BJMS

Borneo Journal of Medical Sciences

Volume 18, Issue 2, May 2024

UMS
UNIVERSITI MALAYSIA SABAH

BJMS
Borneo Journal of Medical Sciences
Volume 18, Issue 2, May 2024

BJMS

Borneo Journal of Medical Sciences

Volume 18, Issue 2, May 2024

ISSN 1985-1758 E-ISSN 2710-7353

PENERBIT UNIVERSITI MALAYSIA SABAH

Kota Kinabalu • Sabah • Malaysia

http://www.ums.edu.my

2024

A Member of the Malaysian Scholarly Publishing Council (MAPIM)

© Universiti Malaysia Sabah, 2024

All rights reserved. No part of this publication may be reproduced, distributed, stored in a database or retrieval system, or transmitted, in any form or by any means, electronics, mechanical, graphic, recording or otherwise, without the prior written permission of Penerbit Universiti Malaysia Sabah, except as permitted by Act 332, Malaysian Copyright Act of 1987. Permission of rights is subjected to royalty or honorarium payment.

Penerbit Universiti Malaysia Sabah makes no representation–express or implied, with regards to the accuracy of the information contained in this journal. Users of the information in this journal need to verify it on their own before utilising such information. Views expressed in this publication are those of the author(s) and do not necessarily reflect the opinion or policy of the Editorial Board and Universiti Malaysia Sabah. Penerbit Universiti Malaysia Sabah shall not be responsible or liable for any special, consequential, or exemplary problems or damages resulting in whole or part, from the reader's use of, or reliance upon, the contents of this journal.

EDITORIAL OFFICE ADDRESS

Chief Editor
Borneo Journal of Medical Sciences
Faculty of Medicine and Health Sciences
Universiti Malaysia Sabah
Jalan UMS
88400 Kota Kinabalu
Sabah, Malaysia
Tel: +60 88 320000 Ext 5620
Fax: +60 88 320928
Email: bjms@ums.edu.my

PUBLISHER

Penerbit Universiti Malaysia Sabah (UMS)
Ground Floor, Library
Universiti Malaysia Sabah
Jalan UMS
88400 Kota Kinabalu
Sabah, Malaysia
Tel: +60 88 320 789
+60 88 320 462
Fax: +60 88 320 446
Email: penerbit@ums.edu.my

BJMS
Borneo Journal of Medical Sciences
Volume 18, Issue 2, May 2024
Journal of the Faculty of Medicine and Health Sciences
Universiti Malaysia Sabah

EDITORIAL BOARD 2024

Editor-in-Chief

Prof. Dr Kamruddin Ahmed
Professor
Department of Pathobiology and Medical Diagnostics
Director
Borneo Medical and Health Research Centre
Faculty of Medicine and Health Sciences
Universiti Malaysia Sabah, Malaysia
Areas of Expertise: Virology, molecular epidemiology, emerging infectious diseases, diagnostics

Editors

Dr Aminur Rahman
Director
Centre for Injury Prevention and Research, International Drowning Research Centre Bangladesh
Areas of Expertise: Public health, drowning prevention

Prof. Dr Chua Tock Hing
Professor
Department of Pathobiology and Medical Diagnostics
Faculty of Medicine and Health Sciences
Universiti Malaysia Sabah, Malaysia
Areas of Expertise: Entomology, forensic entomology, biostatistics, insect phylogeny

Prof. Dr Gulendam Bozdayi
Professor
Department of Medical Microbiology
Faculty of Medicine
Gazi University, Turkey
Area of Expertise: Medical virology

Assoc Prof. Dr Hidekatsu Iha
Associate Professor
Department of Microbiology
Faculty of Medicine
Oita University, Japan
Areas of Expertise: Oncogenic virus, molecular biology

Prof. Dr Hume E. Field
Honorary Professor
Eco Health Alliance Science and Policy Advisor for China and Southeast Asia
The University of Queensland, Australia
Areas of Expertise: Veterinary sciences, epidemiology, emerging infectious diseases

Prof. Dr Kozo Watanabe
Professor
Molecular Ecology and Health, Laboratory
Center for Marine Environmental Studies
Ehime University, Japan
Areas of Expertise: Molecular genetics, eco-epidemiology, biodiversity and evolution

Prof. Dr Malay Kanti Mridha
Professor
Centre of Excellence for Non-communicable Diseases and Nutrition
JPG School of Public Health
Brac University, Bangladesh
Areas of Expertise: Nutrition, maternal, neonatal and child health, non-communicable diseases

Assoc Prof. Dr Michael A. Huffman
Associate Professor
Section of Social System Evolution, Primate Research Institute
Kyoto University, Japan
Areas of Expertise: Alternative medicine, ethnomedicine, zoonoses, host-parasite interactions, one health

Dr Mohammad Azharul Karim
Research Associate
Department of Child Health
College of Medicine
University of Arizona, USA
Phoenix Children's Hospital
PaediatricNeurology,NeurodevelopmentalResearchBarrow Neurological Institute, USA
Areas of Expertise: Human genetics, genotype-phenotype relationship, neurogenetics

Dr Mya Myat Ngwe Tun
Assistant Professor
Department of Virology
Institute of Tropical Medicine
Nagasaki University, Japan
Area of Expertise: Virology

Prof. Dr Papa Salif Sow
Professor
Department of Infectious Diseases
Faculty of Medicine
University of Dakar, Senegal
Areas of Expertise: Infectious and tropical diseases

Prof. Dr Richard Culleton
Professor
Division of Molecular Parasitology
Proteo-Science Center
Ehime University, Japan
Areas of Expertise: Parasitology, malariology

Assoc Prof. Dr Selim Ahmed
Associate Professor
Medicine Based Department
Faculty of Medicine and Health Sciences
Universiti Malaysia Sabah, Malaysia
Areas of Expertise:
Paediatric environmental and infectious diseases

Prof. Dr Shaman Rajindrajith
Professor
Department of Paediatrics
Faculty of Medicine
University of Colombo, Sri Lanka
Areas of expertise:
Paediatricgastroenterology,paediatricnon-communicable diseases

Assoc Prof. Dr Stuart D. Blacksell
Associate Professor
Nuffield Department of Medicine
Oxford University, UK
Areas of Expertise:
Biosafety, laboratory design and development, zoonosis, serology

Assoc Prof. Dr Terrence Piva
Associate Professor
Pathobiology and Skin Cancer Laboratory School of Health Sciences and Biomedical Sciences
RMIT University, Australia
Areas of Expertise:
Skincancer,photobiology,sunburn,melanoma,sunscreens, cancer metabolism, photo immunology

Dr Tom Hughes
Senior Fellow
Project Coordinator Malaysia for Eco Health Alliance
Eco Health Alliance, USA
Areas of Expertise:
Conservation medicine, zoonotic disease surveillance, biosafety and biosecurity

Managing Editors

Assoc Prof. Dr Mohd Firdaus Bin Mohd Hayati
Associate Professor & Deputy Dean (Research & Postgraduate)
Department of Surgical Based Discipline
Faculty of Medicine and Health Sciences
Universiti Malaysia Sabah, Malaysia
Areas of Expertise:
Carcinogenesis, surgery

Dr Sadia Choudhury Shimmi
Senior Lecturer
Department of Biomedical Science and Therapeutics
Faculty of Medicine and Health Sciences
Universiti Malaysia Sabah, Malaysia
Areas of Expertise:
Physiology,complementaryandalternativemedicine,renal system, hepatobiliary system, cardiovascular system

Dr Fong Siat Yee @ Alison
Senior Lecturer
Department of Biomedical Science and Therapeutics
Faculty of Medicine and Health Sciences
Universiti Malaysia Sabah, Malaysia
Areas of Expertise:
Molecular biology, natural products

BJMS
Borneo Journal of Medical Sciences
Volume 18, Issue 2, May 2024
ISSN 1985-1758 E-ISSN 2710-7353

CONTENTS

BJMS
Borneo Journal of Medical Sciences

EDITORIAL

HTLV-1: Neglected Virus in Southeast Asia for Decades

Hidekatsu Iha[1,2]*

[1]The Research Center for GLOBAL and LOCAL Infectious Diseases (RCGLID), Faculty of Medicine, Oita University, 879-5593 1-1 Idaigaoka, Oita, Japan
[2]Department of Microbiology, Faculty of Medicine, Oita University, 879-5593 1-1 Idaigaoka, Oita, Japan

*Corresponding author's email: hiha@oita-u.ac.jp

Received: 31 March 2024

Accepted: 25 April 2024

Published: 19 May 2024

DOI: https://doi.org/10.51200/bjms.v18i2.5060

Keywords: *HTLV-1, Neglected Virus, Southeast Asia, Epidemiologi*

There are more than 100 types of human pathogenic viruses, with seven currently known oncogenic viruses (Hulo et al., 2011). Hepatitis B (HBV)/C (HCV) viruses (Mohamed et al., 2023) and human papillomavirus (Wee et al., 2024) are pathogens of public health concern not only in Malaysia but also in many other countries, while Burkitt's lymphoma (Epstein-Barr virus) and Kaposi's sarcoma (Kaposi's sarcoma-associated herpesvirus) pose serious complications for AIDS patients (Carbone et al., 2022).

Then, what about Human T-cell leukemia virus type 1 (HTLV-1)?

Like human immunodeficiency virus (HIV), HTLV-1 is a retrovirus, once the infection is established, the individual becomes a carrier for life. Similar to HBV, HTLV-1 is transmitted through sexual contact or from mother to child. However, unlike other oncogenic viruses, this virus has the characteristic of transmission through breastfeeding. Given the crucial role of breastfeeding in both nutritional and emotional aspects between mother and infant, it becomes an important source of infection (Nakahata et al., 2023).

Epidemiological studies on HTLV-1 infection have been conducted in many countries, but unfortunately, reliable surveys have been scarce in Southeast Asian countries. However, what has become evident in the past decade is the high prevalence in coastal

regions of China and Taiwan, as well as the discovery of extremely high infection rates in Australian aborigines (Legrand et al., 2022).

HTLV-1 is a virus originating from primates, with infections of its prototype confirmed in African and Asian non-human primates (Gessain et al., 2023). What does it mean to a high prevalence of HTLV-1 in a continent like Australia, where primates are not native?

During the ice age (Zeberg et al., 2024), when sea levels were several hundred meters lower than they are today, it is likely that humans infected with HTLV-1 were moving repeatedly in the region that formed the continent (Sundaland), eventually reaching Australia (Tao et al., 2023). This is evidenced by the presence of the virus among local tribes in Papua New Guinea.

I have been collaborating with the research team at Universiti Malaysia Sabah (UMS) since 2015 to investigate the presence of HTLV-1 infection in Sabah, Malaysian Borneo. If HTLV-1 is found in Sabah, it would pose the following new challenges for us to address in the future:

- How prevalent is HTLV-1 infection in Sabah, and subsequently in Malaysia?
- What proportion of patients previously diagnosed with conventional leukemia or lymphoma actually developed adult T-cell leukemia/lymphoma (ATL) due to HTLV-1 infection?
- What is the origin of HTLV-1 in Southeast Asia? Was it transmitted from humans or was it of simian origin?

We are determined to face these new challenges and to find strategies to elucidate the reality of HTLV-1 infection in Sabah, Malaysia, and Southeast Asia as a whole, and to eradicate HTLV-1.

REFERENCES

Carbone, A., Vaccher, E., & Gloghini, A. (2022). Hematologic cancers in individuals infected by HIV. Blood, 139(7), 995–1012. https://doi.org/10.1182/blood.2020005469

Gessain, A., Ramassamy, J.-L., Afonso, P. V., & Cassar, O. (2023). Geographic Distribution, clinical epidemiology and genetic diversity of the human oncogenic retrovirus HTLV-1 in Africa, the world's largest endemic area. Frontiers in Immunology, 14. https://doi.org/10.3389/fimmu.2023.1043600

Hulo, C., de Castro, E., Masson, P., Bougueleret, L., Bairoch, A., Xenarios, I., & Le Mercier, P. (2011). ViralZone: a knowledge resource to understand virus diversity. Nucleic Acids Research, 39(Database issue), D576-582. https://doi.org/10.1093/nar/gkq901

Legrand, N., McGregor, S., Bull, R., Bajis, S., Valencia, B. M., Ronnachit, A., Einsiedel, L., Gessain, A., Kaldor, J., & Martinello, M. (2022). Clinical and public health implications of human T-lymphotropic virus type 1 infection. Clinical Microbiology Reviews, 35(2). https://doi.org/10.1128/cmr.00078-21

Mohamed, R., Yip, C., & Singh, S. (2023). Understanding the knowledge, awareness, and attitudes of the public towards liver diseases in Malaysia. European Journal of Gastroenterology & Hepatology, 35(7), 742–752. https://doi.org/10.1097/meg.0000000000002548

Nakahata, S., Enriquez-Vera, D., Jahan, M. I., Sugata, K., & Satou, Y. (2023). Understanding the immunopathology of HTLV-1-associated adult T-cell leukemia/lymphoma: A comprehensive review. Biomolecules, 13(10), 1543. https://doi.org/10.3390/biom13101543

Tao, Y., Wei, Y., Ge, J., Pan, Y., Wang, W., Bi, Q., Sheng, P., Fu, C., Pan, W., Jin, L., Zheng, H.-X., & Zhang, M. (2023). Phylogenetic evidence reveals early Kra-Dai divergence and dispersal in the late holocene. Nature Communications, 14(1). https://doi.org/10.1038/s41467-023-42761-x

Wee, H.-L., Canfell, K., Chiu, H.-M., Choi, K. S., Cox, B., Bhoo-Pathy, N., Simms, K. T., Hamashima, C., Shen, Q., Chua, B., Siwaporn, N., & Toes-Zoutendijk, E. (2024). Cancer screening programs in south-East Asia and Western Pacific. BMC Health Services Research, 24(1). https://doi.org/10.1186/s12913-023-10327-8

Zeberg, H., Jakobsson, M., & Pääbo, S. (2024). The genetic changes that shaped neandertals, Denisovans, and modern humans. Cell, 187(5), 1047–1058. https://doi.org/10.1016/j.cell.2023.12.029

BJMS
Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

A 20-Year Autopsy Study of Myocardial Bridging Among Sudden Deaths

Ahmad Shafiie Ahmad Amran[1,2], Faridah Mohd Nor[1], Mohamed Swarhib Shafee[1], Nadiawati Abdul Razak[3]*

[1] Forensic Unit, Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, 56000 Kuala Lumpur, Malaysia.
[2] Department of Forensic Medicine, Hospital Miri, Jalan Cahaya Miri 98000 Sarawak Malaysia.
[3] Forensic Medicine Unit, Faculty of Medicine and Defense Health, National Defense University of Malaysia, 57000 Kem Perdana Sungai Besi, Kuala Lumpur, Malaysia.

*Corresponding author's email: drnadiawati@yahoo.com

Received: 4 December 2023

Accepted: 5 February 2024

Published: 1 May 2024

DOI: https://doi.org/10.51200/bjms.v18i2.5063

Keywords: *Autopsy, forensic pathology, heart diseases, myocardial bridging, sudden death.*

ABSTRACT

Myocardial bridging (MB) is a condition, where the cardiac muscle overlies the intramyocardial segment of the major epicardial coronary artery. This study aims to analyse the demographics and anatomical characteristics of MB within a pool of 2093 sudden cardiac-related death cases examined at the Forensic Unit of Universiti Kebangsaan Malaysia Medical Centre between 2000 and 2019. In this cross-sectional study, postmortem data collected were gender, racial affiliations, MB anatomical properties, and association with cardiac pathologies entered into the statistical software SPSS version 25 for analysis. The prevalence of MB was 12.9%. It was commoner in males (91.5%). MB was predominant between age 21-40 years old (50.2%). Chinese race showed the highest number of recorded MB cases (24.3%) among local races. MB was mostly found in left anterior descending (LAD) artery (98.2%), with the commonest length of 11-20mm (44.6%), depth of 1-5mm (49.8%), and distance from the ostium of 21-40mm (54.0%). The prevalence of isolated MB (43.2%) was nearly comparable to that of MB with cardiac pathologies (56.8%). MB was mostly associated with atherosclerosis (50.1%) and atheroma formation was mostly proximal to MB (78.3%). MB is a common occurrence and commonly found in the LAD as a single entity. It has a higher preponderance in the male gender among the adult population. In conclusion, the findings not only contribute

to a deeper understanding of MB but also hold potential implications for identifying and managing risks related to sudden cardiac-related deaths. It is a pathological condition at a certain length and depth whether it exists as an isolated entity or associated with cardiac pathologies. Atherosclerosis tends to form proximal to MB and might pose a risk for myocardial infarction.

INTRODUCTION

Myocardial bridging (MB) is a condition where the cardiac muscle overlies the intramyocardial segment of the major epicardial coronary artery. It is synonymously described as a myocardial bridge, an intramural coronary artery, a mural coronary artery and a tunnelled artery (Angelini et al., 2002; Bourassa et al., 2003). The medical fraternity is still divided in terms of whether MB is a congenital anomaly or just a common anatomical variant. The prevalence of MB greatly varies based on autopsy data as well as radiography data. For the autopsy, several studies showed a prevalence between 2% to 85.7% (Desseigne et al., 1991; Poláček, 1961).

Even though MB might be found as a single entity, its association with certain cardiac pathologies has been reported such as coronary atherosclerosis, MI, hypertrophic cardiomyopathy or even sudden death (Srettabunjong, 2016; Zhu et al., 2012). Patients with underlying MB are mostly asymptomatic but some of them present with recurrent chest pain or syncope (Abdou, 2011; Daana et al., 2006). The presence of MB is clinically significant if it can be proved that the patient presents with angina and MI, and the coronary angiography record shows >70% systolic compression (Mookadam et al., 2009).

Regarding coronary atheroma formation, MB has been said to promote proximal atherosclerosis whereby the bridged segment of the coronary artery is protected from atherosclerotic plaque formation (Akishima-Fukasawa et al., 2018; Nakaura et al., 2014; Uusitalo et al., 2015). MB is most commonly found in a single coronary artery which is the LAD artery even though some people might have more than one bridging in other coronary arteries (Lujinović et al., 2013).

In the Malaysia setting, so far there is still no study has been done on MB except for two case reports, both in 2010 and 2019 respectively (Ngow & Wan Khairina, 2010; Rohani et al., 2019). Both cases were based on living patients and radiographical imaging findings. Hence, as a starting point, this study will serve as a preliminary study in examining the demographic and anatomical properties of MB in medico-legal autopsies of sudden death cases brought into the Forensic Unit, Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The objectives of this study were to study the prevalence of isolated MB and the prevalence of MB associated with cardiac pathologies.

MATERIALS AND METHODS

The sample population comprised autopsy cases of sudden death cases received at the Forensic Unit, UKMMC between the years 2000 and 2019 (20-year-study). All cases had fulfilled the inclusion criteria i.e. sudden death from cardiac disease including all males and females, regardless of racial affiliations. Additional inclusion criteria were added during data collection as a pending cause of death for autopsy cases with MB is the only positive finding. The exclusion criteria were sudden death other than a cardiac disease, traumatic death with incidental finding of MB, and death of another manner i.e. accidental, suicidal, and homicide cases. All cases were taken from postmortem reports, and the data were analysed by descriptive statistics. The calculation is based on the total number of sudden death cases with MB in relation to the total number of medicolegal autopsies over 20 years and with the total number of sudden death cases with cardiac origin. The socio-demographic data assessed were gender, age groups, and racial affiliations.

Racial affiliations were divided into categories of Malay, Chinese, Indian, others (Malaysian local natives) and foreigners. The description of coronary artery involvement with MB, the length, the depth, and the distance of MB from the ostium. The presence of MB in one or more coronary arteries was also included. MB was also described as isolated MB or associated with cardiac pathologies such as atheroma formation, MI, or hypertrophic cardiomyopathy (HCM). Concerning atheroma formation in MB, its relation to MB in the coronary artery was described and identified. This study was intended to find the relation of MB to gender, age, and racial affiliations and the relation of MB to association with cardiac pathologies (atheroma formation, MI, HCM). The collected data were tabulated and statistically analysed using SPSS version 25. The significance of the difference was tested using the chi-square test. A P value <0.05 was considered statistically significant (S). The study was approved by the UKM Research Ethics Committee (Ref No: UKM PPI.800-11/1/5/JEP-2019-354).

RESULTS

Prevalence

From 2000 to 2019, a total of 6270 medico-legal autopsies had been conducted in UKMMC. Based on the inclusion and exclusion criteria, a total of 2093 cases were selected. Among those cases, MB was recorded in 271 cases which made the prevalence of MB 12.9% over total cardiac-related death and 4.3% over total medico-legal autopsy cases. Throughout the 20 years of data, the range of prevalence of cardiac-related death was from 2.0% to as high as 31.7% (Table 1).

Demographic data

Among those cases with MB, males (91.5%, n=248) showed higher preponderance than females (8.5%, n=23). From the data, it showed that MB was most commonly found between 21 to 40 years old (50.2%, n=136) and was less common in the age group of 1 to 20 years old (3.3%, n=9). It showed that from the record the Chinese races were highest in several cases for recorded MB as compared to other local racial affiliations (24.3%, n=66). MB was present in a quite significant number of foreigner cases which had been autopsied in UKMMC (39.5%, n=107) (Table 2). Single MB was found to appear significantly more frequently in males than females, in young age (1-20 years) and adults (21-40 years) and Indian and Malaysian local natives. However, generalization could not be made to the real population as there were limited data available for age groups and racial affiliations for analysis and comparison (Table 6).

Anatomical properties of MB

In 271 cases that presented with MB, a total of 273 MB was recorded with the majority of them possessing single MB (99.3%, n=269) with only 2 cases with double bridging found (0.7%, n=2). MB tends to develop in the LAD artery (98.2%, n=266) as compared to other coronary arteries. Out of 271 cases with MB, there was a variable number of total MB for length (N=258), depth (N=239) and distance from ostium (N=263) as cases without recorded values were omitted from the calculation. It had been found that MB length was from 11mm to 20mm in most of the cases (44.6%, n=115). In nearly half of the cases, the depth of MB from epicardial fat was to be from 1mm to 5mm (49.8%, n=119). More than half of the MB recorded was located between 21mm to 40mm from the ostium (54.0%, n=142) (Table 3).

MB association with cardiac pathologies

It had been shown in this study that isolated MB (43.2%, n=117) was almost equally equivalent to MB associated with cardiac pathologies (56.8%, n=154). Among those cardiac pathologies, atherosclerosis was more predominantly associated with MB whether present alone or mixed with other cardiac pathologies (50.1%, n=138) (Table 4). Regarding atheroma formation, the data is collected based on its formation in the coronary artery where the MB was present

regardless of its location pertaining to MB. It showed that more than two-thirds of the data had shown the development of atheroma was proximal to the location of MB (78.3%, n=108). For the remaining cases of MB with atherosclerosis, it was not recorded in the autopsy draft whether the atheroma was located within the bridging segment of the coronary artery or distal to it (Table 5). It was noticed that single MB was highly significantly presented as either isolated MB or associated with atheroma formation in the involved coronary artery. However, a similar conclusion did not apply to other cardiac pathologies as available data was limited for analysis and comparison (Table 7).

Table 1: Prevalence of myocardial bridging cases over 20 years.

Year	Autopsy cases	Cardiac-related death	Cardiac-related death with MB	Prevalence over autopsy cases	Prevalence over cardiac-related death
2000	215	38	1	0.5	2.6
2001	262	45	1	0.4	2.2
2002	240	49	1	0.4	2.0
2003	265	42	9	3.4	21.4
2004	279	60	19	6.8	31.7
2005	285	73	13	4.6	17.8
2006	321	116	11	3.4	9.5
2007	235	69	7	3.0	10.1
2008	204	65	9	4.4	13.9
2009	277	85	16	5.8	18.8
2010	263	93	16	6.1	17.2
2011	284	101	17	6.0	16.8
2012	331	116	15	4.5	12.9
2013	333	118	18	5.4	15.3
2014	370	155	17	4.6	11.0
2015	392	187	26	6.6	13.9
2016	360	161	25	6.9	15.5
2017	412	161	16	3.9	9.9
2018	446	165	15	3.4	9.1
2019	496	194	19	3.8	9.8
Total	6270	2093	271	4.3	12.9

Table 2: Demographic characteristics of autopsy cases with myocardial bridging.

Personal Identification	No. of cases (%), N=271
Sex	
Male	248 (91.5)
Female	23 (8.5)
Age group	
1-20	9 (3.3)
21-40	136 (50.2)
41-60	112 (41.3)
61-80	14 (5.2)
Racial Affiliations	
Malay	59 (21.8)
Chinese	66 (24.3)
Indian	33 (12.2)
Others	6 (2.2)
Foreigners	107 (39.5)

Table 3: Anatomical properties of myocardial bridging.

Anatomical properties of myocardial bridging	No. of cases (%)
Single MB (N=271)	
LAD	266 (98.2)
RCA	3 (1.1)
Double MB	
LAD+RCA	2 (0.7)
MB length (mm, N=258)	
1-10	69 (26.7)
11-20	115 (44.6)
21-30	43 (16.7)
31-40	18 (7.0)
41-50	7 (2.7)
>50	6 (2.3)
MB depth (mm, N=239)	
1-5	119 (49.8)
6-10	97 (40.6)
11-15	16 (6.7)
16-20	5 (2.1)
>20	2 (0.8)
MB distance (mm, N=263)	
1-20	64 (24.3)
21-40	142 (54.0)
41-60	46 (17.5)
61-80	10 (3.8)
>80	1 (0.4)

Table 4: Myocardial bridging association with cardiac pathologies.

