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The Correlation between Antibiotic Consumption and Multidrug-Resistant Organism Infection in Tuanku Ampuan Najihah Hospital (HTAN)

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Abstract

Introduction: Antibiotic resistance is a global health issue. The increasing trend of multidrug-resistant organism (MDRO) infections has become a main concern because it will lead to increased healthcare cost, failure of antibiotic treatment and increased mortality rate.

Objectives: To assess the correlation between antibiotic consumption and multidrug-resistant (MDR) infections (extended spectrum beta-lactamase (ESBL)-producing bacterial and MDR *Acinetobacter*) in Tuanku Ampuan Najihah Hospital from 2014 to 2016.

Method: A retrospective study was conducted. Antibiotic consumption data was expressed as the defined daily dose (DDD)/1000 inpatient-day in 6 months while MDRO infection was expressed as the number of ESBL-producing bacterial and MDR *Acinetobacter* cases in 6 months. The correlation between antibiotic consumption and MDRO infection was evaluated using Pearson's correlation coefficient or Spearman rank-order correlation.

Results: The total antibiotic consumption decreased by 60.09% from 458.98 DDD/1000 inpatient-days in Jan-June 2014 to 178.59 DDD/1000 inpatient-days in July-December 2016. The greatest reduction in consumption was observed in carbapenems (-87.91%). During the same period, ESBL-producing bacterial infections increased by almost three-fold but the increase in MDR *Acinetobacter* infections was minimal. The increment of ESBL infection was seen in the Medical, Surgical and Orthopaedic wards while most of the MDR *Acinetobacter* infections were from the Intensive Care Unit / Coronary Care Unit (ICU/CCU) (76%). Statistically significant strong negative correlations were found between ESBL infections and consumption of ciprofloxacin ($r=-0.930$, $p=0.007$) and moxifloxacin ($r=-0.873$, $p=0.023$). There was a significant strong positive correlation between piperacillin/tazobactam consumption and MDR *Acinetobacter* infections ($r=0.839$, $p=0.037$) in ICU/CCU.

Conclusion: Our study did not observe uniform trends in the correlation between the antibiotic consumption and MDRO infections. Besides the strict control of antibiotics use, other factors may also be important in suppressing the emergence of MDRO. More studies should be carried out to help planning for strategies in combating antibiotic resistance.

Keywords: antibiotic consumption, correlation, ESBL, MDR *Acinetobacter*

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Introduction

Antibiotic resistance is an alarming global issue threatening our health (1). Overuse and misuse of antibiotic have been identified as the main cause of the development and spread of antibiotic resistance (2). The call for actions to combat antibiotic resistance is a matter of urgency because of the drying up of the antibiotic pipelines, and the current antibiotics are losing their effectiveness rapidly as a result of the antibiotic resistance (3).

The common multidrug-resistant organisms (MDRO) are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and certain Gram-negative bacilli (GNB) such as extended spectrum beta-lactamases (ESBL)-producing organisms and multidrug-resistant (MDR) *Acinetobacter* (4). In the recent years, infections due to Gram-negative bacteria, especially MDRO, have increased continuously (5). The increasing trend of MDR infections has become a main concern because it leads to the increased risk in

transplant and other surgical procedures that are dependent on the effectiveness of antibiotic, failure of antibiotic treatment, increased healthcare cost due to costlier new antibiotics or prolonged hospitalisation, and increased mortality rate (2,6).

ESBLs are enzymes produced by some Gram-negative bacteria such as *Escherichia coli* and *Klebsiella* species. These enzymes have the ability to hydrolyse extended spectrum cephalosporins such as ceftazidime, ceftriaxone and cefotaxime which commonly act as first line antibiotics for many infections in the hospital. Therefore, any delay in the identification and failure to treat severe infection caused by ESBL-producing bacteria would lead to increased morbidity and mortality (7). Recently, *Proteus mirabilis* also emerged as one of the producers of ESBL (8). Hawser *et al.* found that countries in Asia-Pacific region showed the highest level of antimicrobial resistance. As high as 42.2% of *E. coli* and 35.8% of *Klebsiella* species among the Gram-negative bacilli collected from intra-abdominal infections in the Asia-Pacific region were found to be ESBL positive (9). In Malaysia, the estimated prevalence of ESBLs was 7% to 19% for *E. coli* and 27% to 38% for *Klebsiella* species (10,11).

MDR *Acinetobacter* refers to any *Acinetobacter* species that is resistant to at least one agent in at least three different classes of antimicrobial agents (12). *Acinetobacter* has the ability to survive on both dry and moist inanimate surfaces for as long as five months. It can also grow at different ranges of temperatures and pH values (13). Therefore, its ability to survive in the hospital environment and persist for a long period enable it to be the frequent cause of healthcare associated infection such as pneumonia, meningitis and urinary tract infection (14).

Previous antibiotic exposure may exert selective pressure to eliminate all sensitive strains, which may in turn lead to the development of antibiotic resistance (7,15). For example, excessive cephalosporins use may lead to the emergence of ESBL-producing organisms (7). The most used antibiotic groups in the hospitals is known to be third generation cephalosporins, which were reported to exert predominant selective pressure for the development of resistant *E. coli* and *Klebsiella pneumoniae*. Several studies had also shown positive correlations between quinolones and third-generation cephalosporins use and the acquisition of ESBL-producing strain (7,16,17). Similarly, prior exposure of broad-spectrum antimicrobial agents, such as second and third generation cephalosporins, carbapenems, and fluoroquinolones, is one of the major risk factors for the acquisition of the MDR strains of *Acinetobacter* (5,13,18,19).

To our knowledge, limited studies have been conducted in Malaysia to assess the correlation between antibiotic consumption and MDRO infections. This study aimed to determine the antibiotic consumptions, number of MDR infections, and to assess the correlation between antibiotic consumptions and MDRO infections in the past three years (2014-2016) in Tuanku Ampuan Najjihah Hospital (HTAN). The findings from this study are important to give an overview on the related topic, and to identify possible strategies for future planning in reducing the emergence of MDRO infections.

Method

A retrospective study was conducted from February to December 2017 in HTAN, Kuala Pilah, Negeri Sembilan, a tertiary care major specialist hospital with 317 beds. Three-year data from year 2014 to 2016 was collected for the purpose of this study. Antibiotic consumption and MDRO infection data from all wards, except the emergency department, paediatric and neonatal wards, were included in this study.

Antibiotic Consumption

Antibiotic consumption data was obtained from the Pharmacy Department. These data were extracted from the data collected by the Pharmacy Department for the National Surveillance of Antibiotic Usage reports. These figures comprised actual consumption data rather than purchasing data. Intravenous antibiotics that were frequently associated with the emergence of antibiotic resistance group and available in HTAN were included in this study, namely carbapenems (imipenem and meropenem), quinolones (ciprofloxacin and moxifloxacin), cephalosporins (cefuroxime, ceftazidime, cefoperazone, ceftriaxone, cefotaxime, and cefepime) and beta-lactam/beta-lactamase inhibitor (cefoperazone/sulbactam, ampicillin/sulbactam, piperacillin/tazobactam and amoxicillin/clavulanic acid). The antibiotic consumption data was expressed as defined daily dose (DDD) per 1000 inpatient-days consumed in every 6 months, calculated based on the World Health Organisation ATC/DDD Index (20).

MDRO Infections

The MDRO tracked were ESBL-producing bacteria (ESBL *E. coli*, ESBL *Klebsiella*, ESBL *Proteus*) and MDR *Acinetobacter*. Data was expressed as the number of cases of ESBL-producing bacteria and MDR *Acinetobacter* infections in every 6 months. ESBL-producing bacterial infection data were extracted from the hospital Laboratory Information System (LIS). ESBL infections were defined from ESBL isolates grew from sterile cultures (blood culture, tissue culture, bone culture, cerebrospinal fluid culture). Non-sterile isolates like sputum culture, tracheal aspirate culture, urine culture, pus culture and swab culture were not considered due to the high chance of being a colonizer or contaminant. On the other hand, MDR *Acinetobacter* infections was defined as all MDR *Acinetobacter* infections treated in the ward as the majority of the laboratory cultures were from non-sterile cultures and tend to be repetitive. Therefore, MDR *Acinetobacter* infections data were extracted from the treated MDR *Acinetobacter* cases captured by the Clinical Pharmacy Unit for monitoring purpose since year 2014.

Statistical Analysis

Pearson's correlation or Spearman rank-order correlation coefficient was conducted to assess the correlation between antibiotic consumptions and respective MDRO infections. It is considered statistically significant when the p value is less than 0.05, with a confidence interval of 95%. A correlation coefficient (r) of less than 0.3 indicates a weak correlation, 0.3 to 0.7 indicates moderate correlation and more than 0.7 indicates a strong correlation.

Results

Antibiotic Consumption

Antibiotic consumptions in HTAN from 2014 to 2016 were presented in Table 1. The total antibiotic consumption decreased tremendously from 458.98 DDD per 1000 inpatient-days in Jan-June 2014 to 178.59 DDD per 1000 inpatient-days in July-December 2016 (-61.09%). From 2014 to 2016, cephalosporin group was the main antibiotic group consumed followed by beta-lactam/beta-lactamase inhibitor group. Overall, all antibiotic consumptions had decreased from 2014 to 2016. The greatest reduction in consumption was observed in the carbapenem group (-87.91%), followed by quinolone group (-69.08%), cephalosporin group (-60.73%) and beta-lactam/beta-lactamase inhibitor group (-55.57%). In terms of the individual antibiotic, the greatest reduction in consumption was observed in moxifloxacin (-100%), imipenem (-100%), ceftriaxone (-85.48%), meropenem (-83.28%) and piperacillin/tazobactam (-73.22%).

MDRO Infections

The number of ESBL *E. coli*, ESBL *Klebsiella*, ESBL *Proteus* and MDR *Acinetobacter* infections were summarised in Table 2. Among the four types of infections, MDR *Acinetobacter* showed the highest cases of infection (38.10%) followed by ESBL *Klebsiella* (36.11%).

Table 3 showed the trend of total ESBL and MDR *Acinetobacter* infections in HTAN according to clinical disciplines from 2014 to 2016. From January-June 2014 to July-December 2016, almost three-fold increment was observed for ESBL infections but the increase in MDR *Acinetobacter* infections was minimal. The increment in ESBL infections was notable in the medical, surgical and orthopaedic disciplines.

Table 1: Antibiotic consumption (DDD / 1000 inpatient-day) in HTAN from 2014 to 2016

Antimicrobial Agents	Antibiotic Consumption (DDD / 1000 patient-day)						Difference (%) ^c
	2014 Jan-Jun ^a	2014 Jul-Dec	2015 Jan-Jun	2015 Jul-Dec	2016 Jan-Jun	2016 Jul-Dec ^b	
Quinolone							
Ciprofloxacin	13.64	9.39	6.31	3.02	4.76	4.39	-67.82
Moxifloxacin	0.56	0.60	0.15	0.00	0.11	0.00	-100
Total	14.2	9.99	6.46	3.02	4.87	4.39	-69.08
Cephalosporin							
Ceftazidime	34.74	34.52	20.45	37.32	25.03	19.80	-43.01
Cefepime	21.87	27.07	10.46	10.38	14.47	8.24	-62.32
Ceftriaxone	84.94	101.43	90.67	68.34	35.13	12.33	-85.48
Cefotaxime	1.52	0.59	0.21	0.32	0.11	0.51	-66.45
Cefuroxime	85.63	72.03	42.8	29.31	46.82	49.23	-42.51
Cefoperazone	6.03	9.44	7.54	5.91	5.55	2.08	-65.51
Total	234.73	245.08	172.13	151.58	127.11	92.19	-60.73
Beta-lactam/beta-lactamase Inhibitor							
Cefoperazone/sulbactam	5.05	3.53	0.52	3.63	1.96	1.82	-63.96
Ampicillin/sulbactam	90.61	90.79	81.59	25.95	82.84	42.36	-53.25
Piperacillin/tazobactam	23.82	25.85	29.45	14.10	20.87	6.38	-73.22
Amoxicillin/clavulanic acid	55.58	45.50	54.27	19.24	47.39	27.22	-51.03
Total	175.06	165.67	165.83	62.92	153.06	77.78	-55.57
Carbapenem							
Imipenem	9.69	5.18	5.56	3.11	2.83	0.00	-100
Meropenem	25.30	36.38	22.58	13.03	15.64	4.23	-83.28
Total	34.99	41.56	28.14	16.14	18.47	4.23	-87.91
Total Antibiotic Consumption	458.98	462.30	372.56	233.66	303.51	178.59	-61.09

Note: c = (b-a) / a x 100

Table 2: Number of ESBL *E. coli*, ESBL *Klebsiella*, ESBL *Proteus* and MDR *Acinetobacter* infections (n=252)

Infection	Number of Infection, n						Total, n (%)
	2014 Jan-Jun	2014 Jul-Dec	2015 Jan-Jun	2015 Jul-Dec	2016 Jan-Jun	2016 Jul-Dec	
ESBL	10	20	25	30	34	37	156 (61.90)
ESBL <i>E. coli</i>	0	4	7	8	11	18	48 (19.04)
ESBL <i>Klebsiella</i>	10	16	15	18	18	14	91 (36.11)
ESBL <i>Proteus</i>	0	0	3	4	5	5	17 (6.75)
MDR <i>Acinetobacter</i>	15	18	16	9	19	19	96 (38.10)
Total	25	38	41	39	53	56	252

Table 3: Number of ESBL and MDR *Acinetobacter* infections in HTAN according to disciplines from 2014 to 2016 (n=252)

Discipline	Number of Infection, n						Total, n (%)
	2014 Jan-Jun	2014 Jul-Dec	2015 Jan-Jun	2015 Jul-Dec	2016 Jan-Jun	2016 Jul-Dec	
ESBL							
Medical	3	5	9	10	7	10	44 (28.2)
Surgical	2	3	4	5	13	10	37 (23.7)
Orthopaedics	1	8	6	7	4	11	37 (23.7)
ICU/CCU	4	4	5	4	9	5	31 (19.9)
O&G	0	0	1	4	1	1	7 (4.5)
Total	10	20	25	30	34	37	156 (61.9)
MDR <i>Acinetobacter</i>							
Medical	3	3	2	0	4	2	14 (14.6)
Surgical	0	1	0	0	2	2	5 (5.2)
Orthopaedics	1	1	0	0	0	1	3 (3.1)
ICU/CCU	11	13	14	9	12	14	73 (76.0)
O&G	0	0	0	0	1	0	1 (1.1)
Total	15	18	16	9	19	19	96 (38.1)
Total MDRO Infection	25	38	41	39	53	56	252

Abbreviation: ICU/CCU – Intensive Care Unit/Coronary Care Unit; O&G – Obstetrics and Gynaecology; MDRO – multidrug-resistant organism

Correlation between Antibiotic Consumption and MDR Infection

The correlations between antibiotic consumption and MDRO infection were summarised in Table 4. There were negative correlations between all the antibiotics and ESBL infections. Strong negative correlations were observed between ESBL infections with ciprofloxacin, moxifloxacin, cefepime, ceftriaxone, cefotaxime and cefuroxime, but statistically significant correlation was only observed in ciprofloxacin and moxifloxacin. On the other hand, there were moderate positive correlations between MDR *Acinetobacter* infections with ampicillin/sulbactam and amoxicillin/clavulanic acid, but all were not statistically significant. Moderate negative correlation was observed between ceftazidime consumptions and MDR *Acinetobacter* infections, and it was not statistically significant as well.

In view of majority of the MDR *Acinetobacter* infections were from the ICU/CCU, a sub-analysis of correlation test was done between MDR *Acinetobacter* infections and antibiotic consumptions in ICU/CCU (Table 5). The findings showed statistically significant positive strong correlation between MDR *Acinetobacter* infections with piperacillin/tazobactam consumption in ICU/CCU. Positive moderate but not statistically significant correlations were observed between MDR *Acinetobacter* infections with cefuroxime, ampicillin/sulbactam and amoxicillin/clavulanic acid consumptions.

Table 4: Correlation between antibiotic consumption and MDRO infections in HTAN

Antibiotic	ESBL		MDR <i>Acinetobacter</i>	
	r	P-value	r	P-value
Quinolone				
Ciprofloxacin	-0.930	0.007 *	0.153	0.772
Moxifloxacin	-0.873	0.023 *	0.187	0.722
Cephalosporin				
Ceftazidime	-0.556	0.252	-0.623	0.186
Cefepime	-0.739	0.093	0.195	0.711
Ceftriaxone	-0.791	0.061	-0.330	0.523
Cefotaxime	-0.799	0.056	-0.074	0.889
Cefuroxime	-0.791	0.061	0.361	0.482
Cefoperazone	-0.575	0.232	-0.122	0.818
Beta-lactam/beta-lactamase Inhibitor				
Cefoperazone/sulbactam	-0.649	0.163	-0.392	0.442
Ampicillin/sulbactam	N.A.	N.A.	0.541	0.268
Piperacillin/tazobactam	N.A.	N.A.	0.068	0.898
Amoxicillin/clavulanic acid	N.A.	N.A.	0.440	0.382
Carbapenem				
Imipenem	N.A.	N.A.	-0.203	0.699
Meropenem	N.A.	N.A.	0.075	0.887

* Significant correlation between antibiotic consumption and MDR infections

Table 5: Correlation between antibiotic consumption and MDRO infection in ICU/CCU discipline in HTAN

Antibiotic	MDR <i>Acinetobacter</i>	
	r	P-value
Quinolone		
Ciprofloxacin	0.129	0.808
Moxifloxacin	0.092	0.862
Cephalosporin		
Ceftazidime	0.222	0.672
Cefepime	-0.263	0.615
Ceftriaxone	-0.106	0.842
Cefotaxime	-0.580	0.228
Cefuroxime	0.492	0.321
Cefoperazone	-0.582	0.226
Beta-lactam/beta-lactamase Inhibitor		
Cefoperazone/sulbactam	-0.795	0.059
Ampicillin/sulbactam	0.560	0.248
Piperacillin/tazobactam	0.839	0.037 *
Amoxicillin/clavulanic acid	0.512	0.299
Carbapenem		
Imipenem	-0.111	0.835
Meropenem	0.112	0.833

* Significant correlation between antibiotic consumption and MDR *Acinetobacter* infection

Discussion

The consumption of antibiotics in HTAN was found to decrease tremendously over the past three years of 2014 to 2016, especially in the carbapenem group. Total ESBL-producing bacterial infections increased gradually at the same period of time but not much changes was observed in terms of MDR *Acinetobacter* infections. Negative correlations were found between ESBL infections and quinolones use while positive correlations were found between MDR *Acinetobacter* infections and piperacillin/tazobactam consumption in the ICU/CCU.

The overall decreasing consumption of these antibiotics was due to the implementation of Antimicrobial Stewardship (AMS) in HTAN since January 2015. The programme aimed to improve patient outcomes and optimise antibiotic therapy with the hope to limit the emergence of antibiotic resistance, and hence to reduce MDRO infections without adversely impacting the quality of patient care (17). AMS activities conducted included antibiotic rounds by the medical consultants and clinical pharmacists weekly to fortnightly, restrictions in antibiotic use such as carbapenem use restriction, encouragement of intravenous to oral antibiotic conversion and de-escalation of antibiotics based on patient's condition and culture and sensitivity test results. Furthermore, antibiotic request form was required for all newly started broad-spectrum antibiotics and justification for their continuation after 72 hours of initiation. The antibiotics involved were imipenem, meropenem, piperacillin/tazobactam, cefoperazone/sulbactam, cefepime, cefoperazone, ceftazidime and ceftriaxone.

Previous studies suggested that prior exposure to third generation cephalosporins and quinolones could lead to the emergence of ESBL-producing strains, and thus the restriction of antibiotics use is needed to reduce the level of antibiotic resistance (7,16,17). Our result of decreasing antibiotic consumption with increasing ESBL infection was similar to the study conducted by Hyle *et al.* (22), which showed that prior antibiotic use was not independently associated with ESBL *E. coli* and *Klebsiella* infections. The only independent risk factor for ESBL *E. coli* and *Klebsiella* was the species of infecting organism. Molecular analysis from their study also indicated close genetic relatedness of *K. pneumoniae* isolates and this suggested that horizontal spread is important in the emergence of ESBL *E. coli* and *Klebsiella*. The antibiotic-resistance genes will still exist in the environment through the bacteria that have since replicated even if the specific antibiotic is no longer introduced (23). This may explain why ESBL infection in HTAN was still high despite the reduction in all antibiotic consumption.

Results from our study also suggested that there might be other causes besides antibiotic consumption that led to the increase in ESBL infections in HTAN. Previous studies have shown that the risk factors for nosocomial acquisition of ESBL-producing organism infections were age 65 years or higher, dementia, diabetes, accommodation in a ward or room with other patients with ESBL-producing organisms infection, history of recent hospitalisation, prolonged hospital stay and prolonged duration of presence of medical devices in the patient body such as urinary catheters, endotracheal tubes and central venous lines (19,24,25). In order to reduce the risk of transferring MDRO from colonisation to infection sites, the frequency of procedures that carry such risk should be minimised (26).

Administration of broad-spectrum antimicrobial agents, particularly third-generation cephalosporins, carbapenems, and fluoroquinolones were usually considered as one of the major risk factors for the acquisition of the MDR strains of *Acinetobacter* (5,13,19). Carbapenem consumption could modify the bacteria flora in patients and encouraged the infection and/or colonization of resistant bacteria (19). Nevertheless, our results only showed significant positive correlation between consumption of piperacillin/tazobactam and MDR *Acinetobacter* infections. This was similar with the study done by Chan *et al.* (27) which showed that prior use of piperacillin/ tazobactam was also found to be a significant risk factor for the emergence of extensively drug-resistant *Acinetobacter baumannii*.

The increasing incidence of MDR *Acinetobacter* infections in hospitals might be due to the ability of this organism to survive in dry inanimate surfaces for a long period, from three days to five months. They possess fimbriae or lipopolysaccharide side chains that can attach to the human epithelial cells and form biofilm when they are in contact with plastic and glass surfaces (28,29). These mechanisms facilitate the colonisation of *Acinetobacter* in patients or equipments used in medical care such as catheter. Therefore, ICU patients can acquire MDR *Acinetobacter baumannii* from an ICU room previously occupied by a carrier of these bacteria (30). Other risk factors included prolonged hospital stays, support with mechanical ventilation and exposure to infected or colonised patient in neighbouring hospital (13).

To minimize the horizontal spread of MDRO, greater attention should be placed on the early identification of such isolates and reducing the transmission through active infection-control surveillance in the hospital. The modes of transmission of MDRO among the patients include airborne, direct or indirect contact with contaminated equipment, contaminated environment or the contaminated hands of healthcare workers in the hospital. Failure of health care workers to practice aseptic technique (e.g., hand washing and changing gloves after examining a patient) was a leading contributor to the spread of drug-resistant organisms in hospitals (31). An adequate infection-control level of the nursing staffs and correct hand hygiene practices are important in minimising the risk of inter-patient spread of infections. Screening should be done for patient transferred from

other hospitals or residential homes and to detect readmitted patient who are previously found to be a carrier of MDRO (26). This is important because HTAN was part of the hospital cluster programme in Malaysia since 2016. Within a hospital cluster, resources of a few hospitals could be shared and patients may be transferred between the hospitals to improve the clinical outcome and efficiency of resources use.

This was a preliminary study done retrospectively in a non-electronic based hospital. The antibiotic consumption data was recorded manually, thus the chance of discrepancy may exist. Secondly, the acquisition of antibiotic resistance and the emergence of ESBL-producing bacteria and MDR *Acinetobacter* may not occur parallelly with the antibiotic consumption. Furthermore, the reduction of ESBL and MDR *Acinetobacter* infections may take some time to be reflected from the reduced antibiotic consumption. Hence, the results should be interpreted with caution.

Conclusion

The consumption of antibiotics in HTAN has reduced from 2014 to 2016. The number of ESBL-producing bacterial infections has increased during the same period but the changes in the number of MDR *Acinetobacter* infections was minimal. The cases of ESBL infections were negatively correlated with quinolones use while MDR *Acinetobacter* infections were positively correlated with piperacillin/tazobactam consumption in the ICU/CCU. This showed that besides the strict control and reducing the consumption of antibiotics, other factors may also be important in suppressing emergence of MDR organisms. More studies should be carried out to identify the other possible contributing factors in order to aid future planning of strategies in combating antibiotic resistance.

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Conflict of Interest Statement

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Knowledge, Awareness and Perception about Contraception among Pharmacy Staffs: A Single Centre Experience

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Abstract

Introduction: Healthcare professionals play a vital role in instilling the right concept of contraception to the patients. Therefore, it is crucial for pharmacy staffs to emphasise the importance of contraception and changing the misconception of contraceptive usage.

Objective: This study aimed to assess the knowledge, awareness and perception of contraception among pharmacy staffs in a tertiary care hospital in Kelantan.

Methodology: This was a cross-sectional study involving the pharmacy staffs in Hospital Raja Perempuan Zainab II (HRPZ II) from March to June 2018. A validated, self-administered questionnaire from previous literature was utilised. It comprised of four sections namely demographic data, knowledge, attitude and perception towards contraception. The inclusion criteria were all pharmacy staffs which consisted of fully registered pharmacists, provisionally registered pharmacists and pharmacist assistants.

Results: A total of 130 questionnaires were distributed and 100 were returned which yielded a response rate of 77%. The mean (standard deviation (SD)) age of the study population was 32.0 (8.0) years old. Most of the respondents were female (n=72, 72%), degree holder (n=78, 78%) with the service duration of more than three years (n=62, 62%). The mean (SD) score of knowledge was 5.39 (1.34) with 74% (n=74) of respondents managed to obtain good knowledge of contraception. The mean (SD) score of awareness was 22.02 (2.64) with only 18% (n=18) of respondents having good awareness about contraception. Finally, the mean (SD) score of perception was 33.43 (3.21) with only 31% (n=31) of respondents scoring good perception regarding contraception. The correlation between the three domains showed that only awareness score was significantly associated with perception score ($r=0.292$, $p=0.004$).

Conclusion: Overall, knowledge, awareness and perception about contraception among pharmacy staffs in HRPZ II were still unsatisfactory. Continuing professional education is required to ensure that all pharmacy staffs are adequately informed regarding this topic.

Keywords: knowledge, awareness, perception, contraception, pharmacy

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Introduction

Contraception, also known as birth or fertility control, prevents pregnancy by interfering with the normal process of ovulation, fertilization, and implantation. There are various types of contraceptives that act at different points of the process (1). Contraceptive use offers protection against unplanned pregnancies and sexual transmitted diseases acquisition (2,3). Factors such as efficacy, safety, non-contraceptives benefits, cost and personal considerations influence patient's choice of contraceptive method (1).

