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Aims and Scope	Greater Mekong Subregion Medical Journal is an online and printed, peer reviewed international scientific journal published by Mae Fah Luang University. The journal aims to publish articles in the field of basic and advanced clinical research in medicine and related health sciences, medical education as well as community medicine in Thailand, international and especially in countries of Greater Mekong Subregion. Manuscripts submitted to Greater Mekong Subregion Medical Journal will be accepted on the conditions that the author must not have previously submitted that paper to another journal elsewhere. The journal will not charge for any submission. The reproduction or copy of the articles included the pictures should be under the permission of the publisher.
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Publication Ethics

Publication ethics of Greater Mekong Subregion Medical Journal (GMSMJ)

Greater Mekong Subregion Medical Journal presents articles in the field of basic and advanced clinical research in medicine and related health sciences, medical education as well as community medicine in Thailand and international, especially in countries of Greater Mekong Subregion.

The journal publishes 3 issues a year: Issue 1 (January - April), Issue 2 (May - August) and Issue 3 (September -December). All submitted research articles and review articles will be evaluated by a single blinded peer-review process and reviewed by 2 experts who have knowledge, expertise, and experience in the field of medicine and related health sciences prior to publication. The journal encloses the information of authors and reviewers. In case of a difference of evaluation, the article evaluation will be considered and given a final decision.

Greater Mekong Subregion Medical Journal establishes the roles and duties for three different groups in the process of article publication: author (s), editor, and reviewers. The following information is given to the three groups of people so that they will strictly abide by its benefits of those concerns, including readers and others in academia.

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- Author (s) must report the occurred facts without distorting or giving any false information.
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Original Article

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Greater Mekong Subregion Medical Journal

Comparative Study on the Detection of Short Chain Fatty Acids in Fecal Samples from Patients with Type 2 Diabetes Mellitus: An Insight into Diabetic Kidney Disease Compared with Normal Kidney Function

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Abstract:

Background: The role of the gut microbiota in metabolic health was increasingly recognized. Short-chain fatty acids (SCFAs) – including propionic acid, acetic acid and butyric acid – are vital metabolites produced by gut microbiota. These SCFAs play a pivotal role in energy metabolism, glucose homeostasis, and systemic inflammation. The link between gut microbiota and human health, especially in the context of metabolic disorders like Type 2 Diabetes Mellitus (T2DM) and Chronic Kidney Disease (CKD), has garnered significant attention in recent years.

Objective: This study aimed to compare the levels of SCFAs in fecal samples from three distinct patient groups: 1) Type 2 diabetic patients with diabetic kidney disease, 2) Type 2 diabetic patients with normal kidney function, and 3) Hypertensive patients without diabetes with normal kidney function.

Materials and Method: A total of thirty-nine participants were involved in this research, categorized into three distinct groups. Fecal samples were collected, immediately frozen, and processed for the extraction of SCFAs. The concentrations of SCFAs were determined using a gas chromatography-mass spectrometry (GC/MS) system.

Results: The study evaluated the concentrations of three pivotal SCFAs in stool samples across the three patient groups. While there were nuanced variations in the concentrations of acetic, butyric and propionic acids among the groups, an ANOVA test revealed no statistically significant differences in SCFA concentrations among them.

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Conclusion: While this study provides foundational insights into the SCFA landscape across specific health conditions, the absence of significant disparities prompts contemplation. The multifactorial nature of SCFA production, influenced by disease states, diet, genetics and other environmental factors, underscores the need for further investigative depth. Future research might delve deeper into the potential therapeutic implications of modulating gut microbiota and SCFA profiles in managing metabolic disorders.

Keywords: Diabetic Kidney Disease, Gut Microbiota, Short-chain Fatty Acid, Type 2 Diabetes Mellitus

Introduction

The link between gut microbiota and human health has been a subject of interest in recent years. The gut microbiota, often referred to as the "hidden organ" plays a significant role in various metabolic disorders, including Type 2 Diabetes Mellitus (T2DM) and chronic kidney disease (CKD).[1,2] One key area of focus is on short-chain fatty acids (SCFAs) - primarily propionic, acetic, and butyric acids - as these bacterial metabolites are associated with a wide range of physiological functions.[3]

Recent studies have shown that SCFAs play a crucial role in maintaining gut barrier integrity, modulating immune responses, and influencing metabolic processes, which can have significant implications for systemic health and disease.[4,5] Furthermore, alterations in the gut microbiota and SCFA profiles have been linked to the development and progression of T2DM and CKD.[6] In addition to these roles, emerging research has highlighted the potential of gut microbiota as a therapeutic target in T2DM. Certain anti-hyperglycemic agents and traditional Chinese medicine have been found to exert hypoglycemic effects by altering the gut microbiota composition, thereby improving glucose metabolism.[2] Moreover, studies have identified a particular ganglioside profile associated with early diabetic kidney disease in T2DM patients, further emphasizing the complex interplay between metabolic disorders and gut microbiota.[7]

In light of these findings, this study seeks to further explore this association by comparing the levels of these SCFAs in the feces of patients in three distinct groups: 1) Type 2 diabetic patients with diabetic kidney disease, 2) Type 2 diabetic patients with normal kidney function, and 3) Hypertensive patients with normal kidney function without diabetes.

Materials and method

This research involved forty-five participants, divided into three distinct categories. *Group A (DN)* was made up of fifteen individuals diagnosed as Type 2 Diabetes Mellitus with diabetic kidney disease. The definition of diabetic kidney disease is the diabetic patient who has a spot urine sample for microalbumin equal to or greater than 30 mg/g creatinine, and an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2.[8] *Group B (DM)*, which served as a control group, comprised of fifteen patients with Type 2 Diabetes Mellitus with normal kidney function. The definition of normal kidney function is a spot urine sample for microalbumin less than 30 mg/g and an eGFR greater than 60 mL/min/1.73 m^2.[8] *Group C (HT)*, consisted of fifteen hypertensive patients without diabetes and having normal kidney function. The participants were a diverse group of men and women who resided in Chiang Rai province, Thailand. The recruitment phase ranged from March 2022 to February 2023.

Inclusion Criteria: Group A (DN) included individuals with type 2 diabetes mellitus, aged 35-70, who had a spot urine sample for microalbumin equal to or greater than 30 mg/g creatinine, and an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2. Group B (DM) consisted of individuals with type 2 diabetes mellitus, aged 35-70, who had a spot urine sample for microalbumin less than 30 mg/g and an eGFR greater than 60 mL/min/1.73 m^2. Group C (HT) included hypertensive individuals, aged 35-70, who had a spot urine sample for microalbumin less than 30 mg/g creatinine, and an eGFR greater than 60 mL/min/1.73 m^2.

Exclusion Criteria included the recent use of antibiotics within 30 days prior to stool sample collection, current gastrointestinal symptoms such as diarrhea, bloody diarrhea, melena, chronic abdominal pain, nausea, or vomiting, use of antacid or proton pump inhibitors to reduce gastric acid secretion, and use of prebiotics and/or probiotics.

Withdrawal Criteria included the use of antacid or proton pump inhibitors and the use of prebiotics and/or probiotics during the study period.

Informed Consent and Ethical Approval: The study was conducted following the principles outlined in the Declaration of Helsinki posing minimal health risks to the participants. All participants in the study gave their informed consent prior to enrollment and participation. The study protocol received approval from The Mae Fah Luang University Ethics Committee on Human Research, as evidenced by a certificate of approval (COA: 045/2022).

Sample Preparation

Fecal samples were collected from each participant using sterile containers. The samples were immediately frozen at -80°C until further processing. For the extraction of SCFAs, approximately 1 gram of each fecal sample was weighed and homogenized in 1 mL of distilled water. The homogenate was then centrifuged at 12,000 rpm for 10 minutes at 4°C. The supernatant was collected and acidified with 25% metaphosphoric acid to a final concentration of 5%. The acidified samples were kept at 4°C for 30 minutes to allow for the precipitation of proteins and were then centrifuged again under the same conditions. Two-methyl-butyric-acid (Sigma-Aldrich, USA) was added to each vial to reach a final concentration of 0.001 M. 2-methyl-butyric-acid was added as an internal standard (IS) to correct for injection variability between samples, and minor changes in the instrument response. All vials were stored at – 20°C before GC analysis.

GC/MS Analysis

The analysis of SCFAs was performed using a gas chromatography-mass spectrometry (GC/MS) system. The GC/MS was equipped with a capillary column (30 m x 0.25 mm, 0.25 μm film thickness). The oven temperature was initially set at 80°C, then increased to 180°C at a rate of 10°C/min, and finally to 200°C at a rate of 5°C/min. The temperatures of the injector and detector were set at 250°C and 280°C, respectively. Helium was used as the carrier gas at a flow rate of 1 mL/min. The mass spectrometer was operated in electron impact mode at 70 eV. SCFAs were identified by comparing their retention times and mass spectra with those of standards. The concentrations of SCFAs were calculated based on the peak area ratios of the SCFAs to the internal standard. The mass spectrometer was set to scan mode at m/z 100–300 and selected ion monitoring mode at m/z 60 for acetate, butyrate maintaining for 4.72 min, 7.34 min respectively, as well as m/z 73 for propionate for 5.90 min. The results were then normalized to the dry weight of the fecal samples.

Statistical analysis

All statistical analyses were performed by GraphPad Prism 8.0. The results were expressed as means with standard deviation (SD). ANOVA was used for normally distributed continuous variables. The correlation difference between variables was analyzed by Spearman's R coefficient. The association between fecal level with the clinical index was examined via binary logistic regression analysis, based on the median level of fecal or serum SCFAs. P value < 0.05 was considered statistically significant.

Results

Baseline characteristics among the three groups

Although 45 participants were initially enrolled in the study - with 15 participants in each group, some stool sample were not qualified for processing. There were 39 stool samples in remain, with 13 participants in Group A (DN) and 12 in Group B (DM) and 14 in Group C (HT). The mean age of 39 total participants was 55.0 years, ranging from 39 to 67 years. The average blood pressure was 138/78 mmHg and the average BMI was 26.46 kg/m^2.