	No. of cases (%), N=271
Isolated MB	117 (43.2)
MB associated with	
Atherosclerosis (AS)	116 (42.8)
Myocardial infarction (MI)	9 (3.3)
Cardiomyopathy (CM)	7 (2.6)
Mixed	22 (8.1)

Table 5: Atheroma formation in relation to myocardial bridging.

	No. of cases (%), N=138
Proximal to MB	108 (78.3)
Unknown relation to MB	30 (21.7)

DISCUSSION

MB is one of the medical entities that has been a topic of debate for many years people tend to discuss as simply as whether it is an anomaly or just a common variant of coronary artery or to an extent conducting a study on assessing its physiological role in promoting myocardial ischaemia in a heart (Tarantini et al., 2018). One of the topics of interest in MB is the study of its prevalence which has been conducted widely all around the globe, using autopsy or radiography.

Most prevalence of MB found in the works of literature was based on the direct dissection of the formalin-fixed heart with the given value from 34.5% to as high as 85.7% (Loukas et al., 2006; Poláček, 1961). However, a retrospective study of the relationship between MB and sudden death in a series of 930 medico-legal cases in 1991 showed a prevalence of only 2% MB among those cases (Desseigne et al., 1991). The prevalence of MB in this study was 4.3% over total medico-legal cases was considered comparable to that study. The prevalence of MB over total cardiac-related death which is the main focus of this study was 12.9% which was not in agreement with those studies with direct heart dissection mentioned earlier. There was no specific prevalence pattern over the 20 years of our data collection.

We could appreciate that the male gender always showed higher preponderance than the female gender in terms of the presence of MB in the coronary artery. From this study, the male gender was more predominant with 248 (91.5%) cases out of 271 cases of sudden death with MB. In 2006, a study on the relationship of MB to coronary artery dominance by Loukas M. et al on 200 human hearts showed that MB was present in 69 hearts and among those number, 59 hearts were from a male body which made up about 85.5% (Loukas et al., 2006). Furthermore, Akishima-Fukusawa Y. et al 2018 conducted a study on 150 human hearts regarding MB's influence on atherosclerosis development in the LAD of the normal heart. The data from that study showed MB was present in 93 hearts and from that number, the heart which originated from a male was 65 hearts (Akishima-Fukasawa et al., 2018).

Sudden death cases with MB came from an adult age group which was between 21 to 40 years old as seen in this study. This is in accordance with a study by Morales A.R. et al the mean age of the study population was 31.0 (Morales et al., 1993). However, our data was not correlated with few studies in terms of age range where their range of mean age was from 51.0 to 71.4 (Akishima-Fukasawa et al., 2018; Kim et al., 2010; Micić-Labudović et al., 2015;

Mookadam et al., 2009).

For anatomical properties of MB, our data showed MB was mostly dominant in the LAD, followed by the Right Coronary Artery (RCA) then in both coronaries. These findings are in agreement with a few studies that demonstrated similar findings (Job et al., 2016; Loukas et al., 2006; Swaroop et al., 2014). It has been supported by Lujinovic A. et al who demonstrated that single bridging is commoner than more than one bridging (Lujinović et al., 2013). Even though MB might be present as triple bridging in certain people, our data did not accord with that fact. However, a study by Loukas M. et al observed two hearts with triple bridging among 69 human hearts with bridging (Loukas et al., 2006). An almost similar finding was recorded in 2014 when Swaroop N. et al observed two human hearts with triple bridging among 35 human hearts that present with MB (Swaroop et al., 2014). Nevertheless, the highest case recorded for triple bridging was from a study by Ferreira A.G et al way back in 1991 with a total of five human hearts (5.5%) presented with triple bridging among 50 human hearts MB (Ferreira et al., 1991).

In terms of MB parameters such as the length, depth from epicardial fat and distance from ostium, all literature found were discussing mainly the former two of the parameters most probably because both of them have more physiological effects on coronary blood flow and cause ischaemia in the myocardium. Our study observed that MB length was most commonly measured from 11mm to 40mm and its depth was from 1mm to 5mm. The commonest location of MB in our study was at the middle of LAD (21mm-40mm). Our data is supported by a study in 1961 where the recorded length and depth for MB were from 10mm to 20mm and a maximum depth of 5mm respectively (Poláček, 1961). This is later supported by Lujinovic A. et al the study observed a mean length and depth for MB was 14.64mm and 1.23mm respectively (Lujinović et al., 2013). In 2015, another study by Micić-Labudović J. et al found that the average length for MB was 21.85mm and its depth was 3.74mm which is again in agreement with our study (Micić-Labudović et al., 2015). Mookadam F. et al observed that mid-LAD MB was the commonest pattern with 54.4% among his study population and this finding is almost similar to our result with 54.0% MB located in the middle part of LAD (Mookadam et al., 2009).

To prove that MB at a certain length and depth would contribute to myocardial lesions we used a study by Morales A.R. et al back in 1993 as an example. This study involved 39 human hearts with MB in LAD which was then divided into Group 1 and Group 2. Group 1 consisted of 22 hearts with myocardial lesions whether observed grossly and/or microscopically, while Group 2 consisted of 17 hearts without myocardial lesions. The myocardial lesions could be any one or more of the following; interstitial fibrosis, replacement fibrosis, contraction band necrosis, and/or increased vascular density in areas of focal fibrosis. Group 1 had an average length and depth of 2.4cm and 0.31cm respectively. Meanwhile, Group 2 had an average length and depth of 1.9cm and 0.18cm respectively. From these, it had been suggested that deep intramural LAD was abnormal rather than a normal anatomical variant due to its association with myocardial lesions (Morales et al., 1993).

One of the objectives of this study was to study the prevalence of isolated MB and the prevalence of MB associated with cardiac pathologies. It is evident from this study that isolated MB was almost equally prevalent to MB associated with cardiac pathologies with a value of 43.2% out of 271 sudden cases with MB. Therefore, its role in contributing to sudden death cases is not neglectable.

A study of isolated MB was performed using corrected TIMI frame count (CTFC) in 2013, in which a higher CTFC value indicated a decrease in coronary blood flow volume, and

a lower CTFC indicated a normal coronary flow. Results showed significantly higher CTFC in LAD, compared to the control group, which proved that coronary blood flow in MB patients was reduced in comparison to normal coronary arteries (Daoud & Wafa, 2013).

Another related study was conducted by Mookadam F. et al in 2009 on the clinical relevance of isolated MB by reviewing their coronary angiography reports. The severity of MB was categorized into three groups characterized by percentages of systolic compression on LAD, which are group I (< 50% compression), group II (50–70% compression) and group III (compression ≥70%), and these groups were followed up for 12 months. The study revealed that patients with systolic compression of ≥ 70% were associated with angina and MI. It was concluded that MB was not a benign variation of coronary anatomy based on the findings (Mookadam et al., 2009).

The above finding was in agreement with a study in 2010 by Kim S.S. et al. where 308 patients with isolated MB were followed up for about 37 months. The findings on unstable angina pectoris and MI were common presentations in patients with MB, which was in agreement with the study by Mookadam F. et al. It was also shown that patients with MB had a higher incidence of readmission compared to the control group, where the predictors of readmission were long (length) MB and spontaneous vasospasm on the coronary angiogram (Kim et al., 2010).

From this study, we found that MB was mostly associated with atheroma formation with a total of 138 cases out of 275 cases of sudden death cases with MB, whether the atheroma is isolated or associated with MI or cardiomyopathy. Our study observed that atheroma formation proximal to MB was recorded in at least 108 cases out of 138 cases with a percentage of 78.3%. Our data is in agreement with a study by Nakaura T. et al. in 2014 where the study observed that MB in the mid-LAD is considered a significant independent risk factor for coronary atherosclerosis formation in proximal LAD, other than age and diabetes mellitus in 188 patients by MDCT angiography (Nakaura et al., 2014).

Findings on atheroma formation at the proximal segment of the LAD artery or proximal to the MB entrance were also supported by Uusitalo V. et al. and Akishima-Fukasawa Y. et al (Akishima-Fukasawa et al., 2018; Uusitalo et al., 2015). However, according to Sun J.L. et al., MB is not a significant risk factor for coronary atherosclerosis, when compared to traditional cardiovascular risk factors, even though the study had agreed on the role of MB in promoting proximal atherosclerosis (Sun et al., 2013). The bridged segment of the coronary artery usually was spared or protected from atherosclerotic plaque formation (Nakaura et al., 2014) but it was not observed in this study as it was not clearly stated in the record whether the bridged segments of the coronary artery were spared or not.

We had observed a few cases of sudden death with MB where they were associated with atherosclerosis and MI at the same time. There was one study by Ishikawa Y. et al. in 2009 to see the anatomic properties of MB that predispose to MI which could support our observation. This study involved 100 autopsied MI hearts which were divided into MI hearts with MBs [(MI+)(MB+) group] and MI hearts without MBs [(MI+)(MB-) group]. The control group for the study was 200 normal hearts, 100 with MBs [(MI-)(MB+) group] and 100 without MBs [(MI-)(MB-) group]. It was observed that MB with greater thickness and greater MB muscle index was more significant in the (MI+)(MB+) group than the (MI-)(MB+) group. (MI+)(MB+) group had shown a greater intima-media ratio within 1.0 cm of the left coronary ostium than the other groups. It has been proved that from this study MB muscle index is associated with a shift of coronary artery disease more proximally in a proximal

LAD with MB, thus increasing the risk of MI (Ishikawa et al., 2009).

In this study, a few cases of sudden death cases with MB were associated with cardiomyopathy, which is most probably referring to hypertrophic cardiomyopathy (HCM) based on the heart weight in the autopsy draft. This association might be incidental and of no significant relevance based on the study in 2003 by Sorajja P. et al. where follow-up of 425 HCM patients (64 patients with MB) for about 7 years had observed no increased risk of death, including sudden cardiac death among HCM patients with MB as compared to HCM patients without bridging (Sorajja et al., 2003).

In another study in 2009, an assessment of 255 hearts comprised of 115 hearts with HCM and 140 controls, it was observed that MB was a frequent component of phenotypically expressed HCM, but no evidence of systemic association with HCM-related sudden death. Nevertheless, their finding could exclude the possibility of MB contributing to increased risk in certain patients (Basso et al., 2009).

That study was further supported by a retrospective study in 2014 by Tian T. et al.. The data was collected among 298 adult patients who were diagnosed with HCM from 1999 to 2011 and 34 of them presented with MB based on coronary angiography. With average follow-up for 4 years, it was observed that the presence of bridging in HCM patients was not evidently associated with all-cause death, cardiovascular death, sudden cardiac death, or deterioration of heart failure. Therefore, despite of common presentation of MB in HCM patients, it was not a predictor for adverse clinical outcomes (Tian et al., 2014).

MB is a quite common occurrence in our population and is commonly found as a single entity in the LAD. It seems that it has a higher preponderance in male gender among the adult age group. It is a pathological condition at a certain length and depth whether it exists as an isolated entity or is associated with cardiac pathologies, especially atherosclerosis. Atherosclerosis tends to form proximal to MB and might pose a risk for MI.

CONCLUSION

This study has illuminated the demography and anatomical properties associated with MB. The segment of a coronary artery proximal to a segment with MB is at increased risk of atherosclerosis. It was noticed that single MB was highly significantly presented as either isolated MB or associated with atheroma formation in the involved coronary artery. The findings not only contribute to a deeper understanding of MB but also hold potential implications for identifying and managing risks related to sudden cardiac-related deaths. This extensive research stands as a valuable resource, providing a nuanced perspective on this critical aspect of forensic medicine and cardiovascular health.

CONFLICT OF INTEREST

All the authors don't have any conflict of interest. No benefits have been received from a commercial party related directly or indirectly to the study.

ACKNOWLEDGEMENTS

The authors would like to extend special gratitude to the Forensic Unit, Universiti Kebangsaan Malaysia for having access to cases for this research study.

REFERENCES

Abdou, M. (2011). Myocardial bridging causing ischemia and recurrent chest pain: a case report. International Archives of Medicine, 4(1), 1-6.

Akishima-Fukasawa, Y., Ishikawa, Y., Mikami, T., Akasaka, Y., & Ishii, T. (2018). Settlement of stenotic site and enhancement of risk factor load for atherosclerosis in left anterior descending coronary artery by myocardial

bridge. Arteriosclerosis, Thrombosis, and Vascular Biology, 38(6), 1407-1414.

Angelini, P., Velasco, J. A., & Flamm, S. (2002). Coronary anomalies: incidence, pathophysiology, and clinical relevance. Circulation, 105(20), 2449-2454.

Basso, C., Thiene, G., Mackey-Bojack, S., Frigo, A. C., Corrado, D., & Maron, B. J. (2009). Myocardial bridging, a frequent component of the hypertrophic cardiomyopathy phenotype, lacks systematic association with sudden cardiac death. European heart journal, 30(13), 1627-1634. https://doi.org/10.1093/eurheartj/ehp121

Bourassa, M. G., Butnaru, A., Lespérance, J., & Tardif, J. C. (2003). Symptomatic myocardial bridges: overview of ischemic mechanisms and current diagnostic and treatment strategies. Journal of the American College of Cardiology, 41(3), 351-359.

Daana, M., Wexler, I., Milgalter, E., Rein, A. J., & Perles, Z. (2006). Symptomatic myocardial bridging in a child without hypertrophic cardiomyopathy. Pediatrics, 117(2), e333-e335. https://doi.org/10.1542/peds.2005-1388

Daoud, E. M., & Wafa, A. A. (2013). Does isolated myocardial bridge really interfere with coronary blood flow?. The Egyptian Heart Journal, 65(2), 65-70.

Desseigne, P., Tabib, A., & Loire, R. (1991). Myocardial bridging on the left anterior descending coronary artery and sudden death. Apropos of 19 cases with autopsy. Archives des Maladies du Coeur et des Vaisseaux, 84(4), 511-516.

Ferreira, A. G., Trotter, S. E., König, B., Decourt, L. V., Fox, K., & Olsen, E. G. (1991). Myocardial bridges: morphological and functional aspects. Heart, 66(5), 364-367.

Ishikawa, Y., Akasaka, Y., Suzuki, K., Fujiwara, M., Ogawa, T., Yamazaki, K., ... & Ishii, T. (2009). Anatomic properties of myocardial bridge predisposing to myocardial infarction. Circulation, 120(5), 376-383.

Job, C., Prasanna, M. B. & Nandagopalan, P. A. A Study of Myocardial Bridges on the Coronary Arteries. 3, 1782–1783 (2016).

Kim, S. S., Jeong, M. H., Kim, H. K., Kim, M. C., Cho, K. H., Lee, M. G., ... & Kang, J. C. (2010). Long-term clinical course of patients with isolated myocardial bridge. Circulation Journal, 74(3), 538-543.

Loukas, M., Curry, B., Bowers, M., Louis Jr, R. G., Bartczak, A., Kiedrowski, M., ... & Wagner, T. (2006). The relationship of myocardial bridges to coronary artery dominance in the adult human heart. Journal of anatomy, 209(1), 43-50. https://doi.org/10.1111/j.1469-7580.2006.00590.x

Lujinović, A., Kulenović, A., Kapur, E., & Gojak, R. (2013). Morphological aspects of myocardial bridges. Bosnian journal of basic medical sciences, 13(4), 212.

Micić-Labudović, J., Atanasijević, T., Popović, V., Mihailović, Z., Nikolić, S., & Puzović, D. (2015). Myocardial bridges: A prospective forensic autopsy study. Srpski arhiv za celokupno lekarstvo, 143(3-4), 153-157. M

Mohd Rohani, M. F., Mohamed Yusof, A. K., & Hashim, H. (2019). Correlation Between Functional Myocardial Perfusion Imaging and Anatomical Cardiac CT in a Case of Myocardial Bridging. Cardiovascular Imaging Asia, 3(1), 27-29.

Mookadam, F., Green, J., Holmes, D., Moustafa, S. E., & Rihal, C. (2009). Clinical relevance of myocardial bridging severity: single center experience. European journal of clinical investigation, 39(2), 110-115.

Morales, A. R., Romanelli, R., Tate, L. G., Boucek, R. J., & de Marchena, E. (1993). Intramural left anterior descending coronary artery: significance of the depth of the muscular tunnel. Human pathology, 24(7), 693-701.

Nakaura, T., Nagayoshi, Y., Awai, K., Utsunomiya, D., Kawano, H., Ogawa, H., & Yamashita, Y. (2014). Myocardial bridging is associated with coronary atherosclerosis in the segment proximal to the site of bridging. Journal of Cardiology, 63(2), 134-139. https://doi.org/10.1016/j.jjcc.2013.07.005

Ngow, H. A., & WMN, W. K. (2010). Anterior Myocardial Infarction Associated with Myocardial Bridging in a Young Man. IIUM Medical Journal Malaysia, 9(2).

Poláček, P. (1961). Relation of myocardial bridges and loops on the coronary arteries to coronary occlusions. American heart journal, 61(1), 44-52.

Sorajja, P., Ommen, S. R., Nishimura, R. A., Gersh, B. J., Tajik, A. J., & Holmes, D. R. (2003). Myocardial bridging in adult patients with hypertrophic cardiomyopathy. Journal of the American College of Cardiology, 42(5), 889-894. https://doi.org/S0735109703008544 [pii]

Srettabunjong, S. (2016). Myocardial bridging of coronary arteries: sudden unexpected deaths in a 24-year-old man. Rom. J Leg Med, 24, 83-86.

Swaroop, N., Poornima, G. C., & Shashanka, M. J. (2014). Study of myocardial bridges in

the hearts of the human cadavers. Global Journal of Medical Research, 14(1), 25-28.

Sun, J. L., Huang, W. M., Guo, J. H., Li, X. Y., Ma, X. L., & Wang, C. Y. (2013). Relationship between myocardial bridging and coronary arteriosclerosis. Cell biochemistry and biophysics, 65, 485-489.

Tarantini, G., Barioli, A., Nai Fovino, L., Fraccaro, C., Masiero, G., Iliceto, S., & Napodano, M. (2018). Unmasking myocardial bridge–related ischemia by intracoronary functional evaluation. Circulation: Cardiovascular Interventions, 11(6), e006247.

Tian, T., Wang, Y. L., Zou, Y. B., Wang, J. Z., Sun, K., Zhang, W. L., ... & Song, L. (2014). Myocardial bridging as a common phenotype of hypertrophic cardiomyopathy has no effect on prognosis. The American journal of the medical sciences, 347(6), 429-433.

Uusitalo, V., Saraste, A., Pietilä, M., Kajander, S., Bax, J. J., & Knuuti, J. (2015). The functional effects of intramural course of coronary arteries and its relation to coronary atherosclerosis. JACC: Cardiovascular Imaging, 8(6), 697-704.

Zhu, C. G., Liu, J., Liu, W. D., Xu, Y. L., Wu, N. Q., Guo, Y. L., ... & Li, J. J. (2012). Myocardial infarction caused by myocardial bridging in a male adolescent athlete. Journal of Cardiovascular Medicine, 13(2), 138-140.

BJMS
Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

A Cross-Sectional Descriptive Study: Proportion of Authenticity and Complete Product Information of FarmaTag Hologram on Registered Pharmaceutical Products among Selected Mainstream Medicines' Sellers in the State of Sabah (ProvoS)

Ahmad Firdaus Bin Shahari*, Anitha a/p Uthayakumaran, Zulhilmi Farhan Bin Zulkefli, Muhamad Fikri Bin Bakhtiar, Lavinia Kong Jin Qi

Pharmacy Enforcement Branch, Sabah State Health Department, Kota Kinabalu, 88590 Kota Kinabalu, Sabah, Malaysia

*Corresponding author's email: afirdaus.s@moh.gov.my

Received: 7 September 2023

Accepted: 27 March 2024

Published: 1 May 2024

DOI: https://doi.org/10.51200/bjms.v18i2.5066

Keywords: *FarmaTag hologram, registered pharmaceutical products, authenticity, complete product information, Sabah*

ABSTRACT

FarmaTag Hologram is a two-dimensional QR code sticker that is required on all registered pharmaceutical products (RPP) in Malaysia. By scanning the QR code, the authenticity and product information of the hologram are displayed. However, FarmaTag holograms with incomplete product information may be susceptible to being misused by manufacturers/distributors/suppliers (MDS) for different pharmaceutical products, unregistered pharmaceutical products, or counterfeit products. In addition to misusing, these callous acts may lead to consumer distrust, doubt, and a lack of confidence in the authenticity of RPP. A cross-sectional descriptive study was conducted among Selected Mainstream Medicines' Sellers in the State of Sabah between January 2022 and September 2022 to evaluate the proportion of authenticity and complete product information of FarmaTag Hologram on registered pharmaceutical products (RPP) available among selected Mainstream Medicines' Sellers (MMS) in the state of Sabah. The total sample size was 5048 registered pharmaceutical products. There was no formal sample size calculation performed because this was the first study to explore this topic. All samples being selected from MMS were authentic (100%), which included 31.7% (n = 1600) from

private medical clinics, 18.8% (n = 948), from retail pharmacies, and 49.5% (n = 2500) from Non-Pharmacy Drug Stores (NPDS). However, only 268 (5.3%) samples were found to have complete product information. The findings of this study provide preliminary information to relevant authorities on the authenticity and complete product information of FarmaTag Hologram on registered pharmaceutical products among selected MMS in the state of Sabah.

INTRODUCTION

In Malaysia, all pharmaceutical products must be registered with the Ministry of Health Malaysia (MOH) before they can be sold over the counter or marketed to consumers (Pharmaceutical Services Programme, 2015). Registered pharmaceutical products are guaranteed in terms of Safety, Quality and Efficacy (Pharmaceutical Services Programme, 2015). Based on recorded data, the value of unregistered pharmaceutical products seized from 2012 until 2014 showed an increasing trend (Zulkifli et al., 2016). To combat this issue, in 2005, the Pharmacy Service Program under MOH introduced and launched the usage of a label which was more intricate to copy. This led to the appointment of Mediharta Sdn. Bhd., a Malaysian registered company, came up with the idea of using the Meditag Hologram on all registered pharmaceutical products. The Meditag Hologram has the following features: a) security features such as multi-channel hologram and b) multi-layer security, with overt and semi-covert design aspects. Previously all registered pharmaceutical products only displayed the registration number of the pharmaceutical product (Lancaster, 2006). This was not effective in countering the problems posed for the following reason: the registration number can be easily copied and the public will be in a dilemma in determining the authenticity of pharmaceutical products (Shah et al., 2010).

Since the hologram was introduced, it underwent evolution to combat unregistered pharmaceutical products in the Malaysian market. The usage of Meditag Hologram was implemented and carried out from 2005 until 31st August 2019. On 1st September 2019, it was replaced by FarmaTag Hologram by Techno Secure Print Sdn Bhd (Label Keselamatan Hologram FarmaTagTM, 2021). The FarmaTag Hologram is the latest development of hologram which complies with all MOH safety features (Soal dan jawab, n.d.). This new hologram comes with a matrix bar-code, also known as a two-dimensional bar-code or quick response, QR code, which is a machine-readable optical label that can include data about the object to which it is attached (Hung et al., 2020). With this technology, relevant information about pharmaceutical products can be stored. QR codes are a simple, effective way to distribute information (Czuszynski & Ruminski, 2014). They are quick and convenient for mobile device users (Liu & Liu, 2006; Bate et al., 2011). As mobile devices become more prevalent, this application will make it easier for buyers to authenticate the legality of pharmaceutical products. The QR code on this FarmaTag hologram may be read by the "FarmaChecker" application, which is free to download from the Google Play Store, Apple App Store, or Huawei App Gallery (Shah et al., 2010). Similarly, users can obtain product information for registered pharmaceutical items by scanning the FarmaTag hologram's QR code which is accessible to the public. The legitimacy of the FarmaTag hologram may be easily verified by anyone. The FarmaChecker app allows customers to acquire real-time and quick authentication. When the FarmaTag Hologram is scanned, it displays FarmaTag information such as the serial number, PIN, product maker, product manufacturer or importer, and product information. This application also allows consumers to do instant reporting for unrecognized and/or fake labels detected anytime and anywhere.

However, inadequate product information provided by MDS causes consumer uncertainty as they question whether the product is genuine or not, and

there is a risk of hologram misuse. MDS, for example, may repurpose FarmaTag holograms for other products, such as unregistered pharmaceuticals or counterfeit goods.

Evaluating the authenticity and complete product information of FarmaTag holograms found on registered products is important to help overcome the risk of counterfeit pharmaceutical products. This study is important and beneficial to provide supplementary information regarding the authenticity of the hologram used as well as the completeness of product information provided after scanning the FarmaTag hologram.

Even if similar studies have been completed in other areas of the world, there is still a need to undertake this study in Malaysia, notably in the State of Sabah, due to distinction in terms of system and technological improvements. To the best of our knowledge, no such research has yet been undertaken in Malaysia.