The two important indicators in achieving universal access in reproductive health are increasing contraceptive prevalence rate and reducing the unmet need for family planning (4). Contraceptive prevalence rate has been growing rapidly in many developing countries but has yet to achieve the level of usage that exists in the developed countries (3). In Malaysia, the use of all available contraceptive methods is 55% and for modern methods is 32%. This figure is much lower when compared to global rate and less than the neighbouring countries (5).

Among the predictors which contribute to the underuse of contraceptives are patient preferences and health system factors. Another important reason is the amount of information regarding contraceptive methods that women receive from their healthcare providers (6). This includes pharmacy staffs who also play an essential role in providing correct and complete information on contraceptives. Often, they are regarded as an important source of information for women who are considering using contraceptives. Therefore, it is vital that they should be trained and have expertise in the area of comprehensive contraception counselling (7,8).

Poor communication happens when healthcare providers provide inconsistent and inaccurate information about contraception (9). Thus, pharmacy staffs with insufficient knowledge on contraception would miss the opportunity to educate women and became a potential barrier that prevents them from receiving proper counselling session (7,10). Providing erroneous information can dramatically affect the adherence to contraceptives (10). As a consequence, this will reduce the quality of family planning care for patients (6) and decrease their access to contraceptives (11).

A study conducted in United Arab Emirates showed that pharmacists had poor knowledge of proper use and missed dose instructions along with several misconceptions of oral contraceptive pills (10). Amin (2016) reported an alarming finding whereby there was no pharmacist in Egypt who managed to answer all questions about contraceptives correctly (7). So far, both works were carried out abroad among community pharmacists (7,10). In Malaysia, there is still inadequate literature regarding this topic especially in the context of pharmacy staffs in government sector. Therefore, we aimed to evaluate the level of knowledge, awareness and perception about contraception among pharmacy staffs in Hospital Raja Perempuan Zainab II (HRPZ II), Kelantan.

Methods

This was a cross sectional study conducted for a period of four months from February to May 2018. The survey involved all pharmacy staffs working in HRPZ II which included Fully Registered Pharmacists (FRP), Provisionally Registered Pharmacist (PRP) and pharmacist assistants. Those who were on leave during the study period were excluded. A self-administered questionnaire was adopted from previous literature and permission to use the research instrument was obtained from the corresponding author (12).

The questionnaire consisted of 3 domains namely knowledge (8 items), awareness (7 items) and perception (10 items). Each correct answer for the knowledge domain would receive 1 mark and a score of 0 was given to wrong or “do not know” response. This yielded a range of score of 0 to 8 with a score of 5 or more regarded as having good knowledge. All items in the awareness and perception domains were scored on a five-point scale ranging from 1 (strongly agree) to 5 (strongly disagree). The range of score for awareness domain was 7 to 35 with a score of 25 or more termed as high awareness. Whereas for perception, the score could range from 10 to 50 with good perception defined as a score of 35 and higher.

The data was entered and analysed using IBM SPSS Statistics version 22.0. All categorical data were presented as frequencies (n) and percentages (%) while continuous variables were expressed as mean and standard deviation (SD). Association between variables (knowledge, awareness and perception scores) were tested using Pearson’s correlation. A *p*-value of <0.05 was considered as statistically significant.

This research was approved by the Ministry of Health Malaysia (MOH) Medical Research and Ethics Committee (MREC) and was granted with the National Medical Research Register (NMRR) ID number of NMRR-18-830-40309. Permission to conduct the study at the site was obtained from the Hospital Director. Data were reported in a collective manner in the form of journal articles with no reference to a specific individual.

Results

A total of 130 questionnaires were distributed (67 FRP, 38 PRP and 25 pharmacist assistants) and 100 were returned which yielded a response rate of 77%. The mean (SD) age of the study population was 32.0 (8.0) years old. Most of the respondents were female (n=72, 72%), degree holder (n=78, 78%) with the working experience of more than three years (n=62, 62%). About half of the them were FRP (n=54, 54%) of the age 20 to 30 years old (n=54, 54%) and married (n=55, 55%) with average income of RM3,000 to RM5,000 (n=53, 53%) (Table 1).

Table 1: Demographic characteristics of the respondents (n=100)

Variables	n (%) / mean (SD)
Age, years, mean (SD)	32.0 (8.0)
Gender, n (%)	
Male	28 (28)
Female	72 (72)
Marital status, n (%)	
Single	45 (45)
Unmarried	55 (55)
Position, n (%)	
FRP	54 (54)
PRP	23 (23)
Pharmacist assistant	23 (23)
Working experience, n (%)	
Less than 1 year	18 (18)
1 to 3 years	20 (20)
More than 3 years	62 (62)
Education level, n (%)	
Diploma	20 (20)
Degree	78 (78)
Master	2 (2)
Income, n (%)	
RM1000 to RM3000	19 (19)
RM3001 to RM5000	53 (53)
More than RM5000	28 (28)

Abbreviation: FRP – Fully Registered Pharmacists; PRP – Provisionally Registered Pharmacist

The mean (SD) score of knowledge about contraception was 5.4 (1.3). Almost all respondents had heard of contraceptive method (n=99, 99%), and majority knew about IUD (n=86, 86%), condom (n=97, 97%) and oral contraceptive (n=86, 86%). Most of respondents were still unsure regarding the fact that birth control pills could not reduce the risk of cancer in women (n=56, 56%). Many of them answered wrongly for items “it is safe to have sex during infertile period i.e. during Day 1 to Day 12”, “a woman will not be able to get pregnant for at least two months after she has stopped taking birth control pills” and “in order to get birth control pills, a woman must have a pelvic exam” (47%, 45% and 45%, respectively) (Table 2). Overall, only a total of 74% (n=74) of respondents managed to obtain good knowledge regarding contraception (Table 5).

Table 2: Knowledge about contraception among the respondents (n=100)

Items in the Knowledge Domain	Correct response, n (%)	Incorrect response, n (%)
1. Have you ever heard of contraceptive method? #	99 (99)	1 (1)
2. The risk of getting certain types of cancer in women can be reduced by birth control pills	44 (44)	56 (56)
3. A woman will not be able to get pregnant for at least two months after she has stopped taking birth control pills	55 (55)	45 (45)
4. Male condoms can protect against sexually transmitted diseases	76 (76)	24 (24)
5. Common side effects of contraceptive pills include weight gain and mood swing	88 (88)	12 (12)
6. It is safe to have sex during infertile period i.e. during day 1 to day 12	53 (53)	47 (47)
7. There is an increased risk of breast cancer in women taking oestrogen-containing oral contraceptive	69 (69)	31 (31)
8. In order to get birth control pills, a woman must have a pelvic exam	55 (55)	45 (45)

The question was followed by: ‘If yes, please tick the method: condom, oral contraceptive, implant, hormone injection, IUD, others (please specify).’

The mean (SD) score of awareness about contraception was 22.0 (2.6). Respondents believed that both genders were responsible to use contraceptive method and that contraceptive methods could bring more benefit to health (96% and 71%, respectively). They mainly had misconceptions regarding “the use of contraceptive methods in young people will increase the risk of infertility in the future” and “contraceptive pills do not guarantee 100% contraception” (76% and 43%, respectively) (Table 3). In general, a small number of 18% (n=18) of respondents had good awareness regarding contraception (Table 5).

Table 3: Awareness about contraception among the respondents (n=100)

Items in the Awareness Domain	Strongly agree, n (%)	Agree, n (%)	Not sure, n (%)	Disagree, n (%)	Strongly disagree, n (%)
1. Only women are responsible to use contraceptive method	0 (0)	2 (2)	2 (2)	47 (47)	49 (49)
2. Contraceptive methods bring more damage than benefit to health	1 (1)	4 (4)	24 (24)	60 (60)	11 (11)
3. Contraceptive methods can protect the health of family and society *	18 (18)	49 (49)	26 (26)	7 (7)	0 (0)
4. The use of contraceptive methods in young people will increase the risk of infertility in the future	5 (5)	34 (34)	37 (37)	20 (20)	4 (4)
5. Contraceptive pills do not guarantee 100% contraception *	9 (9)	21 (21)	13 (13)	41 (41)	16 (16)
6. Women’s experiences of side effects linked to changes in contraception use i.e. changing to a safer form of contraceptive *	9 (9)	56 (56)	30 (30)	4 (4)	1 (1)
7. Discussion about contraception with spouse is embarrassing	4 (4)	10 (10)	9 (9)	55 (55)	22 (22)

* Reverse scoring items

Table 4: Perception about contraception among the respondents (n=100)

Items in the Perception Domain	Strongly agree, n (%)	Agree, n (%)	Not sure, n (%)	Disagree, n (%)	Strongly disagree, n (%)
1. According to Islamic teaching, the use of contraceptive method is considered a permissible action *	24 (24)	53 (53)	20 (20)	3 (3)	0 (0)
2. It is unnecessary to purchase contraceptives	1 (1)	15 (15)	19 (19)	55 (55)	10 (10)
3. Courage is needed to purchase condoms from pharmacies, conventional shops or dispensaries	25 (25)	47 (47)	16 (16)	11 (11)	1 (1)
4. Using condoms will create less sexual pleasure during sexual intercourse	16 (16)	18 (18)	58 (58)	5 (5)	3 (3)
5. Change in male attitude i.e. to participate in contraception, may increase contraceptive prevalence in some areas *	16 (16)	50 (50)	32 (32)	2 (2)	0 (0)
6. Contraceptives may reduce fear of unplanned pregnancy and afford woman the freedom to enjoy sexual relationship fully *	30 (30)	50 (50)	16 (16)	2 (2)	2 (2)
7. Contraceptives allow women to pursue higher education by delaying pregnancy and gain some measure of economic security *	26 (26)	53 (53)	14 (14)	6 (6)	1 (1)
8. It is complicated to use contraceptive methods	4 (4)	12 (12)	22 (22)	50 (50)	12 (12)
9. Sex education including contraception should be introduced in early age *	34 (34)	54 (54)	9 (9)	3 (3)	0 (0)
10. Health care providers must provide counselling on contraceptive methods, mechanism of action, best time to use and possible side effects to all women *	54 (54)	36 (36)	10 (10)	0 (0)	0 (0)

*Reverse scoring items

The mean (SD) score of perception about contraception was 33.4 (3.2). Respondents agreed that sex education including contraception should be introduced in early age (n=88, 88%). They also felt that health care providers must provide counselling on contraceptive methods, mechanism of action, best time to use and possible side effects to all women (n=90, 90%). However, they still hold negative perceptions on “courage is needed to purchase condoms from pharmacies, conventional shops and dispensaries” as well as “using condoms will create less sexual pleasure during sexual intercourse” (88% and 92%, respectively) (Table 4). All in all, only a handful of respondents (n=31) scored good perception regarding contraception (Table 5). The summary knowledge, awareness and perception levels were presented in Table 5.

As for correlation between the three study domains, only the awareness score was significantly but weakly associated with the perception score ($r=0.292$, $p=0.004$). Other variables were not significantly correlated with each other ($p>0.05$) (Table 6).

Table 5: Knowledge, awareness and perception levels of the respondents about contraception (n=100)

Domain	n (%) / mean (SD)
Knowledge Score, mean (SD)	5.4 (1.34)
Knowledge level ^a , n (%)	
Good	74 (74)
Poor	26 (26)
Awareness Score, mean (SD)	22.0 (2.64)
Awareness level ^b , n (%)	
Good	18 (18)
Poor	82 (82)
Perception Score, mean (SD)	33.4 (3.21)
Perception level ^c , n (%)	
Good	31 (31)
Poor	69 (69)

^a Good knowledge was defined as a score of 5 and higher; ^b Good awareness was defined as a score of 25 and higher;

^c Good perception was defined as a score of 35 and higher.

Table 6: Correlation between the study domains (n=100)

Domain	Knowledge score	Awareness score	Perception score
Knowledge score	-	$r=-0.005$ ($p=0.959$)	$r=0.094$ ($p=0.350$)
Awareness score	-	-	$r=0.292$ ($p=0.004$) *
Perception score	-	-	-

* statistically significant

Discussion

This study was conducted in view of the lack of local literature with regards to the topic of knowledge, awareness and perception on contraception among pharmacy staffs. Based on the literature review, previous investigators were more interested in the general population (4,13), students (12,14–16) and other healthcare providers (9,11,17).

Nowadays, the pharmacist’s role in family planning is expanding and becoming increasingly important as the providers of family planning services (18). These functions include educating patients, informing prescribers and facilitating access by giving referrals (7). Pharmacists in any practice setting can screen patients for contraceptive needs and identify patients who may benefit from the optimisation of their contraceptive methods. There are countries who already legalise pharmacist-initiated contraceptives to overcome the contraceptive access limitations. For example, in the United States, such initiative was launched in California, Oregon, Colorado, New Mexico and Maryland since 2013 (8). Having said that, the collaboration and support from other healthcare providers are essential for pharmacy services to be successful (18). In Malaysia,

pharmacist assistants also work hand in hand with the pharmacists (FRP and PRP) in public healthcare facilities to dispense medications to the patients (19). Therefore, it is important that they are also equipped with the adequate knowledge to ensure the correct filling and labelling of medications.

Almost all our respondents were familiar with contraceptive methods. Being the staffs from the healthcare line, this finding was expected as depicted from previous studies among the medical and pharmacy students. They found that all of their participants (100%) had previously heard of the contraceptive methods, with condoms being the most commonly known method (12,20). Our respondents were mostly unaware that birth control pills could not reduce the risk of cancer in women. Apparently, it appears to be an increased risk of breast cancer in women using combined oral contraceptives (21). We also shared similar findings with Elkalmi *et al.* (2015), where most of their subjects were unable to give correct answers to questions “it is safe to have sex during infertile period i.e. during day 1 to day 12”, “a woman will not be able to get pregnant for at least two months after she has stopped taking birth control pills” and “in order to get birth control pills, a woman must have a pelvic exam” (12).

It was noted that a quarter of our study population still lacked knowledge about contraception. This finding was consistent with the work by Amin (2016) that identified considerable gaps in the pharmacists' knowledge in oral contraceptives. The author found that 13% of the respondents did not know the correct answer to any of the questions while no pharmacist were able to answer all questions correctly (7). Elkalmi *et al.* (2015) also found that their participants exhibited a lack in the in-depth knowledge and awareness on contraceptive measures (12). As for Tran and Vo (2018), their study population in Vietnam too had low knowledge and awareness with high number of misperceptions (15). This is concerning since inadequate knowledge would lead to ineffective contraception and unintended pregnancies due to the incorrect use of contraceptives (17).

Our respondents showed poor awareness regarding contraception, which was even lower than the figure reported by Elkalmi *et al.* in 2015 (12). Our respondents were confused over whether contraceptive usage could lead to infertility, as also demonstrated in previous studies. The similar finding was also seen when many of our respondents thought that contraceptive pills could guarantee 100% contraception. On the bright side, however, majority of the subjects in our study and other previous studies agreed on the importance of introducing sex education including contraception in early age and the significance of health care providers to provide counselling services on contraception (12,15,20).

It is undeniable that pharmacists play an integral role in providing contraceptive counselling. The awareness of readily available contraceptive products and methods is vital for pharmacists to educate women and address potential barriers to contraceptive use (22). However, our respondents revealed low levels of awareness and perception on contraception. Both variables were important as they significantly correlated with each other, suggesting that pharmacy staffs with poor awareness may tend to have negative perception. This would generally affect their interest to develop counselling skills on contraception (7). We also found that other variables were not significantly correlated with each other as explained by Atibioko (2018), whereby high level of awareness did not necessary translate to good knowledge about contraception (11).

Our results are slightly worrying as patients are now more ready to seek medical advice from the pharmacy (7,8). Studies have shown that healthcare professional counselling on emergency contraceptives can influence their use among women. Such example is from the analysis of the National Survey of Family Growth data on the use of emergency contraception in the United States. They found that women who received counselling about emergency contraception within the year prior to unprotected sex or birth control failure were 11.7 times more likely to use an emergency contraceptive compared with women who did not receive counselling (95% confidence interval 6.20- 22.15, $p < 0.001$) (23).

There were some limitations in this study. It was a single centre study, although with satisfactory response rate, the small sample captured might not reflect the opinions of all pharmacists and the results could not be generalised to the whole population. Nonetheless, we hope that the findings of this research are worth noting for future reference. Further research is required to establish the results of this study at the national level. A multicentre study involving more facilities from other regions in Malaysia which incorporates probability sampling method is recommended to avoid the potential bias.

Conclusions

Overall, the knowledge, awareness and perception about contraception among the pharmacy staffs in HRPZII were unsatisfactory. Continuing professional education is required to ensure that all pharmacy staffs are adequately informed regarding this topic. For them to get the most out of the educational programmes, they should address the existing gaps in their knowledge, create awareness and instil positive perception. This is important as pharmacy staffs frequently interact with patients and thus have the opportunity to promote effective contraception especially when patients present for emergency contraception, to a hospital for labour and delivery, or to a clinic for chronic disease management. Pharmacy staffs have the responsibility to reinforce their knowledge regarding contraception in order to educate other providers and patients. Assessment of their knowledge, awareness and perception is an important step in designing future training, education, and research endeavours.

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Conflict of Interest Statement

The author declared no conflict of interest. No external organisation was involved in this research project as it was self-funded by the authors.

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Assessment of the Clinical Outcomes of Warfarin Therapy in Two Models of Anticoagulation Services

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Abstract

Introduction: The quality of anticoagulation control is commonly expressed by time spent in the therapeutic international normalised ratio (INR) range (TTR). It is important to ensure the optimal outcome during therapy because the high variability of INR is associated with adverse outcomes.

Objective: This study was conducted to assess the clinical outcomes of warfarin therapy among warfarin treated patients in usual medical care (UMC) and Warfarin Medication Therapy Adherence Clinic (WMTAC) in Kajang Hospital.

Methods: A cross-sectional study of randomly sampled patients from UMC and WMTAC was carried out from May 2013 to May 2014. The primary outcomes were the percentage of time when INR was within the therapeutic range (% TTR) and the percentage of time when INR was within the expanded therapeutic range (% expanded TTR). The secondary outcomes were the number and severity of haemorrhagic and thromboembolic complications, and patients' compliance and defaulter rate.

Results: A total of 78 patients were recruited (45 patients in UMC and 33 patients in WMTAC). The most common indications for warfarin were atrial fibrillation and mechanical heart valves. The TTR was 66.6% for WMTAC and 45.5% for UMC patients ($p < 0.001$) while the expanded TTR for WMTAC was 79% and 55.8% for UMC ($p < 0.001$). There was no significant difference between WMTAC and UMC patients in terms of complications of warfarin therapy. The compliance score showed significant difference with WMTAC patients scored 1.45 and UMC patients scored 2.29. The defaulter rate was significantly lower in WMTAC (3%) compared to UMC (22%) ($p = 0.038$).

Conclusion: The pharmacist-managed WMTAC can help patients to achieve better anticoagulation control, higher compliance to warfarin and lower defaulter rate among patients receiving warfarin therapy. Therefore, more cooperation between the physicians and pharmacists as such should be promoted to explore the potential to improve patient therapeutic outcomes.

Keywords: warfarin, anticoagulation care, warfarin therapy, pharmacist-managed warfarin clinics, medication therapy adherence clinic

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Introduction

Warfarin, a Vitamin K antagonist, is the most widely used anticoagulant in thromboembolic diseases prevention and treatment (1). Treatment with warfarin, however, is challenging due to its narrow therapeutic index, complicated pharmacokinetic and pharmacodynamic profiles as well as drug interactions (2). The quality of anticoagulation control is commonly expressed as the time spent in the therapeutic international normalised ratio (INR) range (TTR). It is important to ensure optimal TTR during therapy because the high variability of INR is associated with adverse outcomes such as thromboembolism and bleeding events (3).

There are two primary models available in Kajang Hospital for managing oral anticoagulation therapy: the physician-managed oral anticoagulation clinics which is the usual medical care (UMC) in most hospitals and the pharmacist-managed Warfarin Medication Therapy Adherence Clinic (WMTAC). WMTAC was introduced as a clinical pharmacy service in the ambulatory care. It serves to enhance patient care for patients on anticoagulation therapy through pharmacist counselling, patient education and close follow-up, thereby

optimising treatment benefits and minimising complications from anticoagulation therapy (4). Several studies found that pharmacist-managed warfarin therapy results in decreased warfarin-related hospital admission, less drug interactions as well as improved patient compliance and anticoagulation control (4-5). High-quality anticoagulant therapy could reduce thromboembolic events while minimising bleeding risk (6). In view of the lack of studies on the effects of pharmacist-managed anticoagulation clinics in our local settings, this study was conducted in Kajang Hospital, Malaysia to assess the clinical outcomes among warfarin treated patients. We compared coagulation control between UMC and WMTAC patients in terms of percentage of time when the INR was within the therapeutic range (% TTR), percentage of time when the INR was within the expanded therapeutic range (% expanded TTR) and the number and severity of haemorrhagic and thromboembolic events. This study also evaluated patients' compliance towards warfarin therapy and the rate of defaulter among warfarin treated patients in both groups.

Method

Usual medical care (UMC) and Warfarin Medication Therapy Adherence Clinic (WMTAC)

A cross-sectional study was carried out in the anticoagulation clinics in Kajang Hospital from May 2013 to May 2014. The anticoagulation clinics were categorized as UMC and WMTAC. UMC was the usual medical clinic managed by the physicians that operates for three days in a week. On the other hand, WMTAC is conducted by the pharmacists on a weekly basis. Patients under the regular follow-up of the UMC clinic will be referred to the WMTAC according to clinical needs.

Both clinics required the patients to have their blood drawn for an INR test during their follow up. The physicians and pharmacists will then assess patients' INR results. For the UMC group, dosage changes and time intervals for INR blood tests were at the discretion of the individual physician based on their knowledge and experience in the management of warfarin. There was no specific dosing guide for UMC.

The pharmacists involved in WMTAC are required to complete a two-week short course on anticoagulation management to equip themselves with the clinical knowledge to assess patients individually to develop patient-specific recommendations. The management of the warfarin therapy was carried out in accordance with the Ministry of Health (MOH) WMTAC Protocol (4). This protocol included evidence-based guidelines for dosage recommendations and intervals for INR testing. The WMTAC pharmacists maintain a list of all the WMTAC patients and a record of patients scheduled for appointment. During the WMTAC appointment, patients were assessed for changes in their medications or diet, signs and symptoms of haemorrhagic or thromboembolic events, missed doses and illnesses. Besides playing an expanded role in patient education and counselling, pharmacists in the WMTAC use the MOH WMTAC Protocol guideline as well as clinical judgement to develop the care plan of dosage change if required. Assessment and recommendations made were documented into the patients' records, which were made available to the physicians. In cases where INR readings are less than 1.0 or more than 4.0, suspicion of serious adverse effects, new clots or serious bleeding, patients will be referred to physician as outlined in the protocol.

Ethical Considerations

Approval to conduct the study was obtained from the Ministry of Health Malaysia (MOH) Medical Research and Ethics Committee (MREC) and the study was registered with the National Medical Research Register (NMRR). Permission from the head of Medical Department was obtained to conduct the study. The patients who met the inclusion criteria were interviewed to assess their compliance. Prior to that, a consent requesting them to willingly participate in the study was obtained. Participants were explained the purpose of the study and assurance of anonymity in the management of data. In addition, they were allowed to ask questions about the interviews. All data collection and information were remained confidential according to the ethical requirements.

Study Population

Eligible patients were screened for recruitment based on inclusion criteria which were adults aged 18 years and above, on warfarin therapy for at least 3 months and under follow up of anticoagulation clinics for at least 3 months. There should be at least two INR readings taken not more than 6 weeks apart. Patients taking warfarin for antiphospholipid syndrome were not included in this study. INR readings taken during hospitalization and during temporary planned interruptions were excluded. It was predicted that the physician-managed

anticoagulation service in UMC would achieve the target INR in about 50% of the time (9-10). Hence, a sample size of 45 patients in each group would be required to have a statistical power of 80% and α error of 0.05 to detect the difference.

Study Outcomes

The primary outcomes were the percentage of TTR and expanded TTR of patients in the WMTAC group compared to the UMC group. The percentage of time patients' INR in therapeutic range reflects INR control over time. The percentage was obtained by dividing the number of INRs within the target range for each patient with the overall number of INRs during that selected time interval. The expanded therapeutic INR range was defined as the therapeutic range INR ± 0.2 , where dosage adjustment is not required because such variation is not considered clinically significant (1). Thus, the percentage of TTR and expanded TTR of patients were calculated using equation, as follows:

$$\% \text{ TTR} = \frac{\text{Number of INR within the target range}}{\text{Total number of INR}} \times 100$$

$$\% \text{ expanded TTR} = \frac{\text{Number of INR within the } \pm 0.2 \text{ target range}}{\text{Total number of INR}} \times 100$$

The secondary outcome measurement included adverse events or complications, patients' compliance and defaulter rate. Thromboembolic and haemorrhagic adverse events are possible complications of warfarin adverse events. Thromboembolic event is defined as any embolic or thrombotic cerebrovascular accident, deep vein thrombosis, pulmonary embolism or other systemic thromboembolic events detected during the study period. Cases which do not require hospitalisation were classified as minor events whereas those require hospitalisation were classified as major events. Major bleeding was defined as bleeding episode which requires hospitalisation whereas minor bleeding does not require further intervention. Minor bleeding includes mild bruising, nose bleeding, gum bleeding, haematuria and rectal bleeding (7).

Warfarin Compliance-Assessment Scale (WCAS) developed by Huber *et al.* from the Community Anticoagulation Therapy Clinic was used to measure the patient's compliance towards warfarin therapy. It is a compliance tool that assigns points to the various aspects of medication use, diet, and alcohol use. The tool provides an objective measure of patient compliance with warfarin therapy. Lower score indicates higher compliance (8). On the other hand, rate of defaulter is defined as the percentage of scheduled appointments defaulted by patients during the study period. The percentage was obtained by dividing the number of appointments missed by patients with the total number of appointments made by UMC or WMTAC during the study period.

Data Collection

Simple random sampling technique was used to recruit sample in this study. Since the hospital does not have a computerized data system, the list of patients who were on warfarin therapy was captured manually from the patients' medical files and prescriptions. The patients who met the inclusion criteria were interviewed to assess patients' compliance using WCAS. In addition, a data collection form was used to extract data from patients' medical records, which include patients' demographics, medical illness, indications for warfarin, INR target, duration of therapy, risk factors for bleeding or thromboembolic events, concurrent medication, occurrence of haemorrhagic and thromboembolic complications after initiation of warfarin as well as the number of appointments made and missed during the study period.