Both Group A (DN) and Group B (DM) had poor glycemic control (HbA1C were 8.4% and 8.2% respectively. All three groups were obese (average BMI was 26.5 kg/m^2). In comparisons between groups, the Group A (DN) was rather older than the Group B (DM). Significant differences were observed in creatinine, eGFR and urine microalbumin levels among the three groups, based on the study's design and enrollment criteria. However, blood pressure, BMI and inflammatory marker (CRP) levels did not differ significantly among the three groups (Table 1)

Comparisons of fecal and serum SCFAs among the three groups

Our study evaluated the concentrations of three pivotal short-chain fatty acids (SCFAs) - acetic, butyric and propionic - in stool samples across three distinct patient groups (Table 2). For acetic acid concentrations (Figure 1), Group A (DN), consisting of individuals with Type 2 Diabetes Mellitus with diabetic kidney disease, exhibited a concentration of 1111.791 ± 179.119 μmol/g dry weight. In comparison, the control group, Group B (DM), which includes patients with Type 2 Diabetes Mellitus with normal kidney function, showed a slightly lower concentration of 1061.101 ± 148.689 μmol/g dry weight. Meanwhile, Group C (HT), made up of hypertensive patients with normal kidney function, had concentrations closely mirroring Group A (DN) at 1115.751 ± 177.345 μmol/g dry weight. For butyric acid (Figure 2), Group A (DN) had a concentration of 18.378 ± 4.173 μmol/g dry weight, Group B (DM) displayed 17.333 ± 4.725 μmol/g, and Group C (HT) showed 18.019 ± 3.879 μmol/g. Lastly, for propionic acid (Figure 3), in Group A (DN), the concentration was 11.624 ± 3.418 μmol/g dry weight, Group B (DM) ehibited 12.299 ± 5.157 μmol/g, and Group C (HT) aligned closely with Group A (DN) at 11.557 ± 4.728 μmol/g. Notwithstanding these nuanced variations, an ANOVA test revealed no statistically significant differences in SCFA concentrations among the groups.

Table 1 Comparison of clinical and biochemical features between 3 groups: Group A (DN), Group B (DM), Group C (HT)

	Group	Mean	S.D.	p-value
Age	A	58.2	7.4	
	B	51.3	6.7	0.039*
	C	56.6	6.9	
BMI	A	27.2	3.8	
	B	26.1	3.9	0.886
	C	26.1	4.2	
s-BP	A	138	13	
	B	139	17	0.936
	C	138	22	
d-BP	A	79	9	
	B	80	7	0.840
	C	77	11	
eGFR	A	44	11	
	B	102	14	0.001*
	C	92	13	
Cr	A	1.6	0.7	
	B	0.7	0.2	0.001*
	C	0.8	0.2	
UMA	A	574	841	
	B	27	38	0.001*
	C	10	6	
CRP	A	2.4	1.9	
	B	2.2	2.9	0.493
	C	2.1	1.1	
HbA1c	A	8.4	2.1	0.683‡
	B	8.2	1.5	
FPG	A	176	114	0.242‡
	B	175	51	

Kruskal-Wallis statistics for analysis of difference of median between 3 groups
‡Mann-Whitney statistics for analysis of difference of median between 2 groups (DN and DM)
*statistical significance
note: Cr = creatinine (mg/dL), eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2), UMA = urine microalbumin (mg/gCr), s-BP = systolic blood pressure (mmHg), d-BP = diastolic blood pressure (mmHg), BMI = body mass index (kg/m^2), CRP = c-reactive protein (mg/L), HbA1c = glycosylated hemoglobin (%), FPG = fasting plasma glucose (mg/dL)

Table 2 The concentration of short-chain fatty acids (SCFAs) in different groups

Fecal SCFAs	DN (13)	DM (12)	HT (14)	P
Acetate (μmol/g)	1111.79 ± 179.12	1061.10 ± 148.68	1115.75 ± 177.34	NS
Propionate (μmol/g)	11.62 ± 3.41	12.29 ± 5.15	11.55 ± 4.72	NS
Butyrate (μmol/g)	18.37 ± 4.17	17.33 ± 4.72	18.01 ± 3.87	NS

SCFAs concentration is expressed as Mean± SD (μmol/g); NS represents that the difference is not significant ($p > 0.05$)

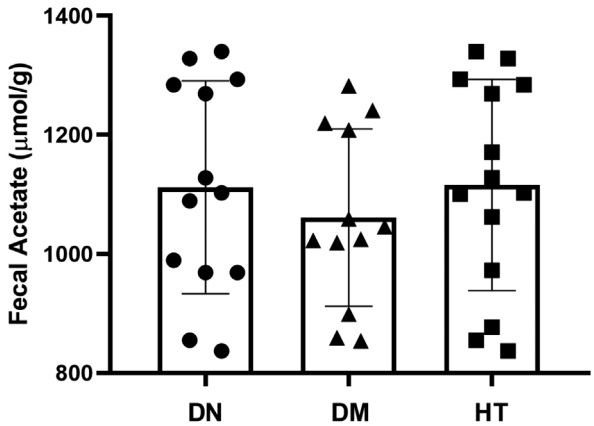

Figure 1 Acetic acid concentrations across patient groups. The figure illustrates the concentrations of acetic acid (in μmol/g dry weight) in fecal samples from three distinct patient groups: DN (Type 2 diabetic patients with diabetic kidney disease), DM (Type 2 diabetic patients with normal kidney function) and HT (Hypertensive patients with normal kidney function without diabetes). The bars represent mean concentrations, and the error bars denote standard deviations.

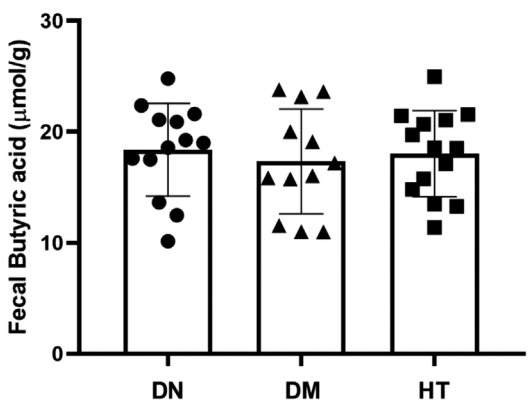

Figure 2 Butyric acid concentrations across patient groups. The figure displays the concentrations of butyric acid (in μmol/g dry weight) in fecal samples from the three patient groups: DN, DM, and HT. The bars indicate mean concentrations, while the error bars represent standard deviations.

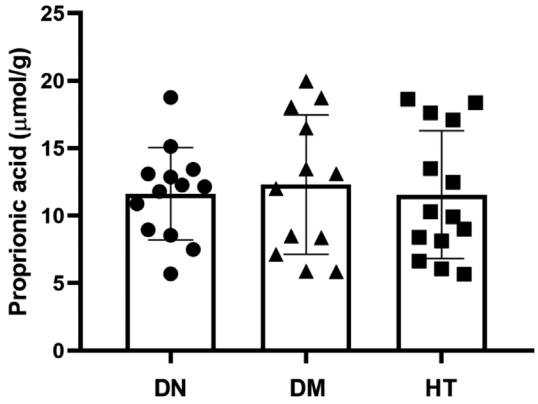

Figure 3 Propionic acid concentrations across patient groups. The figure showcases the concentrations of propionic acid (in μmol/g dry weight) in fecal samples from the three patient groups: DN, DM and HT. The bars depict mean concentrations, and the error bars indicate standard deviations.

Discussion

The role of short-chain fatty acids (SCFAs) in modulating gut and metabolic health has been a subject of increasing scientific scrutiny. Our findings, which revealed nuanced yet statistically non-significant variations in SCFA concentrations across distinct clinical cohorts, align with the broader scientific discourse on this topic.

SCFAs, primarily produced from the microbial fermentation of dietary components, play a pivotal role in shaping the biochemical profile of the diet, influencing both gut and host metabolism.[9] Acetic acid concentrations across our cohorts, particularly the similarity between the DN and HT groups, resonate with previous studies suggesting shared gut microbial signatures between conditions like hypertension and diabetes.[10] Butyric acid, renowned for its anti-inflammatory properties and its role in maintaining gut barrier integrity, showed consistent concentrations across our cohorts. This observation is in line with the understanding that SCFAs, especially butyric acid, are essential for gut integrity, regulating luminal pH, mucus production and providing fuel for epithelial cells.[11] The consistency in propionic acid concentrations across the groups further underscores the multifaceted role of SCFAs in metabolic health. SCFAs, including propionic acid, have been implicated in a range of physiological processes, from glucose homeostasis to immunomodulation.[12]

Several factors may explain the lack of significant differences in SCFAs concentration in our study: (1) *Renal Function Variations:* participants in the diabetic kidney disease (DN) and diabetes mellitus (DM) group showed a slight difference in their estimated glomerular filtration rate (e-GFR). The DN group had an e-GFR of 44 mL/min/1.73 m^2, while the DM group had a higher e-GFR of 102 mL/min/1.73 m^2. Additionally, the average creatinine level in the DN group was 1.62 mg/dL, in comparison with 0.72 mg/dL in the DM group. These subtle differences in renal function could have influenced on the SCFAs concentration. If the study had involved participants with more advanced kidney damage, such as those in stage 5 chronic kidney disease (CKD) with an e-GFR below 15 mL/min/1.73 m^2, we may have observed more pronounced differences in SCFAs concentration (2) *Dietary Patterns:* The study did not assess the dietary pattern in

all participants, despite the fact that most lived in the same geographical area. This region, located in northernmost part of Thailand, is home to a diverse, multicultural population consisting the people originated from Laos, Myanmar, Chinese, Hill tribes people and people from central and northeastern part of Thailand which made it very difficult to evaluate participants dietary habits accurately.[13-14] Future studies should include more detailed dietary assessments for each participant that need laborious effort and time for preparation, considering both household and individual factors. Such information would provide a valuable insight into how dietary patterns could influence the SCFAs concentration between groups.