MATERIALS AND METHODS

This was a cross-sectional descriptive study. The study was granted approval by the Medical Research and Ethics Committee (MREC) (22-02874-GMT) registered with the National Medical Research Register (NMMR) and given a registration number NMRR ID-22-02874-GMT. Data was collected from routine inspection of MMS in the state of Sabah from January 2022 until September 2022 as secondary data. The total number of MMS inspected was 1262 premises which included private clinics, private hospitals, private pharmacies and NPDS. The list of 400 private clinics and private hospitals was provided by Cawangan Kawalan Amalan Perubatan Swasta (CKAPS) which included 393 private clinics and seven private hospitals. The list of 237 private pharmacies which have applied for Poison License A in the state of Sabah was obtained from My.Pharma-C system. For NPDS, 625 premises were conveniently selected by Pharmacy Enforcement Branch (PEB) officers during a routine inspection. For private clinics, we excluded veterinary clinics, dental clinics and aesthetic clinics. Furthermore, 'for-cause' inspections of all aesthetic clinics and all NPDS that are currently under investigation by the Sabah Pharmacy Enforcement Branch were excluded from this study as well as they did not undergo routine inspection.

From each Mainstream Medicines' Seller MMS, officers scanned four (4) selected registered pharmaceutical products. So there were 1600 samples from private clinics/ private hospitals, 948 samples from private pharmacies and 2500 samples from NPDS. In conclusion, the total number of registered pharmaceutical products scanned was 5048 samples as seen in Table 1. All 5048 samples were included in the study. Apart from sampling, the officers also investigated other aspects of the MMS to ensure their practices complied with the Malaysian Laws on Poisons and the Sale of Drugs. The FarmaTag Hologram of each selected sample was scanned using the FarmaChecker apps. PEB officers filled a data collection form in Microsoft Excel software 2010. A data collection form, used to collect data related to the objectives of this study, was created. The form consists of the date of inspection, type of MMS premises, number of products scanned, the authenticity of the hologram, and product information.

Data analysis

The IBM SPSS Statistics (Version 28) was used to analyse all data. For both objectives, the results were presented as frequencies and percentages.

Ethics approval

On February 21, 2023, the Malaysia Research Ethics Committee (MREC) of the Ministry of Health reviewed and approved the study under registration number 22-02874-GMT. The principal investigators were the only ones with access to all the data, and they were

Table 1: Census sampling method was carried out for the selection of 5048 samples from 1262 premises of MMS.

MMS		
Private clinics (GP)/ Private Hospitals	**Private pharmacies (Poison License A premises)**	**NPDS**
400 premises	237 premises	625 premises
Total MMS (400 + 237 + 625) = 1262 premises		
FarmaTag Hologram on RPP scanned by FarmaChecker apps		
400x4 =1600	237x4=948	625x4=2500
Total FarmaTag Hologram on RPP scanned (1600 + 948 + 2500) = 5048 samples scanned		

GP: General practitioner

only used for research. The Malaysian Good Clinical Practise Guideline and the Declaration of Helsinki's ethical guidelines were followed when conducting the study.

RESULTS

For the proportion of authentic FarmaTag holograms on registered pharmaceutical products, a total of 5048 samples of registered pharmaceutical products were scanned throughout this study. A summary of the authenticity of the FarmaTag hologram and complete product information on registered pharmaceutical products are seen in Table 2. All samples being selected from MMS were authentic (100%), which includes 31.7% (n=1600) from private medical clinics, 18.8% (n=948) from retail pharmacies and 49.5% (n=2500) from NPDS. However, only 268 (5.3%) samples were found to have complete product information. More than half of the samples (79.8%) were from NPDS and the remaining were from private pharmacies (20.2%) and none from private clinics and private hospitals.

Table 2: The proportion of authentic and complete product information of FarmaTag hologram on RPP..

Variable	Number of MMS scanned for RPP	Number of FarmaTag holograms on RPP scanned	Number of authentic FarmaTag holograms on RPP found in the MMS	Number of complete product information on FarmaTag Holograms found in the MMS
	n (%)	n (%)	n (%)	n (%)
MMR	N = 1262	N = 5048	N = 5048	N = 268
Private medical clinics	400 (31.7%)	1600 (31.7%)	1600 (31.7%)	0 (0.0%)
Private pharmacies	237 (18.8%)	948 (18.8%)	948 (18.8%)	54 (20.2%)
Non-pharmacy drug store	625 (49.5%)	2500 (49.5%)	2500 (49.5%)	214 (79.8%)

DISCUSSION

Ten per cent (10%) of the world's pharmaceuticals have been estimated to be counterfeit (Bate et al., 2011). This global problem is responsible for around one million deaths annually and has a market value of up to $200 Billion (O'Hagan et al., 2018). Pharmaceuticals are vulnerable to counterfeiting due to the high intensity of the pharmaceutical industry and high demand. The data available confirms this. According to the 2019 Organisation for Economic Co-operation and Development/European Union Intellectual Property Office (OECD/EUIPO) report, pharmaceuticals were the 10th most counterfeited product category out of 97 recorded product categories between 2014 and 2016. In 2016, the global trade in counterfeit pharmaceuticals was valued at USD 4.4 billion. This amounts to 0.84% of total global pharmaceutical imports (OECD, 2020). According to the OECD/EUIPO customs seizures database (2019), United States brands were disproportionately affected by the trade in counterfeit pharmaceutical goods from 2014 to 2016. They were followed by the European economies of the United Kingdom, France, Austria, Germany, and Switzerland. This result is not surprising given that the United States, Switzerland, Germany, and France are the world's largest pharmaceutical producers. According to the United Nations Industrial Development Organization's (UNIDO) Industrial Statistics Database, the United States accounted for 37.6% of global pharmaceutical output in 2016, making it the world's leading producer of pharmaceutical products and medicines. It was followed by Switzerland (14%), Germany (8.9%), and France (6.8%) (OECD, 2020).

India, China and some Far East Asian Economies, including Vietnam, Indonesia, Pakistan and the Philippines, appear to be the main producers of counterfeit pharmaceuticals traded worldwide. India remains the primary source economy for counterfeit pharmaceuticals, making up 53% of the total seized value of counterfeit pharmaceutical products and medicines worldwide in 2016 (up from 53% in 2011-2013). It was followed by China (30% in 2014-2016 compared to 33% in 2011-2013), the United Arab Emirates (4% in both periods), and Hong Kong (China) (4% versus 3%) (OECD, 2020).

The Pharmaceutical Association of Malaysia reported in 2005 that 5% of prescription medicines, including eye drops, inhalers, and erectile dysfunction medications, were counterfeit (Stevens & Mydin, 2013). Pfizer conducted a market survey on its innovator drugs (Viagra, Norvasc, and Lipitor) in Malaysia in 2006, which revealed that 4.8% were counterfeited products (Zulkifli et al., 2016). In 2015, the Malaysian Ministry of Health revealed that 5.2% of over-the-counter medicines were counterfeit (Ting et al., 2018).

The goal of this study was to evaluate the proportion of the authentic and complete product information of FarmaTag Hologram on RPP available among selected MMS in the State of Sabah. We used the census sampling method to select all 5048 Farmatag Holograms on RPPs scanned during routine inspections by PEB officers.

We discovered that 100% of the samples had authentic FarmaTag holograms and only 5.3% of these samples had complete product information which was 268 samples. Samples with complete information were found mostly in private pharmacies, 20.2% (54 samples) and NPDS, 79.8% (214 samples). None of these samples were detected in private clinics and private hospitals. These stark differences are due to the majority of the samples with complete product information in the Farmatag Hologram are from over-the-counter and traditional medicines, which are more commonly sold in private pharmacies and NPDS, as opposed to private clinics and private hospitals, which are more focused on providing and selling controlled medicines.

From this data, we found that most of the MDS failed to complete the product information of the FarmaTag hologram on their registered pharmaceutical products. These may be due to a lack of awareness from the MDS on the importance of completing the product information besides no clear and transparency on instruction and regulation from the regulator and enforcement, resulting in MDS takes these things for granted. This is particularly important where counterfeits can pose health hazards.

Limitation of study

Although the proportion of authentic FarmaTag holograms was found to be 100%, this result should be interpreted conservatively. The result should not serve as a sole benchmark to show that the state of Sabah is free from non-authentic FarmaTag holograms. First, this study excluded the premises which had undergone 'for-cause' inspection. Second, the results were subjected to bias as the PEB officer selected the NPDS and samples (registered pharmaceutical products) according to their preferences. Furthermore, due to time constraints during routine inspection, only four (4) samples were selected in each premise regardless of how many registered pharmaceutical products were found in that premise. Moreover, there were possibilities that PEB officers scanned the same products at different premises especially NPDS where less variation of registered pharmaceutical products available could be found. Future study is recommended to use a random sampling method in choosing premises and samples.

CONCLUSION

We discovered that all of the samples had an authentic FarmaTag hologram as a result of this research. Despite this, most of the scanned holograms had insufficient product information. There are risks of MDS having a tendency to recycle authentic holograms on different, unregistered, or counterfeit pharmaceutical products, which is one of the drawbacks of having incomplete product information. As a result, despite the use of authentic holograms, the authenticity and safety of the RPP are called into question. Furthermore, this may cause consumer distrust, doubt, and a lack of confidence in the RPP's authenticity. The findings of this study will be useful in detecting poor product information displayed by MDS, resulting in immediate corrective action. This research could help policymakers implement new policies such as MDS must compulsorily complete product information before their products enter the market. Policymakers can also establish new requirements for the next Hologram company tender. This study can serve as a basis for the next national multi-centre research project. This is important to collect data on the authenticity and complete product information of FarmaTag Hologram on RPP across Malaysia.

CONFLICT OF INTEREST

The authors declared no competing interests.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to the Director General of Health Malaysia YBhg. Tan Sri Dato' Seri Dr Noor Hisham Bin Abdullah for his approval to publish this manuscript. The authors are obliged to thank the Director of Sabah State Health Department YBhg. Datuk Dr Rose Nani Binti Mudin and Deputy Director of Sabah State Health Department (Pharmacy) Dr Liau Siow Yen for their approval of the data collection of this study and unconditional support in this study. Last but not least, credit to all enumerators from the Sabah Pharmacy Enforcement Branch who devoted their efforts unreservedly in the data collection process to make this study possible.

FUNDING

This study did not receive any specific grant. All the overhead expenses were covered by the

operating fund of the Pharmacy Enforcement Branch, Sabah State Health Department.

REFERENCES

Arasa, A. J., & Rose, W. J. (2015). Factors contributing to substandard medical products in Kenya. Strategic Journal of Business and Change Management, 2(38), 748-66.

Asiah, B. (2009). Counterfeit Medicine: A Threat to the Public Health and Pharmaceutical Industry. In International Conference on Corporate Law (ICCL).

Bate, R., Jin, G. Z., & Mathur, A. (2011). Does price reveal poor-quality drugs? Evidence from 17 countries. Journal of Health Economics, 30(6), 1150-1163. https://doi.org/10.1016/j.jhealeco.2011.08.006

Czuszynski, K., & Ruminski, J. (2014). Interaction with medical data using QR-codes. 2014 7th International Conference on Human System Interactions (HSI) (pp. 182-187). IEEE https://doi.org/10.1109/HSI.2014.6860471

Hung, S. H., Yao, C. Y., Fang, Y. J., Tan, P., Lee, R. R., Sheffer, A., & Chu, H. K. (2020). Micrography QR codes. IEEE Transactions on Visualization and Computer Graphics, 26(9), 2834-2847. https://doi.org/10.1109/TVCG.2019.2896895

IBM Corp. (2021). IBM SPSS Statistics for Windows (Version 28.0) Armonk, NY [Computer software]. IBM Corp.

Label Keselamatan Hologram FarmaTagTM. (2021, August 2). Program Perkhidmatan Farmasi. https://www.pharmacy.gov.my/v2/ms/entri/label-keselamatan-hologram-farmatagtm.html

Lancaster, I. M. (2006). Use and efficacy of DOVIDs and other optical security devices. Optical Security and Counterfeit Deterrence Techniques VI (pp. 271-277). SPIE. https://doi.org/10.1117/12.648416

Liu, Y., & Liu, M. (2006). Automatic recognition algorithm of quick response code based on embedded system. Sixth International Conference on Intelligent Systems Design and Applications (pp. 783-788). IEEE. https://doi.org/10.1109/ISDA.2006.253712

Meehl, O. J. (2020). A first study on the suitability of volume holograms for use as integral security features on pharmaceuticals [Master's dissertation, Ohio State University]. OhioLINK Electronic Theses and Dissertations Center. http://rave.ohiolink.edu/etdc/view?acc_num=osu1593622852698023

Pharmaceutical Services Programme. (2015). New hologram Meditag. Ministry of Health Malaysia. https://www.pharmacy.gov.my/v2/en/content/new-hologram-meditag.html

O'Hagan, A., & Garlington, A. (2018). Counterfeit drugs and the online pharmaceutical trade, a threat to public safety. Forensic Research & Criminology International Journal, 6(3), 151-158. https://doi.org/10.15406/frcij.2018.06.00200

OECD. (2020). Trade in Counterfeit Pharmaceutical Products. OECD Publishing.

Shah, R. Y., Prajapati, P. N., & Agrawal, Y. K. (2010). Anticounterfeit packaging technologies. Journal of Advanced Pharmaceutical Technology & Research, 1(4), 368-373. https://doi.org/10.4103/0110-5558.76434

Soal Dan Jawab. (n.d.). Technosecureprint. https://www.technosecureprint.com/src/file/faq.pdf

Stevens, P., & Mydin, H. H. (2013). Fake medicines in Asia. Emerging Markets Health Network. https://www.ideas.org.my/wp-content/uploads/2021/04/Fake-Medicine-Asia-Feb-2013.pdf

Ting, C. Y., Loo, S. C., Sim, S. T., Tee, E. C., Hassali, M. A., Abd Jabar, A. H. A., Adruce, S. A. Z., & Talin, B. A. (2018). Unregistered medical products detected by Malaysia's pharmacy enforcement division during routine inspection: a cross-sectional study among selected mainstream medicines' retailers in the state of Sarawak. Pharmaceutical Medicine, 32, 143-148. https://doi.org/10.1007/s40290-018-0229-7

Zulkifli, N. W., Aziz, N. A., Hassan, Y., Hassali, M. A., Bahrin, N. L. Z., & Ahmad, A. (2016). Are we on the right track?: Overview of unregistered drugs in Malaysia. Journal of Pharmacy Practice and Community Medicine, 2(4), 107-115. https://doi.org/10.5530/jppcm.2016.4.2

BJMS
Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

Emergency Haemorrhoidectomy in Acute Haemorrhoidal Crisis: A Tertiary Centre Experience

Muhd Yusairi Kamarulzaman[1]*, Fatin Nur Laily Rosli[1], Nil Amri Mohamed Kamil[1], Wan Khamizar Wan Khazim[1], Michael Pak Kai Wong[2]

[1] Colorectal Unit, Department of Surgery, Sultanah Bahiyah Hospital, Ministry of Health Malaysia, 05460 Alor Setar, Kedah, Malaysia
[2] Department of Surgery, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, 15200 Kota Bharu, Kelantan, Malaysia

*Corresponding author's email: dryusairi@moh.gov.my

Received: 26 December 2023

Accepted: 24 January 2024

Published: 1 May 2024

DOI: https://doi.org/10.51200/bjms.v18i2.5067

Keywords: *Anal diseases; Benign anal disease; Emergency; Haemorrhoids; Haemorrhoidectomy*

ABSTRACT

Acute haemorrhoidal crisis refers to painful, irreducible prolapsed haemorrhoids. On the best of hand, surgical treatment of acute haemorrhoidal crisis could still risk complications of bleeding and worse, incontinence. Our study aimed to look at the short-term outcomes of emergency excisional haemorrhoidectomy for acute haemorrhoidal crisis at a colorectal centre. This is a retrospective study conducted at a tertiary centre in the northern state of Malaysia from January 2015 to December 2020. The medical record was traced from the medical record unit and the operation theatre list for all patients with surgical treatment for an acute haemorrhoidal crisis. Sociodemographic data and complications rate were collected with 12 months follow-up. There were 51 patients identified from the registry and 29 out of those were male. The median age was 41 (20-82) years old. In addition, 26% (n=13) of the females were pregnant at presentation. Five patients had previous haemorrhoidal procedures performed. The median operating time was 35 (15-143) minutes with the length of hospital stays of 4 (2-10) days. The early complications were seen in 17 patients with bleeding (5.9%) and urinary retention (27%). The 12-month recurrence rate was 7.8% with median Wexner incontinence scores of 0 (0-3). The emergency excisional haemorrhoidectomy in acute haemorrhoidal crisis is safe and effective for immediate symptomatic relief with an

acceptable low self-limiting complication rate. dy.

INTRODUCTION

Haemorrhoids is a common anorectal condition characterised by symptomatic enlargement and displacement of vascular cushion in the anal canal. Between 4.4% and 36.4% of the general population are affected by haemorrhoids (Elnaim et al., 2019; Loder et al., 1994). Acute hemorrhoidal crisis refers to painful, prolapsing, and irreducible haemorrhoids due to constriction and eventual blockage of the haemorrhoid venous return (Theodoropoulos et al., 2013). Further congestion of these vascular cushions leads to pain and subsequently anal spasms, preventing it from reduced spontaneously (Ng et al., 2020). This is the vicious cycle of acute haemorrhoidal crisis from progressive haemorrhoidal prolapsed. Conservative treatment includes ice-packing, sitz baths, sugar dressing, laxatives and adequate analgesia. The aim is to reduce the haemorrhoid swelling, release the strangulation and alleviate the pain, which would take several days to resolve. The symptoms are usually persistent and recur which elective surgery may eventually needed.

Emergency haemorrhoidectomy is less popular, and many surgeons avoid as concerns regarding in¬creased risks of anal stenosis, sphincter damage, and portal pyae¬mia following acute surgical intervention (Ng et al., 2020). Majority of these patient who had a successful initial non-operative management would have recurrent symptoms, if further surgical intervention was not offered. Nevertheless, non-surgical treatment may fail and progress to ruptures, haemorrhage, gangrene and ulceration, causing prolonged patient suffering and increasing hospital stays. Furthermore, few studies have proven that emergency haemorrhoidectomy is a safe and effective procedure that allows rapid symptoms relief and a short hospital stay, comparable to elective haemorrhoidectomy. No local study has been carried out to address the validity of this common dilemma. Henceforth, we conducted a retrospective study to evaluate the outcomes and complications for those presented with acute haemorrhoidal crisis underwent emergency excisional haemorrhoidectomy.

MATERIALS AND METHODS

The study was done in a specialized colorectal surgery unit at a tertiary centre in the northern state of Malaysia. We collected data between January 2015 and December 2020 for patients who presented with an acute haemorrhoid crisis, defined as painful prolapsed haemorrhoids that may be associated with thrombose, bleeding, or ulceration. A total of 51 patients underwent emergency haemorrhoidectomy; either Milligan-Morgan or Ferguson, operated by the registrars, general surgeons or colorectal surgeons. Patient data like demographic, clinical complaints, perioperative data, and complications such as acute urinary retention, bleeding, anal fissure, recurrence, anal stenosis, anorectal abscess and incontinence were analysed. The Wexner incontinence score was used to assess the incontinence. All patient data were retrospectively collected through Electronic Hospital Information System (eHIS) and the patients' folder. In addition, a follow-up telephone interview was conducted for patients who did not attend the final assessment (1 year after the operation). The data were compiled and analysed using Microsoft Excel (version 2016). This study was approved by Medical Research & Ethics Committee with an approval number of NMRR ID-23-00427-7XQ.

RESULTS

Table 1 presents the demographic data and clinical characteristics statistics. There were 29 males and 22 females with a median age of 41 (range 20-82) years old. In addition, 26% of the patients from our cohort were pregnant. Five patients had previous haemorrhoid procedures; one had a stapled haemorrhoidopexy, and

four had rubber band ligation. The majority of the patients complained of painful prolapsed haemorrhoids with minimal bleeding on presentation.

A total of 72.5% of patients in (American Society of Anesthesiologists (ASA) class I and the rest in ASA II to IV. The median operating time and hospital stays were 45 minutes and 4 days, respectively. The median waiting time to surgery was 2 (0-4) days and the post-operative in patient stay was 1 (0-7) days. There was one patient stays for 7 days after closed haemorrhoidectomy because of secondary haemorrhage with haematoma requiring re-exploration and evacuation of clots.

The postoperative complications shown (Table 2) were early complications, most commonly reported as the urinary retention 27%, required no intervention and postoperative bleeding 5.9% with no transfusion required. The median incontinence scores were 0 (0-4) for pre-operative period and 0 (0-3) during 12-month postoperative assessment. There were 4 patients (7.8%) had recurrence at 12-month follow-up.

Table 1: Demographic, clinical and operative data.

Socio-demography	**n (% / range)**
Age in years, median (range)	41 (20-82)
Gender, n (%)	
Male	29 (56.8%)
Female	22 (43.2%)
Pregnant	13 (59.1%)
Not Pregnant	9 (40.9%)
Duration of hospital stay in days, median (range)	**4 (2-10)**
Duration from admission to surgery in days, median (range)	2 (0-4)
Duration from operation to discharge in days, median (range)	1 (0-7)
Previous haemorrhoid intervention, n (%)	
Rubber band ligation	4 (7.8%)
Stapled haemorrhoidopexy	1 (2%)
ASA classification, n (%)	
I	37 (72.5%)
II	12 (23.5%)
III-IV	2 (4%)
Type of Anaesthesia, n (%)	
General Anaesthesia	13 (25.5%)
Spinal Anaesthesia	38 (74.5%)
Type of Haemorrhoidectomy, n (%)	
Milligan-Morgan	22 (43.1%)
Ferguson	29 (56.9%)
Total Excised Columns of Haemorrhoids, median (range)	2 (1-3)
Operative time in minutes, median (range)	35 (15-143)

Table 2: Complications

Complications	n (%)
Early (< 7 days postoperatively)	
Secondary haemorrhage	3 (5.9%)
Urinary retention	14 (27.5%)
Late (> 7 days postoperatively)	
Anal fissure	2 (4%)
Recurrence	4 (7.8%)
Wexner Incontinence Score	**Median (range)**
Pre-op	0 (0-4)
12 months post-op	0 (0-3)

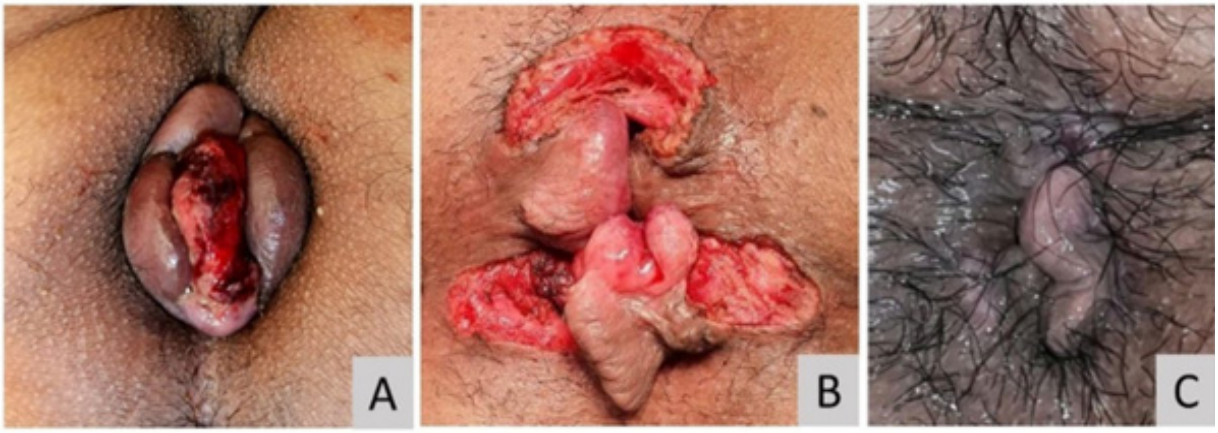

Figure 1: Acute haemorrhoidal crisis (A), excisional haemorrhoidectomy (b), and post-operation 3-month after excisional haemorrhoidectomy (C).

DISCUSSION

Emergency excisional haemorrhoidectomy comes with negative implication for their risks of secondary haemorrhage, anal incontinence, anal stricture, and recurrences. The profound challenges in identifying the plane of the haemorrhoids which were oedematous and gangrenous during acute haemorrhoidal crisis imposes anxiety to many general surgeons and patients (Hardy & Cohen., 2014). Many adopted watch and wait strategy until the oedema subsides prior to subjecting the prolapsed haemorrhoids for the excisional haemorrhoidectomy. On the contrary, in the past we have learned that there was no statistically significant in complication rate comparing emergency and elective excisional haemorrhoidectomy with the contradicting benefits that the emergency procedure could provide rapid pain relief and shorter hospital stay compared to non-operative treatment in acute haemorrhoidal crisis (Hardy & Cohen., 2014; Eu et al., 1994; Lai et al., 2006)). The post operative infection rates were equivalent when performing excisional haemorrhoidectomy in emergency or elective settings (Pattana-arun et al., 2009). Immediate surgical intervention reduced the prolonged recovery during the non-operative management, henceforth, improved the early return to work and reduced economic burden. However, the non-operative approach may be favourable among pregnant patients when calculated maternofoetal risks outweighs the benefit of the operation (Hardy & Cohen., 2014).

Urinary retention was the most reported early complication in our study (n=14) which

resolved spontaneously after 48 hours by hot compression or clean intermittent catheterisation. This is consistent with the commonest complication reported in the past for both elective and emergency surgery especially among the closed excisional haemorrhoidectomy compared to energy-devise excisional haemorrhoidectomy (Simillis et al., 2009). About 75% of our cohort had the procedure done under spinal anaesthesia which could have contributed to the self-limiting acute urinary retention. The median hospital stay was four days, and it was comparable to previous study with the duration of hospital stays between 3 to 5 days (Borse & Dhake 2016). However, in our cohort, some patients required longer stay due to longer emergency waiting time as they were prioritised against more life-threatening emergency procedures.