Statistical analysis

Statistical analysis was performed using SPSS version 20. Descriptive statistics was used to describe the demographic characteristics of the patients. For INR control, the mean and standard deviation (SD) value for the percentage days in range was calculated for all the patients who were included for INR control analysis. The default rate, % TTR and % expanded TTR were analyzed using independent t-test with 0.05 set as the level of significance. The differences in complications and compliances between the two groups were analyzed using Chi-square test.

Results

For UMC group, 63 out of 102 patients screened met the inclusion criteria. Out of 63 patients, 45 patients were randomly selected. Out of 43 WMTAC patients screened, 33 patients who met the inclusion criteria were included, making a total of 78 patients in the study. The demographic data showed that the baseline characteristics were similar between the groups. The majority of the warfarin treated patients were male (45.5% in WMTAC and 64.4% in UMC) and Malay (60.6% in WMTAC and 55.6% in UMC). The most common indications for warfarin were atrial fibrillation (AF) and mechanical heart valves. Of the 78 patients recruited, three patients had individually narrowed INR targets, i.e. 2.0 to 2.5 and 2.5 to 3.0.

Table 1: Demographic characteristics of the study population (n=78)

Variables	WMTAC, n (%)	UMC, n (%)	X ² -stats (df)	P-value
Gender			2.792 (1) ^a	0.09
Male	15 (45.5)	29 (64.4)		
Female	18 (54.5)	16 (35.6)		
Age			7.083 (5) ^b	0.214
31-40	1 (3.0)	1 (2.2)		
41-50	6 (18.2)	5 (11.1)		
51-60	3 (9.1)	17 (37.8)		
61-70	8 (24.2)	11 (24.4)		
71-80	11 (33.3)	9 (20.0)		
81-90	4 (12.1)	2 (4.4)		
Race			0.483 (2) ^a	0.785
Malay	20 (60.6)	25 (55.6)		
Chinese	9 (27.3)	12 (26.7)		
India	4 (12.1)	8 (17.8)		
Warfarin indication			0.643 (6) ^b	0.996
AF	23 (69.7)	31 (68.9)		
Mechanical heart valve	6 (18.2)	5 (11.1)		
AF & MVR	2 (6.1)	1 (2.2)		
DVT	0	2 (4.4)		
PE	0	1 (2.2)		
MI/ACS	0	1 (2.2)		
Others	2 (6.1)	4 (8.9)		
Risk factors for thromboembolism or bleeding			8.183 (4) ^b	0.085
Hypertension	19 (57.6)	12 (26.7)		
Diabetes mellitus	3 (9.1)	1 (2.2)		
Previous cardiovascular accident	0	1 (2.2)		
Hypertension & Diabetes mellitus	2 (6.1)	10 (22.2)		
Nil	9 (27.3)	21 (46.7)		
INR range target			1.182 (3) ^b	0.757
2.0-3.0	25 (76)	40 (89)		
2.0-2.5	1 (3)	1 (2)		
2.5-3.0	1 (3)	0		
2.5-3.5	6 (18)	4 (9)		

^a Chi-square test; ^b Chi-square test (Yate's)

Abbreviation: AF – atrial fibrillation; MVR – mechanical valve replacement; DVT – deep vein thrombosis; PE – pulmonary embolism; MI – myocardial infarct; ACS – acute coronary syndrome

Table 2 summarised the anticoagulation control of WMTAC and UMC patients. The frequency of INR assessment was significantly higher in WMTAC patients, with mean 12 (SD 2.9) INR assessments per patient, compared to UMC patients who had mean 7.7 (SD 3) INR assessments per patient over 12 months (p<0.001). The mean difference between the two groups was 4.3 tests (95% confidence interval (CI) 3.00-5.61). The anticoagulation control was significantly better in WMTAC patients, with 65.1% of them achieving the target INR as compared to 46.0% among UMC patients (p<0.001). In relation, the mean percentage TTR was significantly higher in WMTAC patients (66.6% (SD 13.6%) versus 45.5% (SD 21.4%), p<0.001). The mean difference was

21.1% (95% CI 12.7-29.6). Similar results were obtained in terms of the percentage of expanded TTR (79.0% (SD 12.9%) versus 55.8% (SD 22.9%), $p < 0.001$). The mean difference was 23.2% (95% CI 14.3-32).

The complications of warfarin therapy were presented in Table 3. There was no significant difference between WMTAC and UMC patients in terms of complications of warfarin therapy. The compliance score showed a significant difference between the two groups with WMTAC patients scored 1.45 (SD 0.97) and UMC patients scored 2.29 (SD 1.23) ($p = 0.002$), indicating that WMTAC patients had better compliance (Table 4). The mean difference between the groups was -0.8 (95% CI -1.4 - -0.3). As shown in Table 5, the follow up default rate was significantly lower in the WMTAC group (3.0%) compared to patients in the UMC group (22.2%) ($p = 0.038$). Ten out of 45 UMC patients defaulted their follow-up appointment at least once during the study period while only one of the 33 WMTAC patients did not attend their appointment once.

Table 2: Anticoagulation control of in WMTAC and UMC patients (n=78)

Variables	WMTAC (n=33)	UMC (n=45)	Statistics (df)	P-value
No. of INR readings, n	395	346	3.24 (1) ^{a#}	0.072 ^a
INRs test / patient, mean (SD)	12.0 (2.9)	7.7 (3.0)	6.394 (76) ^{b*}	<0.001 ^b
INRs within range, n (%)	257 (65.1)	159 (46.0)	27.354 (1) ^{c#}	<0.001 ^c
% TTR, mean (SD)	66.6 (13.6)	45.5 (21.4)	4.986 (76) ^{b*}	<0.001 ^b
% Expanded TTR, mean (SD)	79.0 (12.9)	55.8 (22.9)	5.216 (76) ^{b*}	<0.001 ^b
INRs < 1 unit from target, n (%)	0	11 (3.2)	7.482 (1) ^{c#}	0.006 ^c
INRs > 5, n (%)	5 (1.3)	2 (0.6)	1.522 (1) ^{c#}	0.217 ^c

^a Chi-square test; ^b Independent t-test; ^c Chi-square test (Yate's); # data presented in X²-stats (df); * data presented in t-stats (df)

Abbreviation: INR – international normalised ratio; SD – standard deviation

Table 3: Complications of warfarin therapy among WMTAC and UMC patients (n=78)

Variables	WMTAC, n (%)	UMC, n (%)	X ² -stats (df) ^a	P-value ^a
Number of haemorrhage episode			0.993 (2)	0.609
0	30 (90.9)	35 (77.8)		
1	3 (9.1)	8 (17.8)		
2	0	2 (4.4)		
Severity of haemorrhage complications			0.005 (1)	0.943
Minor	3 (9.1)	8 (17.8)		
Major	0	2 (4.4)		
Number of thromboembolic episodes			0.025 (1)	0.874
0	32 (97)	45 (100)		
1	1 (3)	0		

^a Chi-square test (Yate's)

Table 4: Compliance assessment of WMTAC and UMC patients

Variables	WMTAC	UMC	Statistics (df)	P-value
Compliance score, mean (SD)	1.45 (0.97)	2.29 (1.23)	-3.125 (76) ^{a*}	0.002 ^a
Compliance Score, n (%)			8.616 (4) ^{b#}	0.071 ^b
0	5 (15.2)	4 (8.9)		
1	14 (42.4)	8 (17.8)		
2	8 (24.2)	13 (28.9)		
3	6 (18.2)	11 (24.4)		
4	0	9 (20.0)		

^a Independent t-test; ^b Chi-square test (Yate's); * data presented in t-stats (df); # data presented in X²-stats (df)

Table 5: Default rate of WMTAC and UMC follow up

Clinics	Number of default (%)	X ² -stats (df) ^a	P-value ^a
WMTAC	1 (3.0)	4.313 (1)	0.038
UMC	10 (22.2)		

^a Chi-square test (Yate's)

Discussion

The results from our study indicated better control of INR values among WMTAC patients as they spent more time in both the TTR and the expanded TTR compared to the UMC group. These differences were statistically significant. There were several studies which compared pharmacist managed anticoagulation services to usual care. The studies that supported our findings include two randomised controlled trials and three observational studies. In one randomized controlled trial conducted in Canada, patients were allocated to either anticoagulation clinics with a pharmacist in three tertiary hospitals (n = 112) or to their family physician practices (n = 109). Patients followed up in the anticoagulation clinics were within the expanded therapeutic range more than patients managed by family physicians (82% vs 76%, p < 0.05). High risk INR values (defined as being <1.5 or >5.0) were more often observed in patients managed by family physicians (40% vs 30%, p < 0.05) (9). In another study conducted in Hong Kong, patients were randomized to either a pharmacist managed anticoagulation clinic (n = 68) or physician managed service (n = 69). This randomized controlled trial found higher TTR among patients in the pharmacist managed group than the physician managed group (64% vs 59%, p < 0.001) (10).

The three observational studies were conducted in Canada, United States and Malaysia respectively. The Canadian research is a prospective cohort study where patients (n = 125) referred to the pharmacist Anticoagulation Management Service (AMS) with at least four months anticoagulation management prior to referral were included in a pre- and post-analysis of anticoagulation control. The anticoagulation control in the AMS improved compared to the standard care before referral (66.5% vs 48.8%, p <0.0001) (11). The study conducted by Rudd *et al.* in the United States (n=996) reported significantly improved patients anticoagulation control in pharmacist managed anticoagulation clinics as measured by the TTR (12).

A retrospective cohort study conducted in a tertiary hospital in Malaysia found that WMTAC (n=92) had significantly higher %TTR compared to UMC (n=92) (65.1% vs 48.3%, p<0.05). These findings were similar to our study. Moreover, the study also showed that the rate of admission due to warfarin complications and bleeding incidences were reduced in the pharmacist-managed group although it was not significantly different. These findings were similar to our study as there was no significant difference between WMTAC and UMC patients in terms of complications of warfarin therapy. In our study, however, two patients (4.4%) from the UMC group were hospitalised due to hemorrhagic complications of over-warfarinisation. Major haemorrhagic complications were not reported among the warfarin treated patients in the WMTAC group. Three patients (9.1%) from the WMTAC group and eight patients (17.8%) from UMC group were reported to have minor complications such as bruises, gum-bleeding, haematuria, black stool and rectal bleeding.

Compliance assessment is important as warfarin has multiple drug and food interactions and requires frequent laboratory monitoring. Our study used an assessment questionnaire (WCAS) to measure patients' compliance in taking warfarin (8). Our findings showed that WMTAC patients had significantly better compliance towards warfarin therapy compared to UMC patients. This could be attributed to the role of pharmacists in the WMTAC on clinical counselling, patient education, strict INR monitoring, standardized follow-up and comprehensive pharmaceutical care for warfarin treated patients in accordance with protocol (13).

Our study further investigated the default rate among the warfarin treated patients which was not reported by other studies. Findings showed that UMC patients had higher defaulter rate as compared to patients in the WMTAC group. This may be due to the high patient loads and long waiting time in the medical clinics. Hence, WMTAC service can be viewed as a solution to help to share the burden of increasing patient loads. In view of the benefits of WMTAC, such collaborative efforts involving the pharmacists and physicians could be an effective structure for the optimisation of anticoagulation management (14,15). The cooperation between

physicians and pharmacists, not only in anticoagulation management but also in other therapeutic groups, should be considered and expanded to optimise patients' therapeutic outcomes.

There were a few limitations that should be considered. In this study, the WMTAC group was unable to achieve the calculated sample size. Nevertheless, all the WMTAC patients who met inclusion criteria were recruited and post-hoc power analysis revealed more than 80% power. Our study was not powered to detect differences in bleeding or thromboembolic complications between the two groups. Other potential limitation included self-reporting of compliance by the patients. Future research could consider evaluating the effectiveness of WMTAC in a larger cohort and determining the cost effectiveness of WMTAC services.

Conclusion

The pharmacist-managed WMTAC service was able to help patients to achieve better anticoagulation control, higher compliance towards warfarin and lower default rate. These results warrant its effectiveness and continuity in future practice. Therefore, more cooperation between the physicians and pharmacists like the WMTAC services should be promoted to explore the potential to improve patient therapeutic outcomes.

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Conflict of Interest Statement

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

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Evaluation of Egami Risk Scores in Predicting Intravenous Immunoglobulin (IVIG) Resistance in Malaysian Paediatric Population with Kawasaki Disease

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Abstract

Introduction: Egami score has been used in various countries to predict the resistance to intravenous immunoglobulin (IVIG) in paediatric patients with Kawasaki Disease (KD), but it has not been validated in Malaysia.

Objective: To evaluate the use of Egami Scores in predicting IVIG resistance in the Malaysian paediatric population with KD.

Methods: Retrospective data of children admitted for KD and received IVIG within 10 days of the onset of illness from 2008 to 2015 was collected from two hospitals in Kedah, Malaysia. IVIG resistance was defined as fever more than 37.5°C for more than 36 hours or recurrent fever following a period of defervescence after the administration of initial IVIG. Egami scores were assigned based on patients' demographic and laboratory parameters. Patients with Egami scores of 0 to 2 were categorised as low risk while patients with 3 points and above were categorised as high risk of IVIG resistance.

Results: Egami risk scores were calculated for 57 KD patients with complete data. Nine of these patients (15.8%) had IVIG resistance while 48 were IVIG responders. The median Egami scores for IVIG resistant patients and IVIG responders were 3 (inter-quartile range (IQR) 1-3) and 1 (IQR 1-2) respectively ($p=0.055$). Among the nine IVIG resistant patients, three (33.3%) were categorised in the low-risk group and six (66.7%) were in the high-risk group. Among the IVIG responders, 37 patients (77.1%) were categorised as having low risk for IVIG resistance and 11 patients (22.9%) were in the high-risk group ($p=0.015$). Therefore, the Egami score could predict IVIG resistance with a sensitivity of 66.7%, specificity of 77.1%, positive predictive value of 35.3% and negative predictive value of 92.5%.

Conclusion: The Egami score was able to predict IVIG resistance but it may not be sensitive enough to be applied as the only method of prediction.

Keyword: Egami score, IVIG resistance, Kawasaki disease, Kawasaki prediction score

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Introduction

Kawasaki disease (KD) is an acute inflammatory syndrome predominantly affects children younger than 5 years old (1). It is characterised by five days of fever with other clinical features, including non-exudative bilateral conjunctival injection, erythema of the lips and oral cavity, atypical rash, oedema or erythema of hands and feet, and cervical lymphadenopathy (2). The aetiologies of KD remain unknown, but it has been reported to substitute acute rheumatic fever as the leading cause of acquired heart disease among children in developed countries (3). The potentially fatal complications of KD may include coronary artery (CA) dilatation and aneurysm formation (4).

In principal, the primary objective in the treatment of acute KD is to minimise the risk of developing CA lesions and prevent further complications (5). It has been suggested that prompt treatment using high dose (2g/kg) intravenous immunoglobulin (IVIG) during the initial 10 days of illness will provide immediate

suppression of the acute-phase inflammatory reaction in KD, resulting in lower incidence of CA aneurysms and less coronary damage (6,7). However, several studies also highlighted that 13 to 21 percent of patients receiving IVIG tend to develop persistent fever or recrudescence upon completion of the initial IVIG administration. Such patients are considered to have IVIG resistance or refractory KD (8-11), and these patients have the greatest risk of developing CA aneurysms (12, 13). Thus, early identification of patients who has high tendency of developing IVIG resistance is important in order to provide alternative options such as the use of other anti-inflammatory therapies, including corticosteroids (14) or anti-tumour necrosis factor (TNF)- α therapy (15).

Evaluation of the likelihood of patients developing IVIG resistance can be performed using several established risk scoring algorithm, including the Fukunishi score(16), Egami score(8), Kobayashi score(9), and Sano Score(10) from Japan, San Diego score(13) from America and the most recent Formosa score(17) from Taiwan. The duration of illness prior to initial treatment, age, inflammatory markers, liver enzyme and blood counts are among the common variables included in most of the scoring system. Kobayashi and Sano scores additionally account for the level of aspartate aminotransferase (AST). A recent study by Sleeper *et al.* showed that when all the three existing Japanese scoring systems (Kobayashi Score, Egami Score and Sano score) were used to predict IVIG resistance in the North American population, the scores displayed good specificity but low sensitivity of less than 45%. Of which, the Egami scores demonstrated the highest sensitivity and specificity as compared to the other scoring methods (18).

To explore the potential of using Egami score to predict IVIG resistance in the local setting, it is important to externally validate the Egami score in the multi-ethnic Malaysian population. Hence, in this study, we aimed to evaluate the use of Egami Scores in predicting IVIG resistance in the Malaysian paediatric population.

Methods

A retrospective study was performed using the medical records of KD patients who were admitted between 2008 to 2015 in the two selected general hospitals at the northern region of Malaysia, namely the Sultan Abdul Halim Hospital and Sultanah Bahiyah Hospital. The classification of KD patients in this study was based on the clinical diagnosis in accordance to the modified American Heart Association criteria, which includes five or more days of fever and the presence of at least four out of the five principle clinical features (non-exudative bilateral conjunctival injection, erythema of the lips and oral cavity, atypical rash, oedema or erythema of hands and feet, and cervical lymphadenopathy), or the presence of less than four clinical features when CA disease is detected through echocardiography or coronary angiography (19).

KD patients who received the initial dose of 2g/kg IVIG within 10 days of the onset of illness were included into the study. Patients were categorised as IVIG resistance with the presence of fever more than 37.5°C lasting more than 36 hours or recurrent fever following a period of defervescence after the administration of initial IVIG. The complete data on admission details, age, sex, duration of fever (in days), complete blood count, erythrocyte sedimentation rate (ESR), albumin, total bilirubin, alanine aminotransferase (ALT), C-reactive protein (CRP) and echocardiogram results were obtained and screened. Patient's CA status was confirmed upon echocardiogram done during the acute phase and any repeated echocardiogram at six to eight weeks period by a certified paediatric cardiologist.

Egami scores were assigned based on patients' demographic and laboratory parameters. In the Egami algorithm to predict IVIG resistance, scores were recorded in the scale of 0 to 5 points. Patients with Egami scores of 0 to 2 were categorised as having low risk of IVIG resistance while patients with 3 points and above were categorised in the high-risk group. The Egami scores were assigned according to the following criteria: ALT \geq 80IU/L (2 points), day of illness at initial IVIG day 4 or earlier (1 point), CRP \geq 8mg/dL (1 point), platelet counts \leq 30.0 x 10⁴/mm³ (1 point) and age \leq 6 months (1 point).

Statistical Package for the Social Science (SPSS) Version 21.0 was used for data analysis. Demographic and descriptive data were presented as mean with standard deviation (SD) or medians with inter-quartile range (IQR) for continuous data, and frequency (n) with percentage (%) for categorical data. Student T-test was used to compare the resistance to IVIG for normally distributed variables and Mann-Whitney U test was used for the non-normally distributed variables. Fisher exact test and Chi Square test were applied to compare the categorical risk score (number of points) distributions by IVIG re-treatment status. Statistical significance was set at 0.05. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the score were calculated.

Results

From 2008 to 2015, there were a total of 99 patients with the diagnosis of KD who received IVIG. However, only 88 patients were included in this study. Seven patients were excluded as IVIG were given only after 10 days of illness, two were excluded following incomplete data on temperature charting, and another two were excluded due to lack of record on the criteria fulfilment for Kawasaki Disease.

Figure 1 showed the number of KD and IVIG resistance cases from 2008 to 2015. The highest number of KD cases were recorded in 2014 and 2015, with 16 and 15 cases respectively. Of the total included patients, there were 12 patients (13.6%) with IVIG resistance. Seven patients had persistent fever (temperature >37.5°C) for more than 36 hours and 5 patients had recurrent fever after a period of defervescence.

In the baseline characteristics of study populations (Table 1), a vast majority were Malays (73.9%) followed by Chinese (20.5%) and Indians (5.7%). In terms of gender, there were higher proportion of males both in the IVIG resistance group (83.3%) and IVIG responder group (60.5%). The median age for IVIG resistance group were found to be 8.5 months whereas the IVIG responder group was 12 months.

Figure 1: The number of KD and IVIG resistance in two northern Malaysia hospitals from 2008 to 2015 (n=88)

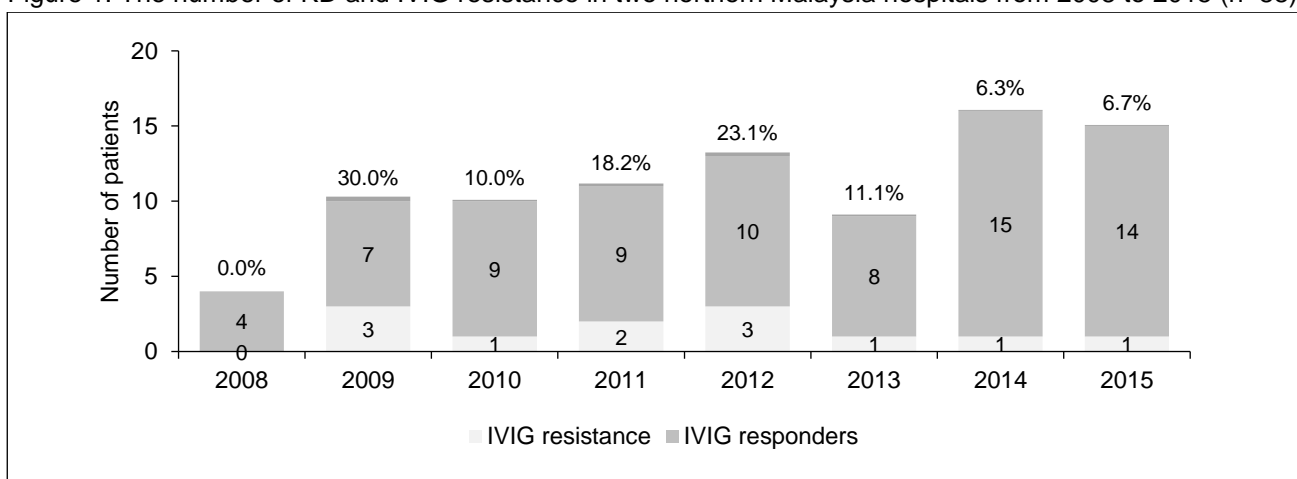


Table 1: The baseline characteristics of IVIG resistance and IVIG responders (n=88)

Variables	IVIG resistance (n=12)	IVIG responders (n=76)	P-value
Age at diagnosis, month, median (IQR)	8.5 (4.8-34.3)	12.0 (8.3-27.0)	0.327 *
Illness days of initial IVIG, median (IQR)	6 (5-7)	6 (5-8)	0.829 *
Gender, male:female	5:1	1.5:1	0.198 **
Type of Kawasaki disease, n (%)			1.00 **
Complete	10 (83.3)	63 (82.9)	
Incomplete	2 (16.7)	13 (17.1)	
Race, n (%)			0.724 **
Malay	10 (83.3)	55 (72.4)	
Non-Malay	2 (16.7)	21 (27.6)	
Presenting symptom, n (%)			
Conjunctivitis	11 (91.7)	64 (84.2)	0.685 **
Rashes	9 (75.0)	67 (88.2)	0.359 **
Extremities changes	9 (75.0)	49 (64.5)	0.744 **
Oral mucosal changes	10 (83.3)	71 (93.4)	0.242 **
Lymphadenopathy	8 (66.7)	63 (82.8)	0.397 **

*Mann-Whitney test; ** Fishers's Exact test

Abbreviation: IVIG – intravenous immunoglobulin; IQR – inter-quartile range

The comparison of the laboratory values between the two groups found that IVIG resistance patients have significantly higher white blood cell count ($p=0.038$), higher neutrophil percentage ($p=0.004$), and higher total bilirubin ($p=0.022$). The lymphocytes, however, was significantly lower in the IVIG resistant group ($p<0.001$) (Table 2).

Echocardiogram results were available in 85 of the patients. The results showed that more than half of the patients (68.2%) identified to have normal CA. CA dilatation were found in 20% of patients, medium CA aneurysms in 10.6% of patients and 1.2% patients developed giant CA aneurysm. Comparison of the presence of CA aneurysm showed that a significant difference was found between the IVIG resistant group and the IVIG responder group. Significantly higher number of patients (50%) of the IVIG resistant group developed CA aneurysms as compared to the IVIG responders (5.5%) ($p<0.001$) (Table 3).

Table 2: Laboratory values of IVIG resistance and IVIG responders (n=88)

Variables	IVIG resistance (n=12)	IVIG responders (n=76)	P-value
WBC count ($10^9/L$) ^a	17.9 (14.5-22.1)	14.0 (11.4-17.5)	0.038 *
Hemoglobin (g/dL) ^b	10.8 ± 1.7	11.0 ± 1.1	0.756 †
Hematocrit (%) ^b	32.1 ± 5.6	33.1 ± 3.5	0.550 †
Platelet ($10^9/L$) ^a	432 (363-554)	425 (291-510)	0.488 *
MCV (fl) ^a	77.7 (75.0-80.3)	77.6 (75.7-80.8)	0.980 *
MCH (pg) ^a	25.9 (25.2-26.5)	25.8 (24.2-26.7)	0.863 *
MCHC (g/dL) ^a	33.3 (32.7-34.3)	33.0 (32.0-34.0)	0.351 *
Lymphocytes (%) ^a	16.6 (11.1-22.3)	31.3 (21.1-39.6)	<0.001 *
Neutrophil (%) ^a	74.6 (68.9-80.2)	58.2 (50.8-68.7)	0.004 *
ESR (mm/h) ^b	71.1 ± 38.1	78.5 ± 27.3	0.474 †
CRP (mg/L) ^a	130.7 (97.2-151.8)	106.2 (57.1-148.4)	0.334 *
Serum Albumin (g/dL) ^b	3.1 ± 0.7	3.3 ± 0.6	0.297 †
Total bilirubin (umol/L) ^a	15.0 (8.4-43)	7.0 (5.0-12.0)	0.022 *
ALT (IU/L) ^a	88.0 (13.5-110.5)	26.0 (14.5-94.5)	0.605 *
Sodium (mmol/L) ^a	133 (132-136)	134 (132-136)	0.892 *

^a data presented in median (IQR); ^b data presented in mean (SD); *Mann-Whitney test; †Independent-T test
 Abbreviation: IVIG – intravenous immunoglobulin; WBC – white blood cell; MCV – mean cell volume; MCH – mean cell haemoglobin; MCHC – mean cell haemoglobin concentration; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; ALT – Alanine Aminotransferase

Table 3: The presence of CA aneurysms in IVIG resistance and IVIG responders (n=85)

Characteristic	Total (n=85)	IVIG resistance (n=12)	IVIG responders (n=73)	P-value
Presence of CA aneurysms				< 0.001 **
Yes	10 (11.8%)	6 (50.0%)	4 (5.5%)	
No	75 (88.2%)	6 (50.0%)	69 (94.5%)	

** Fisher’s Exact test
 Abbreviation: IVIG – intravenous immunoglobulin; CA – coronary artery

There were incomplete laboratory data to calculate the Egami scores in 31 patients. Egami risk scores were calculated for 57 patients with complete data. The median Egami score for IVIG resistant patients and IVIG responder were 3 (IQR 1 to 3) and 1 (IQR 1 to 2) respectively (Table 4). The Fisher’s Exact test showed that the Egami score was significantly associated with IVIG resistance in our patients ($p=0.015$). The Egami score could predict IVIG resistance with a sensitivity of 66.7%, specificity of 77.1%, positive predictive value (PPV) of 35.3% and negative predictive value (NPV) of 92.5% (Table 4).