Conclusion

While our study provides foundational insights into the SCFA landscape across specific health conditions, the absence of significant disparities prompts contemplation. The multifactorial nature of SCFA production, influenced by disease states, diet, genetics, and other environmental factors, underscores the need for further investigative depth.

Funding

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Conflict of Interest

The authors declare no conflict of interest of this study.

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สำนักวิชาแพทยศาสตร์ มหาวิทยาลัยแม่ฟ้าหลวง
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Exploring Constraints in Logistics Operations of Public Hospitals in Mountainous Areas of Northern Thailand

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Abstract:

Background: Thai public hospitals in highland rural areas are experiencing difficulties in logistics operations due to the mountainous geography and scarcity of resources compared to hospitals in the city center.

Objective: This paper aims to explore the constraints in logistics operations that Thai public hospitals located in rural mountainous areas are experiencing.

Materials and Method: A qualitative study using 3 case study hospitals from three highland border cities in northern Thailand was conducted in this study. The onsite observation and interviews were conducted at the hospital to explore operational constraints in seven logistics activities based on the framework of the World Health Organization.

Results: All sample hospitals have no centralized logistics coordination system, while I.T. systems cannot integrate the data between front and back-office systems. The inventory system of all hospitals cannot access the actual use rate of medicines and medical supplies. The systematic forecasting procedure of future consumption and the warehouse storage system does not exist. Lastly, transportation operations are faced with long driving times on dangerous roads, and there is a risk of landslides when servicing patients' referral systems to the urban hospital.

Conclusion: The result of this paper is an initial step in an attempt to reduce the gap between populations in the rural-urban quality of life through better hospital operations by exploring and understanding constraints experienced by mountainous public hospitals.

Keywords: Hospital logistics, Hospital management, Mountainous, Rural

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Introduction

The geography of the northern region is different from that of other areas of Thailand. It's mostly a mountainous highland area and is bordered by two neighboring countries: Myanmar and Laos PDR. Although the Universal Cover Scheme (UCS) was introduced in Thailand in 2002 as a social health insurance program, making most services at public hospitals free of charge, aiming at an equal chance of having the same healthcare standard across the country[1], the rural-urban inequality still found existing in various aspect.[2-3]

A number of papers focus their study on an inequality between rural and urban hospitals.[4-6] However, finding what difficulties public hospitals in mountainous rural areas, which is the shared geography of Thailand border cities in the north, are experiencing due to their location context receive less attention from researchers, especially in the area of hospital logistics operations.

Hospital logistics operations are defined as activities that enable purchasing, inventory management, and replenishment of goods and services surrounding medical services to patients[7], ensuring resource availability at any treatment place.[8] In short, the hospital logistics system helps ensure that its clinical services are always available for patients by efficiently managing all related hospital operations.

Hospital logistics systems are embedded in entire hospital operations, making it even more challenging to scope which operations should be included in this paper. A previous study has highlighted the inefficiency of Thai public hospitals' logistics operations.[9] Later, the study was extended and found that public hospitals in Thailand still rely on manual information exchange processes, causing slow and inaccurate data exchange in the supply chain.[10]

A study of the hospital logistics framework[11] states that the hospital has two primary operations. Firstly, clinical care services are a core treatment process by medical professionals, including physicians and nurses. Secondly, non-clinical services include support services, such as management of medicines and medical supplies, and administration services, such as purchasing management, information technology, transportation services, etc. Being a hospital in mountainous rural areas makes it even more challenging for the logistics system to ensure all non-clinical services will always be available for clinical services with the highest patient safety requirements.

Therefore, this paper is the first step in an attempt to reduce the gap between populations in the rural-urban quality of life through better hospital operations. The objective is to explore and understand what constraints in hospital logistics operations of Thai public hospitals in mountainous areas are experiencing. Although this paper did not develop a novel methodology, it is only a qualitative exploration with in-depth interviews and onsite observation. Still, the result is a body of knowledge that will help point out the actual constraints of public hospitals in mountainous areas for future studies.

Methodology

This paper has reviewed an international standard and found a standard developed by the World Health Organization called Hospital Readiness Checklist for COVID-19.[12] This standard has been used in many papers.[13-15] Although it's not a dedicated guidebook only for hospital logistics operations, we found it's capable of being our framework for assessment since *hospital logistics* is one of the modules in that guidebook. It comprises seven sub-operations, which will be used as a scope of study in this paper.

The operation guidelines in each scope are as follows;

1) Logistics coordination: the hospital is recommended to designate a coordination system that can ensure a mechanism for prompt internal and external transportation services, prompt maintenance and repair services of medical equipment, and prompt services for purchasing and refilling supplies.

2) I.T.: Hospitals should be able to maintain an updated inventory of all equipment, supplies, and pharmaceuticals. Establish a shortage alert and reordering mechanism.

3) Inventory management: Hospitals should have a clear inventory policy to ensure the timely use of inventory and avoid loss from expiration.

4) Forecasting: the hospital is advised to estimate the consumption of essential equipment, supplies, and pharmaceuticals.

5) Purchasing: The hospital is advised to use an effective purchasing system to ensure prompt delivery of suppliers.

6) Storage: the hospitals must identify the physical space within the hospital for storage and ensure effective operations to guarantee the availability of essential items under storage conditions.

7) Transportation: In the recommended action of the guidebook, hospitals must ensure an effective transport system for patients and supplies in both intra-hospitals and inter-hospitals.

Study Participants and Procedure

This paper selected three mountainous rural district hospitals (also known as small community hospitals) from 3 border cities in northern Thailand to be a case study hospital. The characteristics of each hospital are as follows: **Hospital 1** has a bed capacity of 30 beds with four full-time doctors (three interns and one specialist who also works as hospital director), located in a highland agricultural district with a distance of 2.5 hours of driving time far from the city center at the altitude of 750 meters above sea level. **Hospital 2** has a bed capacity of 20 beds with three full-time doctors (two interns and one specialist who also works as hospital director), located in a highland forestry district with 3 hours of driving time far from the city center, at an altitude of 950 meters above sea level. **Hospital 3** has a bed capacity of 20 beds with three full-time doctors (two interns and one specialist who also works as hospital director), located in a mountainous travel-destination district with 2 hours of driving time far from the city center, at an altitude of 730 meters above sea level. All hospitals have an average of 250 outpatients per day.

The research team communicates with the hospitals through an official email containing research details and asks permission to conduct this research. After that, request a hospital representative experienced with hospital logistics operations from the predetermined questions included in the official letter who is willing to participate in an interview. Finally, the research team communicated and verified their positions and voluntary participation via authorized hospital contact details.

Data Collection and Analysis

The data were collected from interviews with each hospital representative (including the director of the administration department, director of pharmacy, director of nursing, and director of the I.T. department) conducted in January 2023 using an open-ended question on constraints they are experiencing in seven areas of their hospital logistics operations as scoped by WHO's guidebook. The interviews were conducted onsite, face-to-face, at the hospital, and took about 90 minutes per hospital. Hospitals were asked to explain each operation's details and the difficulties experienced when

performing them. Secondly, the onsite observation at the hospital with selected representatives was also conducted to validate and confirm the information collected from the first step, which took another 60-120 minutes per hospital. The interviews were recorded digitally and transcribed verbatim. All researchers with previous qualitative research experience brainstormed and carefully discussed the interview results by comparing them with the recommended guidelines by WHO. Lastly, the results were verified with each hospital representative as per the data validation process.

Results

Table 1 The result of constraints found in each operation

Operations	Constraints
1. Logistics Coordination	- No designated person in the organization chart - Unclear roles in hospital logistics operations
2. I.T.	- No staff with software development skill - The back-office is not integrated with the hospital's primary operations system
3. Inventory management	- Unable to access the actual use rate
4. Forecasting	- Systematic forecasting procedure has not existed
5. Purchasing	- Location constraints make vendors lose interest in bidding - Location constraints make longer purchasing lead time
6. Storage	- No systematic storage system
7. Transportation	- Location constraints make a referral system between hospitals challenges - No transporters for internal transport

Logistics Coordination

The result found no designated person for internal logistics coordination in the organization chart of all sample hospitals, and each department needs to manage its own department. This is because they don't have enough personnel to handle this type of overlapping operation since budget allocation for job positions from the government was proportionate to the population size in each area, which population size in mountainous districts is considered extremely small compared to city hospitals. This constraint creates many inefficient operations, including a shortage of stock, since each ward needs to monitor and decide when and how much stock should be replenished.

Information Technology

Although all three hospitals are located in a mountainous rural area, they all have quality internet networks in both wired and wireless versions. What was found to be the constraints related to the hospital information technology system is lacking I.T. staff with software development skills. All hospitals found have only information technology staff with skills in fixing everyday problems, such as installing printer drivers and Wi-Fi

connections. etc. However, no hospital has staff with software development skills, leading to a lack of software that can integrate between the back-office software, like the quantity of medicine purchased and remaining in the warehouse, all running with different software from the front-office software where physicians prescribe the medicines and supplies for patients.

Inventory management

A constraint differentiating case study hospitals from city hospitals is the inability to access the actual use rate of medicines and medical supplies. Their inventory software cannot access the actual use rate of medicines that physicians prescribed to each patient, but it can only see the replenishment rate from each ward's request to the central warehouse for re-stocking purposes. Relying on the ward's replenishment rate instead of the actual use rate of patients will lead to fault and inefficient inventory control.

Forecasting

Forecasting is a critical logistics operation that uses mathematical models to ensure adequate procurement for future consumption. However, a systematic forecasting procedure does not exist in any sample hospitals. This hospital system that only relies on self-estimation of purchasing staff will create a risk of inventory shortage, especially in mountainous areas where purchasing lead time is much longer than in city hospitals. This is because all hospitals never attempt to recruit staff with forecasting skills since they all never acknowledge the importance of forecasting.

