to ensure their appropriate usage. Hence, the objective of this study was to determine the appropriateness of IV PPIs use in two non-ICU adult wards of Labuan Hospital.

Methods

This is a prospective observational study which was conducted in two non-ICU adult wards of Labuan Hospital. The study was registered with the National Medical Research Register (NMRR) and the approval by the Ministry of Health Malaysia (MOH) Medical Research and Ethics Committee (MREC) was obtained prior to the initiation of the study.

The inclusion criteria of this study were patients more than18 years of age who were admitted in the two non-ICU adult wards (internal medicine, surgery, or orthopaedic) of Labuan Hospital, and received IV PPIs. Paediatric patients and outpatients were not enrolled in the study. Patients who were admitted to ICU before transferring to these two non-ICU wards were also excluded. Prescriptions of IV omeprazole were excluded as well as it was only reserved for paediatric patients.

One sample proportion level sample size formula has been used to calculate the sample size in this study (11,12): $n=Z^2P(1-P)/d^2$. We estimated a 95% confidence interval and a power of 80%. Therefore Z was 1.96 and d was 0.05. Based on the results of our 10 participant pilot study that was conducted in July 2016, it was estimated that 90% of the prescription of IV PPI was inappropriate. Therefore, we set the P as 0.9 and the calculated sample size was 138. We adjusted the sample size to account for dropouts (d set at 0.2) by using the formula: N1=n/(1-d). Based on above calculation, our targeted sample size was 180.

Table 1: Appropriate indications for IV PPIs

Appropriate indication	Dosage	Notes
1. Non-variceal upper gastrointestinal bleeding following therapeutic endoscopy	IV Pantoprazole / Esomeprazole 80mg STAT followed by an infusion of 8mg hourly for 72 hours	- It is appropriate in those who could not undergo an endoscopy for clinical reasons (clinically unstable or other comorbidity precluding endoscopy). - If re-bleeding occurred, diagnosed on clinical and / or endoscopic grounds, the patient is allowed to receive IV PPI for an additional 72 hours.
2. Gastroesophageal reflux disease in patient with esophagitis and/or severe symptom of reflux	IV Pantoprazole / Esomeprazole 40mg OD for up to 10 days	It is only appropriate when the oral route is not possible.
3. Healing of duodenal or gastric ulcer	IV Pantoprazole 40mg OD or IV Esomeprazole 20-40mg OD	It is only appropriate when the oral route is not possible.
4. Prevention of gastric and duodenal ulcers associated with nonsteroidal anti-inflammatory drug (NSAID) treatment, in patient at risk	IV Pantoprazole / Esomeprazole 20mg OD up to 10 days	It is only appropriate when the oral route is not possible.
5. Pathological hypersecretion conditions including Zollinger-Ellison syndrome	IV Pantoprazole 80mg BD-TDS or IV Esomeprazole 40mg BD	It is only appropriate when the oral route is not possible.

Abbreviation: STAT - immediately; OD – once a day; BD - twice a day; TDS - three times a day

The data collection was carried out over seven months (July 2016 – January 2017) using universal sampling method. Data such as gender, age, days of hospitalisation, past and current medical history, all concurrent medications during IV PPI administration, oral or nil by mouth (NPO) status during IV PPI use and information about IV PPI use (indication, duration, dose, specialty of the prescriber and prescriber status) were recorded using a structured data collection form. Both the medication charts and clinical notes were examined by the data collector to identify the indications of IV PPIs prescription.

The indication of IV PPIs recorded was then compared against a set of "Appropriate indications for IV PPIs" (Table 1). The appropriate indications were developed based on the Ministry of Health Drug Formulary, product prescribing information, relevant guidelines and published articles (5,13-19).

Results

A total of 181 patients were identified to have received IV PPI in the two non-ICU adult wards of Labuan Hospital from July 2016 to January 2017. Of those, 64 patients were discharged from the wards before the data collection by the investigators. Therefore, only 117 medication charts and clinical notes were reviewed.