Egami score was subsequently used to predict patient’s CA abnormalities. Patients were classified as having normal CA versus abnormal CA (includes CA dilatations, medium CA aneurysms and giant aneurysms) for comparison (Table 5). Egami score was found to be higher among those in the abnormal CA group, with a median Egami score of 3 (IQR 1-3) as compared to those in the normal CA group with a median score of 1 (IQR 1-2). The sensitivity was 52.2%, the specificity was 85.3%, PPV was 70.6%, and NPV was 72.5%.

To further validate the Egami scores in this study population, patients were further categorised as those presented with CA aneurysms (medium aneurysms and giant aneurysms) and those without CA aneurysms (normal CA and CA dilatation) (Table 6). The median Egami score was 3 (IQR 1-3) for patients with CA aneurysms compared to those with no CA aneurysms with a median Egami score of 1 (IQR 1-2). When the patients were categorised into the low-risk and high-risk groups according to their Egami scores, there was an association with CA aneurysms (p=0.015). The sensitivity was 66.7%, specificity was 77.1%, PPV was 35.3%, and NPV was 92.5%.

Table 4: Comparison of Egami scores in IVIG resistance and IVIG responders (n=57)

Characteristic	Total (n=57)	IVIG resistance (n=9)	IVIG responders (n=48)	Z statistics	P-value
Egami score, median (IQR)	1 (1-3)	3 (1-3)	1 (1-2)	-1.922	0.055 **
Egami score, n (%)					
0	5 (8.8)	0 (0.0)	5 (10.4)		
1	26 (45.6)	3 (33.3)	23 (47.9)		
2	9 (15.8)	0 (0.0)	9 (18.8)		
3	15 (26.3)	6 (66.7)	9 (18.8)		
4	2 (3.5)	0 (0.0)	2 (4.2)		
Risk group, n (%)					0.015 †
Low risk (0-2)	40 (70.2)	3 (33.3)	37 (77.1) ^a		
High Risk (≥3)	17 (29.8)	6 (66.7) ^b	11 (22.9)		

** Mann-Whitney Test; † Fisher’s Exact Test; ^a Specificity; ^b Sensitivity
Abbreviation: IVIG – intravenous immunoglobulin; IQR – inter-quartile range

Table 5: Comparison of Egami scores by normal CA and abnormal CA status (n=57)

Characteristic	Total (n=57)	Abnormal CA (n=23)	Normal CA (n=34)	Z statistics	P-value
Egami Score, median (IQR)	1 (1-3)	3 (1-3)	1 (1-2)	-1.861	0.063 **
Egami Score n (%)					
0	5 (8.8)	2 (8.7)	3 (8.8)		
1	26 (45.6)	8 (34.8)	28 (52.9)		
2	9 (15.8)	1 (4.3)	8 (23.5)		
3	15 (26.3)	11 (47.8)	4 (11.8)		
4	2 (3.5)	1 (4.3)	1 (2.9)		
Risk group, n (%)					0.002 †
Low risk (0-2)	40 (70.2)	11 (47.8)	29 (85.3) ^a		
High Risk (≥3)	17 (29.8)	12 (52.2) ^b	5 (14.7)		

** Mann-Whitney test; † Chi-Square test; ^a Specificity; ^b Sensitivity
Abbreviation: CA – coronary artery; IQR – inter-quartile range

Table 6: Comparison of Egami scores by the presence of CA aneurysms (n=57)

Characteristic	Total (n=57)	CA aneurysms (n=9)	No CA aneurysms (n=48)	Z statistics	P-value
Egami Score, median (IQR)	1 (1-3)	3 (1-3)	1 (1-2)	-1.922	0.055 **
Egami Score n (%)					
0	5 (8.8)	0 (0.0)	5 (10.4)		
1	26 (45.6)	3 (33.3)	23 (47.9)		
2	9 (15.8)	0 (0.0)	9 (18.8)		
3	15 (26.3)	6 (66.7)	9 (18.8)		
4	2 (3.5)	0 (0.0)	2 (4.2)		
Risk group, n (%)					
Low risk (0-2)	40 (70.2)	3 (33.3)	37 (77.1) ^a		0.015 [†]
High Risk (≥3)	17 (29.8)	6 (66.7) ^b	11 (22.9)		

** Mann-Whitney Test; [†] Fisher's Exact Test; ^a Specificity; ^b Sensitivity
 Abbreviation: CA – coronary artery; IQR – inter-quartile range

Discussion

The present study provides a comprehensive account of validation of Egami Score to predict IVIG resistance among children with KD in Malaysia. In this study, the prevalence of IVIG resistance was 13.6% and this was similar to the result of studies previously conducted in Japan and United States, which reported the IVIG resistance range between 13-21% (8-11).

In our study, the Egami score could predict IVIG resistance with a sensitivity of 66.7%, specificity of 77.1%, PPV of 35.3% and NPV of 92.5%. Therefore, by applying the Egami scoring system on the multi-ethnic Malaysian paediatric patients, it is predicted that 66.7% of patients with IVIG resistance will be categorised as the high-risk group while 77.1% of patients who were IVIG responders will be categorised as the low-risk group. In other words, if a patient is categorised as high risk according to the Egami score, the likelihood to develop IVIG resistant is 35.3%, whereas for those in low risk group, the likelihood to respond to IVIG would be 92.5%. If the Egami scoring system can be applied to predict IVIG resistance among the Malaysian paediatric population who has KD, it will help in planning early interventional therapies and prevent the occurrence of CA aneurysms. Previous literature has reported on the use and efficacy of single dose methylprednisolone (30mg/kg/day) in combination with IVIG (2g/kg for 1 day) plus Aspirin (30mg/kg/day) as primary treatment for those predicted to be at high risk of IVIG resistance based on Egami score. The regimen has been shown to lower the incidence of CA abnormalities and IVIG resistance (20).

The Egami Score was well established in Japan and using the Egami score of three points and above as cut off point has been shown to be 78% sensitive and 76% specific to predict IVIG resistance in the Japanese population (8). Our findings showed a similar specificity with that of the Japanese population, but with lower sensitivity. Another study conducted by Sleeper *et al.* in the North American population(18) also showed low sensitivity and moderate to high specificity. A recent study on Western Mediterranean population in Catalonia, Spain reported 26% sensitivity and 82% specificity, with the NPV of 85% and PPV of 22% (21). On the other hand, In another study based on 182 patients from US Midwest, Egami score was found to have a sensitivity of 22% and a specificity of 95% (22). An older study by Tremoulet *et al.* reported sensitivity of 33.3% and specificity of 89.3% when applied to their Asian patients(13).

The difference in the sensitivities and specificities observed in the different studies are probably due to the different definition of IVIG resistance that were used. In our study, patients were defined as having IVIG resistance based purely on the body temperature (>37.5°C). In the Japanese population, patients were defined as having IVIG resistance if CRP did not reduce by more than 50% within 48 hours after the initial IVIG treatment (8). CRP was not included in the analysis of the current study because the measurement of CRP was not repeated after 48 hours in most of the patients. However, studies from the North America and San Diego population defined IVIG resistance as having persistent or recrudescence fever of ≥38°C instead of ≥37.5°C, and the reduction in CRP value was not considered (13,18). In contrast, the study by Sánchez-Manubens *et al.*, IVIG resistance is defined as patient who required a second dose of IVIG, and was not based on the rise in

body temperature (21). Thus, it would be more meaningful if future studies with standardised definition of IVIG resistance could be performed to enable direct comparison.

In this study, CA involvement was found to be higher with 31.8% compared to those reported in other studies where CA involvement were only seen in 15-20% of patients with KD (23,24). Another study done in Malaysia in 2012 also found similar results where only 28.6% of patients had CA abnormalities (25). IVIG resistance is a significant risk factor for CA aneurysms (12,13). In our study, the incidence of CA aneurysms ranged between 5.5% among IVIG responders to 50% among IVIG resistant patients. A study from Japan found that CA aneurysms ranged from 0% in IVIG responders to 29.2% in IVIG resistant patients (8). In a San Diego study, the incidence of CA aneurysms were reported as 3% in IVIG responders to 15% in IVIG resistance (26). Another study by Loomba *et al.* among Midwestern US population also found that the incidence of CA aneurysms to range between 4.8% in IVIG responder to 12% in IVIG resistant patients (22). Collectively, these results show that IVIG resistance increases the incidence of CA aneurysms, though at different rate.

According to the Japanese Ministry of Health, CA is classified as abnormal when the internal lumen diameter is more than 3mm in children younger than 5 years or more than 4 mm in children 5 years or older, when the internal diameter of any segment measures at least 1.5 times that of an adjacent segment or when the CA lumen is clearly irregular(8). Egami score was reported to have the sensitivity of 61% and specificity of 81% in predicting CA lesions in the Japanese study (8). In this study, however, we considered CA aneurysms and obtained similar sensitivity and specificity (67% and 77% respectively). Studies done by Sleeper *et al.* on the other hand, found no significant association between Egami score and CA abnormalities (18).

In the current study, patients with IVIG resistance have significantly higher level of WBC, total bilirubin, percentage of neutrophils, and lower percentage of lymphocytes. Percentage of neutrophil is a risk factor for IVIG resistance in calculating the Kobayashi Score (9) and Formosa Score (17) while increased total bilirubin is a risk factor for resistance in the Sano Score (10). A recent prospective study on the impact of neutrophil-lymphocyte ratio (NLR) in predicting the outcomes of Kawasaki disease showed that IVIG resistant patients demonstrated significantly higher NLRs in the acute febrile phase and 2 days after IVIG treatment as compared to IVIG responsive patients (27). Based on our result, this indicated that high neutrophil level could be a predictive factor for IVIG resistance. However, in view of the small number of patients with IVIG resistance in this study, regression analysis was not performed. Further studies with larger sample size should be carried out and regression analysis could be done to confirm this. A new scoring system incorporating risk factors such as WBC, neutrophil, lymphocyte, and bilirubin can be developed to obtain higher sensitivity and specificity for our population.

There are several limitations in this study. The low incidence of KD was due to partial records retrieval following the change in the record system in 2008. Due to the retrospective nature of the study, it is impossible to retrieve laboratory results on the standard days of illness (day one being day when fever start). To reduce the bias due to the day laboratory data were obtained, all the laboratory data were obtained before IVIG was given, and statistical test was done to make sure that there was no significant difference in the days the laboratory data were obtained for the IVIG resistance group and the IVIG responder group (median day 5 of illness, $p= 0.995$). This was because during data collection for this study, it was observed that the number of days of illness may affect the Inflammatory marker values and platelet counts. This could be explained by the changes of clinical laboratory values over the acute and subacute phases of the illness (28). The onset of thrombocytosis is common in the second week of fever (29). Another limitation of this study was that the complete laboratory data was not available for all patients which further reduced our sample size and this may also be a source of bias.

Conclusion

The validation of Egami score in the Malaysian population to predict IVIG resistance showed that the Japanese scoring system was significantly associated with IVIG resistance in our patient population. However, the Egami score was not sensitive enough to be applied as the only method for the prediction of IVIG resistance among the paediatric patients with KD. Further studies are needed to develop better predictive models for our population so that early identification of patients with the risk of IVIG resistance and CA aneurysms are possible.

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Conflict of Interest Statement

This research received no grant from any funding agency in the public, commercial or not-for-profit sectors. The Author(s) declare(s) that there is no conflict of interest

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An Evaluation of The Impact of Diabetes Medication Therapy Adherence Clinic (DMTAC) in Tangkak

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Abstract

Introduction: The Diabetes Medication Therapy Adherence Clinic (DMTAC) is an ambulatory care service provided by pharmacists to assist diabetic patients in achieving better glycaemic control and medication adherence. Personalised care including counselling and education on medications, disease and lifestyle modifications are provided.

Objective: The objective of this study was to evaluate the impact of DMTAC among poorly controlled diabetic patients at the Tangkak district government health clinics.

Methods: A retrospective cohort study was conducted at Klinik Kesihatan Payamas and Klinik Kesihatan Sagil. The impact of DMTAC were evaluated in terms of glycaemic control, laboratory parameters and medication understanding. The medication dose, frequency, indication and time (DFIT) score was used to measure patients' medication understanding level. The changes in patients' HbA1c, blood pressure, lipid parameters and DFIT score before DMTAC enrolment and post forth DMTAC visit were determined. Data was analysed using SPSS software.

Results: Eighty DMTAC patients were included in this study. A significant reduction in HbA1c was detected among the patients after receiving at least four DMTAC counselling sessions (mean difference -1.02%, 95% confidence interval (CI) -1.42 – -0.61, $p < 0.001$). Medication DFIT score rose from 97.65% to 99.46% (mean difference 1.81, 95% CI 0.71 – 2.91, $p < 0.05$) following the completion of at least four DMTAC visits. No statistically significant difference was detected in blood pressure and lipid parameters (total cholesterol, TGL, LDL, HDL) before and post DMTAC visits. A slight decrease in BMI was detected across the study duration, but it was not statistically significant.

Conclusion: This study showed that the DMTAC programme significantly improved glycaemic control and medication understanding among the diabetic patients which could translate into substantial benefits in patient morbidity and mortality as well as savings in health care costs.

Keywords: DMTAC, HbA1c, medication understanding score, diabetic patient, glycaemic control

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Introduction

Diabetes mellitus is a chronic disease caused by insulin deficiency and insulin resistance. It is presented as chronic hyperglycaemia state commonly associated with other metabolic derangements. Poorly controlled diabetes may lead to serious macrovascular and microvascular complications. Diabetes is known to be a multifactorial disease with both non-modifiable and modifiable risk factors. These include genetic, sedentary lifestyle, obesity and unhealthy diet (1).

In recent years, diabetes has become one of the alarming non-communicable diseases due to its rapidly increasing trend. According to the World Health Organization (WHO), the number of adults with diabetes has increased from 108 million in 1980 to 422 million in 2014 globally (1). In line with the global pattern, the National Health and Morbidity Survey 2015 (NHMS V) reported that the prevalence of diabetes among Malaysian adults has reached 17.5% in 2015 compared to 15.2% in 2011 as reported in NHMS IV (2,3). Globally, 12% of the

health expenditures were estimated to be used in diabetes care in 2010. In Malaysia, 16% of the total healthcare cost was estimated to be spent on diabetes in 2010 (4). Despite the huge sum of healthcare budget being spent on diabetes, it is still causing many deaths worldwide. In 2012, 3.7 million deaths worldwide were caused by diabetes and its complications (1).

In view of high impact of diabetes, the Ministry of Health Malaysia (MOH) has introduced Diabetes Medication Therapy Adherence Clinic (DMTAC) service in the primary health clinics and hospitals in 2004. It is an ambulatory care service provided by the pharmacists to help diabetic patients to achieve better glycaemic control and medication adherence level. Diabetic patients with poor glycaemic control, indicated as glycosylated haemoglobin (HbA1c) above 8%, are recruited into the programme either by physicians' referral or identified by the pharmacists. Each patient is scheduled to follow-up with the DMTAC pharmacists for at least 8 sessions according to their medications collection date or check-up appointment date. Personalized cares including medication counselling, education on disease and lifestyle modifications are provided. In addition, DMTAC pharmacists perform blood glucose monitoring during each patient visit. Apart from patient education and counselling, DMTAC pharmacists also work together with physicians in monitoring patient's clinical outcome, treatment regime and any drug related problems (5).

The main objective of DMTAC is to improve patient's medication adherence and subsequently improve patient's glycaemic control. Several studies has shown that better diabetic control could be achieved with higher patient's medication adherence (6,7). The key factors to improve a patient's medication adherence are educational activities, effective communication between the patient and healthcare provider and care continuation (6). A few studies in Malaysia demonstrated that better glycaemic control, improvement in metabolic syndrome indicators and medication understanding level were observed in diabetic patients attending the pharmacist-managed DMTAC services (8-10). Similarly, studies carried out overseas involving pharmacist's interventions in diabetes care had also demonstrated prominent improvement in glycaemic control and cardiovascular risk reduction (11-12).

Although quite a number of studies have demonstrated the impact of DMTAC clinic in Malaysia, more concrete evidence are still needed to support the value of DMTAC in the primary health clinic setting, which caters for more than half (56%) of the diabetes care burden in Malaysia (13). Therefore, the objective of this study was to evaluate the impact of DMTAC among poorly controlled diabetic patients following up at the government health clinics under the Tangkak District Health Office. The impact will be assessed from the aspect of glycaemic control, lipid parameters control, blood pressure control and patient's medication understanding level.

Method

A retrospective cohort study was conducted at the Payamas Health Clinic and Sagil Health Clinic in Tangkak district of Johor to determine the impact of DMTAC services among poorly controlled diabetic patients. Approval from the MOH Medical Research Ethics Committee (MREC) was obtained and this study was registered with the National Medical Research Register (NMRR) with NMRR-18-2616-44167 (IIR)).

All Type 2 Diabetes Mellitus (T2DM) patients with age 18 years and above, HbA1c level above 8.0% who were registered with the DMTACs at Payamas and Sagil Health Clinic and had completed four DMTAC visits between January 2017 to September 2018 were included into the study. Patients who were lost to follow-up, not completing four DMTAC visits or patients who did not have pre-DMTAC and post-fourth DMTAC visit laboratory results, blood pressure and medication understanding score were excluded from the study. Universal sampling method was adopted in this study. All potential subjects were selected, reviewed and became the subjects of this study. Hence, no sample size was calculated.

Patient's DMTAC forms and medical records were reviewed. Patients' demographics data, medication regimens and laboratory parameters were retrieved from the records. The impact of DMTAC was measured as the changes in glycaemic control, lipid parameters control, blood pressure control and patient's medication understanding level. Therefore, the primary outcome was to compare the changes in HbA1c before DMTAC enrolment and post fourth DMTAC visit. The secondary outcomes were to determine the changes in total cholesterol (T.Chl), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (TGL), systolic blood pressure (SBP), diastolic blood pressure (DBP) and patient's medication understanding. The last laboratory and examination results prior to DMTAC recruitment were taken as the pre-

DMTAC parameters, while the most recent results documented during DMTAC visit before September 2018 were taken as post fourth DMTAC visit parameters.

To measure patient’s medication understanding and their knowledge to the prescribed medications, assessment via the dose, frequency, indication and time of administration (DFIT) score was used. The score was calculated based on these four elements for every prescribed drug with each element carrying one mark for ‘good understanding’ and 0 mark for ‘unable to understand or recall’. Patients who were able to understand all the four elements of a prescribed drug would score four marks. The total score (denominator) was calculated based on the number of drugs prescribed. The score during the first DMTAC visit was compared to the score during the most recent DMTAC visit before September 2018.

Data was analysed using SPSS software. The difference of the parameters pre-DMTAC and post-fourth DMTAC visit was compared using Paired T-test with the central limit theorem in normality assumption (n>30, normality assumed). A value of p<0.05 was taken as statistically significant.

Results

A total of 305 DMTAC records were reviewed and 80 patients (26.2%) were included in this study. The demographic characteristics and anti-diabetic regimens of the patients were presented in Table 1. The mean age of the patients in this study was 56.69 (SD 7.93). Almost 60% of the patients were obese with BMI more than 27.5 kg/m² and 30% of the patients were at the pre-obese stage. About half of the patients (48.75%) in this study had diabetes for more than 10 years and 32.5% of the patients were living with diabetes for more than five years. Combination therapy (OHA + insulin) was the most used anti-diabetic regimen among the participants.

Table 1: Characteristics of DMTAC patients (n=80)

Variables	n (%) / mean (SD)
Age, year, mean (SD)	56.69 (7.93)
Gender, n (%)	
Male	26 (32.50)
Female	54 (67.50)
Ethnicity, n (%)	
Malay	50 (62.50)
Chinese	14 (17.50)
Indian	16 (20.00)
Body Mass Index (BMI), n (%)	
<18.5 kg/m ² (Underweight)	2 (2.50)
18.5-22.9 kg/m ² (Normal)	7 (8.75)
23.0-27.4 kg/m ² (Pre-obese)	24 (30.00)
27.5-34.9 kg/m ² (Obese I)	35 (43.75)
35.0-39.9 kg/m ² (Obese II)	8 (10.00)
≥ 40 kg/m ² (Obese III)	4 (5.00)
Duration of Diabetes, year, mean (SD)	9.48 (5.11)
Duration of Diabetes, n (%)	
< 5 years	15 (18.75)
5-10 years	26 (32.50)
>10-20 years	39 (48.75)
Marital Status, n (%)	
Married	77 (96.25)
Not married	3 (3.75)
Anti-diabetic Regimen, n (%)	
OHA only	21 (26.25)
OHA + basal insulin	27 (33.75)
OHA + premixed insulin	25 (31.25)
OHA + basal-bolus insulin	4 (5.00)
Insulin only	3 (3.75)

Abbreviation: BMI – body mass index, OHA – oral hypoglycaemic agent, SD – standard deviation

Table 2: Changes in patient outcomes before DMTAC enrolment and after the fourth DMTAC visit

Variables	Pre-intervention, mean (SD)	Post-intervention, mean (SD)	Mean difference (95% CI)	T-statistics (df) *	P value *
HbA1c, %	10.53 (2.21)	9.52 (1.88)	-1.02 (-1.42, -0.61)	-5.02 (79)	<0.001
T.Chl, mmol/L	4.66 (0.90)	4.81 (0.94)	0.15 (-0.042, 0.334)	1.55 (72)	0.126
TGL, mmol/L	1.70 (0.69)	1.76 (0.88)	0.059 (-0.048, 0.165)	1.101 (72)	0.275
LDL, mmol/L	2.68 (0.80)	2.73 (0.80)	0.041 (-0.143, 0.225)	0.445 (72)	0.658
HDL, mmol/L	1.21 (0.30)	1.23 (0.27)	0.0225 (-0.016, 0.061)	1.161 (72)	0.250
SBP, mmHg	134.61 (15.68)	134.36 (19.73)	-0.25 (-4.90, 4.39)	-0.11 (79)	0.915
DBP, mmHg	77.35 (11.62)	77.76 (9.54)	0.41 (-2.46, 3.29)	0.29 (79)	0.776
DFIT score #	97.65 (5.69)	99.46 (2.56)	1.81 (0.71, 2.91)	3.28 (79)	0.002
BMI, kg/m ²	29.42 (6.02)	29.38 (5.85)	-0.04 (-0.42, 0.33)	-0.24 (78)	0.811

* paired T-test; # medication understanding score

Abbreviation: T.Chl – total cholesterol; TGL – triglycerides; LDL – low-density lipoprotein cholesterol; HDL – high-density lipoprotein cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; DFIT – dose, frequency, indication and time of administration; SD – standard deviation; CI – confidence interval

Discussion

A small-scale retrospective study conducted at a DMTAC pioneer facility, the Penang Hospital, which involved 43 DMTAC patients who have completed eight DMTAC visits showed a significant improvement in diabetic control and medication adherence level. Significant reductions in HbA1c, fasting blood glucose (FBG) and low-density lipoprotein cholesterol (LDL) were observed (8). Six years later, a prospective open-labelled randomised study at the same hospital which involved a total of 76 patients showed similar positive outcomes (9). In addition to the single-centred studies, a retrospective study involving 56 DMTAC patients in 14 government health clinics in Kuala Lumpur and Putrajaya also showed a remarkable improvement in HbA1c after attending at least four DMTAC sessions. Besides that, patient’s medication adherence and medication understanding also improved (10). A large scale randomised controlled trial in the United State with 194 patients showed a significant reduction in HbA1c level and blood pressure control after a twelve-month follow up visits with the pharmacists (11). In Australia, a significantly larger improvement in HbA1c level was observed in the intervention group who received DMTAC-like diabetes care by the community pharmacists compared to the control group over 6 months duration (12).

In line with the findings of the few previous studies, this study provided further evidence that DMTAC services run by the pharmacists significantly improved glycaemic control among the poorly controlled diabetic patients. The mean HbA1c reduction was 1.02% pre and post 4th DMTAC visits. One recent study also showed a similar result of 1.03% drop in the mean HbA1c value after four DMTAC sessions with the pharmacists (14). Recognising that these two studies were conducted retrospectively without a control group, a recent meta-analysis with 13 randomised control trials (RCT) from year 2011 to 2015 showed that pharmaceutical care interventions provided by the pharmacists were effective in reducing the HbA1c among T2DM patients (15). Another systematic review with meta-analysis which included 16 both randomised and non-randomised controlled clinical trials also showed that pharmacist’s interventions consisting of diabetes education and medication management significantly reduce HbA1c over control. The magnitudes of HbA1c reduction were greater when the average baseline HbA1c values were above 9%. This could possibly explain the greater reduction of HbA1c in our study compared to the meta-analysis (16).

HbA1c is an important indicator of glycaemic control in diabetic patients over time. Glycaemic control is closely associated with the incidence of diabetic complications. According to the UK Prospective Diabetes Study (UKPDS) 35, every 1% reduction in HbA1c was associated with 21% risk reduction in any end point of death related to diabetes and 37% decrease in the risk for microvascular complications (17). This is particularly important for the diabetic patients with high HbA1c.

