Print ISSN 2549-7588 Online ISSN 2549-7596

Medical and Health Science Journal

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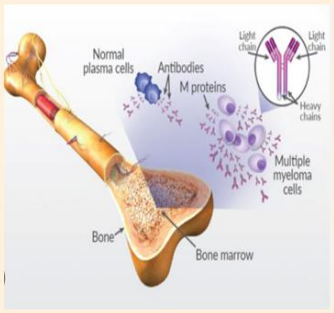

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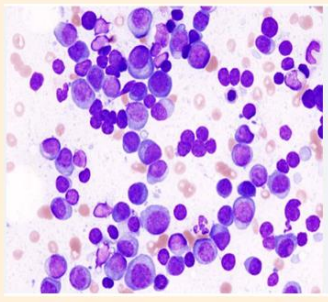

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Volume 08 Nomor 2, August 2024

ORIGINAL ARTICLE

The Impact of Docosahexaenoic Acid (DHA) Supplementation on Calcium Levels in Third Trimester Pregnant Women with Chronic Energy Deficiency (CED): A Correlational Study

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ARTICLE INFO

Article history:
Received :
September,3 2024
Received in revised form:
September, 7 2024
Accepted:
September, 30 2024

Keywords:
Chronic Energy Deficiency (CED), Pregnancy, Docosahexaenoic Acid (DHA), Calcium Levels

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ABSTRACT

Background: Chronic Energy Deficiency (CED) during pregnancy represents a critical health challenge, especially in developing regions, where it significantly threatens maternal and fetal well-being. Docosahexaenoic Acid (DHA), an essential omega-3 fatty acid, plays a pivotal role in fetal neurodevelopment and maternal health. However, the impact of DHA supplementation on maternal calcium levels, particularly among pregnant women affected by CED, has not been extensively studied. This study evaluate the correlation between DHA supplementation and calcium levels in third-trimester pregnant women with CED, with the goal of improving outcomes for this vulnerable population.
Method and Results: This research uses experimental cohort study design with a quantitative approach, using non-probability sampling techniques such as quota and purposive sampling, and involving a total of 24 participants. Statistical analysis revealed a significant increase in calcium levels following DHA supplementation, with a p-value of 0.007 (<0.05), indicating a notable impact of the intervention. The mean calcium levels post-treatment were higher than pre-treatment, demonstrating the efficacy of DHA supplementation in improving calcium levels. Further analysis showed no significant correlation between pre-supplementation calcium levels and Body Mass Index (BMI) ($p = 0.622$, > 0.05). However, a significant correlation was found between post-supplementation calcium levels and BMI ($p = 0.002$, < 0.05). These findings indicate a positive correlation between DHA supplementation and calcium levels in pregnant women with CED during the third trimester. However, further investigation is needed to fully understand the relationship between calcium levels and BMI.
Conclusion: This study lays the groundwork for future research aimed at optimizing therapeutic interventions or supplementation strategies to improve the nutritional status of underweight pregnant women.

Medical And Health Science Journal
Available at http://journal2.unusa.ac.id/index.php/MHSJ ; DOI: 10.33086/mhsj.v7i02.6409
pISSN 2549-7588. eISSN 2549-75961

Introduction

Chronic Energy Deficiency (CED) is a persistent and severe form of undernutrition that affects a substantial number of pregnant women, particularly in developing regions. Characterized by inadequate intake of calories and nutrients, CED poses significant risks to both maternal and fetal health, including increased susceptibility to infections, complications during childbirth, and adverse birth outcomes such as low birth weight and impaired fetal development. The condition underscores the critical need for effective nutritional interventions to support the health and well-being of both mother and child during pregnancy.[1,2]

Pregnant women with CED are pregnant women with nutritional deficiencies such as calories and protein. So that it affects the health of the mother and her baby. Pregnant women can be known to experience CED by looking at UAC (upper arm circumference) and < 23.5 cm. The 4,656,382 pregnant women in Indonesia, 451,350 are at risk of chronic energy deficiency and according to the Ministry of Health in 2020 the incidence rate was 9.7% in 2020. Then the basic health survey in 2018, the prevalence of pregnant women at risk of chronic energy deficiency (CHD) in Indonesia is 17.3 percent.[3]