Patient characteristics and the appropriateness of IV PPI indication were shown in Table 2 and Table 3. Male patient (73.5%) was more than female patient (26.5%). The mean patient age was 51 years old. Most of them were receiving IV Pantoprazole (97.4%). The number of patients from the medical discipline (80.3%) was more than the surgical (18.9%) and orthopaedic (0.9%). The reasons for hospital admission included gastric-related illness, infection, cardiovascular, hepatic, gastrointestinal, renal or pulmonary diseases. About one third (34.2%) of the patients received drugs which may induce gastric ulcer such as anticoagulants, antiplatelets, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids during hospitalisation.

The most common indications for prescribing IV PPIs were gastritis (19.7%), prevention of drug-induced ulcer (19.7%) and gastrointestinal symptoms such as abdominal pain, nausea and vomiting (17.9%). Of the 117 patients that were prescribed with IV PPI, only 17 (15%) were prescribed with the appropriate indications while the indications for PPI in 100 (85%) patients were inappropriate. Among the 10 patients whom IV PPIs were indicated for upper gastrointestinal bleeding (UGIB), all were identified to be appropriately indicated. When the IV PPIs were indicated for GERD / peptic ulcer (5 patients), the indication was appropriate in 4 (80%) of the patients. Nevertheless, when IV PPIs were prescribed for the prevention of drug-induced ulcer and gastrointestinal symptoms, the use of IV PPI was only considered appropriate in 4.4% and 4.8% of the patients respectively.

Table 2: Characteristics of patients (N=117)

Characteristics	n (%) or mean (SD)
Gender, n (%)	
Male	86 (73.5)
Female	31 (26.5)
Age, year, mean (SD)	51 (17.5)
Length of stay, day, mean (SD)	7 (5.4)
Duration of IV PPI use, day, mean (SD)	4 (3.4)

Abbreviation: SD – standard deviation

Table 3: Appropriateness of IV PPI prescription (N=117)

Variable	Patient, n (%)	Appropriate IV PPI prescription, n (%)
Type of PPI prescribed		
Pantoprazole	114 (97.4)	14 (12.3)
Esomeprazole	3 (2.6)	3 (100.0)
Indication of IV PPI		
Gastritis	23 (19.7)	1 (4.4)
Prevent drug-induced ulcer	23 (19.7)	1 (4.4)
Unknown	23 (19.7)	0 (0.0)
GI symptoms	21 (17.9)	1 (4.8)
UGIB	10 (8.5)	10 (100.0)
Pancreatitis / cholecystitis	8 (6.8)	0 (0.0)
GERD / peptic ulcer	5 (4.3)	4 (80.0)
Anaemia	4 (3.4)	0 (0.0)
Diet status		
Oral	79 (67.5)	2 (2.5)
NPO	31 (26.5)	14 (45.2)
Tube feeding	7 (6.0)	1 (14.3)
Past medical history		
NKMI	42 (35.9)	3 (7.1)
Cardiovascular	38 (32.5)	7 (18.4)
Endocrine	12 (10.3)	2 (16.7)
Gastroenterology	8 (6.8)	1 (12.5)
Gastric related	7 (6.0)	4 (57.1)
Pulmonary	4 (3.4)	0 (0)
Renal	3 (2.6)	0 (0)
Others	3 (2.6)	0 (0)
Reason for hospital admission		
Infection	30 (25.6)	1 (3.3)
Cardiovascular	28 (23.9)	2 (7.1)
Gastroenterology	22 (18.8)	2 (9.1)
Gastric related	16 (13.7)	11 (68.8)
Pulmonary	6 (5.1)	0 (0.0)
Endocrine	4 (3.4)	0 (0.0)
Nephrology	4 (3.4)	0 (0.0)
Others	7 (6.0)	1 (14.3)
Concurrent medications		
One blood thinner	20 (17.1)	2 (10.0)
Two blood thinners	4 (3.4)	1 (25.0)
Three blood thinners	14 (12.0)	1 (7.1)
Corticosteroids	1 (0.9)	0 (0.0)
NSAIDs	1 (0.9)	0 (0.0)
No drugs that may induce gastric ulcer	77 (65.8)	13 (16.9)
Discipline		
Medical	94 (80.3)	13 (13.8)
Surgical	22 (18.9)	4 (18.2)
Orthopaedic	1 (0.9)	0 (0.0)
Prescriber status		
Medical officer	104 (88.9)	16 (15.4)
Specialist	13 (11.1)	1 (7.7)