The average baseline HbA1c value in this study (10.53%) was similar to that reported in a recent study conducted at a government health clinic in Johor Bahru, Malaysia (10.61%) (14). These values were higher than the mean HbA1c value among patients treated at hospital-based outpatient diabetic clinic in Malaysia

reported by Mafauzy *et al.* in 2013 which was 8.52% (SD 2.01%) (18). A higher mean value of HbA1c among the patients at government primary health clinics could possibly be due to the limited choice of antidiabetic drugs available. This was shown in the study where hospital have recorded an increase use of Dipeptidyl Peptidase-4 (DPP-4) Inhibitors and analogue insulin, in contrast to the primary health clinics where both drugs are still restricted to be prescribed by the Family Medicine Specialists (FMS) with limited quota allocated. Besides, the low usage (6.25%) of intensive insulin regimens in this study compared to 20.6% in the hospital setting could also explain the higher mean HbA1c value in our patients (18).

According to UKPDS 35, besides glycaemic control, dyslipidaemia, hypertension and smoking also contributed to the cardiovascular risk in diabetic patients (17). Therefore, blood pressure and lipid level control are important in preventing diabetes complications. UKPDS 36 showed that every 10mmHg decrease in the SBP was associated with 12% risk reductions in diabetes related complications, 15% deaths related to diabetes, 11% myocardial infarction and 13% microvascular complications. SBP below 120mmHg was presented with the lowest risk (19).

The implication of pharmacist care on blood pressure control tends to give many different results. A systematic review and meta-analysis of RCTs showed greater reductions in both SBP and DBP among diabetic outpatients who received pharmacist care compared to usual care (20). A recent meta-analysis involving 39 RCTs with 14,224 outpatients has also shown positive outcome in supporting the pharmacists' interventions in improving SBP and DBP control. However, the effect sizes of the pharmacists' interventions on blood pressure control in the individual studies varied from tremendous effect to modest or no effect (21). Similar to our study, a recent study about DMTAC at the Mahmoodiah Health Clinic in Johor, Malaysia also showed no significant changes in blood pressure control (14). One of the possible reasons for this could be the baseline blood pressure in both studies were closely around the recommended target level of blood pressure (135/75mmHg) in the Malaysian Clinical Practice Guidelines (CPG) on Management of Type 2 Diabetes Mellitus (22).

Like blood pressure control, pharmacists' care on the control of cholesterol level also produced a mixed result. Although a meta-analysis demonstrated statistically significant reductions in LDL with pharmacist care, it was with moderate heterogeneity. No statistically significant change in HDL cholesterol was detected in the meta-analysis (20). Similar to our study, the DMTAC study at Mahmoodiah Health Clinic also failed to show a significant change in the lipid level (14). No significant changes in the lipid levels could possibly be due to our baseline lipid profiles that was already meeting the recommended levels for diabetic patients without overt cardiovascular disease in the Malaysian CPG (22). Another possible reason could be due to the infrequent lipid monitoring with an average frequency of once per year causing the delay in optimum treatment. Lastly, the limited anti-dyslipidaemia agents available at the health clinic setting may also contribute to this. The only medication available is Simvastatin tablet with the recommended daily dose of 20-40mg that confers moderate intensity therapy. Agents for high intensity therapy such as Atorvastatin was still restricted to the use by FMS (23).

High calorie diets and sedentary lifestyle are the known risks factors for T2DM. About 90% of the patients recruited in this study were pre-obese or obese. The absence of significant reduction in BMI in this study could possibly due to the poor adherence with lifestyle recommendations provided. A study showed that it was highly prevalent among Malaysian T2DM patients to be non-adherent to the lifestyle modifications suggested (24). Another study showed that only 16.4% of individuals with diabetes adhered to the dietary regimen provided by the dietitians (25). Besides that, it was reported that 54% of Malaysian adults with diabetes were physically inactive (26). In a study conducted among T2DM patients at the Cheras Health Clinic in Kuala Lumpur, only 20% reported practicing high physical activity level with the rest adopting either moderate physical activity level (47%) or low physical activity level (33%) (27). The inefficacy of pharmacist care in reducing BMI was also reported in other DMTAC studies (9,14). Although a meta-analysis of two studies showed a statistically significant benefit of pharmacist care in BMI reduction, there was substantial heterogeneity between studies (20).

As reported in other DMTAC studies, our findings showed that patient's medication understanding score was significantly improved after DMTAC visits (10,14). Medication review done by the pharmacists during the DMTAC sessions had helped the patients to improve their medication knowledge. Longer patient contact time also enabled the pharmacist to reinforce necessary information and subsequently improving their understanding, especially for patients with multiple medications and older age patients (28). A study done in

Singapore by Goh *et al.* (29) demonstrated that the better knowledge and understanding about own medication were found to be beneficial to enhance patients' medication adherence and could ultimately lead to the improvement in glycaemic control.

Several limitations were identified in this study. Small sample size was one of it. This restricted the extrapolation of the finding of this study to the entire diabetic patient population. Besides, as a retrospective observational study, a control group with standard care was not available for comparison to assess the effectiveness of DMTAC programme. The effect of education on metabolic control of diabetic patients may decrease over time after the end of the intervention (22). Future studies should be conducted with a longer follow up period to determine if the impact of DMTAC counselling sessions could sustain after patients were discharged from the DMTAC. Also, larger RCTs that are adequately powered are needed to evaluate the effectiveness of DMTAC programme in metabolic control and to determine the appropriate follow up duration of the DMTAC programme for more sustained positive impact.

Conclusion

As a conclusion, the DMTAC programme can help in improving the glycaemic control and medication understanding among diabetic patients. These positive impacts may translate into substantial benefits in improving patient morbidity and mortality as well as savings on health care cost.

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Conflict of Interest Statement

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

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Benzodiazepine Prescribing Trends among Major Depressive Disorder Patients at the Outpatient Pharmacy of Hospital Bahagia Ulu Kinta

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Abstract

Introduction: Benzodiazepines should only be used as adjunct to antidepressants for the duration of less than four weeks.

Objectives: This study aimed to investigate benzodiazepine prescribing trends among the patients with major depressive disorder (MDD) in Hospital Bahagia Ulu Kinta (HBUK).

Method: This was a cross-sectional study from March 2016 to December 2016. We reviewed all prescriptions at the outpatient pharmacy with the diagnosis of MDD and sorted them per patient basis. Patient demography, drug name, dose and treatment duration were recorded in a data collection form and analysed using SPSS.

Results: A total of 908 prescriptions for 612 MDD patients were reviewed and 313 (51%) of the 612 MDD patients received one or more types of benzodiazepines. Most patients (76.7%) received benzodiazepines for more than four weeks with a median duration of 84 days (interquartile range (IQR) 35-206 days). The median dose of benzodiazepine was 3.57mg (IQR 1.78-7.14mg) of diazepam equivalents per day. Clonazepam was most prescribed, followed by zolpidem and alprazolam. Older MDD patients were prescribed benzodiazepines for a longer duration (median 126, mean rank 334.58) compared to patients of younger age (median 84, mean rank 298.50, $p=0.001$). Chinese MDD patients were also prescribed benzodiazepines for a longer duration (median 112, mean rank 168.54) compared to other ethnicities (median 56, mean rank 129.70, $p=0.0004$).

Conclusion: Notwithstanding guideline cautions, long term prescribing of benzodiazepines in depressed patients remains an occurring treatment pattern in the specialty care. Majority of the depressed patients received benzodiazepines for a period of more than four weeks albeit in low doses. However, short-acting benzodiazepines seem to be a popular choice among physicians as compared to long-acting benzodiazepines.

Keywords: benzodiazepine, depression, prescribing pattern

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Introduction

Major depressive disorder is extremely common in which community-based surveys have estimated the lifetime prevalence from 4.9% to 17% (1,2). Depression incurs substantial public health and economic costs. According to the Clinical Practice Guidelines for the Management of Major Depressive Disorder, major depression disorder (MDD) is defined as a mental health problem that disrupts a person's mood and adversely affects the psychosocial and occupational functioning, which is associated with significant morbidity and mortality (1).

Antidepressants are the recommended pharmacological treatment for depression (2). In Malaysia, antidepressants are offered as the first line measure as they are easily available and are as effective as psychological interventions (1). However, antidepressants' beneficial effects often do not occur in just several weeks, and studies have shown that the adjunctive use of benzodiazepines may confer some benefit in providing more immediate relief (1-3). Nevertheless, benzodiazepines are not free from disadvantages especially with long term use as tolerance, dependence and withdrawal effects can occur (1). Benzodiazepine withdrawal symptoms include anxiety, depression, diarrhoea, constipation, insomnia, irritability, restlessness, poor concentration and occasionally, seizures and symptoms of psychosis. These unwanted effects can be prevented by keeping the dosages minimal and courses short (4). Thus, guidelines have suggested that

benzodiazepines should be used with caution and not to be prescribed for more than two to four weeks when used as adjunct treatment with the antidepressants (1,4-6).

Daily practices in the healthcare settings, however, may not necessarily comply with these guidelines as seen in a study conducted in the United States Department of Veterans Affairs mental health settings by Valenstein and colleagues. The authors reported that depressed patients, especially the elderly patients, were particularly more likely to receive benzodiazepines for more than ninety days despite guideline cautions (2). The same was observed in Hospital Bahagia Ulu Kinta, the largest psychiatric hospital in Malaysia, which is the secondary and tertiary referral centre for the northern states in Peninsular Malaysia. Besides that, a study conducted by Woods *et al.* found that the physicians were prescribing shorter-acting benzodiazepines, which can produce a more intense withdrawal syndrome following chronic administration in preference to longer-acting benzodiazepines (7).

Generally, it is a known fact that many depressed patients are taking benzodiazepines longer than the recommended period but no solid evidence is available. It is also a worrying issue that many depressive patients who come to the pharmacy to collect their supply of medications are more interested in their benzodiazepines instead of their antidepressants. Some patients have even requested the pharmacists to provide extra tablets of benzodiazepine. Thus, this study aimed to identify the benzodiazepine prescribing trends among MDD patients at the outpatient pharmacy of Hospital Bahagia Ulu Kinta (HBUK), Perak. It was hoped that the findings will be able to create awareness not only among the healthcare professionals but also the public, on the trends of benzodiazepine usage among depressed patients in Malaysia.

Method

This was a cross-sectional study on the benzodiazepine prescribing trends among the MDD patients at the outpatient pharmacy of HBUK that was conducted from March to December 2016. In this study, the term 'benzodiazepine' applied to all benzodiazepines available in HBUK which were alprazolam, lorazepam, clonazepam, midazolam, bromazepam and diazepam, as well as zolpidem which is a non-benzodiazepine hypnotics. Zolpidem was included in this study as zolpidem also causes habit forming on prolonged use and is frequently prescribed in HBUK as an alternative to benzodiazepines.

Using the sample size calculator for prevalence study developed by Naing *et al.* 2006, setting the precision level at 5% and confidence level at 95%, the minimum sample size required was 369. During the study period, all prescriptions available at the outpatient pharmacy of HBUK with MDD written as the diagnosis, with and without comorbidities, were included for data collection. The diagnosis of MDD was based on the criteria in the American Psychiatric Association's Diagnostic or Statistical Manual of Mental Disorders V (DSM-5) (1). Prescriptions with benzodiazepines but without any diagnosis written were excluded from the study. All pharmacists involved in the data collection were briefed on how to screen and sort the prescriptions based on the patient selection criteria and then the prescriptions were sorted out per patient basis. A data collection template was designed via Microsoft Excel and data was keyed in directly into the template. Patient demography, drug name, dose and treatment duration were recorded in the data collection form and analysed via SPSS.

Ethical approval from the Medical Research and Ethics Committee (MREC) of Ministry of Health Malaysia (MOH) was obtained and the study was registered in the National Medical Research Register (NMRR). All data collected were kept confidential, and no unique identifiers were collected. The data presented did not identify any individuals and the data used for publication would not review any identity of the subjects. The hard copies of study data were kept locked in a specified cabinet, and the soft copies of the study data were password encrypted to ensure that all information was only accessible by the two investigators and the supervisor for pharmacy research and development in HBUK. Study data will be stored for duration of three years and will be destroyed thereafter.

Patients' demographic characteristics and benzodiazepine prescribing trends were tabulated in a table. Continuous variables were represented as count (n) with percentage and median with interquartile range (IQR) in view of data was not normally distributed while the categorical variables were presented as n with percentage. The mean prescribed dose was calculated by adding up the diazepam-equivalent milligrams dispensed and dividing it by the duration of benzodiazepine prescribed (number of days). The non-parametric Chi-square test was used to determine if differences existed between benzodiazepine usages with each independent variable.

The non-parametric Mann Whitney U test was also used to determine if differences existed between the daily doses and duration of benzodiazepines of each independent variable as the data were not normally distributed. Results were considered statistically significant if the p value is less than or equal to 0.05.

Results

Patients characteristics

A total of 908 prescriptions for 612 MDD patients were identified. Of that, a number of 313 patients (51.1%) received a prescription containing benzodiazepine(s) for at least once during the period of data collection. All MDD patients who were prescribed with benzodiazepine(s) were also on antidepressants. The demographic characteristics of the patients and information about benzodiazepine use were presented in Table 1.

In line with the HBUK’s MDD population, 64.9% (n=397) of the MDD patients included in this study were female. The median age of MDD patients was 52 years (IQR 41-63 years) with 79.2% of them were in the range of less than 65 years. Only 21.6% (n=132) of the depressed patients had a comorbid psychiatric diagnosis in which 11.1% (n=68) had psychosis and 8.2% (n=50) had an anxiety disorder. Other comorbid psychiatric diagnoses were obsessive-compulsive disorder, substance disorder, sleep disorder, borderline personality disorder and adjustment disorder which only made up of 2.3% (n=14) of the overall sample.

As seen in Table 1, older patients were more likely to be prescribed with benzodiazepines as compared to younger patients. Nevertheless, the difference was not statistically significant (p=0.109). Among the three main races in Malaysia (Malays, Chinese and Indians), the Chinese were most likely to receive benzodiazepines. A Chi-square test of independence was performed to examine the relation between race (Chinese and non-Chinese) and benzodiazepine usage. The relation between these variables was not statistically significant (p=0.243). Among the depressed patients receiving benzodiazepines, only 24.2% (n=76) had psychiatric comorbidities. Although depressed patients with concomitant psychiatric comorbidities were more likely to receive benzodiazepines, the differences showed no significance.

Table 1: Benzodiazepine use among patients with MDD by patient characteristics (n=612)

Variable	Patients with MDD (n=612), n (%)	MDD Patients Prescribed with Benzodiazepines (n=313), n (%)	X ² statistics ^a	P-value ^a
Age group			2.575	0.109
<65	485 (79.2)	240 (49.5)		
≥65	127 (20.8)	73 (57.5)		
Ethnicity			1.364 ^b	0.243 ^b
Malay	118 (19.3)	54 (45.8)		
Chinese	417 (68.1)	220 (52.8)		
Indian	61 (10.0)	30 (49.2)		
Others	16 (2.6)	9 (56.3)		
Gender			0.031	0.860
Female	397 (64.9)	202 (50.9)		
Male	215 (35.1)	111 (51.6)		
Psychiatric comorbidity			2.786	0.095
Present	132 (21.6)	76 (57.6)		
Absent	480 (78.4)	237 (49.4)		

^a Chi-square test of independence; ^b Chinese versus other ethnicities

Trends of Benzodiazepine Prescribing

A large portion of users, 94.9% (n=297) received only one benzodiazepine for each prescription they received throughout the period of data collection while only 3.8% (n=12) received two benzodiazepines in each single prescription throughout the period of data collection. One patient was receiving two benzodiazepines concomitantly which was then increased to three benzodiazepines for a period of 6 months and then reduced back to two benzodiazepines. Three patients received prescriptions with a mixture of one and two benzodiazepines throughout the period of data collection.

The median dose of benzodiazepines prescribed was 3.57mg/day (IQR 1.78-7.14mg/day) of diazepam equivalents. A total of 76.7% (n=240) of the patients received benzodiazepines for more than four weeks and the median duration of benzodiazepines prescribed was 84 days (IQR 35-206 days). The doses and durations of benzodiazepine prescribed were presented in Table 2.

No statistically significant difference was observed between the doses of benzodiazepines prescribed and the characteristics of the patients. Older patients received longer duration of benzodiazepines (median 126 days, mean rank 334.58) as compared to the younger patients (median 84 days, mean rank 298.50). The difference was found to be statistically significant (p=0.001). Besides that, Chinese patients received statistically significant longer duration of benzodiazepines (median 112 days, mean rank 168.54) as compared to other ethnicities (median 56 days, mean rank 129.70) (p=0.0004).

Majority of benzodiazepine users received prescription(s) for benzodiazepines for as needed (p.r.n.), which accounted for 60.7% (n=190) of all depressed patients on benzodiazepines. A total of 30.0% (n=94) had regular doses of benzodiazepine prescribed to them while only 9.3% (n=29) of benzodiazepine users were given both as needed (p.r.n.) and regular doses. Clonazepam was the most frequently prescribed benzodiazepine, followed by alprazolam and zolpidem, which can be seen in Table 3.

Table 2: Doses and durations of benzodiazepine among patients with MDD by patient characteristics (n=313)

Variable	Dose of Benzodiazepine, mg/day of diazepam equivalents, median (IQR)	U statistics ^a	P-value ^a	Duration of benzodiazepine, days, median (IQR)	U statistics ^a	P-value ^a
Age group		8037	0.756		6.024	0.001
<65	3.57 (1.78-7.28)			84 (33.5-173.5)		
≥65	4.72 (1.88-6.73)			126 (42-231)		
Ethnicity		6341 ^b	0.690 ^b		7.944 ^c	0.0004 ^c
Malay	4.34 (2.16-7.47)			56 (28-84)		
Chinese	3.72 (1.78-7.14)			112 (42-236)		
Indian	3.57 (1.78-6.87)			97 (43.5-199.5)		
Others	2.50 (1.33-10.22)			49 (28-175)		
Gender		1.056	0.730		9.802	0.176
Female	3.57 (1.85-6.71)			98 (35-224)		
Male	4.04 (1.78-9.59)			84 (35-169)		
Psychiatric comorbidity		8032	0.155		7.756	0.067
Present	4.16 (2.43-7.51)			84 (28-215)		
Absent	3.57 (1.78-7.14)			84 (35-196)		

^a Mann Whitney U test; ^b Malay versus other ethnicities; ^c Chinese versus other ethnicities

Table 3: Types of benzodiazepine prescribed (n=313)

Types of Benzodiazepine	Prescribed Frequency, n (%)
Clonazepam	145 (38.6)
Alprazolam	75 (19.9)
Zolpidem	73 (19.4)
Lorazepam	62 (16.5)
Diazepam	12 (3.2)
Bromazepam	9 (2.4)

Discussion

This study, which examined the usage of benzodiazepines among depressed patients treated in a tertiary psychiatric referral centre, showed high levels of benzodiazepine use and for longer duration than recommended in the guidelines. In this study, benzodiazepine use was more prevalent in the older patients as compared to the younger age group. This finding was similar to a population-level retrospective study of benzodiazepine usage conducted in the United States by Ofelson *et al.* where they found that the percentage that used benzodiazepines increased with age (8). This finding was also similar to other studies where they found that benzodiazepine use was more common among the older patients, which is quite unexpected given that the risks of benzodiazepine increase with age (2,9,10). Valenstein *et al.* reported that this finding was possibly due to the fact that higher portion of older patients had exposure to benzodiazepine(s) and thus were more likely to request these medication(s) from their physicians. Besides that, older patients may also have more difficulty in discontinuing benzodiazepine(s) once they have started. This explains the similar findings with the study by Valenstein *et al.* that older patients received benzodiazepines for a longer duration as compared to the younger patients (2). It is worrying that the median dose received by our older depressed patients was higher as compared to the younger patients although the difference was not statistically significant. This finding was different from the findings by Valenstein *et al.* whereby they reported that even though older patients were more likely to use benzodiazepines than younger patients, they received lower benzodiazepine doses (2). Healthcare professionals may want to address this matter in view of the risks and adverse events related with benzodiazepine use in older patients such as increased risk of vehicular accidents, falls and hip fractures that increased with age, cognitive and psychomotor adverse events or deaths.

Clonazepam was shown to be the most prescribed benzodiazepine among our depressed patients. However, it should be taken into consideration that when this study was conducted, there was insufficient stock of lorazepam due to the review of the import permit of its raw material by the regulatory agency. Therefore, to counter this problem, many patients who were receiving lorazepam in HBUK were converted to clonazepam instead. Taking this into account, the prescribing pattern of benzodiazepines in HBUK leaned more towards the short-acting benzodiazepines. This finding was interesting as in a study carried out in six Asian countries by Tor *et al.*, lorazepam and clonazepam were found to be the top most prescribed benzodiazepines, taking note that lorazepam is a short-acting while clonazepam is a long-acting benzodiazepine (11,12). In another study carried out in Lebanon by Ramadan *et al.*, alprazolam and bromazepam were the most commonly prescribed benzodiazepines, both of which belong to the short-acting group (12,13). Maniam *et al.* reported lorazepam to be the most prescribed benzodiazepine in a study conducted in a university hospital in Kuala Lumpur (14). In addition, according to the Malaysian Statistics on Medicines 2010, the top three benzodiazepines prescribed in Malaysia were alprazolam, zolpidem and lorazepam, which reflect closely to the findings in HBUK (15). It can be seen that Asian countries in general were more in favour of short-acting benzodiazepines as compared to western countries where long-acting benzodiazepines were preferred. Two studies conducted in the United States by Valenstein *et al.* and Gray *et al.* reported that the most prescribed benzodiazepines were diazepam, clonazepam and lorazepam where else in Canada, a cross-sectional study conducted in depressed patients by Rizvi *et al.* showed that clonazepam and lorazepam were the most common benzodiazepines prescribed (2,16,17).

The median dose of benzodiazepines received by our MDD patients was 3.57mg diazepam equivalent per day. According to the Canadian Agency for Drugs and Technologies in Health, high dose of benzodiazepine(s) is defined as doses of more than 10mg diazepam equivalents (18). Janhsen *et al.*, who studied the problems of long-term treatment with benzodiazepines and related substances in Germany, defined high dose of benzodiazepine as 20mg or more of diazepam equivalents (19). Benzodiazepine therapy can give rise to physiologic and psychologic dependence depending on the drug's dosage, duration and potency. Therefore, dependence will develop sooner in a patient receiving a high dosage of benzodiazepine as compared to a patient receiving a low dosage of benzodiazepine (20). Even though this study showed high levels of benzodiazepine use among outpatient depressed patients in HBUK, the dose received by the patients were considered low, and majority received a p.r.n. dose instead of a regular dose, which was less worrying. This finding differed from the findings in the REAP study which was a cross-sectional study conducted across nine Asian countries from 2001 to 2008. In the REAP study, the mean benzodiazepine daily dose prescribed in

Malaysia was 18.7mg (SD 14.1mg) of diazepam equivalents, which was much higher than the median dose prescribed in HBUK (11).

More than one half of the depressed patients received benzodiazepine(s) for more than four weeks with a median duration of 84 days (12 weeks) which was similar to other studies. Factors such as the desire to prevent a distorted physician-patient relationship, lack of time dealing with patients and failure to reassess patients' needs for benzodiazepines could have contributed to this finding. Valenstein *et al.* described that many physicians responded to their patients' requests for continuation of benzodiazepine(s) due to the worries that a good physician-patient relationship will be distorted if they decline the patients' requests (2). Two other studies also found that physicians continue to prescribe benzodiazepine(s) because of insufficient time in dealing with their patients (21,22). Physicians may also began benzodiazepine treatment as an adjunct to the antidepressants in the early stage of treatment and then failed to reassess the patients' need for the medication or may be hesitant to discontinue the medication as their patient is doing better (2). The EMPOWER trial showed that direct-to-consumer education could effectively elicit shared decision making around the overuse of medications that increase the risk of harm in older adults (23). Therefore, counselling about the risk of benzodiazepine dependence to newly diagnosed MDD patients may help to improve the awareness and reduce patients' dependence to the drugs.

To date, there was no published article on benzodiazepine prescribing pattern and usage among the MDD patients in Malaysia. Hence, this study provided important findings to create awareness among the healthcare professionals and public on the extent of benzodiazepine usage among MDD patients in the local setting. Since all prescriptions retained in the pharmacy for the treatment of MDD over the ten months period (March –December 2016) has been accounted for, the findings were highly reliable. There are limitations of this study, however, that should be taken into consideration. All prescriptions received from March 2016 to December 2016 that fit into the study criteria were included to study the benzodiazepines prescribing trend. However, some prescriptions were endorsed without diagnosis being written. Hence, some prescriptions in which patients were diagnosed with MDD could have been missed out in this study. Moreover, there could be a possibility that the patients did purchase benzodiazepines from the private general practitioners or community pharmacies without the hospital's knowledge.

Conclusion

Notwithstanding guideline cautions, long term prescribing of benzodiazepines in MDD patients remains an occurring treatment pattern in the mental health specialty care. Majority of the depressed patients receive benzodiazepines for a period of more than four weeks albeit only in low doses. Short-acting benzodiazepines were popular choices among the physicians of HBUK compared to long-acting benzodiazepines. Further studies are needed to clarify physicians' reasons for long-term treatment with benzodiazepines, the preference of short-acting benzodiazepines and the effectiveness of this practice. Other than that, it will be interesting to explore whether thorough counselling regarding the risk of benzodiazepine dependence with chronic use of benzodiazepines to newly diagnosed MDD patients will help to improve the awareness and reduce patients' dependence on the drugs in Malaysia.

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Conflict of Interest Statement

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Adverse Drug Reactions of Antivenom in Children: Frequency, Types, Severity and the Effectiveness of Pre-medications

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Abstract

Introduction: Antivenom is the only definitive lifesaving treatment for snakebite envenomation. However, the use of antivenom made from animal serum carries the risk of reactogenicity.

Objective: This study aimed to determine the frequency, types and severity of adverse reactions to antivenom following snakebites, and the association between the administration of pre-medications and the occurrence of antivenom-related adverse reactions in children.

Methods: All records of children receiving antivenom in paediatric ward in Hospital Sultan Abdul Halim from June 2011 to May 2016 were retrieved retrospectively from the Electronic Hospital Information System and Records Department. Demographic data, the documentation of snakebite and antivenom given, descriptions of adverse reactions to antivenom and pre-medications prescribed and the outcome of patient following antivenom treatment were recorded. The severity of antivenom reactions were classified as mild, moderate and severe.