In our cohort, there were four recurrences within the 12 months follow-up; two of which complains of per rectal bleeding and the rest experienced prolapsed haemorrhoids. This is earlier than previously reported of 1.8% after 2 years (Gravié et al., 2005). This could be owing to our treatment plan that only the symptomatic prolapsed haemorrhoid column were excised and not all the three columns at the index surgery. None of our patients experienced faecal incontinence or stricture during follow-up which consistent with previous reported low incidence rate of 4.4% after emergency excisional haemorrhoidectomy (Eu et al., 1994).

Our study was limited by the retrospective observational design, which could potentially present with reporting and other confounding bias. There was no control arm to compare the outcome and complications. The strength of our study lies on the high volume of excisional haemorrhoidectomy performed in our specialized centre. In future study design, multi-centre study including those centre that only adopt non-operative approach in acute haemorrhoidal crisis and design a cost-effective analysis to allow us to conclude the cost-effectiveness of this procedure.

CONCLUSION

Emergency excisional haemorrhoidectomy is relevant and relatively safe and effective option to provide immediate symptomatic relieve in managing acute haemorrhoidal crisis with acceptable and self-limiting complication rate.

REFERENCES

Borse, H., & Dhake, S. (2016). A Comparative Study of Open (Milligan-Morgan) Versus Closed (Ferguson) Hemorrhoidectomy. MVP J Med Sci. 3(1): 7.

Elnaim, A. L. K., Wong, M.P.K, & Sagap, I. (2019). The Perils of Haemorrhoids Treatment. IIUM Medical Journal Malaysia, 18(3), 198–206.

Eu, K. W., Seow-Choen, F., & Goh, H. S. (1994). Comparison of emergency and elective haemorrhoidectomy. The British journal of surgery, 81(2), 308–310.

Gravié, J. F., Lehur, P. A., Huten, N., Papillon, M., Fantoli, M., Descottes, B., Pessaux, P., & Arnaud, J. P. (2005). Stapled hemorrhoidopexy versus milligan-morgan hemorrhoidectomy: a prospective, randomized, multicenter trial with 2-year postoperative follow up. Annals of surgery, 242(1), 29–35.

Hardy, A., & Cohen, C. R. (2014). The acute management of haemorrhoids. Annals of the Royal College of Surgeons of England, 96(7), 508–511.

Lai, H. J., Hsiao, C. W., Kang, J. C., Chao, P. C., Wan, C. C., & Jao, S. W. (2006). Emergency Hemorrhoidectomy for Treating Acute Hemorrhoidal Crisis: A Single Institute Experience. J Soc Colon Rectal Surgeon (Taiwan). 17, 87–93.

Loder, P. B., Kamm, M. A., Nicholls, R. J., & Phillips, R. K. (1994). Haemorrhoids: pathology, pathophysiology and aetiology. The British journal of surgery, 81(7), 946–954.

Ng, K. S., Holzgang, M., & Young, C. (2020). Still a Case of "No Pain, No Gain"? An Updated and Critical Review of the Pathogenesis, Diagnosis, and Management Options for Hemorrhoids in 2020. Annals of coloproctology, 36(3), 133–147.

Pattana-arun, J., Wesarachawit, W., Tantiphlachiva, K., Atithansakul, P., Sahakitrungruang, C.,

& Rojanasakul, A. (2009). A comparison of early postoperative results between urgent closed hemorrhoidectomy for prolapsed thrombosed hemorrhoids and elective closed hemorrhoidectomy. Journal of the Medical Association of Thailand = Chotmaihet thangphaet, 92(12), 1610–1615.

Simillis, C., Thoukididou, S. N., Slesser, A. A., Rasheed, S., Tan, E., & Tekkis, P. P. (2015). Systematic review and network meta-analysis comparing clinical outcomes and effectiveness of surgical treatments for haemorrhoids. The British journal of surgery, 102(13), 1603–1618.

Theodoropoulos, G. E., Michalopoulos, N. V., Linardoutsos, D., Flessas, I., Tsamis, D., & Zografos, G. (2013). Submucosal anoderm-preserving hemorrhoidectomy revisited: a modified technique for the surgical management of hemorrhoidal crisis. The American surgeon, 79(11), 1191–1195.

BJMS
Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

Metformin Preserves Function and Histology of Liver in Type 2 Diabetic Rat Model

Wan Amir Nizam Wan Ahmad[1], Nor Asiah Muhamad Nor[2], Nor Hidayah Abu Bakar[3], Liza Noordin[4]*

[1] Biomedicine Programme, School of Health Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia
[2] Faculty of Health Science, Universiti Sultan Zainal Abidin, Gong Badak Campus, 21300, Kuala Terengganu, Malaysia
[3] Faculty of Medicine, Universiti Sultan Zainal Abidin, Medical Campus, 20400, Kuala Terengganu, Malaysia
[4] Department of Physiology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia

*Corresponding author's email: lizakck@usm.my

Received: 18 August 2023

Accepted: 2 February 2024

Published: 1 May 2024

DOI: https://doi.org/10.51200/bjms.v18i2.5061

Keywords: *diabetes mellitus, metformin, lipid profile, liver disease, animal model*

ABSTRACT

Diabetes mellitus (DM) causes significant morbidity and mortality worldwide. Metformin is considered first-line oral therapy for type 2 DM, together with lifestyle modification. The objective of this study was to evaluate the protective effects of metformin on the liver in the type 2 DM rat (T2DR) model. The rats were fed a high-fat diet (HFD) to become obese, followed by a single low dose of streptozotocin (STZ) at 35 mg/kg intraperitoneally to induce T2DR. Twenty-eight male Sprague Dawley (SD) rats were divided into four groups equally (n=7): Control, Obese (obese rats), T2DR (Untreated T2DR), or Met-T2DR (T2DR on oral metformin at 250 mg/kg/day for six weeks). Weekly levels of fasting blood glucose (FBG) were measured. Rats were euthanised, and liver function tests and lipid profiles were measured. The histology of the liver was examined using haematoxylin and eosin staining. The met-T2DR group demonstrated a significant decrease in FBG levels beginning in week 3 and preserved liver function and histology, and lipid profile comparable to control. The effect of metformin in lowering blood glucose was demonstrated, thus controlling diabetes and preventing liver complications. The mechanism of the hepatoprotective effect could be linked to glycaemic control and lipid metabolism.

INTRODUCTION

Diabetes mellitus (DM) has emerged as a global major public concern, with a substantial risk of morbidity and mortality (Tang et al., 2024). Diabetes was estimated to affect 8.8% of adults aged 20 to 79 in 2015, with a predicted increase to 10.4% by 2040. Its prevalence in Southeast Asia is expected to gradually increase from 11.3 percent in 2019 to 12.6 percent in 2045 (Amirudin et al., 2021). Numerous complications that involved macrovascular and microvascular changes have been attributed to DM. Type 2 DM (T2DM) is characterised by progressive loss of β-cell function and mass (Sayyed Kassem et al., 2023) associated with insulin resistance in muscle (Den Hartogh et al., 2023) and adipose tissue (Ahmed et al., 2021). It was previously referred to as 'non-insulin-dependent diabetes', and it accounts for 90–95% of all diabetes cases. T2DM alters insulin resistance and lipid metabolism, which leads to pancreatic β-cell dysfunction (Skovso, 2014).

Proper treatment is necessary to prevent complications by delaying the progression of the disease. Continuous medical care with risk-reduction strategies for various factors is critical in the management of diabetes. The primary goal of DM treatment, which improves the quality of life, are to prevent or delay complications. It is acknowledged that a non-pharmacological approach, lifestyle changes, and the use of pharmacological agents are required in the treatment. Metformin, an oral hypoglycaemic guanide drug, is a first-line treatment for T2DM, particularly in overweight and obese people with a good safety profile (Chandra et al., 2019; Pinyopornpanish et al., 2021). This medicine was used to treat T2DM in the late 1950s, and it is still the drug of choice used by nearly 150 million people. Furthermore, because of its low cost, great efficacy, and weight-loss benefits, this drug has been the first-line oral hypoglycaemic medication for many years (Raqib et al., 2022). The main actions of metformin include suppressing hepatic gluconeogenesis, improving uptake of glucose, and increasing insulin sensitivity (Shaw, 2013; Rena et al., 2017; Baker et al., 2021). The effects of metformin among diabetic patients have been inconsistent, however, several evidence demonstrated the beneficial effects of metformin in previous studies. For example, metformin improved lipid profiles, decreased body weight, decreased hyperinsulinemia, improved endothelial function (Nasri and Rafieian-Kopaei, 2014), and decreased oxidative stress (Abdel-Moneim et al., 2022).

Obesity contributes to the development of T2DM (Lang et al., 2019), whereby a body mass index (BMI) of more than 25 kg/m2 is considered a risk (ElSayed et al., 2023). Diabetic dyslipidaemia in T2DM is associated with lipid metabolism abnormalities such as decreased high-density lipoprotein cholesterol (HDL-C) levels, increased triglycerides (TG), and low-density lipoprotein-cholesterol (LDL-C) (Wu and Parhofer, 2014). Furthermore, insulin resistance has been attributed to the link between the T2DM and development of nonalcoholic fatty liver disease (NAFLD), which may lead to nonalcoholic steatohepatitis, liver fibrosis, and cirrhosis (Pinyopornpanish et al., 2021; Kosmalski et al., 2022). NAFLD, a consequence of lipid acquisition exceeding lipid disposal (Ipsen et al., 2018), is described as fat accumulation in the hepatocytes in patients without excessive alcohol consumption (Marusic et al., 2021). Although the pathogenesis of NAFLD is poorly understood, dysregulation of lipid delivery, hepatic lipid uptake, and oxidation have been linked to promoting lipid deposition in the liver (Marusic et al., 2021). Meanwhile, insulin resistance which is described physiologically as the inability of some tissues to respond to normal insulin levels can cause NAFLD due to impairment of insulin signalling pathways such as insulin receptor substrates (IRSs) and phosphatidylinositol 3-kinase (PI3K)-AKT/protein kinase B (PKB) pathway (Chao et al., 2019). A previous study demonstrated that 12 to 24 weeks of treatment with metformin significantly decreased the BMI, liver enzymes,

liver fat content, and haemoglobin A1c (HbA1c) and improved insulin resistance in NAFLD patients with T2DM (Feng et al., 2017; Zhang et al., 2017; Tian et al., 2018). On the basis of this, the aim of this study was to evaluate the protective effects of metformin on liver function and structure in a type 2 DM rat (TD2R) model.

MATERIALS AND METHODS

Chemicals and reagents Metformin and streptozotocin were purchased from Hovid Bhd, Malaysia, and Sigma Aldrich, Germany respectively. The rat pellet was purchased from Altromin, Germany. Haematoxylin, eosin, and formaldehyde were purchased from Leica Biosystem, USA. Other chemicals were of analytical grade.

Animals

This study included twenty-eight (28) male Sprague-Dawley rats (N=28) weighing 200-250 g and aged 8-10 weeks. Rats were obtained from the Animal Research and Service Centre (ARASC), Universiti Sains Malaysia (USM), Malaysia. The animal procedure was approved by the Institutional Animal Care and Use Committee (IACUC), USM (Ref: USM/ISCUC/2017/9110 (886)). Animals were housed for a week prior to the intervention in a standard polypropylene cage under controlled conditions (23 ± 1°C, 60-70 percent humidity, and 12-hour light-dark cycle) with access to a standard pellet diet and drinking water ad libitum.

Experimental design

The experimental design is shown in Figure 1. Animals were divided into two groups; Control (n=7) and Obese (n=21). The control group was given a standard Altromin diet, while the obese group received a self-prepared high-fat diet (HFD 32% fat) to induce obesity. The standard diet was Altromin pellet (Altromin Spezialfutter GmbH & Co. KG, Lage, Germany) that was composed of soy, wheat and corn with approximately 24% protein, 64%

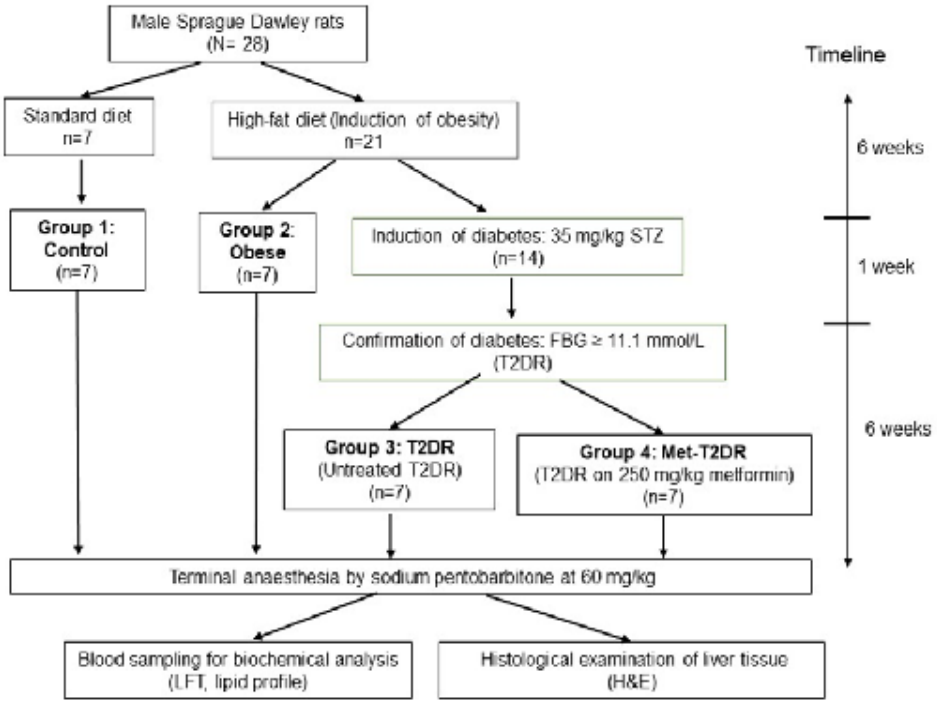

Figure 1: The flow chart of the study. T2DR: Untreated type 2 diabetes mellitus rat, Met-T2DR, T2DR treated with 250 mg/kg/day of metformin, STZ: streptozotocin, LFT: liver function test, FBG: fasting blood glucose, H&E: haematoxylin & eosin.

carbohydrates and 12% fat in terms of caloric content (Zakaria et al., 2022) while for the preparation of HFD, 32 g of ghee (saturated fat from an animal), 300 mg calcium, and 100 IU of vitamin D3 per 100 g of standard rat pellet were mixed well to become dough-like consistency (Noordin et al., 2022). Obese rat has a BMI of more than 0.68 g/cm2 (Nouvelli et al., 2007). BMI was calculated as follows: body weight (g) / length2 (cm2).

Diabetes mellitus was induced in obese rats using streptozotocin (STZ) at 35 mg/kg (i.p) (Noordin et al., 2021). One week following STZ induction, levels of fasting blood glucose (FBG) were measured. FBG levels of more than 11.1 mmol/L were considered diabetes (Cai et al., 2020), and were assigned as T2DR. T2DR were divided into two groups: untreated or treated with metformin at 250 mg/kg orally for six weeks. The dose of 250 mg/kg was based on previous studies that demonstrated a significant decrease in plasma levels of glucose (Roxo et al., 2019; Shen et al., 2020; Noordin et al., 2022). The study groups include Control, Obese, T2DR (Untreated-type 2 diabetes mellitus rat), and Met-T2DR (T2DR treated with 250 mg/kg/day metformin), with seven rats in each group.

The rats from the control group were given a standard diet, while the other rats were given HFD throughout the study. FBG levels were measured weekly by tail pricking in the dorsal vein after an overnight fast (8 hours) using the portable Accu-Check Advantage glucometer. Rats were euthanised at the end of the study by sodium pentobarbitone at 60 mg/kg (i.p). Blood was withdrawn via cardiac puncture for biochemical analysis, and the liver was isolated for histological examination.

Measurement of biochemical parameters

Liver function test, including liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), and lipid profile, including total cholesterol, triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C) were measured in the serum. Blood samples were kept in nonheparinised tubes, left to clot at room temperature, and centrifuged at 1,100 x g for 15 min. Blood samples were sent to B.P. Clinical Lab Sdn. Bhd., Kota Bharu, Kelantan, Malaysia.

Histopathology assessment

Liver tissue was dissected out, rinsed with phosphate buffer solution, and fixed in 10% formalin. The specimen was then embedded in paraffin and sections at a thickness of 2-3 µm. The specimens were put on glass slides and left on a hot plate (HI1220; Leica Microsystems). Then, they were deparaffinised with xylene and dehydrated by a descending ethanol series. After staining with Haematoxylin and Eosin, the sections were dehydrated by an ascending ethanol series followed by xylene.

Statistical Analysis

Data are presented as the mean (Standard Deviation; SD). Results were analysed by one-way analysis of variance (ANOVA) followed by the post hoc Tukey's test and two-way repeated measure ANOVA. Graph Pad Prism software version 9 for Windows (GraphPad, San Diego, CA) was used for analysis. A p-value of < 0.05 was considered significant.

RESULTS

Metformin decreases FBG levels in T2DR

Pre-induction FBG was not significantly different between the groups. One-week post-streptozotocin (STZ) injection (Week 0), FBG levels were higher in T2DR significantly compared to the control group (Table 1). Throughout the six weeks, the FBG levels in the T2DR group remained significantly higher compared to the control ($p<0.001$) and obese ($p<0.001$) groups. Treatment with metformin significantly reduced the FBG levels as compared to T2DR, beginning in week 3 ($p<0.05$). The reduction of FBG with metformin

was comparable to the control group

Table 1: Weekly levels of fasting blood glucose in the experimental groups.

Group	Control	Obese	T2DR	Met-T2DR
Day 0	5.10 (0.49)c	5.62 (0.26)c	17.23 (0.65)	17.80 (1.88)
Week 1	4.69 (0.47)c	5.51 (0.30)c	21.24 (2.78)	17.46 (4.21)
Week 2	4.40 (0.42)c	4.84 (0.58)c	20.56 (3.38)	17.64 (6.98)
Week 3	4.59 (0.29)c	5.49 (0.34)c	23.06 (2.19)	13.34 (6.49)a
Week 4	4.12 (0.22)c	5.29 (0.45)c	22.17 (2.56)	11.64 (6.33)b
Week 5	4.32 (0.30)c	5.50 (0.34)c	22.31 (1.69)	8.98 (4.55)c
Week 6	4.35 (0.39)c	5.69 (0.52)c	22.43 (1.30)	7.53 (3.42)c

Data were analysed by using two-way repeated measures ANOVA. ap<0.05, bp<0.01 and cp<0.001 when compared to T2DR. T2DR, Untreated-T2DR; Met-T2DR, T2DR treated with metformin.

Metformin preserves liver function parameters and lipid profile in T2DR

The liver enzymes increased significantly in the T2DR group compared to the control; including AST, ALT, and ALP. The metformin group had significantly lower levels of all the liver enzymes compared to the T2DR. Meanwhile, TC and TG were significantly higher in the T2DR group compared to the control and obese groups. LDL-C level was significantly higher in the T2DR group compared to the control group. Treatment with metformin significantly reduced TC, TG, and LDL-C levels compared to the T2DR group. However, no significant differences were observed in HDL-C levels between the groups (Table 2). There were also no significant differences in total protein, albumin, globulin, and total bilirubin between the groups.

Table 2: Levels of liver function test parameters and lipid profile in the experimental groups.

Groups	Control	Obese	T2DR	Met-T2DR
Liver function tests				
Total protein (g/L)	66.89 (3.40)	73.00 (8.02)	67.75 (2.56)	68.56 (10.08)
Albumin (g/L)	27.44 (1.67)	29.75 (1.99)	27.13 (0.90)	28.44 (1.81)
Globulin (g/L)	39.44 (5.03)	43.25 (6.50)	40.63 (8.86)	40.11 (9.33)
A/G ratio (g/L)	0.70 (0.09)	0.70 (0.80)	0.69 (0.12)	0.77 (0.12)
Total bilirubin (µmol/L)	1.70 (0.01)	1.71 (0.01)	1.70 (0.01)	1.70 (0.00)
AST (U/L)	123.60 (23.60)a	152.0 (18.19)	173.70 (53.70)	114.0 (25.97)a
ALT (U/L)	68.56 (9.06)b	73.86 (19.45)a	112.00 (37.26)	70.86 (10.84)b
ALP (U/L)	269.00 (44.86)c	454.50 (96.78)c	1539.0 (176.2)	351.0 (275.7)c
Lipid profiles				
Total cholesterol (mmol/L)	1.60 (0.12)c	2.10 (0.24)a	2.88 (0.40)	1.75 (0.20)c
Triglycerides (mmol/L)	1.10 (0.39)b	2.50 (0.94)a	6.40 (3.06)	1.02 (0.22)c
LDL-C (mmol/L)	0.58 (0.28)b	1.53 (2.00)	3.68 (1.83)	1.00 (0.23)a
HDL-C (mmol/L)	0.44 (0.05)	0.60 (0.22)	0.60 (0.07)	0.48 ± 0.10

Data were analysed by using one-way ANOVA. ap< 0.05, bp< 0.01 and cp< 0.001 when compared to T2DR. T2DR, Untreated-T2DR; Met-T2DR, T2DR treated with metformin.

Metformin preserves normal histology of the liver

The histology of the liver is shown in Figure 2. The control rat showed a normal hepatic lobule that consists of polygonal hepatocytes, a regular nucleus, and cytoplasm (Figure 2A). In the obese (Figure 2B) and T2DR (Figure 2C) groups, there were fatty changes seen, which were characterised by the presence of macrovesicular and microvesicular steatosis. The lipid accumulates in the hepatocytes as vacuoles, which have a clear appearance. In addition, ballooning of hepatocytes was seen in the obese and T2DR groups. In the metformin group, the liver tissue was preserved, similar to the control group

DISCUSSION

The present study was successful in developing an animal model of T2DR. The combination of HFD and a low dose of STZ causes minimal dysfunction of the pancreatic β-cell. This method was chosen in this study to develop the T2DM model similar to earlier studies (Fang et al., 2019; Noordin et al., 2021). A low dose of STZ causes mild impairment of insulin secretion, like in the late-stage T2DM. This model exhibits long-lasting and stable hyperglycaemia, making it a widely research tool in the DM study (Guo et al., 2018). T2DM is a metabolic disorder that affects insulin resistance, the function of pancreatic beta-

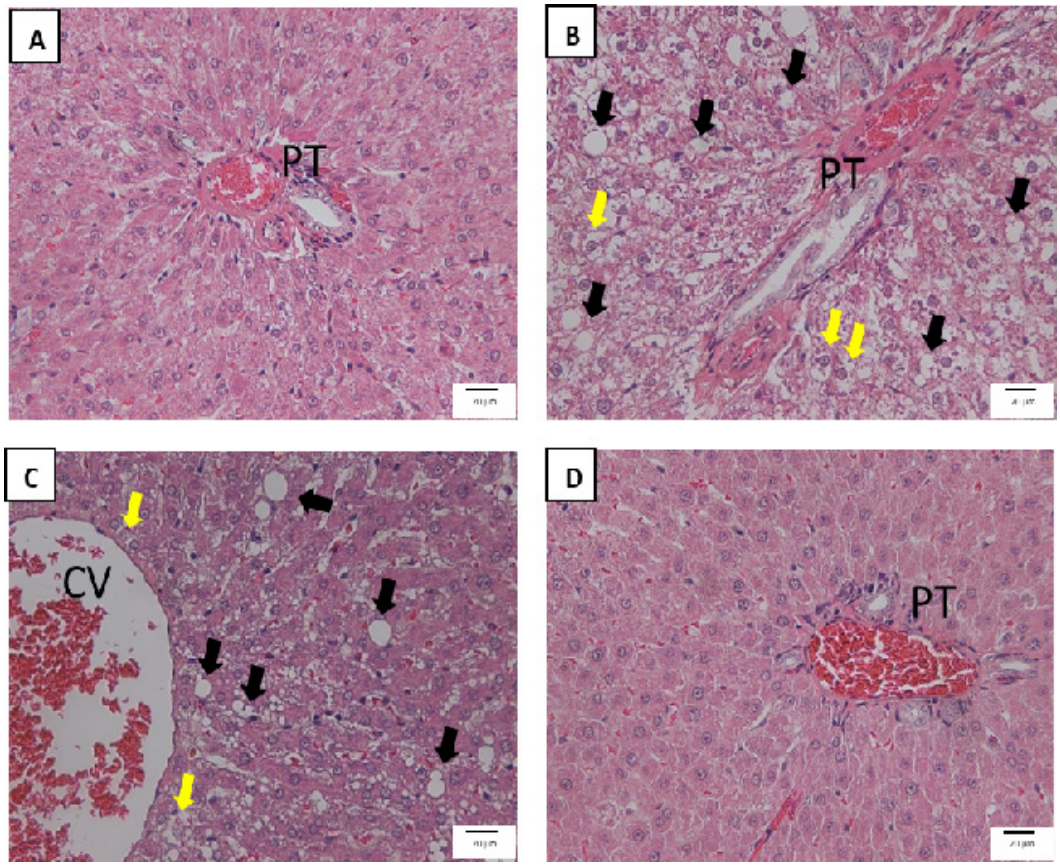

Figure 2: Histopathological sections of liver with Haematoxylin and Eosin staining in all groups. Control (A), Obese (B), T2DR (C), and Met-T2DR (D). Control group shows normal appearance of liver tissue with no pathological changes. Obese and T2DR groups show the presence of lipid droplets while the liver tissue in Met-T2DR group is preserved. T2DR: Untreated-type 2 diabetes mellitus rat, Met-T2DR: T2DR treated with 250 mg/kg/day of metformin. Portal triad (PT), Central vein (CV), Lipid droplets are marked using black arrows, and ballooning of hepatocytes are marked using yellow arrows. Magnification X400, scale bar=20µm.

cell, and lipid metabolism (Skovso, 2014). Obese animals develop insulin resistance, exhibit metabolic characteristics, and develop a disease progression similar to that seen in T2DM patients (Fang et al., 2019). Changes in the biochemical and histology of the liver in diabetic animal models simulate chronic liver disease in humans (Lucchesi et al., 2015).