Docosahexaenoic Acid (DHA), an omega-3 fatty acid, is essential for fetal neurodevelopment and maternal health. DHA plays a vital role in the development of the fetal brain and retina, and it has been associated with positive pregnancy outcomes such as prolonged gestation and reduced risk of preterm birth. Despite its recognized benefits, the impact of DHA supplementation on other physiological aspects, such as calcium metabolism, particularly in pregnant women affected by CED, has not been extensively studied.[4]

Calcium is a crucial mineral required for the development of the fetal skeletal system and the maintenance of maternal bone health. Pregnancy significantly increases the demand for calcium, and deficiencies can lead to serious complications such as gestational hypertension and preeclampsia. In the context of CED, where nutritional deficits are prevalent, understanding how DHA supplementation might influence calcium levels is of particular importance.[5]

This study aims to explore the correlation between DHA supplementation and calcium levels in pregnant women with CED during their third trimester. This research provide insights into potential nutritional strategies and contributing to better health outcomes for mothers and their babies.

Methods

This research uses experimental cohort study design with a quantitative approach, using non-probability sampling techniques such as quota and purposive sampling, and involving a total of 24 participants. The inclusion criteria in this study were pregnant women registered at Made and Simomulyo Health Center (gestational age 28-40 weeks or 3rd trimester) and pregnant women with CED (UAC < 23.5 cm). The exclusion criteria for this study were gestational age less than 28-40 weeks or less than the 3rd trimester and UAC > 23.5 cm, as well as samples that did not routinely take DHA supplements and withdrew from the study.

Results

In this study we conducted several analyses of respondents through the characteristics of respondents age, gestational age, weight, height, body mass index (BMI), calcium pre and post examination.

Table 1 Research Characteristics

Characteristics	N	Minimum	Maximum	Median	Mean	St Deviation
Respondents Age	24	22	39	28	29.37	4,79
Gestational Age	24	28	39	29,0	31,0	3,765
Weight	24	38,0	52,0	43.500	44.258	4,5154
Height	24	144	170	155.50	156.167	7.9052
BMI	24	17,21	18.61	18.3200	18.1079	0.43790
Calcium Pre	24	1.6	13.6	6.700	6.629	2.7765
Calcium post	24	1.2	17.7	8.700	8.842	4.2095

In this research characteristic, the number of respondents was 24 underweight pregnant women. The age characteristics of respondents are in the reproductive age category, namely 22 years to 33 years, then the gestational age represents the three trimesters of pregnancy, from 6 weeks to 27 weeks of gestation, so this study can represent each trimester of pregnancy. The characteristics of height and weight are limited to the underweight category.

Table 2 Normality of Research Data

Characteristics	N	Minimum
Respondents Age	24	.163
Gestational Age	24	<0,0001
Weight	24	.157
Height	24	.336
BMI	24	.001
Calcium Pre	24	.772
Calcium post	24	.888

In the normality test of the research data, it was found that BMI, gestational age, body weight data were abnormal because $p < 0.05$, while pre and post Calcium and Delta data were normal because $p > 0.05$.

Based on the results of the pre and post Calcium data normality test, it was declared normal because the p value> 0.05, so the comparison test used the Paired T test.

Table 3 Comparative Analysis of Calcium Pre and Post Treatment

	Mean ± SD	P
Calcium Pre	6,62 ± 2,77	0,007
Calcium Post	8,8 ± 4,20	

Based on the results of the normality test, the pre Calcium data is normal while BMI is abnormal, so the test of the relationship uses the Spearman test.

Table 4 Analysis of the Relationship Between Pre-Treatment Calcium Levels and BMI

	Mean ± SD	P
Calcium Pre	6,62 ± 2,77	0,723
BMI	18,10 ± 0,437	

Based on the results of the normality test, the post Calcium data is normal while BMI is abnormal, so the test of the relationship between post Calcium and BMI uses the Spearman test.