Purchasing

All sample hospitals have a smaller demand for medicines and medical suppliers than the urban hospital, derived from a smaller population size. This constraint creates a loss of interest in suppliers' bidding system, a one-size-fits-all purchasing procedure from the Ministry of Health since demand is too small to achieve their break-even point within their acceptable time. This results in all three sample hospitals inevitably driving their own vehicle to the city center and purchasing themselves instead of having suppliers deliver to their hospitals.

Storage

All sample hospitals still operate their warehouse without using information technology; a storage location and quantity of stock on hand cannot be checked in the software but only known by warehouse staff through their self-recorded stock card. This system causes difficulty in finding inventory stored in the storage room, such as the outdated inventory status. The persons responsible for all three hospitals say the number of storage items is still manageable using a manual system and see no point in implementing a new technology like a warehouse management system.

Transportation

The results found that all three hospitals had the same distance constraint for inter-hospital transportation since it took them more than 6 hours for each patient referral to the network hospital in their city center. Two hospitals are often faced with landslides during the rainy season that will block the road, and they need to wait for at least two hours before authorities re-open the road. The limited number of ambulances in each hospital will be even less on the day ambulances are on duty to transfer patients to network hospitals since they would not be available for at least one day until it's returned.

At the same time, internal transport operations still rely on traditional manual systems. Nurse in each ward needs to walk and refill their sub-stock themself. For

wheelchairs, a nurse will call the wheelchair counter via the internal phone number. Their request for wheelchair transport e.g., moving a patient from the ward to the parking lot, will be written in the paper, and whenever wheelchair staff, or might be any other male staff who willing to help see requesting notes are awaiting at the wheelchair counter, they will go the location of the user as per requested.

Discussion and Conclusion

This paper observed and interviewed three public hospitals in a mountainous area of three border cities in northern Thailand regarding their hospital logistics operations constraints. The finding revealed constraints in seven logistics operations, including the finding of no designated person for logistics coordination due to budget allocation for full-time staff proportionate to population size. This system differs from city hospitals, where they have a logistics department designated to link each hospital unit, e.g., internal transport, stock monitoring, forecasting, purchasing, and automatic stock replenishment services to ensure all non-clinical services will always be available for clinical services. Suppose such services are available in mountainous hospitals. In that case, a limited number of medical staff will have more time servicing patients instead of managing back-office operations, which the logistics coordinator personnel can centrally manage.

The major constraint of information technology is an inability to integrate data between back-office and front-office software due to the lack of I.T. staff with software engineering skills. This inability also leads to inventory management's constraint from a failure to access the actual use rate of medicines and medical supplies. If the front and back office systems can be integrated, physicians will see how many medicines and supplies are available in the storage area. The purchasing team will have better information for planning its replenishment strategy to ensure no stockout problem. The forecasting function will also benefit from the obtained data. However, all hospitals say attracting specialists willing to work full-time in remote areas is challenging, especially with lower salaries than city hospitals and their current staff is unable to integrate both systems.

The constraint of purchasing operations from suppliers lacking interest in joining the bidding process due to the small quantity demanded of a small mountainous hospital makes their investment infeasible compared to bidding for a city hospital. This is because all Thai public hospitals in mountainous and urban areas have the same one-size-fits-all purchasing procedure via a centralized e-bidding system. The total of six hours of driving time for delivering one box of medical supplies might last six months in mountainous hospitals compared to 10 boxes every week, with only 10 minutes of driving time in the city hospitals, making suppliers lose interest in joining the bid. This paper would suggest developing a purchasing procedure that matches the location contexts of small rural mountainous hospitals.

The storage system of all sample hospitals heavily relies on single warehouse staff, with no real-time digital data available for monitoring, while city hospitals mostly run under the bin-location system. It's a storage system capable of identifying each item's storage location and expiration details, enabling real-time data for inventory control via computer software. Implementing the bin-location system in mountainous hospitals will enable them to lower the risk of shortage and product expiration problems through a notification system.

The transportation system is found to be a direct manual request from the ward to the responsible staff, while the city hospital pulled all requests for both internal and

inter-hospital transport operations into a single centralized software, including requesting wheelchairs or portable beds for stretched patients and requesting sub-stock refilling by picking up inventory from the central warehouse and delivering it to the ward. This pull system will improve the utilization of limited vehicles and staff in mountainous hospitals through better scheduling.

Apart from logistics problems, an inadequate number of doctors, language barriers of local hill tribes population when communicating with hospital staff, and insufficient resources, including lacking laboratory tools and ambulance, are also found to exist in three sample hospitals which is in the same direction with a number of papers that explored rural-urban inequality in Thai hospital operations.[16-18]

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Application of Preventive Medicine in Traffic Medicine

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Abstract:

In the study of traffic medicine, readers need to have a basic understanding of the meaning, boundaries, and branch of preventive medicine as well as concepts and theories associated with preventive medicine, which forms the basis of traffic medicine in order to be able to choose the best principles for treating any health issues. The purpose of this article is to provide an overview of local and international preventive medicine works, various branches of preventive medicine, and the main theories of the nature history of disease, preventive strategies, epidemiologic triad, and spectrum of prevention as well as the applications in traffic medicine. It then provides knowledge and understanding of the fundamental principles of preventive medicine, which is the foundation for higher education in traffic medicine.

Keywords: Epidemiologic triad, Preventive medicine, Preventive strategies, Traffic medicine

Introduction

Preventive medicine, as defined by the American College of Preventive Medicine (ACPM), refers to "the practice of promoting preventive health care to improve patient well-being, with the goals of preventing disease, disability, and death." In the United States, preventive medicine physicians must have knowledge and skills in biostatistics, epidemiology, planning and evaluation of health services, management of health care organizations, research, and preventive medicine practice in clinical settings. Preventive medicine specialists are licensed physicians including, Medical Doctors (MD) and Doctors of Osteopathy (DO). Training is divided into three main specialties; 1) public health and general preventive medicine, 2) occupational medicine, and 3) aerospace medicine.[1]

In Thailand, the training program for preventive medicine residency is managed by the Preventive Medicine Association of Thailand. As of 2024, there are ten specialties for which examinations for certification and proficiency in preventive medicine are offered; 1) epidemiology, 2) travel medicine, 3) aviation medicine, 4) maritime medicine, 5) clinical preventive medicine, 6) public

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health, 7) community mental health, 8) occupational medicine, 9) traffic medicine, and 10) lifestyle medicine.[2] Additionally, there is a related field known as "community medicine," which focuses on the health of populations with an emphasis on preventive and health promotion in communities through primary health care. Community medicine education includes holistic care, lifelong learning, evidence-based practice, interdisciplinary teamwork, and professional ethics to foster sustainable health systems.[3] However, this specialty is not yet included in residency training in Thailand but is integrated into the medical curriculum of various medical schools.

Traffic medicine, a key branch of preventive medicine, is a multidisciplinary and comprehensive field that addresses the development, prevention, and treatment of traffic injuries. It draws on various disciplines, including psychology, sociology, statistics, engineering, biomechanics, law, and medicine. Epidemiology, relevant to both traffic and preventive medicine, plays a crucial role in identifying effective countermeasures for injury control. Big data mining has emerged as an innovative strategy for traffic safety. Recently, forensic traffic injury medicine has integrated clinical medicine, social psychology, and factors related to vehicles, roads, and road users.[4] This article provides an overview of the natural history of disease, preventive strategies, the epidemiologic triad, and the spectrum of prevention, along with their applications in traffic medicine. It also offers essential knowledge and understanding of preventive medicine principles, forming the foundation for advanced studies in traffic medicine.

Key Theoretical Concepts in Preventive Medicine

Working in preventive medicine requires tools to help understand health issues and to find appropriate and effective solutions. Important theoretical concepts in preventive medicine that should be known are as below.

Natural History of Disease[5,6]

The nature of disease progression refers to the development of a disease in an individual over time without treatment. For example, a person infected with HIV will experience disease progression in stages, from the asymptomatic phase, through symptomatic phases, AIDS diagnosis, and ultimately to death. However, the duration of each stage can vary among individuals depending on disease prevention measures and access to treatment. This progression can sometimes be referred to as "the spectrum of disease" and can be categorized into five stages as follows:

1. Underlying stage: This is the stage where the pathogen is present but has not yet spread to others. Pathogens at this stage can cause both communicable and non-communicable diseases. For instance, HIV is a communicable pathogen transmitted through sexual contact, while smoking can lead to lung cancer, which is declared as a non-communicable disease.

2. Susceptible stage: The body has been exposed to the pathogen, but if it has good immunity, infection may not occur.

3. Subclinical stage: The body has been infected and has undergone pathological changes, but symptoms have not yet appeared. In some diseases, even if the patient is asymptomatic, they can still transmit the disease to others, such as with hepatitis B virus and COVID-19.

4. Clinical stage: At this stage, the disease can be diagnosed using standard methods, starting from the onset of symptoms to more severe manifestations.

5. Recovery/disability/death stage: This stage depends on the type of disease and the individual's resistance to it, and it encompasses recovery, disability, or death.

In traffic medicine, the use of the natural history of disease model can be compared to the different stages of an accident: pre-crash, during the crash, post-crash, and the rehabilitation phase to prevent disability. This is combined with the analysis of risk factors that may lead to injuries at each stage in order to plan preventive measures.

Preventive Strategies[5]

Preventive strategies are crucial tools in preventive medicine and consist of five steps:

1. Primordial prevention: This step aims to reduce risk factors for disease across the entire population by focusing on social and environmental conditions. Examples include government measures to increase tobacco taxes, restrict alcohol advertising, and promote healthy food sales in convenience stores.

2. Primary prevention: This involves preventing disease before it occurs in susceptible hosts who are healthy individuals at risk for disease. Methods include immunization, smoking cessation programs, and nutritional supplementation.

3. Secondary prevention: This focuses on early disease detection through screening among healthy populations who have been exposed to pathogens but are asymptomatic. Objectives are to prevent disease progression. Methods include blood pressure measurement, mammography for breast cancer, Pap smears for cervical cancer, and colonoscopy for colorectal cancer.