We also evaluated the potential liver-protective effects of metformin. Metformin is a widely used drug for treating T2DM due to its glucose-lowering effects, safe, and relatively low cost (LaMoia and Shulman, 2021). We found that the levels of FBG remained consistently high throughout the experimental period compared to the control and obese groups. It was demonstrated that metformin significantly reduced FBG levels beginning in week 3.

The liver is the primary site of metformin action, and suppression of hepatic glucose production by metformin is widely accepted for lowering glucose levels in the blood (Horakova et al., 2019; LaMoia and Shulman, 2021). Metformin increases adenosine monophosphate-activated protein kinase activity in the liver and reduces hepatic gluconeogenesis and lipogenesis. Besides lowering blood glucose, metformin also increased peripheral insulin sensitivity (Kristensen et al., 2014), increased muscle metabolic insulin sensitivity (Jahn et al., 2022), and inhibited transepithelial glucose transport in the intestine (Horakova et al., 2019). Most recently, a study on diabetic patients showed that the gut is the primary site of metformin, whereby this drug increases the basolateral intestinal glucose uptake that results in hypoglycaemia in the portal vein and subsequent reduction of glucose production in the liver (Tobar et al., 2023). Metformin is also effective when combined with other glucose-lowering agents; for example, the combination of metformin and glipizide, a second-generation of sulfonylureas, was more potent than a single therapy of metformin in improving glycaemic control and ameliorating oxidative stress (Baker et al., 2021; Abdel-Moneim et al., 2022).

Liver disease has been reported as one of the causes of death in DM patients (Gopal et al., 2014). T2DM is linked to alterations in liver function and lipid profile (Khadke et al., 2019). ALT and AST are recommended as standard indicators of biomarkers and liver function for predicting toxicity. In this study, we observed increased liver enzymes, AST, ALT, and ALP in the T2DR group, indicating an impairment of liver function in this group. In diabetics, elevated ALT and AST levels are related to non-alcoholic fatty liver disease (Mykhalchyshyn et al., 2015). The elevated levels of these transaminases in this study could be attributed to parenchymal liver cells damage (Gopalakrishnan et al., 2020). Treatment with metformin, interestingly, preserved normal liver function, implying that the drug has protective effects on the liver.

Obesity is the leading cause of T2DM, and it contributes to high triglyceride levels and insulin resistance (Gheibi et al., 2017). Insulin resistance and T2DM are associated with lipid abnormalities such as an increase in TC, TG, and LDL-C, as well as a decrease in HDL-C levels (Rosenblit, 2016; Zhang et al., 2017), which was consistent with our study. We also demonstrated that metformin had a significant decrease in TC, TG, and LDL-C compared to the T2DR group, indicating the anti-hyperlipidaemic activity of metformin.

NAFLD is the primary cause of fatty change worldwide, which can be caused by diabetes, obesity, or metabolic syndrome. NAFLD is characterised by fat accumulation in hepatocytes (Firneisz, 2014). Liver changes range from fatty degeneration of liver cells, which comprises of macrovesicular or microvesicular triglycerides accumulation, to steatohepatitis in the advanced stage (Aly and Kleiner, 2011). NAFLD is attributed as the consequence of excessive TG in the cytoplasm of hepatocytes (Benedict and Zhang, 2017),

which may support the presence of fatty change in the T2DR group in this study. Lipotoxicity, inflammation and oxidative stress play a crucial role in the progression of NAFLD (Yang et al., 2019). Metformin preserved the normal histology of the liver, which may be related to lower levels of TC, TG, and LDL-C.

CONCLUSION

Our animal model of T2DR induced by a combination of HFD and a low dose of STZ exhibits hyperglycaemia, liver dysfunction, dyslipidaemia, and liver steatosis. Metformin treatments significantly attenuated the pathological features of T2DM, by lowering blood glucose, protecting liver functions, regulating lipid metabolism, and retaining normal morphology of the liver. These effects could be due to its anti-hyperglycaemic and hypolipidaemic effects, which need further research to elucidate its exact mechanism of action. However, there is a potential limitation to our study whereby we did not evaluate the direct influence of metformin on insulin signalling pathways, which is considered essential for future research.

CONFLICT OF INTEREST

No conflicts of interest.

ACKNOWLEDGEMENTS

The authors would like to thank the Ministry of Agriculture's Herbal Research Grant Scheme (HRGS) for the financial support (project: NH1015S020/USM 304.PPSK.6150169.K123). The authors also acknowledge the facilities and technical assistance of all staff from the Animal and Research Centre (ARASC), Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia.

REFERENCES

Aly, F. Z., & Kleiner, D. (2011). Update on fatty liver disease and steatohepatitis. Advances in Anatomic Pathology, 18(4), 294. https://doi: 10.1097/PAP.0b013e318220f59

Amirudin, N., Aimanan, S. N. M., Kassim, R., & Panting, A. J. (2021). The importance of health information seeking among diabetes patients in Malaysia: A preliminary observation. Malaysian Journal of Social Sciences and Humanities (MJSSH), 6(12), 205-212. https://doi: 10.47405/mjssh.v6i12.1203

Baker, C., Retzik-Stahr, C., Singh, V., Plomondon, R., Anderson, V., & Rasouli, N. (2021). Should metformin remain the first-line therapy for treatment of type 2 diabetes?. Therapeutic Advances in Endocrinology and Metabolism, 12, 2042018820980225. https://doi: 10.1177/2042018820980225

Benedict, M., & Zhang, X. (2017). Non-alcoholic fatty liver disease: An expanded review. World Journal of Hepatology, 9(16), 715. https://doi: 10.4254/wjh.v9.i16.715

Cai, W. D., Ding, Z. C., Wang, Y. Y., Yang, Y., Zhang, H. N., & Yan, J. K. (2020). Hypoglycemic benefit and potential mechanism of a polysaccharide from Hericium erinaceus in streptozotoxin-induced diabetic rats. Process Biochemistry, 88, 180-188.

Chandra, K., Singh, P., Dwivedi, S., & Jain, S. K. (2019). Diabetes Mellitus and Oxidative Stress: A Co-relative and Therapeutic Approach. Journal of Clinical & Diagnostic Research, 13(5). https://doi: 10.7860/JCDR/2019/40628.12878

Chao, H.W., Chao, S.W., Lin, H., Ku, H.C., & Cheng, C.F. (2019). Homeostasis of Glucose and Lipid in Non-Alcoholic Fatty Liver Disease. International Journal of Molecular Sciences, 20(2), 298. https://doi.org/10.3390/ijms20020298

Den Hartogh, D. J., Vlavcheski, F., & Tsiani, E. (2023). Muscle Cell Insulin Resistance Is Attenuated by Rosmarinic Acid: Elucidating the Mechanisms Involved. International Journal of Molecular Sciences, 24(6), 5094.

ElSayed, N. A., Aleppo, G., Aroda, V. R., Bannuru, R. R., Brown, F. M., Bruemmer, D., ... & Gabbay, R. A. (2023). Addendum. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes—2023. Diabetes Care 2023; 46 (Suppl. 1): S19–S40. Diabetes Care, dc23ad08. https://doi.org/10.2337/dc23-S002

Fang, J. Y., Lin, C. H., Huang, T. H., & Chuang, S. Y. (2019). In vivo rodent models of type 2 diabetes and their usefulness for evaluating flavonoid bioactivity. Nutrients, 11(3), 530. https://doi: 10.3390/nu11030530

Feng, W., Gao, C., Bi, Y., Wu, M., Li, P., Shen, S., Chen, W., Yin, T. and Zhu, D. (2017), Randomized trial comparing the effects of gliclazide,

liraglutide, and metformin on diabetes with non-alcoholic fatty liver disease. Journal of Diabetes, 9: 800-809. https://doi.org/10.1111/1753-0407.12555

Firneisz, G. (2014). Non-alcoholic fatty liver disease and type 2 diabetes mellitus: the liver disease of our age?. World Journal of Gastroenterology: WJG, 20(27), 9072. https://doi:10.3748/wjg.v20.i27.9072

Gheibi, S., Kashfi, K., & Ghasemi, A. (2017). A practical guide for induction of type-2 diabetes in rat: Incorporating a high-fat diet and streptozotocin. Biomedicine & Pharmacotherapy, 95, 605-613. https://doi: 10.1016/j.biopha.2017.08.098

Gopal, V., Mandal, V., Tangjang, S., & Mandal, S. C. (2014). Serum biochemical, histopathology and SEM analyses of the effects of the Indian traditional herb Wattakaka volubilis leaf extract on wistar male rats. Journal of Pharmacopuncture, 17(1), 13. https://doi: 10.3831/KPI.2014.17.002

Gopalakrishnan, R., Elumalai, N., & Alagirisamy, R. (2020). Effect of polyherbal drug on oxidative stress and insulin resistance in high-fat diet-induced type 2 diabetic rats. All Life, 13(1), 310-320. https://doi.org/10.1080/26895293.2020.1776772

Guo, X. X., Wang, Y., Wang, K., Ji, B. P., & Zhou, F. (2018). Stability of a type 2 diabetes rat model induced by high-fat diet feeding with low-dose streptozotocin injection. Journal of Zhejiang University. Science. B, 19(7), 559. https://doi: 10.1631/jzus.B1700254

Horakova, O., Kroupova, P., Bardova, K., Buresova, J., Janovska, P., Kopecky, J., & Rossmeisl, M. (2019). Metformin acutely lowers blood glucose levels by inhibition of intestinal glucose transport. Scientific Reports, 9(1), 6156. https://doi: 10.1038/s41598-019-42531-0

Ipsen, D. H., Lykkesfeldt, J., & Tveden-Nyborg, P. (2018). Molecular mechanisms of hepatic lipid accumulation in non-alcoholic fatty liver disease. Cellular and Molecular Life Sciences, 75, 3313-3327.

Jahn, L. A., Hartline, L., Liu, Z., & Barrett, E. J. (2022). Metformin improves skeletal muscle microvascular insulin resistance in metabolic syndrome. American Journal of Physiology-Endocrinology and Metabolism, 322(2), E173-E180. https://doi: 10.1152/ajpendo.00287.2021

Khadke, S. P., Kuvalekar, A. A., Harsulkar, A. M., & Mantri, N. (2019). High energy intake induced overexpression of transcription factors and its regulatory genes involved in acceleration of hepatic lipogenesis: A rat model for type 2 diabetes. Biomedicines, 7(4), 76. https://doi: 10.3390/biomedicines7040076

Kosmalski, M., Ziółkowska, S., Czarny, P., Szemraj, J., & Pietras, T. (2022). The coexistence of nonalcoholic fatty liver disease and type 2 diabetes mellitus. Journal of Clinical Medicine, 11(5), 1375. https://doi: 10.3390/jcm11051375

Kristensen, J. M., Treebak, J. T., Schjerling, P., Goodyear, L., & Wojtaszewski, J. F. (2014). Two weeks of metformin treatment induces AMPK-dependent enhancement of insulin-stimulated glucose uptake in mouse soleus muscle. American Journal of Physiology-Endocrinology and Metabolism, 306(10), E1099-E1109. https://doi.org/10.1152/ajpendo.00417.2013

LaMoia, T. E., & Shulman, G. I. (2021). Cellular and molecular mechanisms of metformin action. Endocrine Reviews, 42(1), 77-96. https://doi.org/10.1210/endrev/bnaa023

Lang, P., Hasselwander, S., Li, H., & Xia, N. (2019). Effects of different diets used in diet-induced obesity models on insulin resistance and vascular dysfunction in C57BL/6 mice. Scientific Reports, 9 (1): 19556. https://doi.org/10.1038/s41598-019-55987-x

Lucchesi, A. N., Cassettari, L. L., & Spadella, C. T. (2015). Alloxan-induced diabetes causes morphological and ultrastructural changes in rat liver that resemble the natural history of chronic fatty liver disease in humans. Journal of Diabetes Research, 2015. https://doi: 10.1155/2015/494578

Marusic, M., Paic, M., Knobloch, M., & Liberati Prso, A. M. (2021). NAFLD, insulin resistance, and diabetes mellitus type 2. Canadian Journal of Gastroenterology and Hepatology, 2021.

Mykhalchyshyn, G., Kobyliak, N., & Bodnar, P. (2015). Diagnostic accuracy of acyl-ghrelin and it association with non-alcoholic fatty liver disease in type 2 diabetic patients. Journal of Diabetes & Metabolic Disorders, 14, 1-7. https://doi: 10.1186/s40200-015-0170-1

Nasri, H., & Rafieian-Kopaei, M. (2014). Metformin: current knowledge. Journal of Research in Medical Sciences: the official journal of Isfahan University of Medical Sciences, 19(7), 658.

Noordin, L., Nor, N. A. M., Bakar, N. H. A., & Ahmad, W. A. N. W. (2021). Metabolic and pancreatic derangement in type 2 diabetic rat. IIUM Medical Journal Malaysia, 20(4). https://doi.org/10.31436/imjm.v20i4.1917

Noordin, L., Wan Ahmad, W. A. N., Muhamad Nor, N. A., Abu Bakar, N. H., & Ugusman, A. (2022). Etlingera elatior flower aqueous extract protects against oxidative stress-induced nephropathy in a rat model of type 2 diabetes. Evidence-Based Complementary and Alternative Medicine, 2022.

Novelli, E. L. B., Diniz, Y. S., Galhardi, C. M., Ebaid, G. M. X., Rodrigues, H. G., Mani, F., ... & Novelli Filho, J. L. V. B. (2007). Anthropometrical parameters and markers of obesity in rats. Laboratory Animals, 41(1), 111-119. https://doi: 10.1258/002367707779399518

Pinyopornpanish, K., Leerapun, A., Pinyopornpanish, K., & Chattipakorn, N. (2021). Effects of metformin on hepatic steatosis in adults with nonalcoholic fatty liver disease and diabetes: insights from the cellular to patient levels. Gut and liver, 15(6), 827.

Raqib, T. M., Polus, R. K., & Mohammad, N. S. (2022). Prevalence of Vitamin B12 Deficiency in Patients with type 2 Diabetes Mellitus on Metformin. Diyala Journal of Medicine, 23(1), 22-32.

Rena, G., Hardie, D. G., & Pearson, E. R. 2017. The mechanisms of action of metformin. Diabetologia; 60 (9): 1577–8. https://doi: 10.1007/s00125-017-4342-z

Rosenblit, P. D. (2016). Common medications used by patients with type 2 diabetes mellitus: what are their effects on the lipid profile?. Cardiovascular Diabetology, 15(1), 95. https://doi.org/10.1186/s12933-016-0412-7

Roxo, D. F., Arcaro, C. A., Gutierres, V. O., Costa, M. C., Oliveira, J. O., Lima, T. F. O., ... & Baviera, A. M. (2019). Curcumin combined with metformin decreases glycemia and dyslipidemia, and increases paraoxonase activity in diabetic rats. Diabetology & Metabolic Syndrome, 11(1), 1-8.

Sayyed Kassem, L., Rajpal, A., Barreiro, M. V., & Ismail-Beigi, F. (2023). Beta-cell function in type 2 diabetes (T2DM): Can it be preserved or enhanced?. Journal of Diabetes, 15(10), 817-837.

Shaw, R. J. (2013). Metformin trims fats to restore insulin sensitivity. Nature Medicine, 19(12), 1570-1572. https://doi.org/10.1038/nm.3414

Shen, X., Wang, L., Zhou, N., Gai, S., Liu, X., & Zhang, S. (2020). Beneficial effects of combination therapy of phloretin and metformin in streptozotocin-induced diabetic rats and improved insulin sensitivity in vitro. Food & Function, 11(1), 392-403.

Skovso, S. (2014). Modeling type 2 diabetes in rats using high fat diet and streptozotocin. Journal of Diabetes Investigation, 5(4), 349-358.

Tang, Y., Feng, X., Liu, N., Zhou, Y., Wang, Y., Chen, Z., & Liu, Y. (2024). Relationship between systemic immune inflammation index and mortality among US adults with different diabetic status: Evidence from NHANES 1999-2018. Experimental Gerontology, 185, 112350.

Tian, F., Zheng, Z., Zhang, D., He, S., & Shen, J. (2018). Efficacy of liraglutide in treating type 2 diabetes mellitus complicated with non-alcoholic fatty liver disease. Bioscience Reports, 38(6), BSR20181304.

Tobar, N., Rocha, G. Z., Santos, A., Guadagnini, D., Assalin, H. B., Camargo, J. A., ... & Saad, M. J. (2023). Metformin acts in the gut and induces gut-liver crosstalk. Proceedings of the National Academy of Sciences, 120(4), e2211933120. https://doi.org/10.1073/pnas.2211933120

Wu, L., & Parhofer, K. G. (2014). Diabetic dyslipidemia. Metabolism, 63(12), 1469-1479. https://doi: 10.1016/j.metabol.2014.08.010

Yang, J., Fernández-Galilea, M., Martínez-Fernández, L., González-Muniesa, P., Pérez-Chávez, A., Martínez, J. A., & Moreno-Aliaga, M. J. (2019). Oxidative stress and non-alcoholic fatty liver disease: effects of omega-3 fatty acid supplementation. Nutrients, 11(4), 872. https://doi: 10.3390/nu11040872

Zakaria, Z., Othman, Z. A., Suleiman, J. B., Mustaffa, K. M. F., Jalil, N. A. C., Ghazali, W. S. W., ... & Kamaruzaman, K. A. (2022). Therapeutic Effects of Heterotrigona itama (Stingless Bee) Bee Bread in Improving Hepatic Lipid Metabolism through the Activation of the Keap1/Nrf2 Signaling Pathway in an Obese Rat Model. Antioxidants, 11(11), 2190.

Zhang, R., Cheng, K., Xu, S., Li, S., Zhou, Y., Zhou, S., ... & Zhou, Y. (2017). Metformin and diammonium glycyrrhizinate enteric-coated capsule versus metformin alone versus diammonium glycyrrhizinate enteric-coated capsule alone in patients with nonalcoholic fatty liver disease and type 2 diabetes mellitus. Gastroenterology Research and Practice, 2017. https://doi: 10.1155/2017/8491742

BJMS
Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

Factors Affecting Health Care Services Utilisation among Rural Population in Sabah, Malaysia

Adilius Manual[1]*, Mohd Yusof Ibrahim[2],Ho Chong Mun[3], Norazah Mohd Suki[4]

[1] Institute for Health Systems Research, National Institutes of Health, Ministry of Health 40170 Shah Alam, Selangor, Malaysia
[2] Faculty of Medicine & Health Sciences, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia
[3] Faculty of Science and Natural Resources, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia
[4] Othman Yeop Abdullah Graduate School of Business, Universiti Utara Malaysia, 27b, Jalan Raja Muda Abdul Aziz, Chow Kit, 50300 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia

*Corresponding author's email: adilius.m@moh.gov.my

Received: 26 November 2023

Accepted: 6 March 2024

Published: 1 May 2024

DOI: https://doi.org/10.51200/bjms.v18i2.5064

Keywords: *health care, healthcare services utilisation, diagnosed, factors, rural population*

ABSTRACT

Malaysia has made significant strides in achieving universal health coverage since gaining independence. However, rural areas in Sabah still confront challenges in accessing adequate healthcare compared to Peninsula Malaysia. This study explores healthcare utilisation patterns among Sabah's rural populace, with a focus on identifying access determinants. Over four months, a household cross-sectional study interviewed 438 respondents, employing geographical units for random sample selection. The questionnaire used was adopted and pre-tested from the National Health and Morbidity Survey 2011 (Healthcare Demand Module). Descriptive statistics and logistic regression were utilised to analyse demographic characteristics and determinants of health utilisation among those reporting one or more diseases (n = 99). The findings underscored age and health limitations as significant predictors of healthcare usage. Despite commendable national health outcomes, resource allocation tends to favour secondary care over primary care in rural regions. Prioritising preventive care at the primary level could enhance overall health outcomes. Understanding healthcare utilisation in rural areas, especially those with heightened poverty rates, is crucial for refining tailored healthcare policies. This study fills a crucial gap in the literature, offering insights to shape effective healthcare interventions for underserved rural populations.

INTRODUCTION

Malaysia's healthcare system has undergone significant evolution since gaining independence, establishing universal health coverage as a cornerstone to ensure unimpeded access to essential services (Mohamad Noh, 2011). Remarkably, it has achieved greater success compared to many other countries in this regard (Rannan-Eliya et al., 2016). Despite overall health improvements nationwide, Sabah, a region with historical ties to British colonisation and now part of Malaysia, continues to face substantial health disparities. In 2018, Sabah reported the highest rates of infant mortality (10.1 per 1,000 live births), toddler mortality (0.6 per 1,000 population), and maternal mortality (18.9 per 100,000 live births) (Ministry of Health, 2021). Challenges also persist in controlling diseases such as tuberculosis and malaria (Goroh et al., 2020; Ministry of Health, 2021; Naserrudin et al., 2023), with a concerning rise in chronic diseases, including diabetes prevalence, hypercholesterolemia, and hypertension (Bakar et al., 2011, 2015).

Effectively delivering healthcare, especially in rural areas, is crucial for addressing both communicable and non-communicable diseases. Public health facilities in rural areas, heavily subsidised, offer accessible care to Malaysians at nominal fees or no cost. However, health access in East Malaysia, particularly in Sabah's rural areas, remains significantly lower than in Peninsula Malaysia (Atun et al., 2016).

The challenge of accessing healthcare due to lower socioeconomic status has significant implications for health outcomes (Nasirin & Lionardo, 2021), often compounded by the higher prevalence of risky behaviours like smoking and drinking (Pampel et al., 2010). In Sabah, where nearly one in five individuals (19.5%) lived below the poverty line in 2019 (Ministry of Economy, 2023), the prevalence of smoking is notably high, reaching 25.3% among individuals aged 15 years and above. Sabah also reports the highest proportion of binge drinkers among adults aged 18 years and older, with a rate of 74.8% (Institute for Public Health, 2019).

These statistics emphasise the importance of scrutinising healthcare utilisation patterns to assess disparities across diverse population characteristics. Madyaningrum et al. identified disparities in outpatient service utilisation in Indonesia, focusing on the correlation between health insurance and visits for economically vulnerable elderly individuals (Madyaningrum et al., 2018). However, there is still an unexplored focus on rural areas with high poverty rates. In South Korea, Ham and Lee found a positive association between lifestyle factors (alcohol consumption, tobacco use) and healthcare provider visits among newly diagnosed hypertensive individuals (Ham & Lee, 2007). Shifting to Malaysia, Anis-Syakira et al. (2022) explored the relationship between socioeconomic position and health service utilisation, specifically in the private health sector across diverse locations (Anis-Syakira et al., 2022).

Despite extensive research exploring healthcare utilisation and its predictors, there remains a notable gap in the literature, specifically in studying variables influencing healthcare usage among rural populations marked by elevated poverty rates. This study delves into the determinants shaping healthcare utilisation patterns among Sabah's rural populace, providing valuable insights for refining policy formulation and healthcare delivery to cater to the distinct needs of these regions. The originality of this research lies in its focused inquiry, which generates insights that transcend conventional national health evaluations.

MATERIALS AND METHODS

The household cross-sectional study, conducted over a period of four months, aimed to address economic challenges and a significant incidence of poverty in a rural area

of Sabah. By division, Nabawan has the highest incidence of poverty, which ranged from 50.8% to 70.8% in 2004 (Institute for Development Studies, 2007b). It is one of the seven interior divisions of Sabah, with a population estimated to be around 32,309 in 2020. Exclusive face-to-face interviews were administered to non-institutionalised residents who had resided in the area for a minimum of two weeks before data collection. Exclusions were applied to individuals in institutional settings, including hotels, hostels, and hospitals, to maintain consistency in the study population.

The determination of the sample size, with a precision of 5%, a confidence level of 95%, and a population variance of 33.2% (representing the population seeking healthcare advice or treatment in Sabah within the last 2 weeks based on Ministry of Health, (2015b), was achieved through a single percentage formula. Considering the finite population in Nabawan, totalling 32,309 (Department of Statistics Malaysia, 2022a), and factoring in a 20% non-response rate, the target sample size was set at 414 respondents. To identify respondents, the research areas were subdivided into Enumeration Blocks (EBs) based on geographical units designated by the National Statistics Department. Each EB comprised approximately 500 to 600 residents, with an average of 80 to 120 Living Quarters (LQs). Six EBs were randomly selected to acquire the necessary respondents from the LQs based on the estimated average of four household members (Aris et al., 2015).

The study employed a questionnaire adopted from the Health Care Demand Module of the 2011 version of the National Health and Morbidity Survey (NHMS), notable for its comprehensive nature compared to other NHMS surveys (Aris et al., 2011). This questionnaire is comprised of two sections. The first section investigated household characteristics, such as telecommunications connectivity, access to electricity, availability of treated water, and socioeconomic quintile, followed by an examination of each household member's sociodemographic profiles. Details regarding the development and validation of the questionnaire are provided in the NHMS technical report (Aris et al., 2011). Prior to conducting interviews, consent was obtained from all respondents as required by the Medical Research Ethics Committee, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah (JKEtika 4/17(2)). Written informed consent was obtained from all the study participants.