Results: Thirty snakebite victims were included in this study. The median age was 8.5 years old and majority (63.3%) of the patients were among between seven to 12 years old. Seventeen subjects developed adverse reactions following antivenom infusion in which 58.8% of the adverse reactions were mild, 23.6% were moderate and 17.6% were severe. The most common adverse reactions were rash (88.2%) followed by itchiness (29.4%) and chest tightness (29.4%). Eleven (36.7%) patients in this study were given pre-medications before the administration of antivenom. The most prescribed pre-medications were the combination of hydrocortisone injection and chlorpheniramine (54.5%), followed by hydrocortisone injection alone (27.3%). The proportion of patient developing reactions (54.5%) after pre-medications was comparable to those without pre-medications (57.9%), and no statistically significant association was observed ($p=1.00$).

Conclusions: The adverse reactions to antivenom were high among the children regardless of the use of pre-medications. Further studies regarding the administration of pre-medications in children and the development of better quality and safer antivenom are warranted.

Keywords: snakebite, envenomation, antivenom reactions, pre-medications

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Introduction

The World Health Organization (WHO) estimated that about 5 million of snakebites occur each year. WHO has recognized snakebite envenomation into Category A of the Neglected Tropical Diseases (NTD-A) on 6th June 2013 (1). Similarly, snakebite injuries are common in tropical developing countries like Malaysia. Among the approximately 40 venomous snake species in Malaysia, Cobra and Malayan pit vipers contribute to most of the cases (2). The incidence of snakebite is highest among the children and young adults and the rate of fatality peaks in vulnerable paediatric and geriatric age groups (3, 4).

Antivenom is the only definitive lifesaving treatment for snakebite envenomation. However, the use of antivenom made from animal serum carries the risk of reactogenicity (5-8). Reported adverse reactions of antivenom include early fatal anaphylaxis, pyrogenic reaction and late allergic reaction (6,9,10-15). The reactions were estimated to occur in 20% of cases and hence, increasing the safety of snake antivenom use is crucial (2,3).

Antivenoms are immunoglobulins derived from the plasma of a horse, mule or donkey (equine) or sheep (ovine) that has been immunised with the venoms of one (monovalent) or more species (polyvalent) of snakes. The Fc fragment of immunoglobulin molecule is responsible for antivenom reactions and its removal produces F(ab')₂ or Fab were believed to potentially reduce the frequency of the reactions (16). The antivenom neutralises snake venom by blocking the venom toxin from interacting with the target tissues (17). It should be given as soon as it is indicated because it can reverse systemic envenoming even if it has persisted for weeks (3, 18). The dosage of antivenom for children is similar to adults (2) as snakes inject the same dose of venom into children and adults (3).

Currently, there is no clear scientific evidence or policy for the use of pre-medications to prevent the adverse reactions of antivenom. The practice of pre-medications with hydrocortisone or antihistamine is not supported by strong evidence. Moreover, there is still controversy on the use of subcutaneous adrenaline as pre-medication for children although a few studies have shown its effectiveness as compared to placebo or other type of pre-medications such as antihistamines and hydrocortisone, or in combinations (9,12,19). As a result, there are variations in the management of snakebite and treatment of antivenom reactions among different settings. Therefore, this study aimed to determine the frequency, types and severity of adverse reactions to antivenom following snakebites, and the association between the administration of pre-medications and the occurrence of antivenom-related adverse reactions in children.

Method

A single-centred retrospective cross-sectional study was conducted in the paediatric ward of Sultan Abdul Halim Hospital in Sungai Petani, Kedah. All children aged 12 years old and below admitted due to snakebite and received antivenom from 1st June 2011 to 31st May 2016 were enrolled except patients whose antivenom were given in the emergency unit or other wards. We also excluded antivenom use without proper documentation or without sufficient detail.

The medical records of paediatric patients admitted due to snakebite were retrieved retrospectively from the Electronic Hospital Information System (e-HIS) and Medical Records Department. All retrieved records were screened for proper documentation. Demographic data, the documentation of snakebite and antivenom given, dilution and method of antivenom administration, descriptions of adverse reactions to antivenom and pre-medications prescribed as well as the outcome of patient following antivenom treatment were recorded into a data collection form.

A grading system developed by Brown (2004) (20) was used to classify the severity of antivenom reactions of the patients. The severity of antivenom reactions were classified as mild, moderate and severe as below:

- Mild – skin and subcutaneous tissues changes such as generalised erythema, urticaria, periorbital oedema, or angioedema;
- Moderate – features suggesting respiratory, cardiovascular, or gastrointestinal involvement, including dyspnoea, stridor, wheezing, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, or abdominal pain; or
- Severe – hypoxia, hypotension, or neurological compromise including cyanosis, oxygen saturation 92% and below, hypotension with systolic blood pressure (SBP) less than 90 mmHg, confusion, collapse, or loss of consciousness.

This study was registered with the National Medical Research Register (NMRR) with the registration number NMRR-16-2737-33694 and ethics approval was obtained from the Ministry of Health (MOH) Medical Research and Ethics Committee (MREC).

The Statistical Package for Social Sciences (SPSS) version 19 was used to perform data analysis in this study. The comparisons of categorical data were carried out by using Fisher's exact test. A P-value of less than 0.05 was considered statistically significant.

Results

Throughout the studied period, 30 children were admitted due to snakebites in Sultan Abdul Halim Hospital. After screening the medical records, all 30 patients were included in the study. The basic characteristics of the study population were shown in Table 1. The median age of the included patients was 8.5 years old and snakebites were most common in the age group of seven to twelve years (n=19; 63.3%). Majority of the study population were male (n=21; 70.0%) and Malay (n=28; 93.3%). The most common bitten areas were finger (n=7; 23.3%) and lower limb (n=6; 20.0%) (Figure 1).

Most of the subjects (86.7%, n=26) were given pit viper antivenom while the remaining received cobra antivenom. As high as 56.7% of our study population (n=17) had developed adverse reactions following the administration of antivenom. With regards to the severity of antivenom reactions, most of the patients (58.8%) developed mild adverse reactions while severe reactions occurred in only three patients (17.6%). Rash was found to be the most frequent adverse reaction and it was reported in 88.2% of those who developed adverse reactions. This was followed by itchiness and chest tightness or bronchospasm in 29.4% of the patients respectively (Figure 2).

Of all 30 patients, 11 patients (36.7%) were given pre-medications before the administration of antivenom. The most prescribed pre-medications in our study were the combination of hydrocortisone injection and chlorpheniramine (54.5%), followed by hydrocortisone injection alone (27.3%). Despite being given pre-medication, adverse reactions of antivenom happened in 54.5% of these patients (n=6), which was comparable to 57.9% of patients (n=11) who did not receive any pre-medication. The Fisher's exact test indicated that the association between the administration of pre-medication and the occurrence of adverse reactions to antivenom was not statistically significant (p=1.00) (Table 2).

Table 1: Characteristics of paediatric snakebite patients receiving antivenom (n=30)

Variable	n	(%)
Age		
< 2 years old	3	(10.0)
2-6 years old	8	(26.7)
7-12 years old	19	(63.3)
Gender		
Male	21	(70.0)
Female	9	(30.0)
Race		
Malay	28	(93.3)
Indian	1	(3.3)
Others	1	(3.3)
Antivenom received		
Pit viper antivenom		
Cobra antivenom	26	(86.7)
Present of Antivenom Reactions	4	(13.3)
Yes		
Mild	10	(33.3)
Moderate	4	(13.3)
Severe	3	(10.0)
No	13	(43.3)
Administration of Pre-medications		
Yes		
Hydrocortisone & Chlorpheniramine	6	(20.0)
Hydrocortisone	3	(10.0)
Adrenaline	1	(3.3)
Normal saline bolus, Hydrocortisone & Promethazine	1	(3.3)
No	19	(63.3)

Figure 1: The frequency of snakebite sites (n=30)

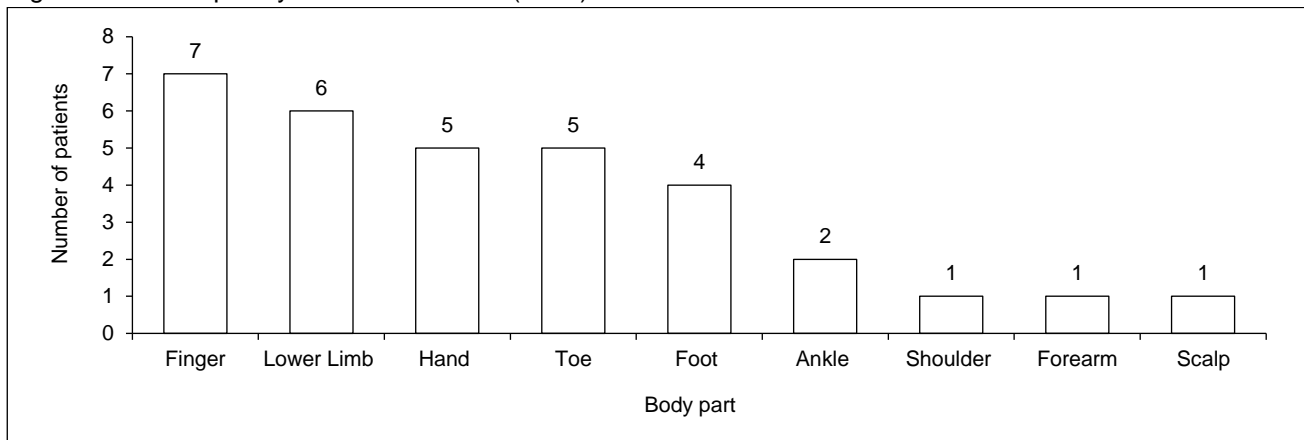


Figure 2: Frequency of adverse reactions to snakebite antivenom (n=17)

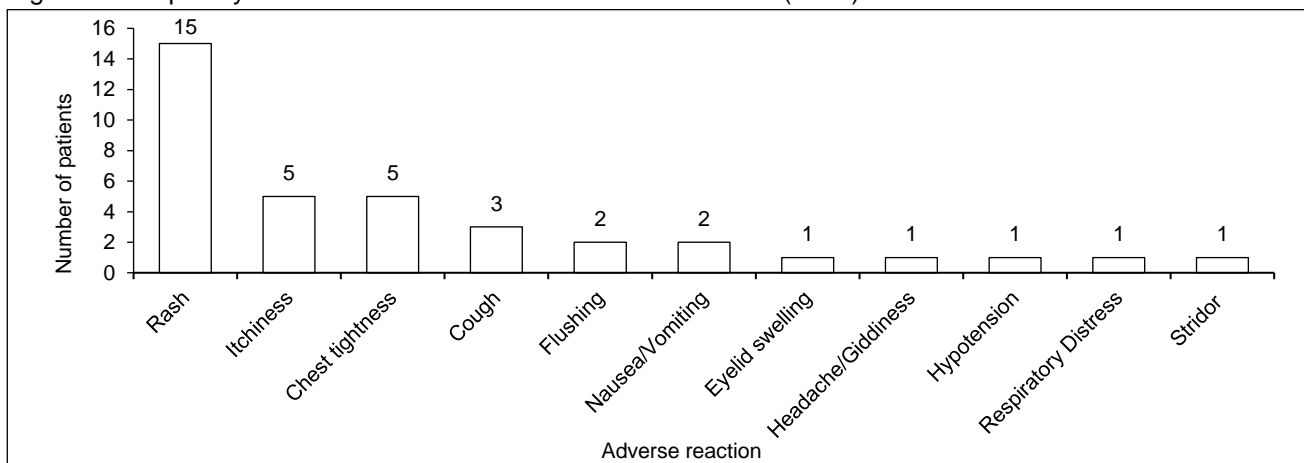


Table 2: The association between the administration of pre-medications and the occurrence of adverse reactions to antivenom (n=30)

Pre-medication	Adverse reaction to antivenom, n (%)		P-value ^a
	Yes	No	
Pre-medication			1.00
Yes (n=11)	6 (54.5)	5 (45.5)	
No (n=19)	11 (57.9)	8 (42.1)	

^a Fisher's Exact test

Discussion

Currently, all MOH hospitals are using the antivenoms manufactured by the Queen Saovabha Memorial Institute, Thailand. This is attributed to the similarity between snake species between both countries (21). The characteristics of our patients were found to be comparable to those observed in most of the studies. For example, the number of male patients were higher than female patients (8,15,22,23). On the other hand, both local and Asian studies proposed that the most common sites of snakebite were lower and upper limbs with majority of the bites occurred while the patients were working or walking outdoor (24-26).

Owing to antivenom antigenicity, as reported by other researchers, 18.4% to 88.4% of patients developed adverse reactions to antivenom (2,15,22,23). Findings from this study actually fell within the range

published by other researchers. Such a high frequency of antivenom reactions probably result from the lack of advancement in antivenom production technology (27). The production methods used have changed very slowly in the past 50 to 60 years (28). Both types of antivenom used in this study were manufactured by the Queen Saovabha Memorial Institute, Thailand. There was no change of antivenom brand throughout the study period. All antivenoms were given through infusion in a stepwise increment of infusion rate as recommended by Malaysia Management Guideline of Snakebites (18).

Most patients with adverse reactions to antivenom in this study presented with rash, itchiness and chest tightness or bronchospasm. Similar presentations of antivenom reactions were observed in Bangladeshi and Australian patients (23, 29). In contrast, Deshpande *et al.* showed that the most common presentation of reaction were chills and rigors in Indian patient (24). In addition, more patients developed tachycardia and tachypnoea in Papua New Guinea, as compared to our study (15). The differences of antivenom reactions reported among patients were likely due to the administration and type of pre-medications used in different countries. There are multiple mechanisms involved in the development of adverse antivenom reactions (30).

At present, there is no strong evidence to support the use of hydrocortisone and antihistamines as pre-medications for snake antivenom (31). Therefore, the routine use of pre-medications is not recommended by our local guidelines unless there are signs of antivenom reactions (2, 18). Nevertheless, approximately one third of our study cohort still received pre-medications prior to antivenom infusion. Hydrocortisone, either given alone or in combination with other agents, appeared to be the most preferred agent in our study. Similar practice was observed in Sri Lanka and Australia (22,29). On the other hand, a study in Papua New Guinea found that the combination of adrenaline and promethazine were commonly used to prevent antivenom reactions (15).

In contrast to our local guidelines, the WHO advocated the routine use of adrenaline as pre-medication since 2016 except in older patients with underlying cerebrovascular disease (3). A systematic review and meta-analysis had also demonstrated that adrenaline plays a positive role in the prevention of early adverse reactions following antivenom administration (32). In addition, a randomised double-blind placebo-controlled trial by Silva *et al.* comparing the effectiveness of pre-medications in adult snakebite victims had reported that pre-treatment with low dose adrenaline significantly reduced the risk of acute adverse reactions to antivenom by 43% at one hour compared to placebo; hydrocortisone or promethazine did not give the same benefit as adrenaline (22). Unlike antihistamine and glucocorticoids which interfere with the mechanisms of antivenom adverse reactions, adrenaline works by directly counteracting the effects produced by mast cell and basophil activation (30). Acting as both α and β adrenoceptors agonist, adrenaline results in the arterial and venous vasoconstriction, increase in cardiac output as well as bronchodilation, hence rapidly reversing bronchospasms, angioedema and severe hypotension observed in anaphylactic shocks (30).

Adrenaline may be effective in reducing antivenom reactions but its safety concern should be addressed before it is used as routine pre-medication in snakebites management. Study on the safety of adrenaline as pre-medication by Dassanayake *et al.* (33) reported a death from suspected intracranial bleeding following adrenaline injection. Furthermore, children, patient aged over 70 years old, patient with hypertension, ischaemic heart disease, arrhythmias or cerebrovascular disease were excluded from the study. This raised the concern on the safety of adrenaline when used as pre-medication in the paediatric population.

In our study, pre-treatment with adrenaline was only observed in one patient and hence the effectiveness of adrenaline as premedication could not be analysed. The different types of pre-medication used among our study population might explain the lack of association between the administration of pre-medications and occurrence of antivenom reactions. Many studies showed that non-adrenaline-containing pre-medications such as hydrocortisone, promethazine or chlorpheniramine alone failed to demonstrate protective role against antivenom reactions (19,22,32,34). Gawarammana *et al.* (19) reported the reduction of antivenom reactions rate among patients treated with the combinations of hydrocortisone and chlorpheniramine, compared to patients treated with hydrocortisone alone and placebo but this study was deemed low statistical power due to small sample size (n=52).

There were a number of limitations faced when carrying out this study. The study was limited by small sample size. Therefore, it may be the reason that the result did not reach any statistical significance. Thus, we need a larger sample size to demonstrate the effectiveness of antivenom pre-medications. Most patients were receiving different combinations of pre-medications and this was potentially the factor for statistical comparisons between individual pre-medication. On top of that, retrieval of patients' record involved both electronic and hand-

written copy that were sometimes inconsistent with each other. Our retrospective design further restricted the assessment of the data accuracy when this happened. As this study was conducted in one centre only, the findings may not truly reflect the trend in Malaysia as a whole.

Conclusion

In conclusion, the adverse reactions to antivenom were high among the children regardless of the administration of pre-medication. Future studies are recommended to explore the effectiveness of pre-medications in the local population in preventing antivenom reactions especially among the children. The adoption of pre-medication recommendations into local snakebite management guideline based on local evidence should be carried out to optimise the therapeutic efficacy of antivenom. Meanwhile, the development of better quality and safer antivenoms are warranted.

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A Study on Potentially Inappropriate Medications in Geriatric Patients Admitted to the Medical Wards in Bentong Hospital Using Beers Criteria

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Abstract

Introduction: Geriatric patients are more susceptible to adverse drug reactions due to the changes in pharmacokinetics and pharmacodynamics in the elderly. The American Geriatric Society (AGS) Beers Criteria were developed to identify potentially inappropriate medications (PIMs) prescribed to the geriatric patients.

Objective: This study was carried out to identify the frequency and risk factors of PIM prescription among the geriatric patients using the AGS Beers Criteria.

Methods: This was a single-centred cross-sectional descriptive study that included patients aged 65 years and above that was admitted to the male and female medical wards of Bentong Hospital, Pahang from August 2018 to October 2018. The case records of the included patients were analysed by referring to the AGS Beers Criteria 2015. Data was analysed using SPSS and multiple logistic regression analysis was used to evaluate the risk factors associated with PIM prescriptions.

Result: A total of 150 patients were included in the study. Among them, 107 (71.3%) received at least one PIM. After excluding the drugs to be used with caution, the frequency of PIMs decreased to 55.3%. The most prescribed PIMs among the geriatric patients in Bentong Hospital were metoclopramide, frusemide and ranitidine. Inappropriate medication use was significantly associated with female gender (adjusted odd ratio 2.64, 90% confidence interval (CI) 1.38 to 5.05, $p=0.014$) and number of medications prescribed per patient (adjusted odd ratio 1.12, 90% CI 1.06 to 1.19, $p=.001$).

Conclusion: The study showed that PIMs prescription constituted a major problem among the elderly patients in Bentong Hospital. Attention needs to be paid to improve healthcare providers' awareness about PIMs for geriatric patients to improve care and minimise adverse drug reactions.

Keywords: geriatric, potentially inappropriate medications, elderly, Beers Criteria

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Introduction

Malaysia is aging fast and the elderly population (65 years old and above) was about 6.2% of the total population in 2017 (1). As Malaysia prepares itself to be an ageing nation when 7% of its population will be 65 years and above in the future, measures have to be taken to overcome the problems and challenges that would arise. One among them would be patient safety, especially in relation to the safety of medications for elderly adults who are more likely to have more than one chronic disease and require concomitant prescription of multiple medications.

The altered pharmacokinetics and pharmacodynamics in the elderly due to aging cause them to be more susceptible to adverse drug reactions. Physiological changes like changes in hepatic and renal functions as well as the decline in total body water lead to an increase in the volume of distribution of lipid-soluble drugs and reduced clearance of lipid-soluble and water-soluble drugs, respectively. These changes may prolong plasma elimination half-life of certain drugs. Significant pharmacodynamic changes such as age-related changes in specific receptors and target sites also lead to the increased sensitivity to drugs. Thus, many drugs are inappropriate for elderly patients because of their pharmacological or potential adverse effects (2). Therefore, this necessitates judicious use of drugs to prevent adverse drug reactions and hence reducing the rate of morbidity in the elderly.

Certain drugs are classified as potentially inappropriate medications (PIM) for the elderly due to their increased risk of adverse drug events when used in this patient group. Several assessment tools have been developed to identify PIMs for older people. The American Geriatric Society (AGS) Beers Criteria 2015 is the most frequently used among those explicit methods to aid the health care providers in safe prescribing. The Beers Criteria have been used internationally over the past three decades to study PIM use. It was first developed in 1991, which included a list of drugs that were likely to cause more harm than benefits in the elderly. The list was based on the consensus of experts from different disciplines like geriatrics, clinical pharmacology, and psychopharmacology using an adopted Delphi method. In 2012, the AGS revised and updated the Beer's list, listing the PIMs into three categories. The first category included drugs to be avoided for many or most older adults regardless of disease or condition. The second category included medications to avoid for older adults with certain diseases or syndromes as these medications may exacerbate the disease or syndrome. The third category included medications that should be prescribed with caution as they have the potential of causing adverse reactions, which may be used if no other alternatives are available (3). The Beers lists were updated again in 2015 with the addition of two major components, which were potentially clinically important drug-drug interactions to avoid and medications to avoid or which dose adjustment is needed based on kidney function (4).

The Bentong Town is a municipality located in the west of Pahang, Malaysia. According to the Census 2010, 5.7% of the Bentong population was 65 years and above (5). The percentage is believed to have increased by the moment due to the substantial improvement in life expectancy throughout the world. In addition, there is an inflow of retirees to Bentong due to its peaceful environment and fresh air. Despite the aging of the population, studies about the prescribing pattern and prevalence of PIM among the geriatric patients were scarce in the state. Therefore, this study was carried out to identify the frequency and risk factors of PIM prescription among the admitted geriatric patients in Bentong Hospital using the AGS Beers Criteria. This study was hope to shed some light on the quality and rationality of drugs prescribing for the elderly patients in the state.

Methods

Study Participants

It was a single-centred cross-sectional descriptive study that was conducted for three months from August 2018 to October 2018 in Bentong Hospital, Pahang. Bentong Hospital is a general government hospital located in the centre of Bentong district.

The study included patients aged 65 years and above that was admitted to the male and female medical wards within the study period. Patients with hospital stay less than 12 hours, who did not receive any medication, admitted for observation only and those who passed away or transferred out within 12 hours of admission were excluded from the study.

Non-probability sampling was used as the sampling technique. The sample size was calculated to be 68 using the Cochran's Formula, based on 50% prevalence rate of PIMs, accounting for a standard error of 10% with a 90% confidence interval. Nevertheless, 150 patients (additional 120%) were targeted in this study taking into consideration of any missing or incomplete data.

Data Collection

Data was collected using a data collection form designed to extract information from the patients' medical records. Patient information including the age, gender, race, diagnosis, comorbid conditions, medication history, duration of hospitalisation and relevant laboratory investigations were extracted from the patient medical record files. Drug information such as the name of drug, strength, frequency, duration together with the starting and ending dates, dosage form and route of administration were extracted from the patient medication charts.

Data Analysis

The entire course of prescribed medications in the patient’s case records during the hospital admission was analysed by referring to the AGS Beers Criteria 2015 to detect any PIMs use in older adults. The categories of PIMs listed in the Beers Criteria (4) were named PIM 1 to PIM 5 in this study, as summarised in Table 1.

Table 1: PIMs listed in the AGS Beers Criteria 2015

Category	Description
PIM 1	Medications to avoid for older adults
PIM 2	Medications for older adults with specific diseases or syndromes to avoid due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome
PIM 3	Medications to be used with caution in older adults
PIM 4	Potentially clinically important non-anti-infective drug-drug interactions that should be avoided in older adults
PIM 5	Non-anti-infective medications that should be avoided or have their dosage reduced according to kidney function in older adults

We performed our analysis using SPSS software version 22. The results were presented as frequency (n) and its respective percentage in the form of tables and figures as appropriate. Multiple logistic regression analysis was used to identify the risk factors associated with PIM prescriptions.

Results

A total of 150 case records of patients aged 65 years and above were reviewed. The demographic characteristics of these patients were shown in Table 1. Out of these 150 patients, 75 were male (50%) and 75 were female (50%). The study revealed that majority of the geriatric patients in Bentong Hospital were Chinese (51.3%), followed by Malay (40.0%) and Indian (8.7%). The age of the patients ranged from 65 years to 93 years, with the average age of 77.21 years. The average number of comorbidities per patient was 2.69 while the average length of hospitalisation was found to be 6.25 days. A total of 2120 medications were prescribed, with an average of 14.13 drugs for each patient.

The prescription of PIMs according to the medication categories listed in the AGS Beers Criteria 2015 was shown in Table 3 and the prescription of PIMs with respect to the characteristics of patients were enlisted in Table 4. Of the 150 patients, 107 received at least one PIM (71.3%). After excluding drugs listed under Criteria 3 of AGS 2015 Beers criteria, namely the drugs to be used with caution in older adults, the percentage of PIMs use was observed to be 55.3%. The most prescribed PIMs according to the PIM categories can be seen in Table 5. The most prescribed PIMs in this study were metoclopramide (category PIM 1), frusemide (category PIM 3) and ranitidine (category PIM 5).

Simple and multiple logistic regression analyses were carried out, and the factors that exhibited significant associations with PIMs were shown in Table 6. The multiple logistic regression revealed that female gender (adjusted odd ratio 2.64, 90% confidence interval (CI) 1.38 to 5.05, p=0.014) and number of medications prescribed (adjusted odd ratio 1.12, 90% CI 1.06 to 1.19, p=0.001) were significantly associated with PIM use.