Table 5 Analysis of the Relationship Between Pre-Treatment Calcium Levels and BMI

	Mean ± SD	**P**
Calcium Post	8,8 ± 4,20	0,002 R = 0,608
BMI	18,10 ± 0,437	

Discussion

DHA increase plasma calcium levels, and thus increase bone mass; hence, our data confirm the valuable effects of PUFAs as the source of DHA on bone formation. Heaney et al. found that ω-3 DHA supplementation increased calcium absorption in humans. DHA maintain Ca and P homeostasis and do not cause disturbances in their nutritional balance. Numerous studies have indicated that DHA and their metabolites play important roles in regulating bone metabolism. The connection between DHA and bone metabolism might be attributed to various suggested mechanisms, including the regulation of osteoclast and osteoblast activity and differentiation, along with alterations in the fatty acid composition of bone cell membranes. DHA have been shown to reduce osteoclast activity while enhancing osteoblast function. Additionally, dietary supplementation with long-chain PUFAs has exhibited a protective effect against bone loss associated with aging.[6] Malondialdehyde, a byproduct of lipid peroxidation, is closely linked with oxidative stress.[7] In our study, DHA treatment significantly reduced oxidative stress across all groups. DHA supplementation notably decreased MDA levels in both serum and liver, as well as reduced hepatic oxidative stress. The reported immunological effects of DHA, including its role in improving pro-inflammatory status and combating oxidative stress, suggest it may help prevent or treat lipid peroxidation.[8] One possible mechanism is that osteocytes influence the development and function of osteoblasts and osteoclasts. Apoptotic osteocytes release pro-inflammatory cytokines like TNF-α, which promote osteoclastogenesis. Treatment with DHA lowered inflammation, and recent research shows that DHA intake effectively reduces inflammatory markers by lowering TNF-α level.[9]

The findings from this study underscore the potential benefits of Docosahexaenoic Acid (DHA) supplementation in improving calcium levels among third-trimester pregnant women with Chronic Energy Deficiency (CED). The results of the Paired T-test comparing calcium levels before and after treatment revealed a p-value of 0.007, which is below the significance threshold of 0.05, indicating a statistically significant difference. The mean calcium levels post-treatment were notably higher than pre-treatment levels, confirming that the administered treatment had a positive impact, leading to an increase in calcium levels. Our findings are consistent with the research conducted by Nami Kim et al., which demonstrated that DHA supplementation enhances the intensity of green fluorescence, a marker of calcium concentration in their study, reflecting an increase in intracellular Ca^{2+} levels.[10] This alignment supports the conclusion that DHA administration contributes to elevated calcium levels. Given the lack of previous research specifically addressing the impact of DHA on calcium levels in underweight pregnant women during the third trimester, our results provide a valuable foundation for future studies.[11]

The significant increase in calcium levels post-supplementation suggests that DHA may influence calcium metabolism, potentially through

mechanisms related to its anti-inflammatory properties and its role in enhancing nutrient absorption.[12] This is particularly relevant in populations with CED, where nutritional deficiencies are prevalent and can have detrimental effects on both maternal and fetal health.[13]

The normality test results showed that pre-treatment calcium levels were normally distributed, while BMI data were not. The analysis resulted in a p-value of 0.622, exceeding the significance threshold of 0.05, suggesting no statistically significant correlation between pre-treatment calcium levels and BMI. However, the analysis of the relationship between post-treatment calcium levels and BMI revealed a statistically significant association. The Spearman correlation coefficient (r) was 0.608, a positive value, indicating that higher post-treatment calcium levels are correlated with higher BMI. The coefficient of 0.608 reflects a strong relationship, accounting for 60.8% of the variance. These findings are consistent with the study by Xiao-hua Ren et al., which demonstrated a significant association between total serum calcium levels and the prevalence of overweight and obesity.[14] In their research, individuals in the highest quartile of serum calcium levels were found to have a higher risk of being overweight or obese compared to those in the lowest quartile. This suggests that elevated serum calcium may be a marker or contributing factor to increased body weight, supporting the correlation observed in our study.[15] In contrast, the study by Abdelmarouf H. Mohieldein et al. found a negative correlation between serum calcium concentrations and BMI ($r = -0.393$, $p = 0.003$), suggesting an inverse relationship that contradicts our findings. This discrepancy highlights the complexity of the calcium-BMI relationship and underscores the need for more targeted research to explore the underlying mechanisms. Notably, no previous studies have specifically examined the relationship between post-treatment calcium levels and BMI in underweight pregnant women during the third trimester. Thus, our findings not only fill a critical gap in the current literature but also lay the groundwork for future research to better understand the physiological and clinical implications of calcium metabolism during pregnancy.[16]

Conclusion

This study demonstrates that Docosahexaenoic Acid (DHA) supplementation in third-trimester pregnant women with Chronic Energy Deficiency (CED) has a significant positive impact on calcium levels. The findings indicate a strong, positive correlation between increased calcium levels following DHA supplementation and Body Mass Index (BMI). However, the study also highlights the need for further research to explore the underlying mechanisms of this relationship and to assess the long-term effects of DHA supplementation on both maternal and fetal outcomes.