Interviews were conducted between February 23 and June 25, 2019, in the Malay language by the main author, with assistance from a locally hired translator when communication in other local languages was necessary. Data entry was facilitated using Epi Info version 7.2.2.6 as the database.

A total of 438 respondents were interviewed for the study, of whom 25.8% (99) reported being diagnosed with one or a combination of the ten health problems, including hypertension, asthma, malaria, diabetes, arthritis, heart disease, TB, stroke, dengue, and renal disease. These conditions were identified based on the NHMS 2011 questionnaire, with no new additions following a pre-test in Nabawan aimed at identifying other common health problems or diseases. Descriptive statistics were employed to illustrate overall healthcare service utilisation, presented as percentages with a 95% confidence interval, across the independent variables studied as indicated in Table 1.

The study analysed the factors associated with healthcare utilisation among the 99 individuals who reported being diagnosed with one or a combination of the ten health problems. Single and multiple logistic regression techniques were utilised. Variables with a significance level of $p<0.25$ in the single logistic regression were included in the preliminary final model, following the methodology outlined by Bursac et al., (2008).

Likelihood ratio tests were then conducted to identify the final variables, retaining those that demonstrated statistical significance in the final regression model. The results of the logistic regression were presented as crude and adjusted odds ratios, along with corresponding 95% confidence intervals.

Multicollinearity was assessed using the Variance Inflation Factor (VIF), and interactions between independent variables were scrutinized. Subsequently, the fitness of the model was evaluated using receiver operating characteristics (ROC) curve analysis, the Hosmer-Lemeshow test, and a classification table.

All analyses were performed using STATA (Stata Corp, College Station, Texas, USA) and a significant level of $p<0.05$ was considered statistically significant throughout the analysis process.

Table 1: Definition of variables.

Variable	Definition	Responses / classification
Sex	Reported gender of the household member	Male; Female
Age	Age group of the household member	18-54; 55-64; 65 and older
Married	Marital status	Yes; No (Single, Divorced, Separated)
Highest education	Highest level of education attained	No schooling; Primary; Secondary; Tertiary
Working	Currently employed or working	Yes (Employed, Self-employed); No (Not working)
Telecommunications connection	Connected to telecommunication lines that enable data, voice, or multimedia connectivity.	Yes; No
Supply of electricity	Connected to the main electricity supply system, including portable generators for home use.	Yes; No
Supply of treated water	Supply of treated water that has undergone a treatment process to make it safe and suitable for consumption and various other purposes. Untreated water sources include rivers, lakes, ponds, or wells that have not been subjected to filtration, disinfection, or other water treatment methods.	Yes; No
Socioeconomic quintile	Household living standards are adjusted using the adult equivalent.	Quintile 1 (Poorest); Quintile 2; Quintile 3; Quintile 4; Quintile 5 (Richest)

Table 1: Definition of variables (continue).

Variable	Definition	Responses / classification
Experienced barrier to health service	Factors that prevent people from acquiring access to health services.	Ill & sought treatment; Ill & did not seek treatment; Did not need health treatment
Self-determination	Ability and right to make their own choices and decisions regarding their healthcare, treatment, and overall well-being.	Yes; No
Reported health status as "good"	Measures present general health and gives answer choices on a Likert Scale.	Yes (Very good, Good) ; No (Moderate, Not good, Very Bad)
Reported to experienced activity limitation	Measures perceived activity limitations of their health condition and gives answer choices on a Likert Scale.	Yes (Severe/unable to perform; Moderate/mild); No (None)
Health services	Utilisation of outpatient care in the last 2 weeks or inpatient care in the last 12 months.	Yes; No

The study analysed the factors associated with healthcare utilisation among the 99 individuals who reported being diagnosed with one or a combination of the ten health problems. Single and multiple logistic regression techniques were utilised. Variables with a significance level of $p<0.25$ in the single logistic regression were included in the preliminary final model, following the methodology outlined by Bursac et al., (2008). Likelihood ratio tests were then conducted to identify the final variables, retaining those that demonstrated statistical significance in the final regression model. The results of the logistic regression were presented as crude and adjusted odds ratios, along with corresponding 95% confidence intervals.

Multicollinearity was assessed using the Variance Inflation Factor (VIF), and interactions between independent variables were scrutinized. Subsequently, the fitness of the model was evaluated using receiver operating characteristics (ROC) curve analysis, the Hosmer-Lemeshow test, and a classification table.

All analyses were performed using STATA (Stata Corp, College Station, Texas, USA) and a significant level of $p<0.05$ was considered statistically significant throughout the analysis process.

RESULTS

A total of 99 respondents (22.6%) who reported ever having been diagnosed with one or more diseases were included in the analysis, and Table 2 presents a detailed overview of the households and members sociodemographic characteristics. The characteristics that were derived from households' questionnaires, reveal a higher proportion of them with telecommunication connectivity, with 86.9% (86) reporting access. The demographic profile shows a nearly equal gender distribution, with 55.6% (55) identifying as female and 44.4% (44) as male. Age distribution is uniform, with the "18–54" age group representing the largest proportion at 50.5% (55) and 87.9% (87) reported being married. A substantial portion of participants (70, 70.7%) were employed. Moreover, a noteworthy 94.9% (94) indicate access to electricity. However,

45.5% (45) of respondents mention a lack of access to treated water. The distribution across socioeconomic categories demonstrates a relatively balanced representation, with approximately 26.3% (26) categorised as belonging to the "poorest" group. The study underscores a prevailing sense of personal autonomy in health decision-making, with 67.7% (67) expressing their independence in health-related choices. Interestingly, a significant majority (85, 85.9%) report no obstacles to accessing healthcare services. Despite 75.8% (75) indicating a positive self-perceived health state, a significant minority (64, 64.6%) reports encountering restrictions in daily activities.

Table 2: Characteristics of respondents.

Characteristics	Frequency	%
Sex		
Female	55	55.6
Male	44	44.4
Age		
18-54	50	50.5
55-64	26	26.3
65+	23	23.2
Married		
No	12	12.1
Yes	87	87.9
Highest education		
No Schooling	23	23.2
Primary	43	43.4
Secondary	25	25.3
Tertiary	8	8.1
Working		
No	29	29.3
Yes	70	70.7
Telecommunication connection		
No	13	13.1
Yes	86	86.9
Supply of electricity including generators		
No	5	5.1
Yes	94	94.9
Supply of treated water		
No	54	54.5
Yes	45	45.5
Socioeconomic level		
Poorest	26	26.3
2	19	19.2
3	14	14.1
4	19	19.2
Richest	21	21.2
Self-decision		
No	67	67.7
Yes	32	32.3
Experienced barrier to health service		
No	85	85.9
Yes	14	14.1
Reported health status as "good"		
No	24	24.2
Yes	75	75.8
Reported to experienced activity limitation		
No	35	35.4
Yes	64	64.6

In the subset of individuals with a medical condition, 39.4% (39) had recently utilised healthcare services. As indicated in Table 3, a notable 89.7% (35) of this subgroup report telecommunication connectivity, and an overwhelming 92.3% (36) have access to electricity. However, 53.8% (21) face challenges in obtaining treated water. Socioeconomic disparities persist, with 33.3% (13) classified as the "poorest." A substantial 69.2% (27) of individuals make autonomous health decisions, and all respondents report no hindrances to accessing healthcare services, ensuring unimpeded healthcare access. Gender distribution remains balanced, and age distribution encompasses individuals aged 18 to 54 (13, 33.3%), 55 to 64 (16, 41.0%), and 65 and older (10, 25.6%). A significant majority (36, 92.3%) of those utilising healthcare services are married. Educational levels vary, with 56.4% (22) completing primary school, 28.2% (11) having no formal education, 12.8% (5) completing secondary school, and

2.6% (1) completing higher education. For employment, 64.1% (25) are working. While 64.1% (25) perceive their health as "good," a notable 79.5% (31) acknowledge activity limitations.

Table 3 shows the results of the logistic regression analysis for healthcare utilisation. Only age, reported health status as good, and reported activity limitation were statistically significant in the bivariate analysis. In the final model, age and health limitations were retained as key predictors. Individuals aged between 55 and 64 exhibited a fourfold increase in the likelihood (AOR =4.328, 95% CI = 1.527–12.269) of utilising health services compared to those in the 18–54 age bracket. For health limitations, individuals reporting such limitations were three times more likely (AOR = 2.982, 95% CI = 1.121–7.937) to utilise healthcare services compared to those without reported health limitations. These findings underscore the significance of age and health limitations as influential factors in predicting healthcare service utilisation within the examined population.

DISCUSSION

Despite Malaysia's relatively modest health spending at four percent of GDP, the health system demonstrates commendable outcomes compared to countries of similar economic standing, such as Brazil, Chile, Estonia, Mexico, and Turkey (Atun et al., 2016; OECD Stat, 2023). However, a concerning issue arises with allocative efficiency, reflecting the optimal allocation of resources within the health system for the best possible outcomes (Atun et al., 2016). A noticeable trend reveals an imbalanced distribution of resources favouring secondary and tertiary healthcare facilities over primary care, resulting in higher costs and suboptimal health outcomes, particularly in rural areas like Nabawan. The prioritisation of curative treatments at the hospital level neglecting preventive and promotive care at the primary level signifies a significant allocative inefficiency, especially in managing Non-Communicable Diseases (NCDs).

In Nabawan, a predominantly rural area, public health facilities play a crucial role in meeting the healthcare needs of the population (Department of Statistics Malaysia, 2022b). However, geographical remoteness and transportation difficulties pose hindrances for those seeking medical assistance. Despite heavy subsidisation of public health services in Malaysia, accessing healthcare remains challenging for rural populations, with notable disparities in resource allocation between primary and secondary healthcare facilities.

The demographic profile of Nabawan suggests a propensity among the elderly and individuals with substantial activity limitations to seek healthcare services. However, the provision of care often lacks emphasis on preventive and promotional strategies. This oversight has significant ramifications, potentially undermining timely interventions among younger demographics with fewer activity limitations. Neglecting preventive measures risks exacerbating complications later in life, increasing the burden on both individuals and the healthcare system.

According to the study, socioeconomic factors did not affect the use of health services. Only those aged 18–64 who reported experiencing activity limitations have higher odds of using health services. Older adults have a greater propensity to seek medical attention for chronic ailments or consultations before and after surgical procedures. However, compared to younger individuals, they display a lower likelihood of pursuing preventative healthcare measures (Hing et al., 2006). Most research reported significant correlations between age and the use of healthcare services (Ani et al., 2008; Blackwell et al., 2009; Nabalamba & Millar, 2007; Stockdale et al., 2007). Nevertheless, the direction of this association varied significantly depending on individuals' traits. For instance, it was discovered that older individuals were

less likely than younger individuals to utilise alcohol, drug, and mental health services (Stockdale et al., 2007). According to other research, older individuals had lower odds of seeing a specialist (Nabalamba & Millar, 2007). A study in the US between ethnic groups showed African-Americans and Latinos older respondents were more likely than their younger counterparts to report having received a doctor's diagnosis for their medical concerns (Ani et al., 2008). The findings among the rural population, with those aged 55 to 64 having a greater likelihood of using healthcare services, could imply that these populations only seek care when experiencing symptoms and rarely for screening or preventive services.

Comparison with other countries, such as Jordan, highlights potential opportunities for a more focused distribution of resources based on health concerns and socioeconomic factors (Rawabdeh & Rawabdeh, 2021). The reallocation of resources towards preventive and promotive care at the primary level holds promise for improving overall health outcomes, particularly in rural regions like Sabah.

Public health services are heavily subsidised in Malaysia, and it is not surprising to observe a need factor such as "activity limitation" determining the use of healthcare services rather than socioeconomic factors. The need-related factor has been closely associated with the use of health services (Newbold et al., 1995). For example, the study by Bennett et al. in the United States showed that activity limitation affects the association between the use of health care services among older adults (Bennett et al., 2009). Similarly, in the study by Heyden et al., in Belgium, a higher utilisation rate among lower socioeconomic groups is due to differences in need (Heyden et al., 2003). Several studies have concluded that self-rated activity limitation acts in tandem with health literacy (Bennett et al., 2009; Reisi et al., 2014; Sørensen et al., 2012).

The Institute for Public Health highlights Sabah's notably high incidence of low health literacy among individuals aged 18 years and older, particularly prevalent in areas with limited educational opportunities or lower income levels (Institute for Public Health, 2019). This lack of health literacy may lead to a diminished understanding of the importance of health services and their potential benefits. Sørensen et al. define health literacy as proficiency in obtaining, comprehending, evaluating, and using health-related information for healthcare, illness prevention, and health promotion (Sørensen et al., 2012). Education and health education are primary contributors to health literacy development.

Advancements in technology have paved the way for enhancing health literacy, notably through eHealth literacy. However, persistent disparities exist in the correlation between self-rated activity limitations and eHealth literacy, potentially attributed to reliance on the health system. Bundorf et al. suggest that internet searches for health information are influenced by factors such as out-of-pocket expenses and opportunity costs, which vary across health systems and could clarify conflicting findings (Bundorf et al., 2006). Moreover, while eHealth literacy significantly contributes to improving health literacy, addressing this among individuals with limited education, unemployment, the elderly, and low-income populations present challenges. A recent study by Qing Liang Goh et al. observed a significant impact on the health literacy of adults with chronic illnesses seeking medical care in Sabah's public health facilities due to the possession of smartphones or laptops (Qing Liang Goh et al., 2022). Moreover, the study found connections between low health literacy and several demographic factors, including older age, lower educational attainment, reduced household income, and lack of insurance coverage. Notably, access to smartphones or computers was shown to notably improve patient health literacy.

Fostering gains in health literacy and promoting informed use of health services pose challenges, particularly among individuals with no formal education, the unemployed, the elderly, and those with low income. In Nabawan, individuals aged 55 to 64 exhibit a notably higher likelihood of utilising healthcare services compared to those aged 65 and older. A study by Liang et al. among adult patients with chronic diseases in Sabah's public health facilities revealed that low health literacy correlated with older age, lower educational levels, reduced household income, and lack of insurance ownership (Liang et al., 2021).

Karim's study in a similar community, aiming to explore their access to health information, found a preference for interactive health talks with healthcare personnel (Karim, 2020). However, inadequate, or uneven distribution of resources allocated to preventive and promotive care at the primary level could impede timely access to appropriate healthcare. Discrepancies, particularly in service quality, often lead to a growing trend where patients seek alternative sources to fulfil their healthcare needs, even at a higher financial cost. This bypassing behaviour, wherein patients directly seek higher-level healthcare facilities without consulting primary care providers for non-critical diseases, results in increased medical costs, compromised care quality, and potential treatment delays (Gotsadze et al., 2005; Pollack et al., 2015). Globally, various factors contribute to this phenomenon, including demographic and socioeconomic factors, provider characteristics, geographic accessibility, service quality, cost considerations, insurance coverage, and drug availability (Xie et al., 2023).

CONCLUSION

Investing in the healthcare system should go beyond infrastructure improvements. It's crucial to promote effective health behaviours and appropriate utilisation patterns, especially among demographics like older individuals and those with activity limitations, as seen in Nabawan. A comprehensive approach, addressing both supply and demand aspects, is essential to meet the needs of rural populations, particularly those facing pre-existing health conditions. This comprehensive strategy involves providing accessible information, enhancing health literacy, and implementing tailored educational initiatives to foster effective demand.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ACKNOWLEDGEMENTS

All authors would like to acknowledge all the village heads and participants for their support and cooperation throughout the data collection.

FUNDING

This study was funded under the Postgraduate Research Grant (UMSGreat) [Project code: GUG0180 – 2/2017].

REFERENCES

Ani, C., Bazargan, M., Bazargan-Hejazi, S., Andersen, R. M., Hindman, D. W. & Baker, R. S. (2008). Correlates of self-diagnosis of chronic medical and mental health conditions in under-served African American and Latino populations. Ethnicity & Disease, 18(2 Suppl 2), S2-105–111.

Anis-Syakira, J., Jawahir, S., Abu Bakar, N. S., Mohd Noh, S. N., Jamalul-Lail, N. I., Hamidi, N.

Table 3: Logistic regression analysis for healthcare utilisation.

Variables	Health services utilisation		Crude			Adjusted		
	Frequency	%	OR	(95% CI)	P-value	OR	(95% CI)	P-value
Sex					**0.491**			
Female	20	51.3	0.752	(0.335-1.692)				
Male (ref)	19	48.7						
Age					**0.010**			
18-54 (ref)	13	33.3						
55-64	16	41.0	4.554	(1.656-12.525)		4.328	(1.527-12.269)	0.006
65+	10	25.6	2.19	(0.775-6.187)		1.804	(0.619-5.266)	0.28
Married					**0.264**			
No	3	7.7	0.473	(0.12-1.867)				
Yes (ref)	36	92.3						
Highest education					**0.489**			
No Schooling	11	28.2	0.875	(0.318-2.411)				
Primary (ref)	22	56.4						
Secondary	5	12.8	0.239	(0.076-0.753)				
Tertiary	1	2.6	0.137	(0.016-1.206)				
Working					**0.247**			
No	14	35.9	1.68	(0.699-4.04)				
Yes (ref)	25	64.1						
Telecommunication connection					**0.489**			
No	4	10.3	0.648	(0.185-2.27)				
Yes (ref)	35	89.7						
Supply of electricity including generators					**0.340**			
No	3	7.7	2.417	(0.386-15.17)				
Yes (ref)	36	92.3						
Supply of treated water					**0.176**			
No	18	46.2						
Yes	21	53.8	1.75	(0.776-3.951)				
Socioeconomic level					**0.472**			
Poorest (ref)	13	33.3						
2	9	23.1	0.9	(0.276-2.941)				
3	4	10.3	0.4	(0.1-1.608)				
4	7	17.9	0.584	(0.175-1.953)				
Richest	6	15.4	0.4	(0.119-1.355)				
Self-decision					**0.790**			
No	27	69.2	1.125	(0.474-2.676)				
Yes (ref)	12	30.8						
Experienced barrier to health service								
No	39	100.0						
Yes	0	0.0						
Reported health status as "good"					**0.031**			
No	14	35.9	2.8	(1.091-7.189)				
Yes (ref)	25	64.1						

Table 3: Logistic regression analysis for healthcare utilisation (Continue).

Variables	Health services utilisation		Crude			Adjusted		
	Frequency	%	OR	(95% CI)	P-value	OR	(95% CI)	P-value
Reported activity limitation					**0.011**			
No (ref)	8	20.5						
Yes	31	79.5	3.171	(1.253-8.027)		2.982	(1.121-7.937)	0.029

Notes: 1. R-square = 10.8%; Area under ROC curve = 70.1%; Hosmer-Lemeshow test, p-value = 0.916; classification table = 68.69%.

2. ref: reference group; OR: odds ratio; CI: confidence interval.

& Sararaks, S. (2022). Factors Affecting the Use of Private Outpatient Services among the Adult Population in Malaysia. International Journal of Environmental Research and Public Health, 19(20). https://doi.org/10.3390/ijerph192013663

Aris, T., Ahmad, N. A., Yusoff, M. F. M., Omar, M. A., Zainuddin, A. A., Selamat, R., Dan, R. M., Khoon, L. Y., Hashim, M. H., Naidu, B. M. & Kamaludin, F. (2011). National Health and Morbidity Survey 2011 (NHMS 2011). Volume 1: Methodology and General Findings (Vol. 1).

Aris, T., Yusoff, M. F. M., Ghani, A. A. A., Hamid, H. A. A., Omar, M. A., Ahmad, N. A., Wong, N. I., Naidu, B. M., Saari, R., Ismail, H., Yeop, N., Zaki, N. A. M., Kassim, N. M., Hashim, M. H., Kay, L. K., Ying, C. Y. & Baharudin, A. (2015). National Health & Morbidity Survey 2015 (NHMS 2015). Volume 1 (Methodology & General Findings) (Vol. 1, Issue 9).

Atun, R., Berman, P., Hsiao, W., Myers, E., Yap, W. A., Subramaniam, S., Abdullah, N. H. & Murad, S. (2016). Malaysia Health Systems Research. Contextual Analysis of the Malaysian Health System. https://www.moh.gov.my/moh/resources/Vol_1_MHSR_Contextual_Analysis_2016.pdf

Bakar, A. K. A., Ghani, A. A. A., Rahman, A. B., Zainuddin, A. A., Jai, A. N., Chandran, A., Razali, A., Baharudin, A., Rosman, A., Naidu, B. M., Ying, C. Y., Jeevenathan, C., Man, C. S., Eugene, C., Paiwai, F., Ismail, F., Othman, F., Mustapha, F. I., Subbarao, G. R. a/l, … Zaini, Z. (2015). National Health & Morbidity Survey 2015 (NHMS 2015). Volume 2 (Non-communicable Diseases, Risk Factors & Other Health Problems).

Bakar, A. K. A., Zainuddin, A. A., Teng, A. K., Awaludin, A., Baharuddin, A., Mahadir, B., Ying, C. Y., Salim, F., Mohamed, F., Mustapha, F. I., Mukhtar, F., Kaur, G., Hamid, H. A. A., Hiong, H. T. G., Haniff, J., Rahman, J. A., Kaur, J., Musa, K. I., Cheong, K. C., … Mohamud, W. N. W. (2011). National Health and Morbidity Survey 2011 (NHMS 2011). Volume 2: Non-communicable Disease (G. Kaur, J. Kaur, N. Odhayakumar, N. Yoep, F. Kamaludin, H. T. G. Hiong, H. Shariff, M. I. Hairon, N. Muhammad, N. A. Ahmad, & T. Aris (Eds.)).

Bennett, I. M., Chen, J., Soroui, J. S. & White, S. (2009). The contribution of health literacy to disparities in self-rated health status and preventive health behaviors in older adults. Annals of Family Medicine, 7(3), 204–211. https://doi.org/10.1370/afm.940

Blackwell, D. L., Martinez, M. E., Gentleman, J. F., Sanmartin, C. & Berthelot, J.-M. (2009). Socioeconomic status and utilization of health care services in Canada and the United States: findings from a binational health survey. Medical Care, 47(11), 1136–1146. https://doi.org/10.1097/MLR.0b013e3181adcbe9

Bundorf, M. K., Wagner, T. H., Singer, S. J. & Baker, L. C. (2006). Who searches the internet for health information? Health Services Research, 41(3 Pt 1), 819–836. https://doi.org/10.1111/j.1475-6773.2006.00510.x

Bursac, Z., Gauss, C. H., Williams, D. K. & Hosmer, D. W. (2008). Purposeful selection of variables in logistic regression. Source Code for Biology and Medicine, 3(1), 17. https://doi.org/10.1186/1751-0473-3-17

Department of Statistics Malaysia. (2022a). Key findings population and housing census of Malaysia 2020. Administration District. Department of Statistics, Malaysia. https://newss.statistics.gov.my/newss-portalx/ep/epFreeDownloadContentSearch.seam?contentId=168491&actionMethod=ep%2FepFreeDownloadContentSearch.xhtml%3AcontentAction.doDisplayContent&cid=334754

Department of Statistics Malaysia, D. (2022b). Key findings population and housing census of Malaysia 2020: Administrative district. https://newss.statistics.gov.my/newss-portalx/ep/epFreeDownloadContentSearch.seam?contentId=168491&actionMe

thod=ep%2FepFreeDownloadContentSearch.xhtml%3AcontentAction.doDisplayContent&cid=334754

Goroh, M. M. D., Rajahram, G. S., Avoi, R., Van Den Boogaard, C. H. A., William, T., Ralph, A. P. & Lowbridge, C. (2020). Epidemiology of tuberculosis in Sabah, Malaysia, 2012-2018. Infectious Diseases of Poverty, 9(1), 1–11. https://doi.org/10.1186/s40249-020-00739-7

Gotsadze, G., Bennett, S., Ranson, K. & Gzirishvili, D. (2005). Health care-seeking behaviour and out-of-pocket payments in Tbilisi, Georgia. Health Policy and Planning, 20(4), 232–242. https://doi.org/10.1093/heapol/czi029

Ham, O. K. & Lee, C. Y. (2007). Predictors of Health Services Utilization by Hypertensive Patients in South Korea. J Family Community Med, 24(6), 518–528. https://doi.org/10.1111/j.1525-1446.2007.00664.x

Heyden, J. H. A. Van Der, Demarest, S., Tafforeau, J. & Oyen, H. Van. (2003). Socio-economic differences in the utilisation of health services in Belgium. 65, 153–165. https://doi.org/10.1016/S0168-8510(02)00213-0

Hing, E., Cherry, D. K. & Woodwell, D. A. (2006). National Ambulatory Medical Care Survey: 2004 summary. Advance Data, 374, 1–33.

Institute for Public Health, I. (2019). National Health and Morbidity Survey 2019 (NHMS 2019): Volume 3 (Non-Communicable Diseases: Risk Factors and other Health Problems) (Vol. 1). http://www.iku.gov.my/nhms-2019

Karim, H. A. (2020). Health literacy among rural communities: Issues of accessibility to information and media literacy. J Komun Malaysian J Commun, 36(1), 248–262.