4. Tertiary prevention: This aims to reduce disease severity and disability, as well as the consequences after disease onset. Examples include foot care for diabetic patients and physical therapy for spinal cord injury patients.

5. Quaternary prevention: This involves ensuring that patients receive appropriate medical care and are not at risk of excessive treatment. An example is the use of antiarrhythmic drugs after myocardial infarction, which can reduce arrhythmias but may increase mortality risk. It also includes evaluating the appropriateness of existing policies.

Disease prevention strategies must be implemented alongside understanding disease progression, as illustrated in Figure 1.

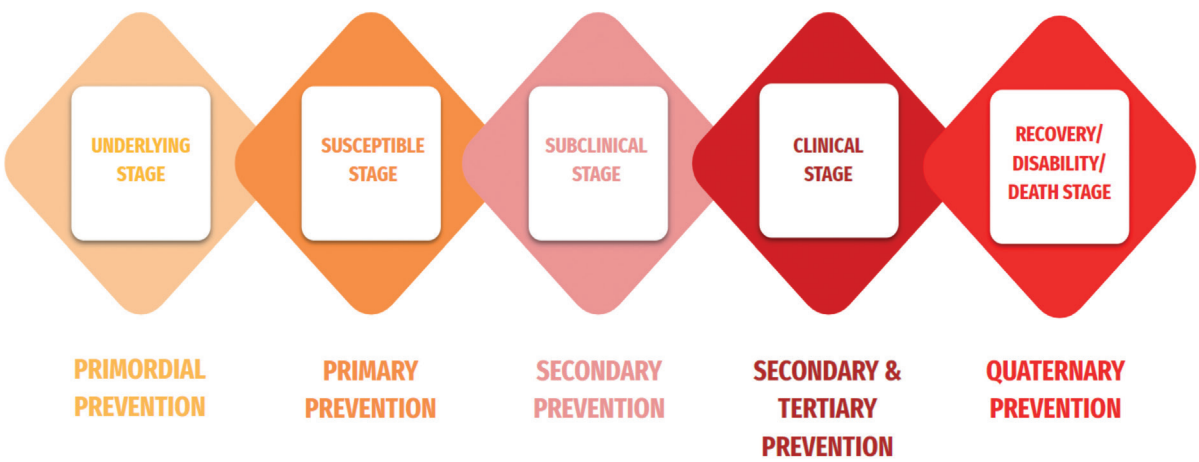

Figure 1 illustrates the implementation of disease prevention strategies alongside the nature of disease progression.

For application in traffic medicine, for example, alcohol consumption increases the risk of accidents, particularly among teenagers. Therefore, the disease prevention strategies can be analyzed as shown in Table 1.

Table 1 shows the preventive strategies of disease at each step.

Preventive Strategies	Problems	Actions
1. Primordial Prevention	Alcohol is sold in the community.	- Restrict alcohol sales advertising. - Increase alcohol taxes.
2. Primary Prevention	Teenagers in the community can easily purchase alcohol.	- Limit the hours for alcohol sales. - Restrict the age of those eligible to purchase alcohol.
3. Secondary Prevention	Some teenagers engage in drinking and driving.	- Identify individuals in the community with drinking behavior and provide training/rehabilitation.
4. Tertiary Prevention	Traffic accident victims suffer from disabilities.	- Promote physical rehabilitation and vocational training.
5. Quaternary Prevention	The rate of injuries and fatalities from traffic accidents continues to rise.	- Review the shortcomings in all the processes that have been implemented.

Epidemiologic Triad[7]

The epidemiologic triad is one of the models used to explain the components of disease occurrence in epidemiology. The triad consists of:

1. Host: This refers to the susceptible host, i.e., the person who is vulnerable to the disease. The susceptibility of each individual varies depending on several factors. The likelihood of exposure to the pathogen depends on personal behavior. For example, individuals who do not wear masks are more likely to contract respiratory infections compared to those who do. Meanwhile, the level of susceptibility and the individual's response to pathogens depend on other factors such as genetic makeup, nutritional status, immunity level, and anatomical characteristics.

2. Agent: This includes pathogens such as bacteria, viruses, parasites, and fungi. However, the presence of a pathogen alone is not enough to cause disease, as several factors contribute to the transition from exposure to disease in a host, such as the pathogen's pathogenicity and the dose of exposure. Nowadays, the definition of an agent in humans is not limited to pathogens but also includes chemicals, physical causes, and various forms of injury. For example, repeated external force applied to the palms and wrists is considered an agent that can cause carpal tunnel syndrome, or alcohol is viewed as an agent that causes liver cirrhosis. In traffic medicine, agents refer to forces that cause injury to the human body, such as high-speed driving or poorly designed vehicles that lack impact-absorbing features during a collision.

3. Environment: This refers to external factors that bring the host and the agent together, such as habitat characteristics, climate, vectors like insects that transmit diseases, socioeconomic status, hygiene,

and access to healthcare. In traffic medicine, the environment refers to driving conditions, such as lighting systems, standard road design, or the presence of obstacles on the road surface.

Disease occurrence results from the interaction between the host and the agent under environmental conditions that favor the transmission of the pathogen to the host, as illustrated in Figure 2.

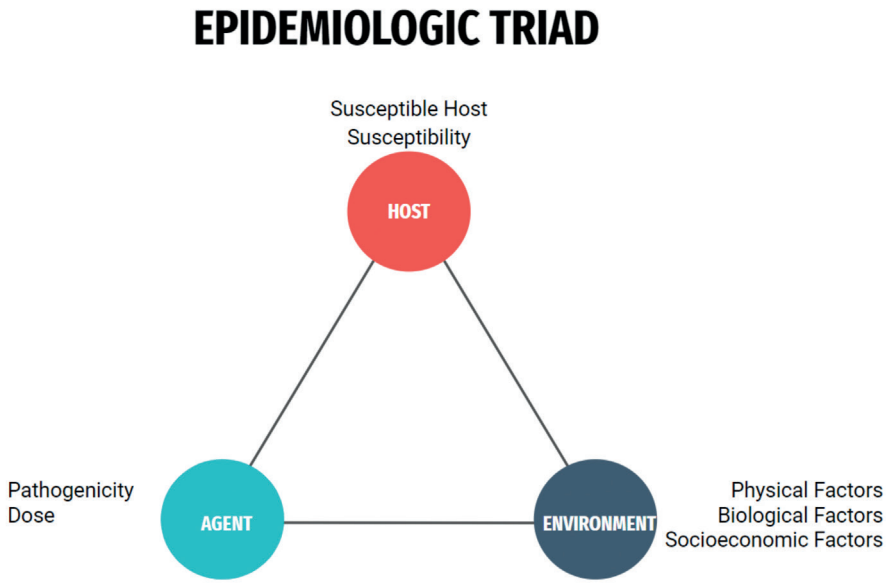

Figure 2 illustrates the relationship between the host, agent, and environment in the epidemiologic triad.

Spectrum of Prevention[8]

The conceptual framework for disease prevention, widely accepted in preventive medicine, was developed by Larry Cohen and Susan Swift. Originally designed for injury prevention, it can also be adapted for the prevention of other diseases. The spectrum of disease prevention consists of six steps:

1. Strengthening individual knowledge and skills: This step involves transferring information and methods for disease or injury prevention to the public to enhance individual capabilities. This is done by professionals or those in authority, such as doctors asking patients during consultations whether they wear helmets while riding motorcycles, along with providing information on injury and mortality rates from traffic accidents. Such recommendations can help reduce injuries or fatalities from traffic accidents.

2. Promoting community education: The purpose of supporting community education is to reach groups of people by providing information and promoting health. This often involves mass communication campaigns aimed at raising awareness and changing attitudes among large populations, such as organizing "exercise days" and "safe driving days."

3. Educating providers: Educating service providers, such as educators, childcare workers, and nursing home staff, is one way to disseminate disease prevention knowledge to the community. These individuals are experts in their fields and have channels to pass on information, skills, and inspiration to those they supervise or serve, thereby spreading knowledge widely.

4. Fostering coalitions and networks: Promoting collaboration and building networks encourages participants to feel confident that projects or ongoing efforts

are likely to succeed, while also reducing competition between groups.

5. Changing organizational practices: Changing organizational practices, such as enforcing laws, health organization policies, and school practices, is a key factor in strengthening community health and safety systems.

6. Influencing policy and legislation: Advocating for changes at the policy or legislative level is the method that can have the most widespread health impact.

Conclusion

Traffic medicine is one of the branches of preventive medicine in Thailand. It is operated by the Preventive Medicine Association of Thailand, with a parallel field working to promote health and well-being. The foundational theories of preventive medicine support the effective implementation of traffic medicine, helping to achieve its goals and contributing to the resolution of public health issues in society.

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Pravalence of Mitragynine in Forensic Autopsy Cases at the Forensic Investigation Center Chulalongkorn University from 2022 to 2023

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Abstract:

Background: Mitragynine is an active compound found in Kratom, a substance experiencing growing usage both in Thailand and globally. While Kratom is commonly perceived as safe with minimal adverse effects, instances of fatalities associated with its use and misuse have been documented.

Objective: Investigating the prevalence of mitragynine in forensic autopsy cases from 2022 to 2023. Analyzing demographic data, causes of death, and proposed lethal level.

Materials and Method: A retrospective study was conducted on the forensic toxicological analysis of 213 forensic autopsy cases from 2022 to 2023 at the Forensic Investigation Center of Chulalongkorn University.

Results: The prevalence of positive mitragynine findings rose significantly from 3.14% in 2021 to 13.39% in the years 2022-2023. The male-to-female ratio was approximately 9:1. The common causes of death were attributed to traffic accidents, undetermined and cardiovascular diseases. Mitragynine concentrations varied widely, ranging from 0.10 to 1,423.23 ng/mL, with a mean concentration of 109.85 ng/mL. However, a definitive proposed lethal level could not be determined based on the data analyzed.