Conflict of Interest

No conflict of interest in this study

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ORIGINAL ARTICLE

Explaining The Correlates of Child Mortality and Under-5 Survival in Nigeria

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ARTICLE INFO

Article history:
Received :
March 19, 2024
Received in revised form:
September 29, 2024
Accepted:
September 30, 2024

Keywords:
Child mortality, child survival, under-5, Nigeria

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ABSTRACT

Background: Survival of children under-5 is among the foremost public health concerns that has been pursued in the Sustainable Development Goals (SDGs). A proper understanding of the correlates of child survival is of paramount relevance to health policy formulation and development of interventions to promote child's health outcomes. This study therefore analysed the determinants of the number of recorded child mortality and survival in Nigeria.

Methods: The data were the Malaria Indicator Survey (MIS) that were collected in Nigeria in 2021. The samples were drawn with multi-stage sampling method following the 2023 Population and Housing Census sampling frame. A total of 14185 housing units were randomly selected of which 13887 were occupied and 13727 were successfully interviewed. In each household, all women belonging to the reproductive ages of 15-49 years were interviewed. A total of 14647 women were eligible, of which 14476 were successfully interviewed (Demographic and Health Survey (DHS), 2021). The data were analyzed using the Negative Binomial regression and logistic regression models.

Results: The logs of the number of dead children were significantly higher ($p<0.05$) for mothers from North West and North East Nigeria, while children from these regions also had a significantly lower probability of surviving. The mothers from urban areas had significantly lower log of dead children while urban children had significantly higher probability of surviving. Mothers with secondary and tertiary education had significantly lower log of dead children, while birth in the past five years and total children born reduced child's survival. Twin children also had a significantly lower probability of surviving while mother's maturity promoted child's survival.

Conclusion: Promotion of child survival in Nigeria requires a concerted effort that disaggregates interventions across Nigerian zones with preferences for those in the north and rural dwellers. In addition, there is the need to promote interventions to assist women with multiple births, promote girl child education and discourage teenage pregnancies.

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Introduction

Substantial progress in some basic indicators of child's health remains a globally authentic parameter for measuring socioeconomic development. Notable among these indicators is under-5 mortality rate, which measures the probability of a neonate dying before the age of five [1].More importantly, the Human Development Index (HDI), which is a composite index computed from life expectancy, education, and Gross Net Income (GNI) are associated with child's health outcomes. However, based on HDI and other economic development parameters, sub-Saharan Africa (SSA) countries are among the poorly rated in the world. Some statistics have shown that in 2021, SSA recorded the least HDI (0.547), while Europe and Central Asia had the highest value (0.796). Therefore, the survival battle of an average child in SSA is significantly complicated by the region's low life expectancy (60.1 years), low education coverage, and very low GNI (US$3699)[2]. More importantly, many SSA children are not fully vaccinated, although national coverages can be widely different with some statistics indicating that 24% for Guinea and 93% Rwanda [3].

A reflection on recent global child mortality statistics reveals a significant improvement, given a 59% decline between 1990 and 2021, when child mortality rates were one death per eleven live births and one death per twenty-six live births, respectively [1].However, a consensus exists among policy makers that more integrated effort should be applied in the fight against under-5 mortality for a better outcome. Specifically, in 2021, about 5 million under-5 children died in the world [1] due to some medical complications from preventable diseases. Moreover, under-5 mortality in SSA is disproportionately high with 3,323,165 and 2,902,961 deaths in 2011 and 2021, respectively [4]. Moreover, in 2021, SSA remains the hotspot of child mortality with one out of every fourteen children likely to die before reaching the age of five[5]. This figure is about fifteen times higher than what is obtainable in some high-income countries, and regrettably places SSA some twenty years behind the tick of time in the global fight against child mortality [5].

Currently, Nigeria is among the SSA countries with the highest under-5 mortality rates. In 2021, estimates showed that under-5 mortality in the country reduced to 111 per 1000 live births, from 133 in 2011. Accordingly, there was a decline in under-5 deaths from 886,075 in 2011 to 852,298 in 2021 [4]. The development implications of these statistics beg for more policy engagements on the identification of effective pathways for ensuring drastic reduction in under-5 mortality. This cannot be over-emphasized because majority of these deaths could have been prevented, should there be some improvements in the efficiency of healthcare service delivery, along with better utilization [6]. Although the Nigerian government is signatory to the Sustainable Development Goals (SDGs), the possibility of achieving the SDG 3, which seeks to reduce child mortality to 25 per 1000 live births in 2030 is perplexingly doubtful.