Liang, G. Q., Ling, T. S., Fiona, F. P. W., How, Y. C. & Yen, L. S. (2021). Health Literacy among Adult Patients with Chronic Diseases in Sabah. Zenodo. https://doi.org/10.5281/zenodo.5357359

Madyaningrum, E., Chuang, Y. C. & Chuang, K. Y. (2018). Factors associated with the use of outpatient services among the elderly in Indonesia. BMC Health Services Research, 18(1), 707. https://doi.org/10.1186/s12913-018-3512-0

Ministry of Economy, M. (2023). Incidence of Poverty by Ethnic Group, Strata and State, Malaysia, 1970-2019. Household Income, Poverty and Household Expenditure. Ministry of Economy (MOE). https://www.ekonomi.gov.my/en/socio-economic-statistics/household-income-poverty-and-household-expenditure

Ministry of Health, M. (2015). National Health & Morbidity Survey 2015 (NHMS 2015). Volume 3 (Healthcare Demand) (Vol. 3). https://doi.org/10.4324/9781315649382-15

Ministry of Health, M. (2021). Health Indicators 2021. https://www.moh.gov.my/moh/resources/Penerbitan/Penerbitan Utama/HEALTH INDICATOR/Petunjuk_Kesihatan_2021.pdf

Mohamad Noh, K. (2011). Primary Health Care Reform in 1CARE for 1Malaysia. International Journal of Public Health Research, 50–56. http://journalarticle.ukm.my/3352/1/special%2520issue%25202011_8.pdf

Nabalamba, A. & Millar, W. J. (2007). Going to the doctor. Health Reports, 18(1), 23–35.

Naserrudin, N. A., Lin, P. Y. P., Monroe, A., Culleton, R., Baumann, S. E., Sato, S., Adhikari, B., Fornace, K. M., Hod, R., Jeffree, M. S., Ahmed, K. & Hassan, M. R. (2023). Exploring barriers to and facilitators of malaria prevention practices: a photovoice study with rural communities at risk to Plasmodium knowlesi malaria in Sabah, Malaysia. BMC Public Health, 23(1), 1316. https://doi.org/10.1186/s12889-023-16173-x

Nasirin, C. & Lionardo, A. (2021). Administering the inclusiveness of neglected low-income urban families to access healthcare services: A qualitative inquiry. Universal Journal of Public Health, 9(5), 263–267. https://doi.org/10.13189/ujph.2021.090508

Newbold, K. B., Eyles, J. & Birch, S. (1995). Equity in health care: methodological contributions to the analysis of hospital utilization within Canada. Social Science & Medicine (1982), 40(9), 1181–1192. https://doi.org/10.1016/0277-9536(94)00229-m

OECD Stat. (2023). https://data.oecd.org/

Pampel, F. C., Krueger, P. M. & Denney, J. T. (2010). Socioeconomic Disparities in Health Behaviors. Annual Review of Sociology, 36, 349–370. https://doi.org/10.1146/annurev.soc.012809.102529

Pollack, C. E., Rastegar, A., Keating, N. L., Adams, J. L., Pisu, M. & Kahn, K. L. (2015). Is Self-Referral Associated with Higher Quality Care? Health Services Research, 50(5), 1472–1490. https://doi.org/10.1111/1475-6773.12289

Qing Liang Goh, Sze Ling Tan, Pui Wun Fiona Fong, Chia How Yen & Siow Yen Liau. (2022). Health Literacy Among Adult Patients with Chronic Diseases in Sabah. Borneo Journal of Medical Sciences (BJMS), 16(3 SE-Original articles), 33 – 42. https://jurcon.ums.edu.my/ojums/index.php/bjms/article/view/3675

Rannan-Eliya, R. P., Anuranga, C., Manual, A.,

Sararaks, S., Jailani, A. S., Hamid, A. J., Razif, I. M., Tan, E. H. & Darzi, A. (2016). Improving health care coverage, equity, and financial protection through a hybrid system: Malaysia's experience. Health Affairs, 35(5), 838–846. https://doi.org/10.1377/hlthaff.2015.0863

Rawabdeh, A. & Rawabdeh, A. A. A. (2021). Presenting a typology of efficiency and their plausible measurement into healthcare systems: A global view. Universal Journal of Public Health, 9(5), 276–286. https://doi.org/10.13189/ujph.2021.090510

Reisi, M., Javadzade, S. H., Heydarabadi, A. B., Mostafavi, F., Tavassoli, E. & Sharifirad, G. (2014). The relationship between functional health literacy and health promoting behaviors among older adults. Journal of Education and Health Promotion, 3, 119. https://doi.org/10.4103/2277-9531.145925

Sørensen, K., Van den Broucke, S., Fullam, J., Doyle, G., Pelikan, J., Slonska, Z., Brand, H. & European, (HLS-EU) Consortium Health Literacy Project. (2012). Health literacy and public health: A systematic review and integration of definitions and models. BMC Public Health, 12(1), 80. https://doi.org/10.1186/1471-2458-12-80

Stockdale, S. E., Tang, L., Zhang, L., Belin, T. R. & Wells, K. B. (2007). The effects of health sector market factors and vulnerable group membership on access to alcohol, drug, and mental health care. Health Services Research, 42(3 Pt 1), 1020–1041. https://doi.org/10.1111/j.1475-6773.2006.00636.x

Xie, W., Liu, J., Huang, Y. & Xi, X. (2023). Capturing What Matters with Patients' Bypass Behavior? Evidence from a Cross-Sectional Study in

BJMS
Borneo Journal of Medical Sciences

REVIEW ARTICLE

Sodium Hypochlorite Irrigation Extrusion in Root Canal Treatment: An Updated Overview

Nur Farhana Wan*, Nurul Ain Ramlan, Noorharliana Mohamed Zohdi

Centre of Comprehensive Care Studies, Faculty of Dentistry, University Teknologi MARA, 47000 Sungai Buloh, Selangor, Malaysia

*Corresponding author's email: wannurfarhana@uitm.edu.my

Received: 13 September 2023

Accepted: 25 January 2024

Published: 1 May 2024

DOI: https://doi.org/10.51200/bjms.v18i2.5065

Keywords: *clinical manifestation, irrigation extrusion, risk factors, root canal, Sodium Hypochlorite accident*

ABSTRACT

Effective endodontic treatment requires the proper choice of instruments and irrigation techniques in chemo-mechanical preparation. Sodium hypochlorite (NaOCl) is the most employed irrigant in endodontic practice, known for its efficiency in disinfecting the root canal system and dissolving organic debris. However, its cytotoxicity poses a drawback, potentially causing acute harm when extruded beyond the apex, a situation referred to as a NaOCl accident. While this occurrence is rare globally, NaOCl extrusion during root canal therapy can lead to severe aftereffects in addition to acute symptoms like pain and swelling. This review paper aims to guide dental clinicians in the early detection and diagnosis of NaOCl accidents, providing appropriate management strategies. The discussion encompasses the prevalence, risk factors, management, complications, and prognosis of NaOCl extrusion beyond the root apex. Recommendations and preventive measures for safely using sodium hypochlorite irrigation during endodontic therapy are also highlighted to ensure better management of hypochlorite accident symptomatology.

INTRODUCTION

Sodium hypochlorite (NaOCl) is the most commonly utilised irrigating solution in endodontic procedures, typically found in concentrations ranging from 0.5 to 5.25%

(Baumgartner & Cuenin, 1992). Its ability to dissolve tissue and its antibacterial properties have made it the preferred choice for cleaning root canals in endodontic therapy (Zehnder, 2006). These attributes allow for effective disinfection when used within the root canal, and no other solution has demonstrated the same level of effectiveness as NaOCl. However, it is essential to note that its cytotoxicity is a well-recognized concern that can result in acute harm if it reaches the periapical area (Guivarc'h et al., 2017). When NaOCl comes into contact with vital tissues, it induces oxidation of the surrounding tissues, leading to rapid hemolysis, ulceration, inhibition of neutrophil migration, and damage to endothelial and fibroblast cells (Pashley et al., 1985).

Wearing the proper personal safety equipment, using a fitted rubber dam, and using high-power suction are preventive methods (Clarkson & Moule, 1998). These precautions help to avoid skin and eye damage, as well as prevention from ingestion and aspiration. The Health Protection Agency Compendium of Chemical Hazards provides management for these injuries. Nevertheless, there remains a potential for the inadvertent release of sodium hypochlorite (NaOCl) into the periapical and soft tissues during root canal therapy.

The extrusion of NaOCl during root canal therapy (RCT) is known as a "hypochlorite accident," and it causes sudden severe symptoms as well as the possibility of catastrophic consequences (Farook et al., 2014). The prevalence of such incidents is uncertain because they are not regularly reported and cannot be diagnosed retrospectively (Guivarc'h et al., 2017). With several randomised control trials conducted worldwide, it is a relatively infrequent event. However, the research found that nearly half of the endodontic practitioners report experiencing at least one NaOCl accident during their work (Kleier et al., 2008).

The intricate anatomy of the head and neck region makes numerous vital structures susceptible to NaOCl accident injuries (Farook et al., 2014). Therefore, general dentists and endodontists need to be well-versed in the risk factors and the management of patients with NaOCl extrusion injuries.

REVIEW

Sodium hypochlorite irrigants

Sodium hypochlorite is an alkaline irrigant with a pH of 11-12. In water, NaOCl ionises to form Na+ and the hypochlorite ion, OCl, which are in equilibrium with hypochlorous acid (HOCl). Chlorine predominates as OCl at high pH levels of 9 and above, while HOCl predominates at acidic and neutral pH levels (McDonnell & Russell, 1999). The antibacterial activity is caused by hypochlorous acid; the OCl ion is less potent than the undissolved HOCl. Hypochlorous acid interferes with several of the microbial cell's vital functions, leading to cell death (McKenna & Davies, 1988). It is a potent agent with effectiveness against many bacteria and can dissolve both living and dead tissue (Senia et al., 1975).

The solution concentration affects NaOCl's capability to dissolve tissue, antibacterial effectiveness, and cytotoxicity. The more concentrated the solution, the more toxic it is to cells (Pashley et al., 1985). More significant cytotoxicity was seen with 5.25% NaOCl solutions than 0.5% or 1% NaOCl solutions (Pashley et al., 1985). However, the irrigant's concentration is still up for debate and is still controversial; many authors suggest using sodium hypochlorite at a concentration of 5.25%, whereas others prefer a lower concentration of 3% or even 0.5% (Harrison, 1984). Due to its toxic impact on living tissues, sodium hypochlorite can lead to adverse effects such as hemolysis, skin ulceration, and necrosis. Therefore, it is crucial to exercise caution to prevent the extrusion of NaOCl beyond the root apex (Pashley et al., 1985). For this reason, (Hauman & Love, 2003) recommended utilising larger quantities of low-concentration sodium hypochlorite

(e.g., 0.5–1%) instead of employing highly concentrated solutions (5.25%).

Types of sodium hypochlorite accident

While many studies have commonly referred to the extrusion of sodium hypochlorite (NaOCl) beyond the apex as a "hypochlorite accident" (Guivarc'h et al., 2017), it is essential to note that various other mishaps during root canal irrigation have been documented in the dental literature. According to Hulsmann et al. (2007), these incidents can include damage to the patient's clothing, splashing of the irrigant into the patient's or operator's eye, accidental ingestion of irrigants, extrusion beyond the apex, air emphysema, allergic reactions to the irrigant, and unintentional use of an irrigant as an anaesthetic solution.

Additionally, it is worth mentioning that Zhu et al. (2013) categorised sodium hypochlorite (NaOCl) extrusion accidents into three distinct types. These categories encompass careless iatrogenic injections, such as unintentionally administering NaOCl as a local anaesthetic, the extrusion of NaOCl into the maxillary sinus, and the extrusion or infusion of NaOCl beyond the root apex into the periradicular regions.

Prevalence and incidence of sodium hypochlorite accident

According to a study by Kleier et al. (2008), female patients with a clinical history of pulp necrosis and periapical radiolucency were found to be at a significantly higher risk of experiencing accidents involving maxillary premolar and molar teeth. The study's findings indicated that such accidents occurred more frequently in the maxillary region (accounting for 73% of cases, or n=122) than in the mandibular region (21%, or n=35). Furthermore, these accidents predominantly occurred in the molar or premolar areas (70%, or n=107) compared to the incisor or canine regions (30%, or n=46). When considering the gender of the patients, accidents were more commonly reported among females (69%, or n=99) than males (31%, or n=44). These results align with a recent systematic review by Guivarc'h et al. (2017), which found that sodium hypochlorite (NaOCl) accidents were most frequently observed in females and maxillary teeth.

Aetiology and risk factors of sodium hypochlorite accident

Factors such as open apices, either iatrogenic or anatomic (Becker et al., 1974), undiagnosed perforation (Reeh & Messer, 1989), needle wedging (Balto & Al-nazhan, 2002), and close approximation with surrounding structures such as antral tooth (Becking, 1991) may increase the risk of NaOCl extrusion.

It is crucial to adhere to the apical constriction during the root canal system's apical preparation. The breakdown of apical constriction in situations when this has been over-prepared will elevate the possibility of hypochlorite extrusion (Spencer et al., 2007). A larger apical foramen may also result from root resorption (Hülsmann & Hahn, 2000). It has been observed in NaOCl accidents that the reactions become more severe when NaOCl concentrations are increased (Kleier et al., 2008). This has led to the debate about the ideal concentration of NaOCl.

The precise positioning of teeth about the alveolar bone is of utmost importance, particularly when the root apex might be shielded by thin bone or soft tissue (de Sermeño et al., 2009). In such instances, even a tiny amount of irrigant extrusion can result in symptoms that have the potential to propagate. Compared to men, the lower bone density in women and the thinness of the cortical bone covering the buccal roots of maxillary teeth could explain why NaOCl may extend into nearby soft tissues (Kleier et al., 2008). An explanation for the potential extrusion of NaOCl into the maxillary sinus was provided by Hauman and Love (2003) in their review, where they mentioned that the alveolar bone tends to become thinner with

age, particularly around the tooth apices.

Besides that, the high flow rate of irrigant, needle depth insertion, apical fenestration, horizontal root fracture, and presence of periapical lesion may also contribute to the risk of NaOCL accident (Boutsioukis et al., 2013).

Until now, most clinical case documentation has been unsystematic, with specific important details omitted (Guivarc'h et al., 2017). This finding is by the study done by Boutsioukis et al. (2013), who reviewed the factors influencing NaOCl extrusion during RCT, and they concluded that the available literature did not allow for the establishment of conclusive findings but instead led to speculation about the risk factors.

Complications

Allowing sodium hypochlorite to settle on vital tissues can lead to a chemical burn. Short exposure may trigger a minimal inflammatory response. In contrast, prolonged exposure or using a higher concentration solution can result in a more significant inflammatory reaction, ultimately causing necrosis in the affected tissue.

Typical clinical manifestation of sodium hypochlorite accident (Hülsmann & Hahn, 2000; Phillip et al., 2022; Spencer et al., 2007):

i. Sever, sudden pain with a burning sensation.
ii. Rapid swelling of nearby soft tissues, with the possibility of spreading to the upper lip, infraorbital region, and bruising on the side of the face.
iii. Continuous bleeding from the root canal
iv. Profound internal bleeding leading to skin and mucosal haemorrhaging (ecchymosis)
v. A taste resembling chlorine and discomfort in the throat after injecting into the maxillary sinus.
vi. Risk of subsequent infection.
vii. The possibility for reversible anaesthesia or paraesthesia.

Sequelae of symptomatology by Khandelwal & Ajitha (2020):

i. Patients present with sudden, intense pain and swelling.
ii. Swelling typically begins minutes to hours after the incident and can be extensive, spreading within and outside the affected tooth area. In some cases, it may even hinder the ability to open the eye on the same side.
iii. Hematomas, tissue necrosis, and infections are typically the subsequent symptoms that may emerge hours or days after the extrusion. Hematomas on the face often result from extensive internal bleeding caused by haemolysis. Consequently, neurological signs like sensory and motor impairments can be expected after an extrusion.
iv. Ophthalmic symptoms such as eye pain, blurred vision, double vision, and coloured patches on the cornea may manifest. These symptoms are commonly associated with the canine and central incisor in the upper jaw.

Other complications include:

i. iTissue necrosis from the chemical burn caused by NaOCl can lead to a secondary healing phase, ultimately forming scars. (Hulsmann et al., 2007).
ii. Acute sinusitis is likely due to endodontic therapy involving the maxillary sinus. Therefore, the congestion of the maxillary sinus is a critical indicator of irrigant damage to the sinuses. Symptoms can range from the taste and smell of sodium hypochlorite to severe sinus congestion and intense discomfort (Ehrich et al., 1993)
iii. Neurological complications such as paraesthesia and anaesthesia may arise, affecting the trigeminal nerve's infraorbital, inferior dental and mental branches. NaOCl can cause permanent nerve damage, resulting in a loss of motor or sensory function. (Chaudhry et al., 2011) (Pelka & Petschelt, 2008)
iv. upper airway obstruction is risky (Bowden et al., 2006).

Ecchymosis and its anatomical relationship

Swelling and ecchymosis are typically the characteristics of NaOCl extrusion into the periradicular tissues. Swelling could be perceived as a defensive tissue reaction when a hyperosmotic and cytotoxic solution is extruded into the periradicular tissues (Zhu et al., 2013). The cytotoxicity of NaOCl caused ecchymosis as a potent solvent for organic materials, which resulted in the blood vessel walls' disintegration and subcutaneous soft tissues' haemorrhage.

It is interesting to note in various literature regarding the location of ecchymosis following incidents of NaOCl extrusion, precisely the absence of ecchymosis in the soft tissues immediately above the endpoint of the tooth affected by the extrusion. According to numerous case reports by Zhu et al. (2013), ecchymosis commonly appears around the mouth's angle and the periorbital region (both upper and lower eyelids). This ecchymosis often follows the path of superficial venous blood vessels. The extent of ecchymosis can vary depending on the quantity and concentration of NaOCl that enters the venous system and the specific location of the affected venous components and associated tissues. In more severe cases, ecchymosis may extend into other body parts, such as the neck and chest regions (Zhu et al., 2013).

It is essential to know how NaOCl extrusion could enter the venous vasculature. According to a new hypothesis by Zhu et al. (2013), the apical pressure produced by positive-pressure irrigation delivery systems at the periapex must be greater than the venous pressure in the neck's superficial veins. When this apical fluid pressure surpasses the venous pressure in the facial veins, the irrigant can enter a portal of entry within the facial venous vasculature. It is important to note that normal central venous pressure typically has a much lower average value (ranging from 1 to 7 mmHg, with a mean of approximately 5.88 mmHg) as reported by (Baumann et al., 2005). Consequently, extruded NaOCl would naturally flow into a vein via the path of least resistance, following the principles of pressure gradients.

Prognosis and healing

As stated by Becking (1991), patients typically require a few weeks to recover from the initial indications and persisting symptoms such as pain, swelling, hematoma, and tissue necrosis. However, discomfort and swelling can persist for as long as 30 days, and in certain instances, as Markose et al. (2009) reported, it may take up to 4 months for the swelling to entirely subside. Mucosal healing might extend to 60 days (Hülsmann & Hahn, 2000), and in some scenarios, it might even result in fibrosis and scar tissue formation, potentially leading to disfiguring scarring. In cases of paraesthesia, complete resolution may take several months.

Management of sodium hypochlorite accident

Addressing NaOCl extrusions seemed to rely mainly on empirical approaches (Guivarc'h et al., 2017). The lack of a documented standard treatment protocol may be due to the rare occurrence of these complications (MS, 2016). It is fascinating to note that most guidelines for managing NaOCl accidents are from the oral maxillofacial department. Therefore, as the first operator, general dental practitioners and endodontists need to know the management and clinical signs of NaOCl extrusion to allow fast and proper management to reduce the severity of the complications.

The first step in managing a NaOCl accident is to elucidate the situation to the patient (MS, 2016). This stage is crucial when managing the aftermath of such an incident. Additionally, record every aspect of the incident, such as the type of irrigation needle used, the usage of a rubber dam, the duration of the work, and the volume and concentration of NaOCl. Consider taking medical photos to support these notes.

The course of treatment will be decided based on the seriousness of the situation (Farook et al., 2014). Long-acting local anaesthetics and analgesics, such as nonsteroidal anti-inflammatory medications and paracetamol, could alleviate pain (Chaugule et al., 2015; Phillip et al., 2022). For the management of severe pain, a flexible prescription that alternates between ibuprofen and paracetamol at intervals of four hours may be helpful. Prescription of a prophylactic antibiotic is advised to avoid secondary infections that could arise as a result of tissue necrosis or hematoma in the affected tissues (Farook et al., 2014). Steroid usage may be suggested to regulate the acute inflammation process (Chaugule et al., 2015).

Advise the patient to apply cold compression on the first day to reduce swelling and warm compression the following day to increase circulation (Hulsmann et al., 2007). Hospitalisation is advised in the event of an obstruction of the upper airway. It will be required to intubate the patient and give them steroids and antihistamines intravenously (Farook et al., 2014).

A summary of the management of NaOCl accidents by Hulsmann et al. (2007) and (Phillip et al., 2022): Patient education regarding the cause, nature, and severity of the problem

i. Promptly flush the canal with saline solution to effectively dilute and rinse away any residual hypochlorite in the canal.
ii. Pain management through the use of analgesics and local anaesthesia.
iii. In extreme situations, consider referring to the hospital.
iv. Applying cold compresses externally to reduce oedema.
v. After a day, switch to warm compresses and regularly gargle with warm water to enhance localised systemic circulation.
vi. Provide daily instructions for managing the recovery process.
vii. Antibiotics may be considered, mainly when there is a high risk of infection or signs of secondary infection
viii. The use of antihistamines and corticosteroids is discretionary.
ix. Typically, it is possible to continue endodontic treatment using sterile saline or chlorhexidine as irrigants.

Preventive measures

The existence of any risk factor that could predispose to the formation of a NaOCl accident, such as perforations, resorption, immature apices, or any other circumstances, must be adequately investigated by the clinician (Ehrich et al., 1993). Previous studies have suggested various precautions to reduce the potential side effects of using NaOCl. The recommended preventive measures are replacing NaOCl with another irrigant, using a lower NaOCl concentration, and avoiding wedging the needle into the root canal. Aside from that, the irrigation needle should be 1-3 mm shorter than the working length, a side-vented needle should be used for root canal irrigation, and excessive pressure should be avoided during irrigation (Kleier et al., 2008; Phillip et al., 2022; Spencer et al., 2007).

According to Boutsioukis et al. (2013), a literature search on factors affecting NaOCl extrusion during RCT regarding the pressure during irrigation causing extrusion is very subjective. It is interesting to explore the fluid dynamics of NaOCl irrigants to know the relation between the flow rates and pressure driven by the fluids. A study by Park et al. (2013) presented a simulated root canal model to measure the magnitude of apically-directed fluid pressure associated with using different needle delivery systems. This study reported that the apical fluid pressure increased with fluid flow rates.

A new hypothesis by Zhu et al. (2013) concluded that the use of a 30G close-ended side-vented needle with a positive pressure irrigant delivery approach, inserted 1 mm short of the working length, resulted in producing positive fluid pressures at the tooth apex that

escalated non-linearly with increasing irrigant flow rate. When the irrigant flow rate remains below 3.4 ml/min, the fluid pressure generated remains below the average blood pressure value within the intraosseous space, around 30 mmHg. In other words, even when there is a patent apical foramen and variations in the facial venous vasculature anatomy, using a non-binding side-vented needle with an irrigant flow rate below 3.4 ml/min is unlikely to lead to a classic NaOCl accident. Conversely, using the same needle at flow rates exceeding 3.4 ml/min can create a more significant pressure gradient than the intraosseous space, which could lead to the extruded NaOCl entering a facial vein.

Summary of preventive measures (Phillip et al., 2022):

i. Employing a rubber dam consistently.
ii. Accurately measuring files to the appropriate working length.
iii. Placing stoppers for irrigation syringes slightly short of the working length (1-2mm).
iv. Utilizing needles with safe ends (side-vented needles).
v. Employing the index finger, not the thumb, to depress the syringe plunger.
vi. Ensuring the syringe is not lodged in the canal by employing an in-and-out motion during irrigant dispensing.
vii. Facilitating the passive movement of the syringe to enable the irrigant to flow around the needle, back into the access cavity, and subsequent aspiration.
viii. Instruct the patient to inform the operator or nurse if they experience an unpleasant taste during treatment.
ix. Opt for a lower concentration of sodium hypochlorite (between 0.5% and 5.25%) to mitigate potential adverse reactions.

Recommendations

As a recommendation for the prevention of NaOCl accidents, the use of a negative pressure irrigation system such as the EndoVac system or modified apical negative pressure (mANP) was proven to minimise the risk of extrusion of root canal irrigant (Farhana et al., 2023; Jamleh et al., 2016; Rahman et al., 2023). Standardising the data information in future case reports is also recommended for further analysis of sodium hypochlorite accidents. Guivarch et al. (2017) proposed a template that can fulfil this goal and clarify the way for greater comprehension of the factors, management, and prognosis of hypochlorite accidents.

CONCLUSION

Even though the extrusion of NaOCl during root canal treatment is rare, its consequences can be severe. Therefore, assessing teeth before initiating root canal treatment is essential to identify potential risks that could lead to extrusion accidents, enabling the implementation of appropriate preventive measures. Understanding the mechanics of a typical NaOCl accident will empower clinicians to make informed decisions regarding irrigation delivery techniques during root canal disinfection. Additionally, this knowledge can guide manufacturers in developing and improving their irrigation systems to ensure the utmost safety and efficiency in root canal irrigation procedures.