Conclusion: The increasing use of kratom, coupled with the rising number of deaths associated with its consumption, necessitate a comprehensive reassessment of its safety profile. A thorough study on its safe usage, including potential positive effects and adverse reactions, is imperative. Additionally, regulatory measures governing kratom distribution and consumption require re-evaluation to ensure public safety and mitigate the risks associated with its use and misuse.

Keywords: Mitragynine, Kratom, Prevalence, Forensic autopsy

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Introduction

Kratom *(Mitragyna speciosa)* is a tropical plant indigenous to Southeast Asia. In Thailand, tradition use of kratom is prevalence in the southern region, as an herb for increasing energy, reducing fatigue, relieving pain, antidiarrhea and recreational purposes to enhance euphoric, sociability and sexual desire.[1] Kratom was classified and controlled as a schedule 5 substance under Thailand's Narcotic Act of 1979. However, kratom was removed from the list of prohibited narcotic substance in 2021.[2] This alteration in classification has contributed to the increasing popularity of kratom. Since kratom is perceived to be safe and illegal in many countries, it has been popular in recent years globally and classified as a new psychoactive substance (NPS).[3]

Mitragynine is an active component of kratom leaves. It acts as opioid receptors agonist, alpha2-adrenoreceptor agonist and 5-HT_{2A} receptor antagonist. The use of kratom has been linked to various adverse reactions, including agitation, tachycardia, nausea, drowsiness, lethargy, hypertension, confusion, seizures, and in rare instances, renal failure and cardiac arrest.[1,4]

Several case reports linking mitragynine-related death have indicated polysubstance uses. Cotinine, diphenhydramine, ethanol, mirtazapine, naloxone, o-desmethyltramadol, propylhexedrine, quetiapine, temazepam were among the substances identified in polydrug cases, with mitragynine concentrations ranging from 10 to 4,800 ng/mL.[5,6] Our investigation into the presence of mitragynine in forensic autopsy cases aims to elucidate related demographics, causes of death, and potentially establish a lethal level of mitragynine. The study site is situated in Bangkok, the capital city of Thailand.

Materials and method

This retrospective study was conducted using forensic toxicological analysis of 213 forensic autopsy cases obtained from the Forensic Investigation Center at Chulalongkorn University during the years 2022 and 2023. The study focused on examining demographic information, causes of death, and the presence of co-exposure substances in the analyzed cases.

The forensic toxicological analysis of drugs and narcotics in blood was conducted using a validated LC/MS-MS method by the Forensic Toxicology Laboratory within the Department of Forensic Medicine at Chulalongkorn university.

Statistical analysis

Mean, median and range were analyzed by Microsoft Excel 2021.

Results

Among the 1,591 forensic autopsy cases examined, mitragynine was detected in 213 cases, comprising 13.39% of the total sample. The majority of these cases were Thai nationality, accounting for 193 cases (90.61%), followed by individuals from other Asian countries, totaling 15 cases (7.04%), with the remaining 5 cases (2.35%) attributed to individuals of other nationalities. Of the cases with positive mitragynine findings, 197 were male and 16 were female, resulting in an estimated male-to-female ratio of 9:1. The demographic data are summarized in Table 1.

The predominant co-exposure substances detected alongside mitragynine included caffeine, antihistamines, ethanol, methamphetamines, and benzodiazepines. Notably, instances of sole mitragynine use were not observed within the examined cases. Additionally, other substances identified in this study encompassed

sildenafil, metformin, amlodipine, quetiapine, gabapentin, zolpidem, LSD, and cocaine, as detailed in Table 2. During the study period, new psychoactive substances (NPS) such as estazolam, fentanyl, JWH-073, and methcathinone were also identified.

The related causes of death observed in the analyzed cases predominantly included traffic accidents, undetermined circumstances, and cardiovascular diseases, as depicted in Table 3.

The concentrations of mitragynine detected in the bodies of the individuals examined ranged from 0.10 to 1,423.23 ng/mL (mean 109.85 ng/mL), as shown in Table 4.

Table 1 Demographic data of forensic autopsy cases with the presence of mitragynine

Year	Demographic data					
	Gender		Age (years)		Nationality	
	Male	Female	range	mean	Thai	Others
2022	88 (91.7 %)	8 (8.3 %)	3 mo. -66 y	32.83	87 (90.6 %)	9 (9.4 %)
2023	109 (93.2 %)	8 (6.8 %)	15 – 74	33.76	106 (90.6 %)	11 (9.4 %)

Table 2 Substances found in the forensic toxicological analysis along with mitragynine

Drugs and narcotics	2022	2023
Caffeine	49	86
Antihistamine	40	50
Ethanol	36	26
Methamphetamine	21	16
Benzodiazepine	12	13
Morphine	7	8
Tramadol	7	14
Ketamine	10	6
THC	0	3
Others	26	37

Table 3 Causes of deaths attributed to mitragynine

Cause of death	2022	2023
Traffic accident	27 (28.1 %)	35 (29.9 %)
Cardiovascular disease	16 (16.7 %)	23 (19.7 %)
Undetermined	19 (19.8 %)	32 (27.4 %)
Asphyxia	9 (9.4%)	10 (8.5 %)
Fall	5 (5.2 %)	5 (4.2 %)
Gun shot	3 (3.1 %)	3 (2.6 %)
Drowning	4 (4.2 %)	0
Others	13 (13.5 %)	9 (7.7 %)
Total	96	117

Table 4 Mitragynine concentration in forensic autopsy cases

Year	Gender	Mitragynine level (ng/mL)	
		range	mean
2022	male	0.19 – 1,198.73	134.49
	female	0.35 - 675	111.26
2023	male	0.10 – 1,423.23	118.58
	female	0.29 – 487.56	75.07

Discussion

The true prevalence of kratom use and misuse remains uncertain. However, based on the findings of this study between 2022 and 2023, kratom was detected in up to 13.39% of the forensic autopsy cases, compared to 16 cases out of 510 (3.14%) in the year 2021.[2] Traffic accidents, cardiovascular diseases, and undetermined causes were identified as the major causes of death, with mitragynine potentially exerting direct or indirect effects contributing to these outcomes. In some cases of asphyxia and gunshot fatalities, mitragynine was identified as a coincidental finding.

A study conducted at Ramathibodi Hospital, another forensic center in Bangkok, spanning from 2015 to 2019, revealed the presence of mitragynine in approximately 1% (24 from 2,160) of the autopsy cases, predominantly affecting 96% of males.[7] The most common cause of death identified in the study was traffic accidents, with concurrent poly-drug usage being notably prevalent.

A case report detailing a single mitragynine-associated death revealed a blood mitragynine level of 950 ng/mL.[8]

It is critical to state the lethal concentration of mitragynine because of the potential effects of co-intoxicants, variation in individual metabolism, and methamphetamine and opioid tolerance. Postmortem change of mitragynine has not been clearly studied. Data on redistribution, stability, and other factors essential for

interpreting cases are currently unavailable. The synergistic toxicity of mitragynine in conjunction with other drugs targeting opioid and adrenergic receptors in the central nervous and cardiovascular systems may contribute to severe adverse effects and potential lethality.

Notably, our study revealed instances where individuals with mitragynine levels exceeding 1,000 ng/mL were still alive, while a death case report documented a single use with a level of 950 ng/mL. Conversely, some cases in our study exhibited mitragynine levels below 100 ng/mL but were complicated by co-intoxication and underlying diseases. Due to the diverse factors influencing the effects of mitragynine, a definitive proposed lethal concentration of mitragynine could not be established based on the available data. However, based on case reports highlighting the adverse effects of kratom ingestion on traffic safety and its association with fatalities, we propose that a blood concentration of mitragynine exceeding 25 ng/mL should be established as the cutoff point for driving impairment. Furthermore, levels surpassing 1,000 ng/mL may be indicative of sole mitragynine intoxication leading to death.[9]

Given these complexities and the absence of established toxic and lethal levels, it is the responsibility of forensic pathologists and toxicologists to meticulously gather and analyze all pertinent data to accurately interpret the effects of mitragynine found in each case.

In other Southeast Asian countries, kratom remains illegal and is regulated in Laos, Malaysia, Myanmar, Singapore, and Vietnam. In contrast, it is legal in Cambodia, the Philippines, and Indonesia.[10]

Analyzing the benefits and adverse effects of kratom reveals that some of its medicinal uses do not offer advantages over standard and traditional treatments. Most users consume kratom for recreational purposes or in conjunction with other narcotics. Although this study was conducted in the capital city, it may reflect trends in other major cities, suggesting an increasing use of kratom. Therefore, we recommend that kratom be regulated under narcotics legislation, as it has been in the past.

Conclusion

The number of deaths were attributed or possibly associated with kratom use or misuse. Traffic accident, undetermined and cardiovascular diseases were noted with mitragynine findings. Polysubstance use could be traced back to the original kratom product. The growing use and misuse of kratom, particularly following its removal from the Narcotic Act in Thailand, pose significant concerns. Therefore, there is a pressing need to reassess both the safety protocols surrounding its use and the regulatory framework governing its distribution and consumption.

Conflict of interest

The authors declare they have no conflicts of interest with the content of this article.

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Case Report

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Acute Fever with Painful Swelling of Leg in Alcoholic Cirrhosis Patient

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Abstract:

Patients with liver cirrhosis are susceptible to bacterial infection. The common infection sites are spontaneous bacteremia, urinary tract infection, pneumonia, soft tissue infection and spontaneous bacterial peritonitis. Gram-negative bacteria such as *Escherichia coli and Klebsiella* spp. were the most common microorganisms causing bacteremia in cirrhotic patients. *Vibrio, Aeromonas*, and *Campylobacter* spp. occasionally caused bacteremia in cirrhotic patients, but these individuals are at great risks for invasive infections. The vibrios are found in marine and surface waters. Aeromonads are inhabitants of aquatic ecosystems, worldwide, and are found in fresh and brackish waters. The campylobacters are found in many species of animals, including many domesticated animals. Here we report a case of soft tissue infection from *Aeromonas hydrophila* in liver cirrhosis patient which caused rapidly progressive septicemia and shock.