Moreover, a proper understanding of the correlates of child survival from the maternal and household perspectives can assist healthcare policy makers in their quests towards reduction in child mortality. The bedrock of such analyses has been the conceptual framework that was proposed by Mosley and Chen [7], which integrates some

economic, social, biological, and environmental factors into a set of proximate determinants that influence child survival through some exogenously defined maternal, paternal, health system and child factors. In Nigeria, there are rural-urban differences in households' access to orthodox healthcare services, with significant impacts on the timeliness of seeking medical care and sickness treatment outcomes. Child survival is promoted by timeliness of healthcare service utilization [8-10], and engagement of competent nurses and doctors during child's delivery [11-12]. It had been reported that residence in urban are as improves survival of child [8,13,14]. Similarly, some regional variables can influence child survival through some peculiar geographical and environmental features. More specifically, in Nigeria, northern zones had been found to have a higher level of [15,16]. Some authors have also integrated religion as a factor influencing child mortality [13], while maternal and paternal education will reduce child mortality and redefine the magnitude of the contributions of other socioeconomic factors to child's survival [17-19].

Maternal age and the age at first birth are concrete reflections of the extent of mother's physical, emotional, psychological, and financial maturity. These attributes are essential for the promotion of child's survival [20,21]. Moreover, teenage mothers are often inexperienced in child-raising matters, thereby increasing their likelihood of recording preventable child mortality. Other studies have found that households' wealth index [21-23], income, waste disposal methods, sources of drinking water [20,24] and the type of sanitation practices [20,23-25] are key determinants of child survival. The wealth of the households and associated housing attributes are essential for raising a child. Therefore, children that are raised in poor homes are likely to be deprived in some essential nutritious foods and health promoting facilities like clean water, improved sanitation, and clean environment.

Furthermore, some inherent child's factors have been found to influence child survival. These include the order of birth [26], child's age [27], gender [26] and being a singleton or twins. Some authors have reported that a higher birth order increases the probability of child survival [26]. However, others found male child to have a lower chance of surviving [28,29], although female child was reported to have a lower surviving chance by other authors [30]. Twin child had been found to have a lower probability of surviving, when compared to singleton. This can be traced to resource constraints and the tendency of some twins to have low weights. In some other studies, altitude increased the probability of child's survival [27]. It had been noted that mortality in high altitude areas may be promoted by a high risk of hypoxaemia at infancy and when the child suffers from acute lower respiratory infections [31].

The objective of this paper is to analyse the maternal and other socioeconomic variables that influence child mortality and under-5 survival. It was hypothesized that maternal and child's characteristics do not significantly explain child mortality and under-5 survival. The paper is a robust contribution to the growing body of knowledge on child survival by utilizing the most recent dataset to articulate the correlates of these vital health outcomes in one of Africa's hotspots for child mortality. The study approached the analyses at the maternal level with consideration of the determinants total child's deaths and at child's

level, with the analysis of the determinants of child's survival.

Methods

1. The data and sampling procedures

This study used the dataset for the 2021 Malaria Indicator Survey (MIS). Although the survey's main objective is to evaluate progress in some basic malaria indicators, being an offshoot of the conventional Demographic and Health Survey (DHS), it integrates some conventional health indicators like child's survival, mortality, and other health outcomes. The 2021 survey was the third MIS to be conducted in Nigeria, since 2010 when the first data were collected. The survey was based on the proposed 2023 Population and Housing Census sampling frame. The multi-stage sampling method was adopted. The first stage comprised of a random selection of 568 clusters with 373 rural areas and 195 from urban areas. The second stage involved listing of all the households in each of the selected clusters, from where 25 households were randomly selected for interview. Therefore, across the country, a total of 14185 housing units were randomly selected of which 13887 were occupied and 13727 were successfully interviewed. In each household, all women belonging to the reproductive ages of 15-49 years were interviewed. A total of 14647 women were eligible, of which 14476 were successfully interviewed [32].