Table 2: Demographic characteristics of the elderly patients (n=150)

Variables	n	(%)
Gender		
Male	75	(50.0)
Female	75	(50.0)
Race		
Malay	60	(40.0)
Chinese	77	(51.3)
Indian	13	(8.7)
Age		
65 – 69 years	44	(29.3)
70 – 74 years	31	(14.0)
75 – 79 years	42	(28.0)
≥ 80 years	33	(22.0)
Number of comorbidities per patient		
≤ 1	29	(19.3)
2	34	(22.7)
3	45	(30.0)
4	30	(20.0)
5	12	(8.0)
Length of hospitalisation		
1 – 5 days	95	(63.3)
6 – 10 days	33	(22.0)
11 – 15 days	9	(6.0)
≥ 16 days	13	(8.7)
Number of medications prescribed per patient		
1 – 5	11	(7.3)
6 – 10	44	(29.3)
11 – 15	42	(28.0)
≥ 16	53	(35.3)

Table 3: Prescription of PIMs according to AGS Beers Criteria 2015 medication categories (n=150)

Category	Patients prescribed with PIMs, n (%)
PIM 1	77 (51.3)
PIM 2	6 (4.0)
PIM 3	52 (34.7)
PIM 4	5 (3.3)
PIM 5	22 (14.7)

Table 4: Prescription of PIMs according to AGS Beers Criteria 2015 medication categories and the demographic characteristics of elderly patients (n=150)

Variable	PIM 1	PIM 2	PIM 3	PIM 4	PIM 5
Gender					
Male	38 (50.7)	4 (5.3)	21 (28.0)	3 (4.0)	9 (12.0)
Female	39 (52.0)	2 (2.7)	31 (41.3)	2 (2.7)	13 (17.3)
Age					
65-69 years	25 (56.8)	1 (2.3)	14 (31.8)	4 (9.1)	4 (9.1)
70-74 years	14 (45.2)	2 (6.5)	13 (41.9)	0 (0)	4 (12.9)
75-79 years	18 (42.9)	1 (2.4)	12 (28.6)	0 (0)	7 (16.7)
≥ 80 years	20 (60.6)	2 (6.1)	13 (39.4)	1 (3)	7 (21.2)
Number of comorbidities					
≤ 1	16 (55.2)	2 (6.9)	7 (23.8)	2 (6.9)	6 (20.7)
2	14 (41.2)	2 (5.9)	12 (35.3)	1 (2.9)	5 (14.7)
3	20 (44.4)	0 (0)	15 (33.3)	0 (0)	6 (13.3)
4	19 (63.3)	1 (3.3)	15 (50.0)	2 (6.7)	3 (10.0)
5	8 (66.7)	1 (8.3)	5 (41.7)	0 (0)	2 (16.7)
Length of hospitalisation					
1 – 5 days	45 (47.4)	4 (4.2)	36 (37.9)	4 (4.2)	13 (13.7)
6 – 10 days	17 (51.5)	2 (6.1)	8 (24.2)	1 (3.0)	7 (21.2)
11 – 15 days	7 (77.8)	0 (0)	4 (44.4)	0 (0)	2 (22.2)
≥ 16 days	8 (61.5)	0 (0)	4 (30.8)	0 (0)	0 (0)
Number of medications prescribed					
1 – 5	3 (27.3)	0 (0)	0 (0)	0 (0)	0 (0)
6 – 10	16 (36.4)	4 (9.1)	13 (29.6)	1 (2.3)	7 (15.9)
11 – 15	19 (45.2)	0 (0)	16 (38.1)	1 (2.4)	6 (14.3)
≥ 16	39 (73.6)	2 (3.8)	23 (43.4)	3 (5.7)	9 (17.0)

Note: values were presented as n (%)

Table 5: The most prescribed PIMs according to AGS Beers Criteria 2015 medication categories (n=150)

Category	Medicine	n (%)
PIM 1	Metoclopramide	51 (34.0)
	Diphenhydramine	11 (7.3)
	Mineral oil	10 (6.7)
	Hyoscinamine	6 (4.0)
	Atropine	6 (4.0)
	Prazosin	6 (4.0)
	Chlorpheniramine	5 (3.3)
	Others	9 (6.0)
	PIM 2	Ranitidine
Alprazolam		1 (0.7)
Verapamil		1 (0.7)
PIM 3	Frusemide	49 (32.7)
	Aspirin	6 (4.0)
PIM 4	Ranitidine	1 (0.7)
	Lorazepam	1 (0.7)
PIM 5	Ranitidine	18 (12.0)
	Tramadol	3 (2.0)
	Fondaparinux	1 (0.7)

Table 6: The factors of PIMs prescription by simple and multiple logistic regression model

Variable	Simple Logistic Regression			Multiple Logistic Regression *		
	B	Crude OR (90% CI)	P value	B	Adjusted OR (90% CI)	P value
Gender						
Male	0.0	1	0.049	0.0	1	0.014
Female	0.73	2.07 (1.13-3.82)		0.97	2.64 (1.38-5.04)	
Number of medications prescribed per patient	0.10	1.11 (1.05-1.17)	0.002	0.11	1.12 (1.06-1.19)	0.001

* Forward LR Multiple Logistic Regression model was applied. Multicollinearity was checked and not found. Interaction was found between gender and number of medications. Hosmer–Lemeshow test, (p=0.539), classification table (overall correctly classified percentage=74.7%) and area under the ROC curve (74.9%) were applied to check the model fit.

Discussion

The results of this study showed that PIM prescription was common among the elderly inpatients in Bentong Hospital. Among our study population, as many as 71.3% received at least one PIM listed in the AGS Beers Criteria 2015. However, if we exclude drugs listed in category PIM 3, namely the drugs to be used with caution in older adults as these drugs were not considered as PIMs to be avoided, the percentage of patients prescribed with PIMs was observed to be 55.3%. This figure was lower than a Korean study (6) but higher than most of the other similar studies (7-9). The higher prevalence could be attributed to the fact that this study utilised Beers criteria 2015 which was a more comprehensive list than Beers criteria 2012 used in the other studies.

Drugs in category PIM 1 which included PIMs to avoid for older adults, formed a majority of inappropriate use of medications, followed by category PIM 3 which was drugs to be used with caution and category PIM 5 which was PIMs to be avoided or adjusted according to creatinine clearance. This was comparable to a study by Narvekar *et al.* which showed that majority of PIMs use were listed under Criteria 3, followed by Criteria 1 and Criteria 5 (9).

It was observed that, in general, as the number of comorbidities increased, the percentage of PIMs use also increased, which conformed to category PIM 1 and category PIM 3. However, this increasing trend of PIMs use was not observed for category PIM 2, PIM 4 and PIM 5, in contrast to the findings by Hwang *et al.* and Narvekar *et al.* (8,9). We also observed that with the advancement of patients’ age, no increased incidences of PIMs prescription were noted, in contrast to the study by Lin *et al.* (10). When we looked at the use of PIMs with respect to the length of hospitalisation, interestingly, there was an increased use of PIMs up to 15 days of hospitalisation, followed by a drop beyond 15 days of hospitalisation. This was similar to the findings by Narvekar *et al.* (9). Besides that, we also noted that as the number of medications prescribed per patient increased, the prescription of PIMs also increased, which was observed for all categories of PIMs in the Beers list. This corresponded with the observations made by Hwang *et al.* and Lin *et al.* (8,10). Geriatric patients are more likely to be in poor health and need multiple medications, which may have contributed to the increased risk of receiving PIMs.

The most prescribed PIMs in this study were metoclopramide, frusemide and ranitidine. Metoclopramide is usually given to patients prescribed with tramadol as a prophylaxis against emesis which is a common side effect of tramadol. Metoclopramide, however, should be avoided in the elderly unless indicated for gastroparesis, as the drug can cause extrapyramidal effects and the risk may be higher in frail older adults (4). The most common “drug to be used with caution” prescribed was frusemide. Frusemide is a loop diuretic which may cause hyponatremia. Therefore, it is advised to monitor the sodium level closely while an elderly patient is on the drug (4). On the other hand, for category PIM 5 medications which are PIMs to be avoided or have their doses adjusted according to the kidney functions, we found that ranitidine was most often being prescribed inappropriately. According to the Beers Criteria, the dose of ranitidine should be reduced for older patients with creatinine clearance below 50mL/min as ranitidine will undergo renal excretion and in patients with renal impairment, it will accumulate in the body and may lead to mental status changes (4,11).

The results described in the multiple variable regression analysis revealed that the factors associated with a PIM use included female gender and the number of medications prescribed during the patient’s

hospitalisation. It was unclear why female patients were more likely to be prescribed a PIM compared to male patients. Therefore, further studies are needed to examine how gender differences may predict inappropriate drug use. It is possible that women tend to be more concerned with their health and may report pain and symptoms of depression more often than men, which exposed them to a higher risk of PIM prescriptions (12). Multiple logistic regression also revealed that the number of medications prescribed seem to be one of the important factors in predicting PIM prescription. Therefore, since elderly patients often require higher number of medications to treat their diseases in the wards, PIMs should be considered during the prescribing process.

Based on the high prevalence of PIMs prescribing observed in this study, efforts must be made to improve the prescribing practice for elderly patients. It would be important for physicians to consider avoiding PIMs and to select better-tolerated alternatives with less adverse effects for the elderly patients. The use of PIMs should be avoided in the elderly as this will lead to higher rate of adverse drug reactions among them, which is also associated with increased healthcare costs (7,13). The use of Beers Criteria in conjunction with other tools such as the 'Screening Tools of Older Persons' potentially inappropriate Prescriptions' (STOPP) and 'Screening Tool to Alert doctors to Right Treatment' (START) criteria is recommended to allow reduce PIMs prescription among the geriatric patients (14). In addition, a systemic strategy can be developed to prevent medication-related complications. For example, common interactions can be listed in the wards to guide doctors to consider PIMs in their clinical decision making. It is essential to encourage the prescriber to be aware of PIMs in their day-to-day clinical practice to deliver better health care to the geriatric population.

Despite the high prevalence of PIMs use among the warded geriatric patients as demonstrated in this study, PIMs were not seriously considered as an important issue during the prescribing process for older patients. Drugs can affect quality of life and morbidity in the elderly. Therefore, judicious prescribing needs to take into consideration the risk-benefit ratio to minimise iatrogenic complications in the aged. A better understanding of ageing physiology and pharmacology is necessary for primary care physicians to adopt in their practice in caring for this subgroup of patients. As iatrogenic complications are more common and more serious among the elderly than among younger patients, the avoidance of PIMs with a high risk of adverse drug effects represents an important strategy.

This study had several limitations. First, since this was a single-centred study, the sample was statistically small and the overall prevalence of PIMs in the state of Pahang could not be estimated in this study. Additionally, the Beers Criteria were developed for the United States, different populations may not share the same effects or adverse effects for some of the listed medications. Finally, there may be drugs that are PIMs for Asian or Malaysian elderly but not listed in the Beers Criteria .

Conclusion

This study gave us a remarkable insight into the current status of drug prescribing for the geriatric patients in Bentong Hospital. High frequency of PIMs use constituted a major problem among the elderly patients with the most prescribed PIMs being metoclopramide, frusemide and ranitidine. Female gender and higher number of medications prescribed per patient were the risk factors associated with PIM prescription for the elderly patients. Since PIM exposure is a key element to ensure care quality, attention needs to be paid improve prescribers' awareness about PIMs for geriatric patients. More studies should be conducted to investigate PIMs use the in outpatient departments, other healthcare facilities, specialties, and even private practitioners.

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Conflict of interest statement

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

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Oral Opioid for Pain Relief after the Discontinuation of Post-operative Pain Treatment Modalities

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Abstract

Introduction: There is insufficient evidence or recommendation to guide the best approach to convert non-oral post-operative pain management to oral analgesics.

Objective: This study aimed to assess the use of oral opioids after the discontinuation of non-oral post-operative pain treatments, their effectiveness in post-operative pain relief and the occurrence of opioid related side effects.

Method: This was a retrospective cross-sectional study involving all adult post-operative patients discharged from the operation theatre from January to June 2016 on post-operative pain treatment with epidural infusion of local anaesthesia with or without strong opioid, Patient Controlled Analgesia (PCA) and subcutaneous injection of strong opioids. Information on the type of oral analgesics, pain score on movement and opioid related side effects were collected from patients' medical record. The effectiveness of pain relief was defined as pain score on movement less than 4 at 24 hours after the conversion of non-oral post-operative pain treatments to oral opioids.

Results: Of 677 patients' charts reviewed, 497 patients fulfilled the inclusion criteria. After the discontinuation of non-oral post-operative pain treatments, most patients were prescribed with strong opioids, with 58.1% using Morphine syrups and 7.4% using Oxycodone capsules. Tramadol capsules, a weak opioid, were given to 32.6% of patients while 1.8% of them did not receive any opioid. Pain assessment at 24 hours after the conversion to oral analgesics found that 92.6% of patients were able to maintain pain score on movement below 4 with a mean score of 2.01 (standard deviation 1.15). Minor opioid related side effects were reported in 49 patients (10.0%). The most common side effects were nausea and vomiting (5.9%), dizziness (2.3%) and constipation (1.2%).

Conclusion: The use of oral opioids after discontinuation of post-operative pain treatment was very common and was able to provide adequate pain relief with low occurrence of minor side effects.

Keywords: strong opioid, post-operative pain, safety

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Introduction

Post-operative pain is a common experience in more than 80% of patients who undergo surgical procedure (1). Effective post-operative pain control is an essential component of patient care that can lead to shortened hospital stays, reduced hospital cost, early mobilisation and increased patient satisfaction (2). Inadequate pain control, apart from being inhumane, can affect the quality of life, functional recovery, increase the risk of post-surgical complications such as prolonged rehabilitation and risk of persistent post-surgical pain thus may result in increased morbidity or mortality (1,3,4).

Another important approach to effective acute pain post-operative pain management is to utilise an appropriate assessment tool. Pain assessment and reassessment are required to provide optimal post-operative pain care. Pain score measured at rest and movement will give an indication regarding the effectiveness of analgesics and the need for changes in analgesic dose (1,5). A 10-point Numerical Pain Rating

Scale, where 1 is no pain and 10 is the worst possible pain imaginable, has been used and accepted nationally. The aim for pain score at rest and on movement is 4 or less out of 10 points (5).

Immediate post-operative pain treatments involve a variety of pain relief modalities including the use of Patient Controlled Analgesia (PCA), intrathecal opioid, peripheral nerve block and epidural administration of local anaesthetics with or without strong opioid. The choice of post-operative pain treatment modalities usually depends on the type of operation, type of patients and availability of the machines. Neuraxial analgesia such as epidural and spinal (intrathecal opioid) is recommended in major thoracic and abdominal procedures, particularly in patients at risk for cardiac complications, pulmonary complications, or prolonged ileus. Epidural analgesia is at advantage as it can be performed as a continuous infusion compared to spinal analgesia that is limited to a single dose of administration. PCA is usually offered to patients who require analgesia for a few days and have adequate cognitive function to understand the device and its safety limitations. In normal practice, post-operative pain treatment modalities will be stopped or weaned off when patients can tolerate fluid intake and is able to take oral analgesics (4,5). PCA will be discontinued when patients demonstrate adequate pain control (1,4,5). In patients with epidural analgesics, the removal of epidural usually occurs after 48 to 70^h hours after which the risk of infection increases (6).

There is insufficient evidence or recommendation to guide on how best to approach the discontinuation and conversion of post-operative pain treatment modalities to oral analgesic. The common oral analgesic used is Paracetamol and Non-steroidal anti-inflammatory drugs (NSAIDs) regardless of patient's pain score due to the fear of misused, addiction and side effects of opioid (1). When discontinuing patients from the post-operative pain treatment modality, the issue that needs to be addressed is what type of oral analgesics to start on patients. Converting to a wrong type of analgesic during this transition period can be problematic as it can create interruptions in analgesic delivery that contribute to ineffective post-operative pain management and delay patient's rehabilitation.

Oral opioids can be highly effective and can be used to rapidly wean a patient off parenteral therapy once the patient is able to tolerate orally, thereby allowing early rehabilitation and earlier discharge from the hospital. While they are very effective analgesics, opioids are not considered as the ideal drugs in the post-operative setting due to the limitations and concerns about their use (7). The use of opioids may lead to many undesirable side effects such as sedation, respiratory depression, nausea and vomiting, hypotension and bradycardia, pruritus, and inhibition of bowel function. The American Pain Society in its new Guidelines on the Management of Post-operative Pain also encourages the physicians to limit the use of opioid therapy to moderate to severe acute post-operative pain (1). They recommended physicians to provide appropriate monitoring of sedation, respiratory status, and other adverse events in patients who receive systemic opioids for postoperative analgesia (1).

In Sultan Ismail Hospital Johor Bahru, the most common post-operative pain management are PCA of Morphine or Fentanyl, epidural infusion of local anaesthesia with or without strong opioid and subcutaneous injection of Morphine or Oxycodone. When patient can tolerate orally, these post-operative pain treatment modalities will be discontinued by the Acute Pain Service and converted to oral analgesics such as oral weak opioid or strong opioid based on the patient's pain score on movement. The oral opioids available in Sultan Ismail Hospital Johor Bahru include Tramadol, Morphine and Oxycodone. Currently there is no data on the common type of oral opioids prescribed after discontinuation of post-operative pain treatment modality. Therefore, this study was done to assess the use of oral opioids after the discontinuation of non-oral post-operative pain treatment and its effectiveness in achieving the targeted pain score on movement in post-operative patient. The secondary objective was to assess the occurrence of any opioid related side effects in patients prescribed with oral opioids. Findings from this study can assist physicians to prescribe appropriate oral analgesics in order to maintain adequate pain relief in post-operative patients.

Methods

This cross-sectional study involved all adult post-operative patients discharged from the operation theatre with post-operative pain treatment managed by the Acute Pain Service from January 2016 to June 2016. Patients with epidural infusion of local anaesthesia with or without strong opioid, PCA and subcutaneous injection of strong opioids as post-operative pain managements were included in this study. Post-operative patients discharged less than 24 hours after started with oral analgesic were excluded from this study.

A retrospective data collection on patients' demographics, types of oral analgesics prescribed after the discontinuation of non-oral post-operative pain treatments, pain score and any opioid related side effects were done from patient's electronic medical record and recorded into the data collection forms. Information regarding pain score and opioid related side effects recorded by the Acute Pain Service as part of the routine practice was collected. A ten-point pain score, where zero is no pain and ten is the worst possible pain imaginable was used. The pain score collected was the pain score on movement 24 hours after being started with oral analgesics. In this study, the effectiveness of pain relief in post-operative patients was defined as pain score less than 4 on movement as suggested in Pain Management Handbook, Ministry of Health Malaysia published in October 2013 (5). The common opioid-related side effects include nausea, vomiting, constipation, respiratory effects and pruritus.

A descriptive analysis was used in this study. Data were expressed as percentage (%), frequency (n), and mean with standard deviation (SD) where appropriate.

Results

Of 677 patients' charts reviewed, 497 patients fulfilled the inclusion criteria and were eligible for analysis. The mean age of the included patients was 43.94 (SD 16.9) years old with most of them being female (61.6%). Most of the patients were on PCA (57.1%) as post-operative pain treatment followed by epidural Infusion of local anaesthetic with or without strong opioid (35.6%), and regular subcutaneous injection of strong opioid (7.2%). The characteristics of patients included in this study were presented in Table 1.

The mean duration of non-oral post-operative pain treatment used before being converted to oral medications was 2.78 (SD 1.13) days. After the discontinuation of these modalities, most of the patients were prescribed with oral opioids. Morphine syrup (58.1%) was most frequently prescribed followed by Tramadol capsule (32.6%) and Oxycodone capsule (7.4%). This study found that 9 (1.8%) patients were not prescribed with any opioid as shown in Table 2.

Table 1: Patient demographic characteristics (n=497)

Variable	mean (SD) / n (%)
Age, year, mean (SD)	43.94 (16.9)
Gender, n (%)	
Male	191 (38.4%)
Female	306 (61.6%)
Post-operative pain treatment, n (%)	
Patient Controlled Analgesia (PCA)	284 (57.1%)
Epidural Infusion of local anaesthetic ± strong opioid	177 (35.6%)
Subcutaneous of strong opioid	36 (7.2%)

Abbreviation: SD - standard deviation; ± - with or without

Table 2: Oral analgesics used after the discontinuation of post-operative pain treatment modalities in the wards and as discharge medications (n=497)

Type of oral analgesic	Inpatient, n (%)	Discharge, n (%)
Strong Opioid		
Morphine Syrup	289 (58.1)	42 (8.5)
Oxycodone Capsule	37 (7.4)	11 (2.2)
Weak Opioid		
Tramadol Capsule	162 (32.6)	394 (79.3)
Non-opioid	9 (1.8)	50 (10.1)

Despite the high percentage of patients started with strong oral opioid after the discontinuation of post-operative pain management modalities, only 53 (10.7%) patients remained on strong opioid upon discharged from hospital. 394 patients (79.3%) were discharged with weak opioid and 50 patients (10%) were successfully discharged from hospital with no opioid.

Pain assessment 24 hours after the conversion from non-oral post-operative pain treatments to oral analgesics found that 460 patients (92.6%) were able to achieve the targeted pain score of less than 4 on movement with the mean pain score of 2.01 (SD 1.15). Most of the patients reported pain score of 2 on movement (33.4%), followed by pain score of 3 (26.6%), pain score of 1 (22.5%) and zero pain score in 10.1% of the patients as shown in Figure 1.

Among the patients who received oral opioids, minor opioid related side effects were reported in 49 (10.0%) of patients. The side effects were nausea and vomiting (5.9%), dizziness or drowsiness (2.3%), constipation (1.2%), and others (rashes and bronchospasm) in 0.6% patient as shown in Figure 2. Due to the side effects, 24 patients had their medication modified to different medication, and three patients needed dose reduction while other patients continue their medications after successfully managing the side effects with appropriate treatment.

Figure 1: Pain score 24 hours after started with oral analgesics (n=497)

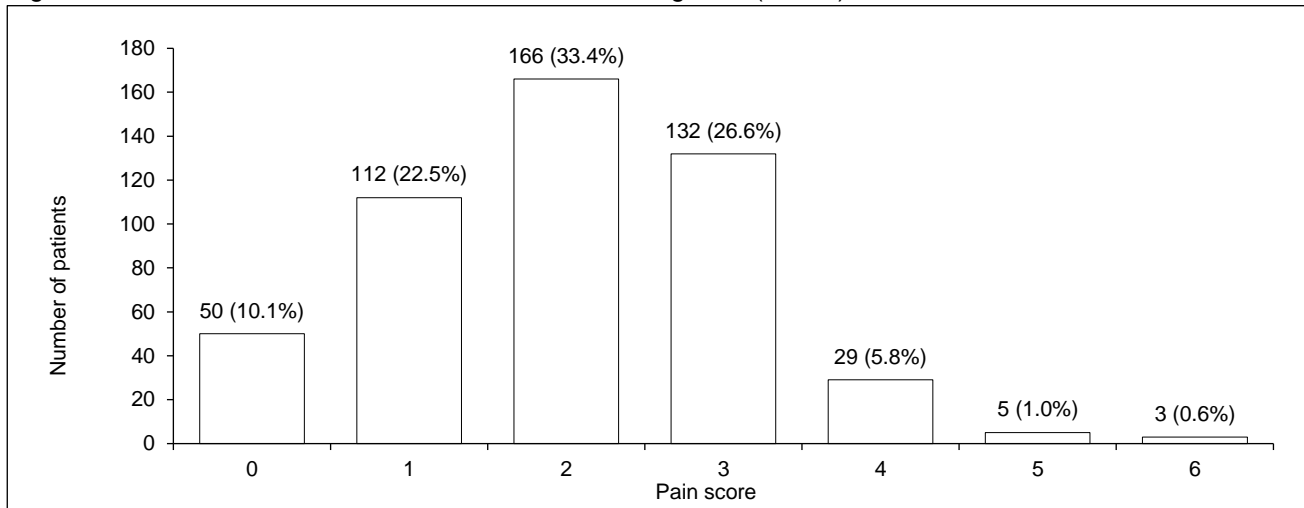
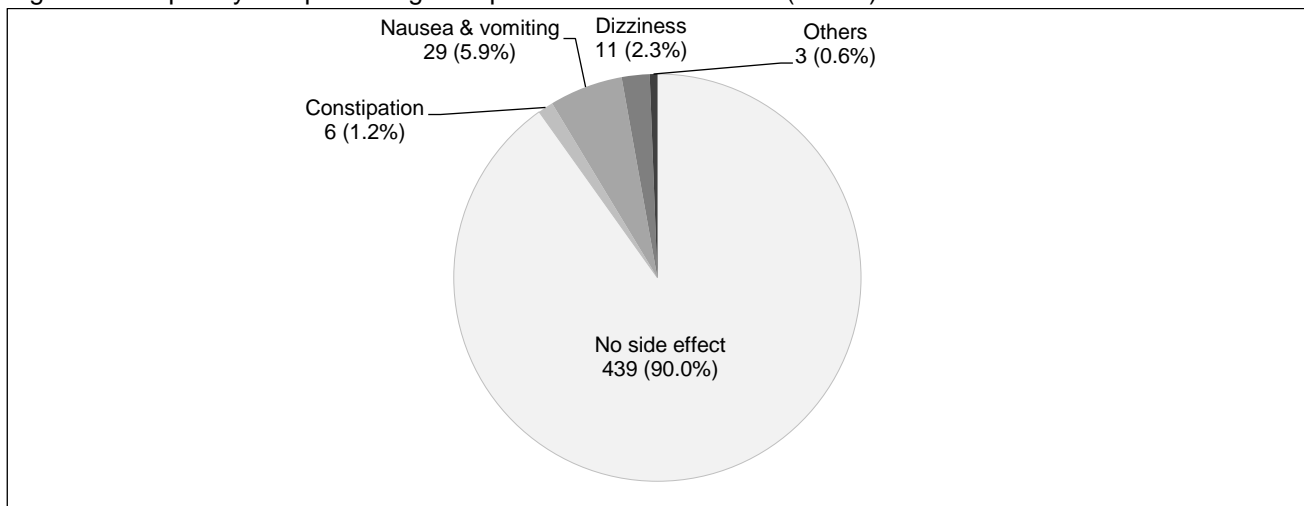


Figure 2: Frequency and percentage of opioid related side effects (n=488)



Discussion

Effective and safe post-operative pain management is very important and is one of the main criteria in the Malaysian Pain Free Program. Some of the reasons for poor pain management include barriers to the use of strong opioid analgesics due to the lack of knowledge among the healthcare providers and controlled substances regulations that govern the prescriptions of opioids (8,9). In Malaysia, as there are few legal issues in the use of strong opioids, the main barriers to effective pain control in Malaysia is related to physicians' and patients' attitudes towards the use of opioids. In a survey of physicians, 46% felt they lacked opioid knowledge, and 64% feared opioid related side effects such as respiratory depression (10).

This study showed that the use of oral opioid is very common in post-operative patients after the discontinuation of non-oral post-operative pain treatment with strong opioids prescribed in 66% of post-operative patients. Most of the patients were started with oral analgesic two days after the procedures. Although intravenous, subcutaneous or epidural routes may be appropriate in the immediate postsurgical period, oral analgesia is usually initiated when feasible and preferred because it is convenient, non-invasive, and cost-effective (1,11).