Keywords: Liver cirrhosis, Aeromonas infection, Sepsis, Septic shock

Introduction

Aeromonas hydrophila, is a facultative anaerobic Gram-negative rod present in fresh and brackish waters which causes opportunistic infections, as well as occasional cases of food- and water-borne illness. *A. hydrophila* is an opportunistic pathogen in humans causing extraintestinal and intestinal infections and is an animal pathogen leading to infections in fish, amphibians, and mammals.[1] It causes a broad spectrum of infections (septicemia, meningitis, endocarditis) in humans, often in immunocompromised hosts, and *Aeromonas* spp. have been associated epidemiologically with travelers' diarrhea.[2] The pathogenic potential of Aeromonas is considered multifactorial and the presence of several virulence factors allows these bacteria to adhere, invade, and destroy the host cells, overcoming the immune host response.[3] Wound and soft tissue infection especially at lower extremities is another manifestation of *A. hydrophila*. Patients usually had history of wading through water. *A. hydrophila* can cause severe localized skin infection. It may present as: folliculitis (pustules) and abscesses, impetigo-like rash with crusting and erosions that leads to ecthyma gangrenosum, cellulitis - redness and swelling involving deeper skin and

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necrotizing fasciitis - a rapidly destructive deep soft tissue and muscle infection. *A. hydrophila* skin infection is treated with antibiotics such as tetracyclines, sulfonamides, trimethoprim + sulphamethoxazole or ciprofloxacin. It is usually resistant to penicillin. An Aeromonas abscess is surgically drained. Recovery is followed by scarring with temporary or permanent hair loss.

Case Presentation

A 63-year-old man, underlying chronic HBV infection and alcoholic liver cirrhosis, Child Class C, living in Chiang Rai, presented with acute onset of fever, swelling and painful of left leg one day. Two hours prior to admission, he developed increasing pain of left calf. He had no diarrhea or abdominal pain. Without improvement after taking paracetamol, he went to the hospital for medical attention. The previous admission was one week before with diagnosis of hepatic encephalopathy. Physical examination at emergency service: BT 39.7°C, BP 88/42 mmHg, PR 136/min, RR 28/min. oxygen saturation on room air was 91%. General appearance: An old man, acutely ill, febrile with tachypnea, good consciousness and orientation. He had moderate dehydration, no anemia but moderate jaundice. He had normal breath sound, regular heart sound and tachycardia. Abdomen exam was unremarkable with negative fluid thrill. Extremities revealed swelling and tenderness at left calf, no erythematous, no discoloration, no crepitus, Homan's sign positive at left leg, left femoral artery 2+, popliteal artery 2+, dorsalis pedis 2+.

Leg circumference	
Right midthigh	Left midthigh
36 cm.	35 cm.
Right calf	Left calf
30.5 cm.	35 cm.

Problem list: Acute febrile with painful swelling of left calf.
Differential diagnosis was 1) deep venous thrombosis 2) Cellulitis

Investigation

Bedside ultrasound deep vein of left leg revealed no thrombosis on left femoral vein, compressible venous, not seen cobble stone appearance or fluid collection at left leg

Complete blood counts: Hct 41.8%, Hb 14.5 g/dL, WBC count 5.81 x 10^9/L, Neutrophil 90 %, Lymphocyte 6 %, Monocyte 3.5%, platelets 100 x 10^9/L

PT 18.4 sec, INR 1.7

BUN 33 mg/dL, Cr 1.47 mg/dL, GFR 50 mL/min/1.73 m^2

Electrolyte: Na 129 mmol/L, K 3.6 mmol/L, Cl 92 mmol/L, HCO3 23 mmol/L, Mg 1.7 mg/dL, Phosphorus 1.7 mg/dL

Liver function test: total protein 5.9 g/dL, albumin 2.7 g/dL, globulin 3.2 g/dL, ALT 79 U/L, AST 106 U/L, ALP 308 U/L, total bilirubin 8.4 mg/dL, direct bilirubin 7.1 mg/dL

Hemoculture: *Aeromonas hydrophila* x 2 specimens sensitive to ciprofloxacin, levofloxacin and tigecycline

Final Diagnosis: Necrotizing fasciitis of left leg caused by *Aeromonas hydrophila* with septicemia and rapidly progressive septic shock

Clinical course

Patient received piperacillin/tazobactam 4 gm intravenously every 4 hours and hydration. After 3 hours of admission, patient developed progressive hypotension and profound shock with alteration of

consciousness and peripheral vasoconstriction. Blood pressure was down to 60/40 mmHg, SpO_2 80%. Abdomen: distended, not tender. Neurological: E1V1M1, pupil 2 mm react to light both eyes. Extremities: Hemorrhagic bleb and ecchymosis was developed on left calf (Figure 1). Then, he had cardiac arrest and received CPR without success and was pronounced death after 24 hours of admission.

Figure 1 Left leg after hospitalization

Discussion

Cirrhosis is associated with several abnormalities in innate and adaptive components of the immune system's response to microbial challenge, leading to a state of acquired immunodeficiency.[4] Cirrhosis can cause sinusoidal fibrosis and capillarization, septal fibrosis with portal-systemic shunts, and Kupffer cell loss.[5] This structural derangement reduces the clearance of endotoxin and bacteria from the blood, leading to bacteremia, metastatic organ infection, and persistent immune system stimulation. A lack of Kupffer cells or of their complement receptors results in uncontrolled bacteremia and increased host death in experimental models.[6] In agreement with these experimental findings, diminished reticuloendothelial system function in cirrhosis has been associated with a greater risk of bacterial infection and lower survival.[7] In cirrhosis, there is coexistence of acquired immunodeficiency and systemic inflammation. The latter results from the persistent stimulation of immune cells and is defined by increased production and enhanced serum levels of pro-inflammatory cytokines and the upregulated expression of cell activation markers.[4] The clinical spectrum of cirrhosis associated immune dysfunction (CAID) varies from a poor response to the bacterial challenge, with

increased susceptibility to bacterial infection accompanied by high mortality, to multi-organ inflammatory damage. The clinical expression of bacteria-dependent events during cirrhosis includes both chronic systemic and organ-specific damage and intercurrent acute insults (i.e. acute-on-chronic).[8,9] It has been demonstrated that the greater the intensity of the cellular and molecular CAID, the greater the risk of severe bacterial infection. This patient presented with acute fever and painful leg swelling. Then, he had rapidly progressive of *Aeromonas hydrophila* septicemia, the possible transmission route might be skin and soft tissue of left leg which resulted in septic shock and multiorgan failure within 24 hours of admission. Although a history of exposure to fresh water is crucial, we did not get the definite history of this. We did not perform Gram stain of the hemorrhagic bleb because the patient was in critical condition. So, early recognition, detection and early intervention especially prompt broad-spectrum antibiotics with hemodynamic resuscitation is mandatory in cirrhosis patients who presented with acute fever and had signs of inflammation in any organs.

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Short Communication GMSMJ Greater Mekong Subregion Medical Journal

The Holistic Care for Heat Exhaustion Patients Associated with Excessive Body Mass Index: A Case Study

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Abstract:

The world today is being greatly impacted by global climate change and warming. Extremely hot weather usually occurs in Asia during the summer months of April and May and is associated with high humidity. People who may be at risk from these conditions include occupations that require working outdoors, such as military and police occupations that require training in the sun and other occupations such as street sweepers and first responders. For factory workers who must work outdoors, heat exhaustion is a condition that is second only to heat stroke, which can be differentially diagnosed by the neurological symptoms and a core body temperature of more than 40^0C. However, if the person who provides initial aid does not think about heat exhaustion and does not provide the correct first aid the condition may increase in severity and become heat stroke, which can be life-threatening. Heat exhaustion is caused by a loss of body water and minerals. If the person is unable to cool down quickly this allows the heat to affect the brain and muscular function, leading to heat stroke. This leads to muscle breakdown (rhabdomyolysis) causing acute kidney injury and hyperkalemia. Severe cardiac arrhythmias can cause sudden death. Patients may have symptoms of vomiting, headache, dizziness, gasping for breath, shortness of breath from the various internal organ dysfunctions.

Keywords: Heat exhaustion, Excessive Body Mass Index

Introduction

Conditions of heat illness (heat-related illness) is a result of the body being unable to dissipate heat in good time. This causes more and more heat to accumulate in the body, resulting in the body's systems functioning abnormally, from the cellular level to various body systems, resulting in various organ systems failing.[1,2] Heat-related illness can be divided into three levels of severity:

1) Heating edema, which is the first sign of heat illness, the patients will experience swelling in the hands and feet. They can notice the tightness of wearing rings or shoes. It usually occurs in the first few days as a warning sign of the body. This

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illness is caused by the dilation of blood vessels in the skin and fluid retention. Many patients may have painful muscle cramps or spasms in the abdomen, arms, or legs.

2) Heat exhaustion can include excessive sweating, clammy skin, a fever of over 38^{0}C (100.4^{0}F), dizziness, headaches, nausea, and a fast, weak pulse. Heat exhaustion can escalate to heat stroke if left untreated. Heat exhaustion is clinically similar to heat stroke, except heat exhaustion patients will have stable consciousness.

3) Heat stroke, is the most serious heat-related illness and requires immediate medical attention. Symptoms include a high body temperature of 39.4^{0}C (103°F) or higher, warm and dry skin, irritability, confusion, headaches, dizziness, staggering, slurred speech, agitation, nausea, vomiting, and a rapid heart rate along with symptoms from abnormal functioning of many organs such as muscular, digestive or circulatory system.[1,3,4] Seizures and loss of consciousness are possible. There are several risk factors for the development of heat stroke, including young age or the elderly, congenital heart disease, lung disease, obesity, and high body mass index or sedentary lifestyle, as well as being not used to hot weather. Certain medications such as diuretics, vasoconstrictors, antihypertensive drugs, (beta-blockers) and psychiatric drugs (antidepressants, antipsychotics and psychostimulants) including amphetamines and cocaine, also predispose to the likelihood of these conditions.