Abbreviation: UGIB - upper gastrointestinal bleeding; GERD - gastroesophageal reflux disease; NPO - nil by mouth; NKMI - no known medical illness; NSAIDs - nonsteroidal anti-inflammatory drugs; GI – gastrointestinal

Discussion

This prospective study demonstrates that inappropriate utilisation of IV PPI therapy was quite frequent in the non-ICU wards at our institution when the indications for IV PPI were compared against a set of "Appropriate indications for IV PPIs". Only 15% of patients received appropriate IV PPI therapy. These results are in keeping with other studies found in the literature (5,7,20).

One of the reasons IV PPIs were prescribed inappropriately was the low adherence to the guidelines regarding PPI prescription (21). In a study carried out by White *et al*. in 2003, up to 36% of doctors were discovered to have prescribed IV PPIs without clear benefit, such as active lower gastrointestinal bleeding (LGIB) and variceal bleeding (22). Zink *et al.* 2005 found that 60% of patients were prescribed with acid suppression therapy without reason or with an inappropriate indication. Inappropriate indications given were low risk or gastrointestinal prophylaxis, pancreatitis, steroid use, LGIB, anaemia, vomiting, inflammatory bowel disease. In Labuan Hospital, most of the IV PPIs were prescribed without a documented indication (19.7%), for gastritis (19.7%), to prevent drug-induced ulcer without concomitant risk factor (19.7%) and to relieve gastrointestinal symptoms such as abdominal pain (17.9%) (23). Another reason for over-utilization of IV PPIs during hospitalisation was its safety and tolerable profile compare to the hazard of gastric ulcer. Ulcer complications can have serious consequences on health such as haemorrhage, confined and free perforation, gastric outlet obstruction and gastric cancer (23,24). The fear of development of ulcer encouraged the utilisation of IV PPIs. Concurrent intake of potentially gastro-toxic compounds might also a contributing factor (25).

It is important to note that IV PPIs is not recommended for stress ulcer prophylaxis (SUP) in non-ICU wards as patients in non-ICU wards rarely meet the two criteria for stress ulcer prophylaxis, namely coagulopathy and respiratory failure requiring mechanical ventilation for more than 48 hours (26-27). Indeed, the risk of bleeding in patients without these two criteria is as low as 0.1% and the prophylaxis can be safely withheld (27). While the guidelines for SUP in ICU patients have been well defined in the medical literature, the perceived benefit from SUP has been extrapolated to patients in non-ICU setting, leading to over utilisation of PPIs and increased overall healthcare costs. This happened when doctors feel that certain non-ICU patients are at a higher risk of developing stress ulcers, such as patients on chronic or high-dose steroids, patients who are septic or potentially septic, and it is easily preventable by PPIs without clear regard for cost-effective provisions of care. However, it is reasonable for clinical judgement to determine if a patient with moderate to severe physiologic stress in the non-ICU setting may ultimately benefit from PPIs, taking into consideration potential risks versus benefits, likelihood of stress ulcer development, cost-effectiveness, and certainly a plan for ensuring that patients are not discharged on PPI without appropriate symptoms or indications for treatment (10).

Grime *et al.* (2001) reported that PPIs were frequently prescribed for non-specific abdominal or chest pain and this was similar to our findings (28). Patients who were admitted for non-gastric related illness were significantly more prone to receiving unnecessary IV PPIs compared to patients who were admitted for gastric related issue. 28% of the patients who received IV PPIs were admitted for cardiovascular diseases such as angina, myocardial infarction, dyslipidaemia and hypertension. 32.5% of the patients were receiving one or more than one type of blood thinners, for example, aspirin. Doctors may prescribe PPIs when patients who receive prophylactic aspirin develop significant gastrointestinal disturbance due to aspirin or have history of peptic ulcer disease. However, this indication is not approved (29). Our study also found that inappropriate prescribing of IV PPI was more prevalent among patients with non-UGIB indications and this scenario also been reported in several other studies (5,7,20). It may be due to the fact that local clinical practice guideline for non-variceal UGIB has been published but not the other non-UGIB illnesses.