CONFLICT OF INTEREST

The authors affirm that they have no conflicts of interest, whether financial or of any other nature.

ABBREVIATIONS

NaOCl – Sodium hypochlorite
RCT – root canal treatment
HOCl – hypochlorous acid
OCl – hypochlorite ion

REFERENCES

Balto, H., & Al-nazhan, S. (2002). Accidental injection of sodium hypochlorite beyond the root apex. Saudi Dent J, 14(1), 36–38.

Baumann, U. A., Marquis, C., Stoupis, C., Willenberg, T.

A., Takala, J., & Jakob, S. M. (2005). Estimation of central venous pressure by ultrasound. Resuscitation, 64(2), 193–199. https://doi.org/10.1016/j.resuscitation.2004.08.015

Baumgartner, J. C., & Cuenin, P. R. (1992). Efficacy of several concentrations of sodium hypochlorite for root canal irrigation. Journal of Endodontics, 18(12), 605–612. https://doi.org/10.1016/S0099-2399(06)81331-2

Becker, G. L., Cohen, S., & Borer, R. (1974). The sequelae of accidentally injecting sodium hypochlorite beyond the root apex. Report of a case. Oral Surgery, Oral Medicine, Oral Pathology, 38(4), 633–638. https://doi.org/10.1016/0030-4220(74)90097-8

Becking, A. G. (1991). Complications in the use of sodium hypochlorite during endodontic treatment. Report of three cases. Oral Surgery, Oral Medicine, Oral Pathology, 71(3), 346–348. https://doi.org/10.1016/0030-4220(91)90313-2

Boutsioukis, Psimma, Z., & Van der Sluis, L. W. M. (2013). Factors affecting irrigant extrusion during root canal irrigation: A systematic review. International Endodontic Journal, 46(7), 599–618. https://doi.org/10.1111/iej.12038

Bowden, J. R., Ethunandan, M., & Brennan, P. A. (2006). Life-threatening airway obstruction secondary to hypochlorite extrusion during root canal treatment. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology, 101(3), 402–404. https://doi.org/10.1016/j.tripleo.2005.06.021

Chaudhry, H., Wildan, T. M., Popat, S., Anand, R., & Dhariwal, D. (2011). Before you reach for the bleach... British Dental Journal, 210(4), 157–160. https://doi.org/10.1038/sj.bdj.2011.90

Chaugule, V. B., Panse, A. M., & Gawali, P. N. (2015). Adverse Reaction of Sodium Hypochlorite during Endodontic Treatment of Primary Teeth. International Journal of Clinical Pediatric Dentistry, 8(2), 153–156. https://doi.org/10.5005/jp-journals-10005-1304

Clarkson, R. M., & Moule, A. J. (1998). Annual costs of hypochlorite used for endodontic irrigation exclusively were obtained from general and specialist endodontic practices to give some idea. Australian Dental Journal, 43(4), 1–7.

de Sermeño, R. F., da Silva, L. A. B., Herrera, H., Herrera, H., Silva, R. A. B., & Leonardo, M. R. (2009). Tissue damage after sodium hypochlorite extrusion during root canal treatment. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology, 108(1), e46–e49. https://doi.org/10.1016/j.tripleo.2008.12.024

Ehrich, D. G., Brian, J. D., & Walker, W. A. (1993). Sodium hypochlorite accident: Inadvertent injection into the maxillary sinus. Journal of Endodontics, 19(4), 180–182. https://doi.org/10.1016/S0099-2399(06)80684-9

Farhana, W. N., Ramlan, N. A., Mahmood, N. Z. N., & Hussein, A. (2023). Positive Pressure and Negative Pressure Irrigation Dynamics with Different Needle Designs Using Computational Fluid Dynamics. Archives of Orofacial Sciences, 18(2), 125–137.

Farook, S. A., Shah, V., Lenouvel, D., Sheikh, O., Sadiq, Z., & Cascarini, L. (2014). Guidelines for management of sodium hypochlorite extrusion injuries. British Dental Journal, 217(12), 679–684. https://doi.org/10.1038/sj.bdj.2014.1099

Guivarc'h, M., Ordioni, U., Ahmed, H. M. A., Cohen, S., Catherine, J. H., & Bukiet, F. (2017). Sodium Hypochlorite Accident: A Systematic Review. Journal of Endodontics, 43(1), 16–24. https://doi.org/10.1016/j.joen.2016.09.023

Harrison, J. W. (1984). Irrigation of the root canal system. Dental Clinics of North America, 28(4), 797–808.

Hauman, C. H. J., & Love, R. M. (2003). Biocompatibility of dental materials used in contemporary endodontic therapy: A review. Part 1. Intracanal drugs and substances. International Endodontic Journal, 36(2), 75–85. https://doi.org/10.1046/j.1365-2591.2003.00631.x

Hülsmann, & Hahn. (2000). Complications during root canal irrigation - Literature review and case reports. International Endodontic Journal, 33(3), 186–193. https://doi.org/10.1046/j.1365-2591.2000.00303.x

Hulsmann, M., RÖDIG, T., & NORDMEYER, S. (2007). Complications during root canal irrigation. Endodontic Topics, 16(1), 27–63. https://doi.org/10.1111/j.1601-1546.2009.00237.x

Jamleh, A., Fukumoto, Y., Takatomo, Y., Kobayashi, C., Suda, H., & Adorno, C. G. (2016). A comparison between two negative pressure irrigation techniques in simulated immature tooth: an ex vivo study. Clinical Oral Investigations, 20(1), 125–131. https://doi.org/10.1007/s00784-015-1489-1

Khandelwal, A., & Ajitha, P. (2020). Management of Sodium Hypochlorite Accident Clinical Practice Guidelines. Drug Invention Today, 13(6), 1216–1219.

Kleier, D. J., Averbach, R. E., & Mehdipour, O. (2008). The Sodium Hypochlorite Accident: Experience of Diplomates of the

American Board of Endodontics. Journal of Endodontics, 34(11), 1346–1350. https://doi.org/10.1016/j.joen.2008.07.021

Markose, G., Cotter, C. J., & Hislop, W. S. (2009). Facial atrophy following accidental subcutaneous extrusion of sodium hypochlorite. British Dental Journal, 206(5), 263–264. https://doi.org/10.1038/sj.bdj.2009.166

Mcdonnell, G., & Russell, A. D. (1999). Antiseptics and disinfectants: Activity, action, and resistance. Clinical Microbiology Reviews, 12(1), 147–179. https://doi.org/10.1128/cmr.12.1.147

McKenna, S. M., & Davies, K. J. A. (1988). The inhibition of bacterial growth by hypochlorous acid. Possible role in the bactericidal activity of phagocytes. Biochemical Journal, 254(3), 685–692. https://doi.org/10.1042/bj2540685

MS, A.-Z. (2016). Sodium Hypochlorite Accident in Endodontics: An Update Review. International Journal of Dentistry and Oral Health, 2(2). https://doi.org/10.16966/2378-7090.168

Park, E., Shen, Y., Khakpour, M., & Haapasalo, M. (2013). Apical pressure and extent of irrigant flow beyond the needle tip during positive-pressure irrigation in an in vitro root canal model. Journal of Endodontics, 39(4), 511–515. https://doi.org/10.1016/j.joen.2012.12.004

Pashley, E. L., Birdsong, N. L., Bowman, K., & Pashley, D. H. (1985). Cytotoxic effects of NaOCl on vital tissue. Journal of Endodontics, 11(12), 525–528. https://doi.org/10.1016/S0099-2399(85)80197-7

Pelka, M., & Petschelt, A. (2008). Permanent mimic musculature and nerve damage caused by sodium hypochlorite: a case report. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology, 106(3), 80–83. https://doi.org/10.1016/j.tripleo.2008.05.003

Phillip, Noman Athwal, Maria Lessani, Alyn Morgan, Pratik Kamalkant Shah, & Sanjeev Bhanderi. (2022). A guide to Good Endodontic Practice. British Endodontic Society, 1(1), 1–83. www.britishendodonticsociety.org.uk

Rahman, W. N. F. W. A., Ramlan, N. A., Mahmood, N. Z. N., & Hamid, A. H. A. (2023). Negative Pressure Irrigation Dynamics between Two Needle Designs using Computational Fluid Dynamics. The Open Dentistry Journal, 17(1), 1–9. https://doi.org/10.2174/18742106-v17-e230420-2022-161

Reeh, E. S., & Messer, H. H. (1989). Long-term paresthesia following inadvertent forcing of sodium hypochlorite through perforation in maxillary incisor. Dental Traumatology, 5(4), 200–203. https://doi.org/10.1111/j.1600-9657.1989.tb00361.x

Senia, E. S., Marraro, R. V, Mitchell, J. L., Lewis, A. G., Thomas, L., & Antonio, S. (1975). Rapid sterilization of gutta-percha cones with 5.25 % sodium hypochlorite. Journal of Endodontics, 1(4), 136–140.

Spencer, H. R., Ike, V., & Brennan, P. A. (2007). Review: The use of sodium hypochlorite in endodontics - Potential complications and their management. British Dental Journal, 202(9), 555–559. https://doi.org/10.1038/bdj.2007.374

Zehnder, M. (2006). Root Canal Irrigants. Journal of Endodontics, 32(5), 389–398. https://doi.org/10.1016/j.joen.2005.09.014

Zhu, W. C., Gyamfi, J., Niu, L. N., Schoeffel, G. J., Liu, S. Y., Santarcangelo, F., Khan, S., Tay, K. C. Y., Pashley, D. H., & Tay, F. R. (2013). Anatomy of sodium hypochlorite accidents involving facial ecchymosis - A review. Journal of Dentistry, 41(11), 935–948. https://doi.org/10.1016/j.jdent.2013.08.012

BJMS
Borneo Journal of Medical Sciences

CASE REPORT

Urgency or Emergency – A Report on Hypertensive Crisis with Severe Retinopathy

Mohd Shaiful Ehsan Shalihin[1]*, Mohd Daud Che Yusof[2]

[1] Department of Family Medicine, Kulliyyah of Medicine, IIUM Kuantan campus, 25200 Kuantan, Pahang, Malaysia
[2] Klinik Kesihatan Beserah, Kampung Pelindung, 26100 Kuantan, Pahang, Malaysia

*Corresponding author's email: shaifulehsan@iium.edu.my

Received: 15 January 2024

Accepted: 6 March 2024

Published: 1 May 2024

DOI: https://doi.org/10.51200/bjms.v18i2.5068

Keywords: *Hypertensive urgency, emergency, dilemma*

ABSTRACT

Hypertensive crisis is a common condition encountered in primary care clinics. It may result from uncontrolled hypertension or a known cardiovascular risk disease but may also be the first occurrence of undiagnosed secondary hypertension. However, there is confusion on the classification of whether certain atypical presentations, particularly in young patients without acute symptoms and exact duration of symptoms, are to be considered as hypertensive urgency or emergency. Some abnormal signs, such as proteinuria or retinopathy, could be signs of an existing progression of underlying chronic disease rather than a manifestation of acute hypertensive crisis. Nonetheless, in any situation where the findings have occurred recently without prior follow-up, they should be treated as if they are signs of an acute hypertensive crisis. Bedside clues, such as concomitant anaemia and proteinuria, are valid evidence for the presence of end-stage renal disease (ESRD) causing the hypertensive crisis, even without the features of fluid overload or failure symptoms. We report the case of a young man presented with an acute hypertensive crisis with an isolated one-month history of blurred vision. Despite the initial dilemma, the case was treated as a hypertensive emergency due to the presence of retinopathy and overt proteinuria. The renal profile later confirmed that the patient had ESRD. This case proves that ESRD is still

possible even in a young patient without a long medical history or other supporting signs. Making the right decision on the first visit saved the patient's life.

INTRODUCTION

Hypertensive crisis is one of the most important acute conditions commonly encountered in primary care (Kotruchin et al., 2022; Taylor, 2015). Its diagnosis is indeed simple and easy to make. However, clinical division into emergency or urgency is sometimes arbitrary and requires individual assessment by the clinician. One of the limitations of primary care is that not all centres can provide all urgent tests or assessment results as soon as possible (Waked et al., 2019). Although the usual bedside investigations sometimes support the diagnosis, they are contrary to the deciding factor for treatment. It becomes more challenging when symptoms are isolated and chronic, but the clinical features are suggestive of an acute condition.

In primary care, the issues of referral indication and shared tertiary care are among the important measures that must be decided at a patient's first visit (Benenson & Bradshaw, 2021). Both hypertensive urgency and emergency are manifested by an acute rise in blood pressure levels exceeding a systolic blood pressure of 180 mmHg or a diastolic blood pressure of 110 mmHg or both (Ministry of Health Malaysia, 2018). Both would share similar symptoms, such as headache, neck pain, blurring of vision, or lethargy. However, the main distinguishing features between the two are the absence of overt symptoms and the signs of acute target organ damage or complication (Nijskens et al., 2020). However, these overt symptoms are still ambiguous, and some patients may present a mixture of mild and overt symptoms (Kotruchin et al., 2022). One example is the changes in visual function detected by fundus examination that reveals hypertensive retinopathy. Although the guideline states that grade IV retinal changes favour emergency, such features can also occur in chronic uncontrolled hypertension, where the decision of whether to admit the patient urgently or not is difficult (Ministry of Health Malaysia, 2018; Taylor, 2015).

Therefore, from the primary care perspective, a holistic rapid assessment is indeed important to obtain more information about the severity of the presentation and its causes (Benenson & Bradshaw, 2021; Waked et al., 2019). This includes the presence of other risk factors, comorbidities, compliance issues, previous readings, and the level of support system at home. However, it becomes more difficult for patients who have no prior follow-up or an underlying medical condition. It became even more unpredictable when detected in the young age group, which falls into the low-risk group. We report a challenging treatment decision in a 28-year-old man who presented with a hypertensive crisis and retinal changes with no other obvious symptoms or known medical problems.

CASE PRESENTATION

A 28-year-old man with no known medical illness presented with a progressive, painless blurring of vision in both eyes for a month. He had no other symptoms suggestive of target organ damage, such as headache, nausea, vomiting, neck pain, chest pain, shortness of breath, reduced effort tolerance, limb weakness, or numbness. There was also no history of a fall, trauma, or fever. He was still able to function as usual despite his condition. He had no similar medical history and no history of hospitalization. There was no significant family history of hypertension or renal disease, nor did family members die at a young age. He is a non-smoker with no history of taking illegal drugs or high-risk behaviour.

On examination upon arrival, he was noted to be pale. His BMI is 22kg/m2. His blood pressure was 200/120 mmHg and remained so even after rest. Repeated readings before referral to a tertiary centre were also similar. His visual acuity in the right eye was only up to hand movement, and in the left eye was the

perception of light. His fundus findings of the right eye show papilledema with soft exudates and central retinal vein occlusion (Figure 1a) and the left eye shows a retinal detachment with papilledema, soft exudates, and central retinal vein occlusion (Figure 1b). Other system examinations were unremarkable.

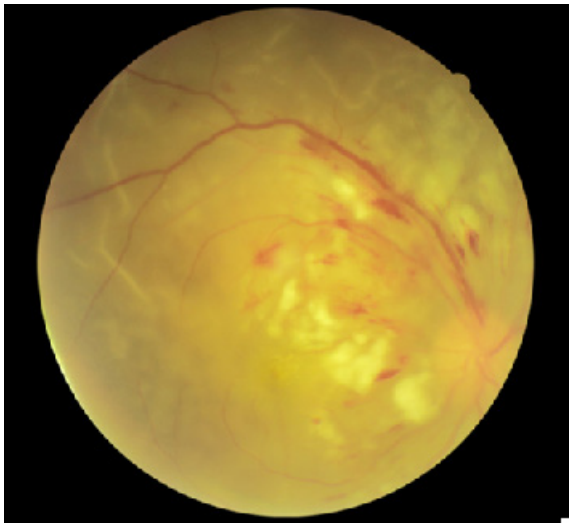

Figure 1a: Fundus photograph of the patient's right eye showing papilledema with soft exudates and central retinal vein occlusion.

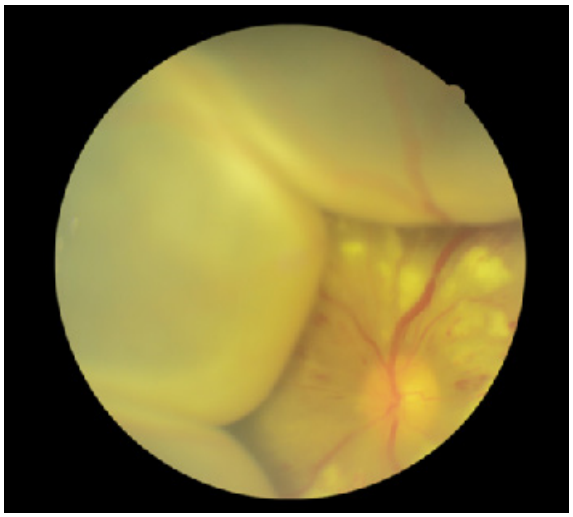

Figure 1b: Fundus photograph of the patient's left eye showing a retinal detachment with papilledema, soft exudates, and central retinal vein occlusion.

His bedside investigations at the clinic revealed normochromic normocytic anaemia (Hb 8.01 g/dL) concomitant to thrombocytopenia. He also had proteinuria (urine protein 3+) and hematuria (urine haemoglobin 1+). His electrocardiography revealed no abnormal findings. However, bedside renal ultrasound managed to show shrunken bilateral kidneys. This case was then referred immediately to the emergency department as a hypertensive emergency and was administered with IV labetalol (20 mg), followed by another 20mg dose for blood pressure stabilization while in transport to the emergency department. Upon arrival at the tertiary, his blood pressure was already stabilized at 180/100 mmHg, and no other anti-hypertensive medication was administered to maintain the blood pressure within that range for the first few hours. He was then warded to the medical ward and noted to have an underlying end-stage renal disease with an eGFR of 2.3 mL/min/1.73 m2. He was then under nephrology follow-up until now.

DISCUSSION

Hypertensive crises are common in primary care (Benenson & Bradshaw, 2021; Waked et al., 2019). They are classified as either hypertensive urgency or emergency, and they require appropriate further management that starts in the primary care clinic. However, the approach of management for the first group may involve the role of observation and initial management in primary care, whereas the other group requires urgent admission and intravenous administration of antihypertensive agents (Ministry of Health Malaysia, 2018; Taylor, 2015).

In this report, the dilemma is to determine the category of the case and the underlying causes. A hypertensive crisis is usually associated with patients having underlying uncontrolled comorbidities (Nijskens et al., 2020). However, the patient in this case has no known underlying medical illness. Although it is clearly stated that the presence of target organ damage is an indicator of a hypertensive emergency, the patient was presented with

only subacute symptoms of blurred vision for one month and no acute symptoms indicating sudden complications, such as acute renal failure, pulmonary oedema, acute coronary syndrome, or encephalopathy (Alley & Schick, 2020). Several studies and guidelines agree that hypertensive retinopathy is equivalent to a hypertensive emergency. Nevertheless, some doubt the relevance of this phenomenon, as it can also occur with non-acutely elevated blood pressure and can be an incidental finding in asymptomatic patients (Nijskens et al., 2020; Pranav Modi & Tasneem Arsiwalla, 2019). Although there were no other alarming signs apart from the fundoscopic retinal changes, this case was treated as an emergency as a precaution. Moreover, the fundoscopic changes were numerous and severe. The patient also had no previous record, as this was the first time, he had sought medical attention. A hypertensive crisis can be the first presentation of secondary hypertension (Siddiqi et al., 2023). Given the patient's young age, non-smoking status, and lack of an unhealthy lifestyle, we are convinced that this patient may have underlying secondary causes of hypertension rather than essential hypertension. The initial bedside tests, especially the urine analysis, suggest underlying renal disorders. At this stage, we are not sure whether the patient has acute renal injury or chronic kidney disease, as he has never been investigated before. However, the concomitant findings of anaemia provide a hidden clue to an underlying chronic kidney disease that may not have been previously recognized.

Studies have shown that renal disease can cause hypertension and vice versa (Sica, 2008). However, which issue comes first in this case is uncertain. Although screening for CKD begins with urine analysis for protein, the patient had no history suggestive of chronic disease progression. It is important to note that kidney disease can also initially present as a hypertensive crisis without any prior symptoms or signs (Alley & Schick, 2020). These mechanisms are often involved in nephrosclerosis, the most common progressive kidney disease leading to end-stage kidney disease (Alley & Schick, 2020; Sun et al., 2019).

The treatment of hypertensive retinopathy in primary care is always referral. The question arises as to whether an urgent or early appointment is required in non-diabetic patients when they come to the clinic. Clinical guidelines recommend emergency referral when a patient is present with sudden severe visual loss or symptoms or signs of acute retinal detachment (Modi & Arsiwalla, 2019; Chillo et al., 2019). The patient, in this case, had severe visual loss (vision up to eye movement) and severe retinal changes. However, we are unsure whether it was sudden, acute, or chronic. Nonetheless, from the primary care perspective, it is appropriate for hospital admission as soon as possible when they are present with severe conditions or alarming signs, regardless of the time of initial presentation. Hypertensive retinopathy is an indicator of the risk of an acute cardiovascular event, such as hemorrhagic stroke (Ramani et al., 2021).

CONCLUSION

Hypertension crisis management aims to reduce blood pressure appropriately within a reasonable time. Regardless of whether it is a hypertensive urgency or emergency, the initiation of hypertensive crisis management should not be delayed. If confusion persists, referral for admission is a good decision by the primary care team, which is vital in saving the patient's life. Continuous education for the public should be implemented to increase their awareness of the early symptoms of hypertension. They should be advised to seek medical attention immediately whenever they feel any abnormal symptoms, whether they are mild or severe. Furthermore, the primary care clinic implementation of the no-wrong-door policy is indeed helpful in accepting any

level of cases at the community level at the earliest possible time.

REFERENCES

Alley, W. D., & Schick, M. A. (2020). Hypertensive Emergency. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470371/

Benenson, I., & Bradshaw, M. J. (2021). Approach to a patient with hypertensive urgency in the primary care setting. The Nurse Practitioner, 46(10), 50–55. https://doi.org/10.1097/01.npr.0000790500.51146.ec

Chillo, P., Ismail, A., Sanyiwa, A., Ruggajo, P., & Kamuhabwa, A. (2019). Hypertensive retinopathy and associated factors among nondiabetic chronic kidney disease patients seen at a tertiary hospital in Tanzania: a cross-sectional study. International Journal of Nephrology and Renovascular Disease, Volume 12, 79–86. https://doi.org/10.2147/ijnrd.s196841

Kotruchin, P., Tangpaisarn, T., Mitsungnern, T., Sukonthasarn, A., Hoshide, S., Turana, Y., Siddique, S., Buranakitjaroen, P., Van Huynh, M., Chia, Y. C., Park, S., Chen, C. H., Nailes, J., Tay, J. C., Wang, J. G., & Kario, K. (2022). Hypertensive emergencies in Asia: A brief review. Journal of clinical hypertension (Greenwich, Conn.), 24(9), 1226–1235. https://doi.org/10.1111/jch.14547

Ministry of Health Malaysia. (2018). Clinical Practice Guidelines Management of Hypertension 5th Edition. Retrieved from https://www.moh.gov.my/moh/resources/penerbitan/CPG/MSH%20Hypertension%20CPG%202018%20V3.8%20FA.pdf

Nijskens, C. M., Veldkamp, S. R., Van Der Werf, D. J., Boonstra, A. H., & Ten Wolde, M. (2020). Funduscopy: Yes or no? Hypertensive emergencies and retinopathy in the emergency care setting; a retrospective cohort study. The Journal of Clinical Hypertension, 23(1), 166–171. https://doi.org/10.1111/jch.14064

Modi, P. & Arsiwalla, T. (2019, January 23). Hypertensive Retinopathy. Nih.gov; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK525980/https://www.ncbi.nlm.nih.gov/books/NBK525980/

Ramani Thiagarajah, Kandasamy, R., & Pulivendhan Sellamuthu. (2021). Hypertensive Retinopathy and the Risk of Hemorrhagic Stroke. Journal of Korean Neurosurgical Society, 64(4), 543–551. https://doi.org/10.3340/jkns.2020.0285

Sica, D. A. (2008). The Kidney and Hypertension: Causes and Treatment. The Journal of Clinical Hypertension, 10(7), 541–548. https://doi.org/10.1111/j.1751-7176.2008.08189.x

Sun, D., Wang, J., Yao, L., Li, Z., & Ohno, S. (2019). Research Progress in Acute Hypertensive Renal Injury by "in Vivo Cryotechnique." Journal of Translational Internal Medicine, 7(4), 132–136. https://doi.org/10.2478/jtim-2019-0027

Siddiqi, T. J., Usman, M., Rashid, A. M., Javaid, S. S., Ahmed, A. B., Clark, D., Flack, J. M., Shimbo, D., Choi, E. H., Jones, D. W., & Hall, M. E. (2023). Clinical Outcomes in Hypertensive Emergency: A Systematic Review and Meta-Analysis. Journal of the American Heart Association, 12(14). https://doi.org/10.1161/jaha.122.029355

Taylor D. A. (2015). Hypertensive Crisis: A Review of Pathophysiology and Treatment. Critical care nursing clinics of North America, 27(4), 439–447. https://doi.org/10.1016/j.cnc.2015.08.003.

Waked, K., Nagge, J., & Grindrod, K. (2019). Managing hypertension in primary care. Canadian Family Physician, 65(10), 725–729. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6788646/