Management

The pathophysiology of heat-related illness occurs when the body is exposed to a sudden increase in temperature, such as in the case of working outdoor in extremely hot weather and high humidity. or during the extreme period of heat wave. The body is unable to adjust to the condition in time, causing heat exhaustion. If the patients receive initial treatment by rest, fluids and mineral supplement, such as ORS (oral rehydration salt), these measures can prevent the development of heat stroke which can be life-threatening. In cases of neurological symptoms such as confusion, seizures, or unconsciousness,[5] heat stroke is the most likely diagnosis. Immediate management is mandatory. Patients should be moved into the shade where the temperature is lower. The patient should be allowed to lie down with both feet elevated. The next step is to lower body temperature by using a cloth moistened with normal temperature water, wiping the body if the symptoms are mild. Be careful when drinking water without mineral salts, because this can cause water intoxication. Patients may experience dizziness or headache from the suddenly decreased concentration of extracellular mineral salts, while the intracellular levels are still concentrated. By osmosis this causes more water to permeate into the cells. Brain cells, in particular, will consequently become swollen (brain edema). To facilitate and increase blood flow back to the heart, patients should be allowed to lie with their feet elevated and their head lower than their body. In cases with muscle cramps, the patients should be placed in a cool place. and drink enough water and apply gentle heat compresses. Massage and stretching of muscles is also helpful.

When the patient is fully conscious, he should drink plenty of water (to 1 liter of drinking water add 1 teaspoon of table salt) to compensate for the salt lost from the body. If the patient is admitted to the hospital, blood electrolytes should be checked. Giving normal saline or 5% dextrose in normal saline intravenously can help patients recover faster. When the patient's symptoms subside, they should not return to working within a high heat environment immediately but should get rest for approximately

1-2 days. Patients should undergo a thorough physical examination and be taught to understand the effect of temperature of the air, especially the heat index value (air temperature and relative humidity, also often referred to as "wet bulb temperature") on the level of operation or exercise. The occurrence of heat exhaustion depends on the level of intensity and the time spent exposed to heat before symptoms of heat exhaustion occurs. This condition may not be caused by a lack of water and minerals, but may be caused by working in the heat alone. This is often found in people who are not accustomed to working in hot weather. Dehydration and salt loss may also be present, or it can be the underlying cause.[2,5] The important mechanism of the development of this disease is the dilation of blood vessels in the skin due to heat. This causes the blood volume in the arteries to be insufficient for adequate return to the heart. This prevents adequate blood pressure and reduced blood circulation to the brain.

Case report

A 27-year-old man, a military officer, was transported to hospital with a chief complaint of losing consciousness 30 minutes before being transferred to the hospital. Present illness: while standing in line for 3 hours, he began to feel restless, dizzy, had headache, sweating profusely, and began to pant. Then he fainted and lost consciousness. He received initial assistance by opening of his airway, wiping with wet towels, and was brought into the shade. He showed no improvement and was still unconscious. Past history: no known underlying diseases. Personnel history: no history of drug or food allergy. He had social drinking 2 times a month and did not drink during the previous week. He rarely smoked. There was no history of heat stroke in the family or a history of sudden death from heart disease in the family. At the hospital, physical examination revealed a young obese man who had regained consciousness and was fully co-operative. Body weight was 118 kg, height 176 cm with BMI of 38 kg/m^2. His vital signs showed rectal temperature of 38.5^{0}C, heart rate of 122/min, respiration 16/min and blood pressure 124/83 mmHg. Oxygen saturation (room air) 96%. He was not anemic, no icteric sclera. His chest, heart and abdominal examination was normal. Skin was remarkably red, dry and showed anhidrosis. He had warm extremities. Neurological examination, GCS was E4M6V5, pupils 3 mm both reacted to light. motor grade V/V all. Sensory and cerebellar signs were unremarkable. DTR 2+ all. Stiff neck was negative. Bedside investigation showed CBG 140 mg/dL, EKG: sinus tachycardia. Echocardiogram bedside: good LVEF. no LV D-shape. no pericardial effusion. IVC collapsibility index more than 50%.

The problem list was alteration of consciousness and hyperthermia. The differential diagnosis was 1) Heat-related illness [Heat stroke] 2) SIRS with sepsis 3) toxic synonym 4) Acute coronary syndrome

Initial investigation: CBC: Hct 48.4% WBC 10.2 x 10^9/L, PMN 45%, L 46%, M 5.1% Platelet 380 x 10^9/L. UA: Color yellow, appearance turbid, Sp.gr.1.020, Glucose negative, Ketone negative, Proteins 1+, Blood 1+, Bilirubin Negative, RBC 5-10 cells/HPF, WBC 1-2 cells/HPF, squamous epithelial 3-5 cells/HPF. PT 13.3 sec. PTT 18.0 sec. INR 1.11, Electrolyte: Na 145 mmol/L, K 3.3 mmol/LCl 102 mmol/L, CO2 22 mmol/L, BUN 14 mg/dL creatinine 1.2 mg/dL, calcium 10 mg/dL, (8.6-10.2) phosphorus 3.7 mg/dL (2.7-4.5), magnesium 1.8 mg/dL (1.7-2.55), LFT: total protein 8.1 g/dL, albumin 5.2 g/dL, total bilirubin 0.48 mg/dL, direct bilirubin 0.17 mg/dL, alkaline phosphatase 93 U/L, CPK 270 U/L,

lactate 3.2 mmol/L, urine amphetamine, marijuana negative, CSF analysis: WBC 2 cells/cu.mm. protein 27 mg/dL glucose 81 mg/dL. Gram stain: No organism found. CSF culture: no growth. Hemoculture: no growth

Emergency room treatment

He received initial cooling with strategic ice packs in the armpit area and neck, which are areas with many blood vessels passing through. Then body cooling by evaporation with a spray, using water at a temperature of 15^0C, and convection by blowing a fan at 45^0C, measuring core body temperature regularly, giving broad spectrum antibiotics because sepsis could not be ruled out, so ceftriaxone 2 gm IV was started after hemoculture, measuring lactate clearance level, and a retained Foley catheter. Initially, the patient felt better when the core temperature was measured at 38.2^0C. Therefore, he was only diagnosed with heat exhaustion, which is second in severity to heat stroke. Then, he was admitted to regular ward for observation. Patients diagnosed with heat stroke, should be admitted to the ICU for close evaluation because this is potentially an emergency and may cause life-threatening complications.

Discussion

This patient was diagnosed with heat exhaustion. The severity of which is secondary to heat stroke. which fits the following diagnostic criteria: core temperature more than 38.3^0C or more, history of exposure to high heat for a long period of time, symptoms including rapid heart rate, headache, dizziness, fainting, loss of consciousness. However, if the disease cannot be confirmed, treatment should be given as for heat stroke. Then a quick diagnosis can be made by measuring the core temperature through the rectum and try to reduce the core temperature as 1-2^0C can reduce the risk of brain damage.[6] In empirical evidence, a method that works well was to immerse patients in ice water. A study by Demartini et al. and colleagues was conducted on marathon athletes. Soaking in cold water at a temperature of 10^0C was not found to have survival benefit.[6] This procedure was not performed in this patient because preparation for a bath or bath is difficult in the emergency room. This patient had the procedure done using the strategic cold pack method, placing ice in areas lot of blood supply such as neck, armpits, and outer legs. He also got the evaporations spray method, spraying cool water at 15^0C followed by fan assisted drying at 45^0C, causing the water to evaporate and carry away the heat.[7,8] There is no empirical evidence of benefit from performing body lavage and cold intravenous infusions.

This patient has a BMI of 38 kg/m^2, which was very high and at risk for heat stroke.[9] Chung studied in soldiers and found that a BMI over 30 had an odds ratio of 4.29 times the chance of heat stroke, and this patient was not familiar with it. Although having a light work only one day, his body was unable to acclimatize, therefore heat exhaustion occurred. The heat environment on that day was 40^0C and relative humidity was 75, putting him at risk due to the high wet bulb temperature. Although this patient's symptoms did not reach the level of heat stroke, it was still necessary for him to stay in the hospital in order to monitor for any late complications.[1]The main life-threatening complication is a heart attack, even in young patient who was in good health.

Elevated body temperature causes pulmonary edema, brain swelling, liver injury and elevated liver enzymes. Liver function will begin to deteriorate until the condition of alopecia occurs or hypoglycemia. Within 24 hours, elevated body temperature can damage the blood

coagulation system and blood vessel walls. Thrombocytopenia, hypoprothrombinemia, hypofibrinogenemia may be detected. These can cause bleeding in various organs.

Higher body temperature causes dehydration along with the destruction of muscle cells (Rhabdomyolysis), causing skeletal muscle to break down so much that kidney failure can occur. Blood flow to the kidneys is also reduced. Therefore, acute tubular necrosis may occur, which may occur several days after injury. The amount of blood that feeds the digestive system (Splanchnic system) decreases, causing loose stools. or bleeding in the digestive tract. During the hospital stay, this patient had a low blood potassium level. A small amount had been corrected orally with potassium elixir and there was no evidence of muscle breakdown with normal CPK values following admission. It was probably caused by heat radiation alone. After 4 days in the hospital, the patient was able to return home. He was advised to lose weight and begin with light work and avoid working with heat exposure because he was at increased risk.

After returning home, he was to refrain from exercising and make an appointment to follow up in 7 days to check that the physical examination and blood results remained normal. He was advised to start exercising in the cold first, then to gradually increase intensity and temperature over 2 weeks. In cases where symptoms recur within 4 weeks, heat tolerance testing may be done to assess return to work where there is a risk of heat exposure. It should be noted that brain's heat regulation mechanism remains dysfunctional for several weeks. Therefore, heat exhaustion can reoccur if the person is still in a hot environment with inappropriate exercise.

Summary

Heat exhaustion is a disease that is second in severity to heat stroke, which can be differentially diagnosed from the symptoms of neurological symptoms and core body temperature lower than 40^0C. If the person providing first aid does not think about heat exhaustion and provide first aid according to general symptoms the condition may develop in severity and become heat stroke, which can be life-threatening.

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