Throughout the study period, we found that most of the non-fasting patients were receiving other oral medications at the same time but were prescribed with IV PPI. In fact, both IV and oral PPIs have similar effects on inhibition of gastric acid secretion. Oral PPIs are as effective as IV PPIs except in bleeding peptic ulcer case which require a continuous infusion to achieve high target pHs to promote clot stabilization (1). In addition, oral PPI brings extra benefits compared to the IV formulation such as lower cost, reduced utilization of hospital resources, and fewer IV related complications (30). The additional costs of intravenous tubing, infusion pumps, and personnel time must be considered when giving IV PPIs to patients (31). These findings highlight the role of the clinical pharmacist in the selection of appropriate candidates for oral PPI.

Craig *et al.* reported that inappropriate prescribing was more common in female patients, surgical admissions and when initiated by junior hospital doctor (7). Nasser *at al.*, however, reported a contradicting result, in which they found that IV PPI was more likely to be inappropriately prescribed in medical rather than

surgical department (30). Afif *et al.* found that there were relationships between increasing patient age, lower mean daily PPI dose, timing of prescriptions and appropriateness of IV PPI therapy (5). However, these variables were not examined in this study.

There were several limitations in our study. Firstly, this study was observational and conducted at a single site, which may limit its generalizability. The results might be biased by the prescribing habits of a relatively small number of doctors. In addition, there were no current established guidelines for the appropriate use of IV PPI in the hospital to evaluate their actual use. Moreover, we assumed that patients with no clear documented indication for PPI use received the drug inappropriately. Since the data in our study were abstracted by chart review from each patient hospitalisation, it is possible that some appropriate utilisation of IV PPIs might be missed when the indications have not been documented in the patient chart.

Conclusion

This study found the high rate of inappropriate use of IV PPIs in Labuan Hospital. Inappropriate prescribing of IV PPIs was observed mainly when the indication was for the prevention of drug-induced ulcer and gastrointestinal symptoms. As a recommendation, we suggest that hospitals should consider developing controlled policies such as formulary restrictions, stop-orders for certain indications and automatic switch-order to oral PPI if patient is receiving oral feeding. At the same time, doctors and pharmacists may work together to review the need of IV PPIs during patients' hospital stay.

Acknowledgement

We would like to thank the Director General of Health, Ministry of Health of Malaysia for his permission to publish this article.

Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

References

1. Pang SH, Graham DY. A Clinical Guide to Using Intravenous Proton-Pump Inhibitors in Reflux and Peptic Ulcers. *Therapeutic Advances in Gastroenterology* 2010; 3:11-22.
2. Prescribing Information for Nexium IV. AstraZeneca 2016.
3. Prescribing Information for Protonix IV. Pfizer 2014.
4. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock. *Society of Critical Care Medicine, European Society of Intensive Care Medicine*. 2013.
5. Afif W, Alsulaiman R, Martel M, Barkun AN. Predictors of Inappropriate Utilization of Intravenous Proton Pump Inhibitors. *Alimentary Pharmacology & Therapeutics.* 2007; pp 609–615.
6. Lai PMS, Wong YY, Low YC, Lau HL, Chin KF, Mahadeva S. Unexplained Abdominal Pain as a Driver for Inappropriate Therapeutics: an Audit on the Use of Intravenous Proton Pump Inhibitors. *PeerJ*. 2014; 451.
7. Craig DGN, Thimappa R, Anand V, Sebastian S. Inappropriate Utilization of Intravenous Proton Pump Inhibitors in Hospital Practice—a Prospective Study of the Extent of the Problem and Predictive Factors. *QJM*. 2010; 327-335.
8. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therapeutic advances in gastroenterology*. 2012; 219-232.
9. Moran N, Jones E, O'Toole A, Murray, F. The Appropriateness of a Proton Pump Inhibitor Prescription. *Irish Medical Journal*. 2013; 326-7.
10. Heidelbaugh J, Inadomi J. Magnitude and Economic Impact of Inappropriate Use of Stress Ulcer Prophylaxis in Non-ICU Hospitalized Patients. *American Journal of Gastroenterology*. 2006; 2200-2205.
11. Al-Subaihi AA. Sample size determination: Influencing factors and calculation strategies for survey research. *Neurosciences*. 2003; 8(2):79-86.
12. Suresh K, Chandrashekara S. Sample size estimation and power analysis for clinical research studies. *Journal of human reproductive sciences*. 2012; 5:7-13.
13. Kaplan GG, Bates D, McDonald D et al. Inappropriate Use of Intravenous Pantoprazole: Extent of the Problem and Successful Solutions. *Clinical Gastroenterology and Hepatology.* 2005; 1207-1214.
14. Cheer SM, Prakash A, Faulds D, Lamb HM. Pantoprazole. *Drugs*. 2003; 101-132.
15. Prescribing Information for Nexium IV. AstraZeneca 2016.