By using appropriate oral analgesic after the discontinuation of non-oral post-operative pain management, it was shown to be successful in maintaining adequate pain relief as clearly demonstrated in this study. The mean pain score reported 24 hours after initiating oral analgesics was 2.01 (SD 1.15) which was much lower than another study done in developing country that reported a mean pain score of 6.72 (SD 1.44) among their post-operative patients (9). They found that poor post-operative pain management was a consequence of inappropriate pain medications prescribed and the absence of strong opioids in their hospital setting. Other than the type of medications, the timing of oral analgesia administration was also crucial to effective pain management for patients during the transition from non-oral post-operative pain treatment to oral analgesics (12). Following the discontinuation of post-operative pain treatment modalities, patients need to be prescribed with regular oral analgesia to ensure adequate pain relief. As needed (p.r.n.) prescription is not encouraged as this may require patients' participation and some patients are less likely to request pain medication even though they were suffering high levels of pain (9).

At the time of transition to oral route of analgesia, patients' pain score should be re-assessed and analgesic requirement should be reviewed regularly in order to achieve post-operative pain management goal. The goal of post-operative pain management is to relieve pain while keeping the side effects to a minimum with pain score aim less than 4 at rest and on movement (5). Pain control on movement in post-operative patients is important and often more difficult to achieve compared to pain at rest. Pain that is not well controlled with movement or activities has major effects on patient's ability to participate in post-operative rehabilitation and return to normal function (1,13). Many studies demonstrate the health benefit and cost saving of getting patients ambulate soon after their operations. It shows that early mobilisation after operation improved physical, psychological, social and organisational outcomes (14). The physical benefits included less delirium, pain, urinary discomfort, urinary tract infection, fatigue, deep vein thrombosis (DVT) and pneumonia. Patients also experienced less anxiety and depression with early mobilisation. While for the organisation benefit, early mobilisation will cause cost reduction, decreased length of hospital stays and lower mortality rates.

Opioids were still the mainstay of post-operative pain therapy in treating moderate to severe pain after major surgery. In this study, Morphine syrup is the most commonly prescribed strong opioid for post-operative patient required strong opioid for pain management as it is the drug of choice and first line treatment in moderate to severe pain that provides effective pain relief, widely tolerated and cheap. In post-operative pain, short acting opioid such as Morphine syrup, Oxycodone immediate release capsule or Tramadol capsule are preferred over long acting sustained released formulation (1). Short acting opioid are recommended and preferred for easy dose titration according to patients need especially during the first 24 hours after operation. Around the clock oral dosing of short acting or immediate release opioids allows stable opioid plasma effective concentration therefore provide adequate pain relief. The use of long acting strong opioid, although provide more stable plasma concentration, is associated with more adverse effects, such as increased vomiting experienced and increased sedation, with no improvement in pain related interference with activity or walking (15).

All opioids have significant side effects that limit their use with the most important side effect being respiratory depression that could result in hypoxia and respiratory arrest. Nausea, vomiting, pruritus and reduction in bowel motility leading to ileus and constipation are also the common side effects of these

medications. Hence, regular monitoring of patients and then adjustment of medications accordingly is essential in patients on opioids post-operatively in order to optimise pain management and prevent or minimize the risk of side effects. Another approach to reduce the occurrence of opioid-related side effects is by using multimodal analgesics by combining opioid with nonopioid drugs with different mechanisms of action such as paracetamol and NSAIDs which can produce synergistic effects resulting in maximum pain relief with minimal opioid consumption (16). It is recommended that in post-operative pain management, all patients should receive regular doses of paracetamol and / or NSAIDs as background analgesia unless contraindicated (17).

In this study, it was found that despite the use of strong opioid, only 10% of the patients reported minor opioid related side effects. Other study also showed low incidence of opioid induced side effects with the most frequent side effects being nausea, constipation and somnolence or drowsiness that can be easily managed without requiring the discontinuation of opioid treatment (18). The side effects during short term administration was found to be age and gender related and depended on the type of opioids as certain opioids produced fewer side effects than the others (19). It was also shown in this study that some patients who required strong opioid were prescribed with Oxycodone as an alternative to Morphine. Oxycodone is more expensive than morphine but produce less side effects, and therefore is reserved for patients with the higher risk of morphine-related side effects such as elderly patients and patients with renal impairment. A review of clinical trials that assessed the effectiveness and safety of oral oxycodone showed that patients receiving oxycodone for acute post-operative pain experienced fewer opioid-related side effects than those on other opioids (16).

It was noted in this study that only a small number of patients were discharged from the hospital with strong opioid (10.7%). This percentage was much lower than a study done by Hance *et al.* where they found that almost 50% of patients were discharged from the hospital after major elective surgeries with an opioid prescription and 3% will continue to use strong opioid for more than three months (20). Patients prescribed with strong opioids upon discharge must be followed up properly to taper down and then wean off the strong opioids to avoid prolonged strong opioid use. The prolonged use of strong opioids is associated with the increased risks of injury, cardiac events and addiction (20). The prescribing of strong opioids as discharge medications in high risk patient therefore should be judiciously done to avoid this risk as well as the emergence of opioid addiction and tolerance in post-operative patients especially in previously opioid naive patients.

This study should be interpreted cautiously considering its limitations. Firstly, the findings lacked important clinical details such as type of operation and dose of oral medications used that will have effect in patients' pain experience. We were also not able to discuss if the use of strong opioid in these patients indicate improving in patient early rehabilitation and preventing them from getting chronic pain. To evaluate the appropriateness of oral strong opioid use in post-operative patient, further studies are needed to profile patients' pain experience after discharged home and the ability of patients to wean off from opioid medications.

Conclusion

The use of oral opioids after the discontinuation of non-oral post-operative pain managements was quite common. It was able to provide adequate pain relief and was safe to be used with low occurrence of minor side effects. Nevertheless, oral opioids should still be used judiciously with appropriate monitoring to avoid any undesirable major side effects that can compromise patient safety.

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Conflict of interest statement

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

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Drug Information Resources Preferred by the Prescribers in Queen Elizabeth II Hospital (HQEII), Kota Kinabalu

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Abstract

Introduction: In line with the increasing drug information resources (DIRs) available for prescribers' reference, the credibility of information obtained towards safe and judicious therapeutic decisions has become a concern.

Objective: To explore DIRs preferred by the Queen Elizabeth II Hospital (HQEII) prescribers and factors identified by the prescribers that determine their choice of DIRs.

Method: This was a cross-sectional, self-administered questionnaire survey involving prescribers working in HQEII from May to July 2018. The questionnaire comprised questions about demographic information, preferred DIRs according to the information required, factors determining the choice of DIRs, frequency of DIRs use and subscription of paid DIRs.

Results: Among the 117 respondents, majority were male (n=66; 56.4%) and medical officers (n=81; 69.2%) with median age of 28 years old (interquartile range=3). The three most preferred DIRs were consistent across all types of required drug-related information, comprising online/mobile medical database, consultation with pharmacists and senior medical officers. Accessibility (n=107; 91.5%), comprehensiveness (n=63; 53.8%) and urgency (n=58; 49.6%) were identified to be the factors influencing the choice of DIR. The most frequently used online/mobile DIRs were My Blue Book (n=54; 46.2%), Medscape (n=51; 43.6%) and UpToDate (n=50; 42.7%). Twenty-eight respondents (23.9%) subscribed to paid online/mobile resources, with UpToDate having the most subscription (n=25; 89.3%). For hardcopy references, Clinical Practice Guidelines (n=39; 33.3%), Sarawak Handbook of Medical Emergencies (n=33; 28.2%) and Oxford Handbook of Clinical Medicine (n=20; 17.1%) were most frequently used. Out of 22 prescribers (18.8%) who purchased hardcopy references, Sarawak Handbook of Medical Emergencies was most purchased by the prescribers (n=10; 45.5%).

Conclusion: Overall, prescribers in HQEII preferred online medical databases or mobile applications and peer consultation over hardcopy DIRs. Healthcare facilities or MOH may consider subscribing to the preferred DIRs to support the access to reliable databases which would facilitate safe and judicious prescribing decisions.

Keywords: drug information resources, prescribers, Hospital Queen Elizabeth II, applications, hardcopy

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Introduction

Health plays a fundamental role in the sustainability and progression of the population worldwide. In line with the increasing population, recent decades have witnessed a growing prevalence of various epidemic outbreaks and chronic diseases, such as malaria, tuberculosis, cardiovascular diseases, diabetes and cancer (1,2). Pharmacotherapy has since become pivotal in the healthcare system and remains the primary mode of treatment until today (3).

Drug explosion in the past decades has widened the range of treatment options for the prescribers. However, in addition to facilitating rationale therapeutic decisions, it has also increased the likelihood of medication errors, such as inappropriate medication, inappropriate dose regimen and polypharmacy (4). It is therefore common for the healthcare professionals (HCP) to look up drug information resources (DIRs) to consolidate their personal medical knowledge when managing a wide variety of health conditions.

There is a wide range of DIRs available for prescribers' reference. These include journals, product information leaflets, reference books, evidence-based guidelines, online databases, mobile applications and interpersonal consultation with other HCPs such as the pharmacists (3,4). The choice of resources used varies among the prescribers, depending on various factors such as the field of practice and accessibility. However, the credibility of resources used has been one of the utmost concerns in making safe and judicious therapeutic decisions (3). Until 2017, there have been approximately 325,000 mobile health applications available for download (5). This is further challenged by the constant invention of new drugs and dissemination of new medical information into healthcare practice (3).

A retrospective review from 2009 to 2012 revealed that over three-quarters of medication errors in Malaysia were attributed to prescribing errors (6). It is therefore important for prescribers to utilise reliable and up-to-date DIRs to avoid prescribing errors and putting patients' health in jeopardy. To date, limited information about the prescribers' preference on DIRs is available. Therefore, the objective of this study was to explore the DIRs preferred by the prescribers in Queen Elizabeth II Hospital (HQEII) as well as the factors identified by the prescribers that determine their choice of DIRs.

Method

This was a cross-sectional, self-administered questionnaire survey involving the prescribers working in HQEII that was conducted from May to July 2018. A questionnaire was developed in English language, content and face-validated, and pre-tested. The questionnaire comprised questions about demographic information, the preferred DIRs according to the type of information required, factors identified by the prescribers that determine their choice of DIRs frequency of online medical database or mobile applications and hardcopy references use, and current subscription of paid DIRs.

Based on the "sample size calculator for prevalence studies" with finite population correction (7), the calculated sample size was 93. The study population were prescribers who were working in the clinics or wards of HQEII during the data collection period and the ones who were involved in prescribing medications. Upon consent, the prescribers were required to complete the questionnaire and return to the investigators on the spot. The questionnaire took approximately 10-15 minutes of each respondent's time.

This study was conducted in accordance to the ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. Ethical approval was obtained from the Ministry of Health (MOH) Medical Research and Ethic Committee (MREC) and the study was registered with the National Medical Research Register (NMRR) before the commencement of research. No identifiable data was collected in the questionnaire. Completed questionnaires were kept by the investigators only for data analysis purpose. No personal information was disclosed during the communication between relevant departments. Individual subjects were not identified when publishing the survey outcomes.

Data analysis was performed using SPSS version 17. Descriptive analysis was used to present the results of this study. Numerical data was presented in mean and standard deviation or median and interquartile range (IQR) depending on data normality. Categorical data was presented as frequency (n) and percentage.

Results

A total of 117 prescribers participated in the study. Sixty-six were male (56.4%) with the median age of 28 (IQR 3.0) years old and the average working experience of 4.2 (SD 2.2) years. Majority of the respondents were medical officers (MO) (n=81; 69.2%) and were from the Medical Department (n=66; 56.4%). The participants' characteristics were summarised in Table 1.

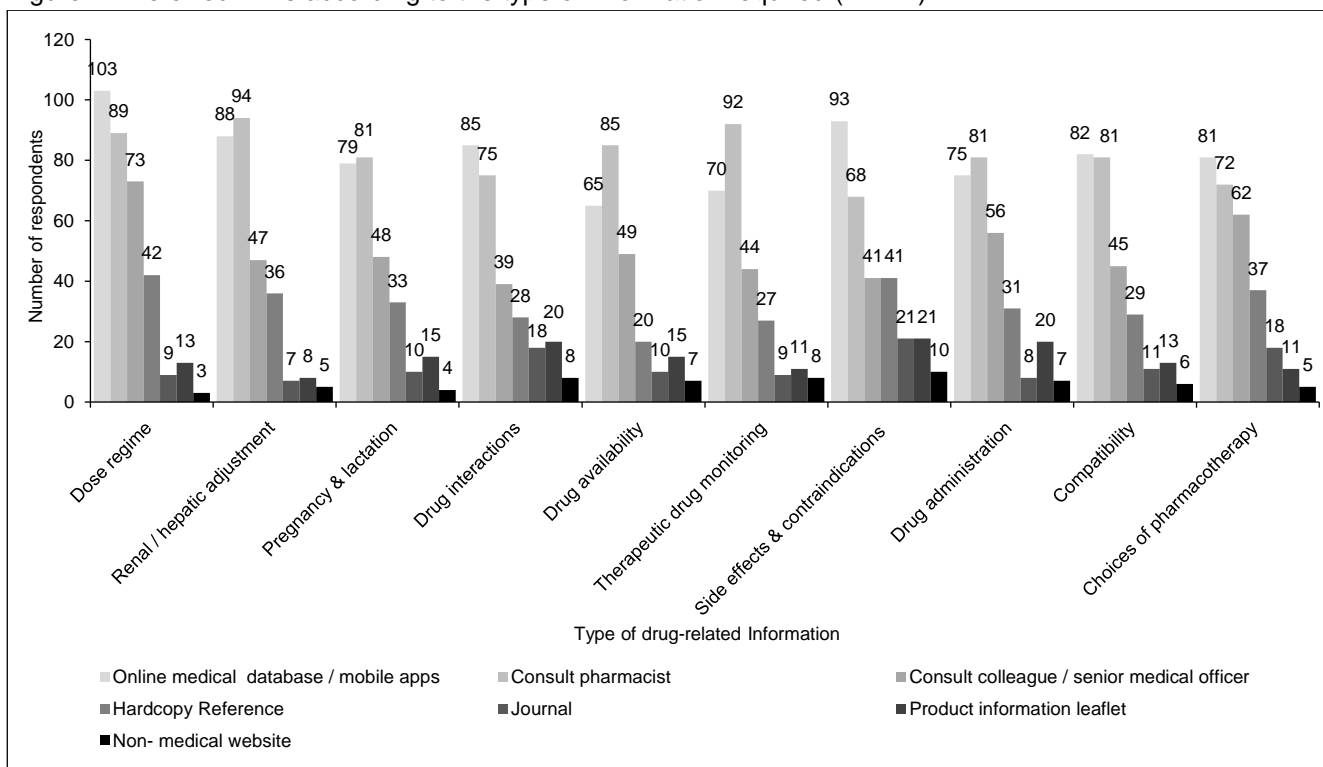
Seven categories of DIRs were outlined in the questionnaire and the respondents were asked to select up to three DIRs of their preference for each type of the drug-related information required. It was found that the three most preferred resources were consistent across all types of drug-related information, which were online medical database or mobile applications, consultation with the pharmacists and consultation with colleague or senior MO (Figure 1). The main factors identified by the prescribers that influence the prescribers' choice of DIRs were found to be accessibility (n=107; 91.5%), comprehensiveness (n=63; 53.8%) and urgency (n=58; 49.6%).

Table 1: Demographic characteristics of respondents (n=117)

Variable	n (%) / median (IQR) / mean (SD)
Gender, n (%)	
Male	66 (56.4)
Female	51 (43.6)
Age, year, median (IQR)	28 (3.0)
Position, n (%)	
Specialist	4 (3.4)
Medical Officer (MO)	81 (69.2)
House Officer (HO)	32 (27.4)
Department, n (%)	
Medical	66 (56.4)
Non-medical	
Cardiology	19 (16.3)
Cardiothoracic	7 (6.0)
Neurosurgery	9 (7.7)
Orthopaedic	10 (8.5)
Surgery	6 (5.1)
Working Experience, year, mean (SD)	4.2 (2.2)

Abbreviation: IQR – interquartile range; SD – standard deviation

Figure 1: Preferred DIRs according to the type of information required (n=117)



In the question about online medical databases or mobile applications, respondents were given the options of “Always”, “Sometimes”, “Rarely” and “Never” to indicate the frequency of using each of the listed online or mobile DIRs. If the resources other than those listed were used, they were asked to specify in the questionnaire. The online resources that were used most frequently were My Blue Book, Medscape and UpToDate, which had the most “Always” and “Sometimes” answers. It was found that Lexicomp was the least used online database (Table 2). Twenty-eight respondents (23.9%) reported subscribing to paid online or mobile

resources. Most of them subscribed UpToDate (n=25; 89.3%), and the remaining three respondents subscribed British Medical Journal (BMJ), Orthobullets and Epocrates (n=1, 3.6% respectively).

Similar to the question about online or mobile DIRs, participants were given the same options to indicate the frequency of using each of the listed hardcopy references. Clinical Practice Guidelines (CPG), the Sarawak Handbook of Medical Emergencies and the Oxford Handbook of Clinical Medicine were “Always” and “Sometimes” used by most of the respondents. Seven participants indicated that they always refer to the Drug Doses booklet, more commonly known as Frank Shann (Table 3). Twenty-two prescribers (18.8%) purchased hardcopy references, and the Sarawak Handbook of Medical Emergencies was the most commonly purchased (n=10; 45.5%), followed by the Oxford Handbook of Clinical Medicine (n=8; 36.4%) and Frank Shann (n=4; 18.2%).

Table 2: Frequency of using online medical database or mobile applications (n=117)

Online / Mobile DIRs	Always	Sometimes	Rarely	Never	Not Answered
My Blue Book	54 (46.2%)	32 (27.4%)	13 (11.1%)	14 (12.0%)	4 (3.4%)
Medscape	51 (43.6%)	47 (40.2%)	10 (8.5%)	4 (3.4%)	5 (4.3%)
UpToDate	50 (42.7%)	34 (29.1%)	15 (12.8%)	13 (11.1%)	5 (4.3%)
MyNAG *	21 (17.9%)	29 (24.8%)	27 (23.1%)	29 (24.8%)	11 (9.4%)
MIMS Gateway	10 (8.5%)	24 (20.5%)	34 (29.1%)	41 (35.0%)	8 (6.8%)
Sanford #	4 (3.4%)	14 (12.0%)	19 (16.2%)	67 (57.3%)	13 (11.1%)
Lexicomp	2 (1.7%)	10 (8.5%)	12 (10.3%)	77 (65.8%)	16 (13.7%)
Micromedex	1 (0.9%)	6 (5.1%)	21 (17.9%)	75 (64.1%)	14 (12.0%)

* MyNAG – National Antibiotic Guidelines; # Sanford – The Sanford Guide to Antimicrobial Therapy

Table 3: Frequency of using hardcopy references (n=117)

Hardcopy DIRs	Always	Sometimes	Rarely	Never	Not Answered
Clinical Practice Guidelines (CPGs)	39 33.3%	55 47.0%	13 11.1%	9 7.7%	1 0.9%
Sarawak Handbook of Medical Emergencies	33 28.2%	46 39.3%	26 22.2%	8 6.8%	4 3.4%
Oxford Handbook of Clinical Medicine	20 17.1%	46 39.3%	26 22.2%	18 15.4%	7 6.0%
CURRENT Medical Diagnosis and Treatment	6 5.1%	18 15.4%	28 23.9%	56 47.9%	9 7.7%
British National Formulary (BNF)	1 0.9%	20 17.1%	32 27.4%	57 48.7%	7 6.0%
Others: Frank Shann*	7 6.0%				

* Drug Doses booklet by Frank Shann

Discussion

The constant invention of new drugs and dissemination of new medical information have been prompting HCPs to look up DIRs in their daily practice. Although studies have documented variable resources used and mixed preferences among the HCPs across the globe (8-15), it was noted that hardcopy texts were generally preferred prior to the digital era. For example, a systematic review of studies conducted in Australia, United States of America, New Zealand, Hong Kong, Greece, Canada, Denmark, United Kingdom and Singapore from 1994 to 2005 revealed that text books were most preferred, followed by colleagues’ advice and electronic resources (8). The trend has, however, changed following the advancement in information technology with the increasing accessibility to the Internet and popularity of electronic devices. In fact, handheld computers such as smartphones and tablets are now widely used by the HCPs to obtain drug related information (13). The authors of Epocrates, one of the most commonly used drug reference application in the Western countries, found that 90% physicians use mobile applications to access to drug information (16). This phenomenon, together with the plethora of mobile health applications, has switched prescribers’ preference of DIR from hardcopy to electronic. This is reflected by the study in Abu Dhabi in 2013, where almost three-quarters of their physicians prefer online

over hardcopy resources (9). In Malaysia, study conducted among hospital pharmacists in 2013 to 2014 revealed that 86.6% of them looked up DI via handheld devices (13). The outcome of our study correlates with these findings, where most prescribers prefer online/mobile resources over hardcopy sources as shown in Figure 1.

Consultation with the pharmacists and colleague or senior MOs are the next preferred DIRs for HQEII prescribers. This finding again correlates with other studies where peer consultation is found to be one of the favourite DIRs. In fact, such preference has been consistent over time even before the digital era (8,9,14,15), due to reasons such as availability and timesaving (14). This could be explained by the HQEII environment where there are usually more than one doctors working in a same shift, enabling instant peer consultation. Most of the wards are also assigned with a clinical pharmacist who joins the doctors' ward rounds, making consultation with pharmacist quicker and easier. Otherwise, the Pharmacy Department at HQEII is also equipped with a Drug Information Centre (DIC) which answers drug-related queries from prescribers. The DIC is easily accessed via phone call through the hospital operator. Similar studies in Malaysia are few and most were limited to the pharmacists. The FrEEDoM Qualitative Study done in the rural primary care setting in Pahang showed similar results to our study, where mobile applications and peers were the common DIRs used by the doctors (15).

Looking into the preference pattern according to the type of drug-related information required, it was found that online or mobile resources are favoured for DI categories of dose regime, drug-drug interactions, side effects and contraindications, compatibility as well as choices of pharmacotherapy. On the other hand, pharmacist consultation is preferred for renal or hepatic dose adjustment, dose for pregnancy and lactation, drug availability, therapeutic drug monitoring (TDM) as well as drug administration. The incline towards online/mobile source is likely due to their increasing comprehensiveness, such as Medscape and UpToDate, which are found to be among the prescribers' most visited applications (13,17). However, prescribers still prefer pharmacist consultation for certain drug information. Of these, well over 90% of HQEII prescribers choose to refer to pharmacists for information on renal/hepatic dose adjustment and TDM. For dose adjustment, it was possibly because of the variable adjustment regimes for different drugs and different extents of renal or hepatic impairment of the same drug. For TDM, it is not surprising that pharmacist referral was the favourite source of information as TDM is managed by Pharmacy Department, where the specially trained pharmacists will perform sample screening, lab result retrieval and interpretation as well as recommendation of dose adjustment to prescribers.

Our study found that prescribers in HQEII used My Blue Book, Medscape and UpToDate more often than other online or mobile resources. Even though My Blue Book had the lowest score for comprehensiveness in the study done by Apidi *et al.* (17), it was still preferred possibly due to the convenience of accessing the basic information necessary for prescribing. Firstly, the database of the application was based on the Ministry of Health Malaysia (MOH) Medicines Formulary which was also known as the Blue Book or FUKKM. The MOH Medicines formulary consists of a list of drugs approved for use in the MOH health institutions. Hence, the use of drugs not listed in the formulary, which requires special authorization by the Director-General of Health (18), can be easily identified through the My Blue Book application. Secondly, information about the categories of prescribers' allowed for each drug is also available on My Blue Book. This is important to ensure that prescribers prescribe medications according to their prescribing category, particularly for medicines that require authorisation by the specialists and consultants. However, My Blue Book is relatively less comprehensive compared to the other online databases as it lacks various information such as dose adjustment, drug-drug interactions, contraindications and precautions. It is also updated less frequently compared to other applications and therefore the information may not be as up-to-date and accurate (17).

Medscape and UpToDate were the other favoured application due to their comprehensiveness. They were among the most comprehensive online tools according to Apidi *et al.* (17). They provide comprehensive information on various drugs, calculations related to medical areas and materials for medical education. They are relatively up to date as the versions and databases of the applications are frequently updated. Another advantage of Medscape is that no paid subscription is needed and it can be used offline (13). Due to these features, Medscape was one of the most frequently used applications among the HCPs worldwide including Malaysia and our setting. The disadvantage of UpToDate is that it requires paid subscription for full access (13,17). Despite the fact that UpToDate and Lexicomp are sharing similar databases, over three quarters of the

prescribers have never used Lexicomp, probably because Lexicomp only contains information specific to individual drug profile, unlike UpToDate which covers not only general drug information, but also diseases-based information. This could explain why UpToDate was the top subscribed online database among the HQEII prescribers.

Among the hardcopy DIRs, CPGs, the Sarawak Handbook of Medical Emergencies and the Oxford Handbook of Clinical Medicine were most frequently used. The preference for the first two resources could be due to the fact that they are constantly updated and tailored to the local practice. More than half of the participants had never used the British National Formulary, unlike physicians in other countries (9), possibly because it does not coincide with local practice. The Frank Shann Drug Doses booklet was also listed by some prescribers as the frequently used reference. It is a quick and easy reference for paediatric dose regime, which is especially important for doctors at the Paediatric Cardiology and Emergency departments. The hardcopy references purchased by prescribers are consistent with the most used references, comprising the Sarawak Handbook of Medical Emergencies, Oxford Handbook of Clinical Medicine and Frank Shann. CPG was not on the list of purchase as they are available for free access online.

Among the factors identified to affect the choice of DIRs, accessibility and comprehensiveness were reflected by their preference of online or mobile resources which contain information on various aspects, can be used offline and without paid subscription. Urgency could be explained by the use of peer consultation in acquiring drug-related information, as the pharmacists and peer doctors are easily accessible at the workplace.

This was a single-centred study at HQEII, hence the results could not be generalised to the prescribers in other health facilities. Exploratory study on the association between factors or barriers and the resources preferred, as well as the relationship between the prescribers' position and DIRs preferred may better facilitate in interpreting the prescribing pattern in HQEII.

Conclusion

The study showed that prescribers in HQEII preferred online medical databases or mobile applications and peer consultation over hardcopy DIRs. Since peer consultation was one of the preferred DIRs, information conveyed may need to be verified against credible resources to ensure the accuracy. Subscription to reliable databases may also be considered by the healthcare facilities or MOH to support the access to the preferred DIRs for accurate information, which would facilitate safe and judicious prescribing decisions.

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Conflict of Interest Statement

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