16. Prescribing Information with Medication Guide for Nexium. AstraZeneca 2008.
17. Prescribing Information for Pantosec IV. Cipla 2013.
18. Clinical Practice Guidelines: Management of Non-Variceal Upper Gastrointestinal Bleeding. 2003.
19. Pharmaceutical Services Programme, Ministry of Health Malaysia. Ministry of Health Malaysia Drug Formulary. 2017. Available at: https://www.pharmacy.gov.my/v2/en/apps/fukkm
20. Sebastian S, O'Morain CA, Qasim A. Appropriateness of Gastric Antisecretory Therapy in Hospital Practice. *Irish journal of medical science*. 2003; 115-117.
21. Magadmi EM, Alnabulsi RK, Dhabab NM, Alsubahi TA, Basheikh MA, Kamel FO. Practice toward and knowledge about proton pump inhibitor prescription in Jeddah, Saudi Arabia. *International Annals of Medicine*. 2018; 2(6).
22. White KT, Storch IM, Mullin GE. Intravenous Pantoprazole: Physician Understanding of Indications and their Prescribing Patterns Leading to Hospital Restrictions. *The American Journal of Gastroenterology*. 2003; S231.
23. Zink DA, Pohlman M, Barnes M, Cannon ME. Long-term Use of Acid Suppression Started Inappropriately During Hospitalization. *Aliment PharmacolTher*. 2005; 1203-1209
24. Vakil N. Peptic ulcer disease. *Merck Manual Professional Version*. 2016.
25. Parente F, Cucino C, Gallus S, et al. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. *Aliment PharmacolTher*. 2003; 1503-1506.
26. Alsultan MS, Mayet AY, Malhani AA, Alshaikh MK. Pattern of intravenous proton pump inhibitors use in ICU and non-ICU setting: a prospective observational study. *Saudi Journal of Gastroenterology*. 2010; 16(4): 275–279.
27. Cook DJ, Fuller HD, Guyatt GH et al. Risk Factors for Gastrointestinal Bleeding in Rritically Ill Patients. *N Engl J Med*. 1994; 377-381.
28. Grime J, Pollock K, Blenkinsopp A. Proton Pump Inhibitors Perspective of Patients and their GPs. *British Journal of General Practice.* 2001; 703-711.
29. Choudhry MN, Soran H, Ziglam HM. Overuse and Inappropriate Prescribing of Proton Pump Inhibitors in Patients with *Clostridium Difficle*-Associated Disease. QJM. 2008; 445-48.
30. Nasser SC, Nassif JG, Dimassi HI. Clinical and Cost Impact of Intravenous Proton Pump Inhibitor Use in Non-ICU Patients. *World Journal of Gastroenterology*. 2010; 982-6.
31. Barletta JF, Erstad BL, Fortune JB. Stress Ulcer Prophylaxis in Trauma Patients. *Critical Care*. 2002; 526-530.

eISSN 2637-1332