The MIS comprised of four questionnaires which were for households, women, biomarkers, and fieldworkers. The data were collected after being pre-tested during some training sections that were conducted for 31 participants between 6-18 September 2021. The main survey trainings were conducted for 214 enumerators, 47 medical laboratory scientists, and 37 nurses between 20 September and 7 October 2021. The MIS data were collected between 12 October and 4 December 2021 in every Nigerian state and the Federal Capital Territory (FCT) by a survey team comprising a supervisor, a medical laboratory scientist, a nurse and two interviewers. The questionnaire, which was originally designed in English was translated into Nigeria's three predominant languages - Hausa, Yoruba, and Igbo. Data from the respondents were entered on phone tablets, registered, verified, and transmitted to the National Population Commission's (NPC) central office. Editing and processing of data were done by CSPro software. Compliance with essential ethical procedures for questionnaire administration was observed and the survey protocols were evaluated and approved by "the National Health Research Ethics Committee of Nigeria (NHREC) and the ICF Institutional Review Board" [32].

2. Estimated models

The negative binomial regression

The correlates of child mortality were analysed with negative binomial regression, which is a hybrid form of the Poisson regression. This model was used to analyse the determinants of the number of dead children reported by each interviewed woman. Following Lord and Park [33], this model is specified for a random variable Yi that follows Poisson distribution as:

$$g(Y_i, \mu_i) = \frac{e^{-\mu}\mu_i}{Y_i!} \qquad .1$$

Where Y_i is a count of the deceased children 0, 1, 2,3, 4, …..k, and μ_i is the mean of the Poisson distribution. The basic assumption of the specification in equation 1 is that the conditional mean and variance are equal. When this is violated, the model is said to be over-dispersed, and an alternative model like negative binomial regression

should be considered. The estimated Poisson regression model using the STATA 17 software is to be subjected to goodness-of-fit test. If this is statistically significant, the model fails the basic assumption of Poisson model and an alternative model, such as the negative binomial regression model should be used. The estimated model is specified as:

$\mu_i = \exp(\beta_0 + \sum_{i=1}^{k} \beta_i X_i + \mu_i)$ .2

In equation 2, X_i are the explanatory variables,β_0 andβ_i are the estimated parameters and u_i is the random error.

Logistic Regression Model

Logistic regression was used to analyse determinants of child survival. The dependent variable was specified as 1 for surviving children and 0 otherwise. The model is specified as:

$log\left(\frac{\pi}{1-\pi}\right) = \gamma_0 + \gamma_i \sum_{i=1}^{d} X_i + e_i$ .3

In equation 3, π denotes the probability of child being alive andγ_0 and $\gamma_i$are the parameters to be estimated, and e_i is the stochastic error term.

Results

The results in Table 1 show the mean of selected demographic variables for the sampled children and mothers. It reveals that 96.38% of all the children born by selected women were alive, while average number of dead children was 0.456. Across the regions, 37.37% of the children and 32.96% of the mothers were from the North West zone. Although South East recorded the lowest percentage of the under-5 children (7.75%), South West reported the lowest percentage for eligible women (8.34%). In addition, urban areas accounted for 27.87% of eligible children and 29.45% of eligible women. Average age of eligible women was 29.30 years, while that for eligible children was 30.03 months. Of all the eligible children, 65.53% and 57.15% had access to improved water sources and sanitation, respectively. Also, among the eligible women, 67.57% and 60.17% had access to improved water sources and sanitation, respectively. Males accounted for 51.38% of the eligible children and only 5.71% were twins. The average altitudes for children and mothers were 325.13 m and 300.58 m, respectively. Also, while 43.62% of the eligible mothers had no formal education, 31.48% and 10.66% had secondary and tertiary education, respectively. Mobile phones were owned by 57.48% of the mothers. Average birth in the past five years was 1.526 and average total children were 3.973.

Table 1 Mean of the selected demographic variables across sampled respondents

Variables	**Coding format**	**Means across the children (n=10988)**	**Means across the mothers (n= 7222**
Alive children	Alive =1, 0 otherwise	.9637557	
Total dead	Number of dead children		.4564808
Regions			
North Central	Yes=1, 0 otherwise	.164444	.1960078
North East	Yes=1, 0 otherwise	.1791391	.1592662
North West	Yes=1, 0 otherwise	.3736697	.3295553
South East	Yes=1, 0 otherwise	.077536	.1357121

South South	Yes=1, 0 otherwise	.1029472	.0960926
South West	Yes=1, 0 otherwise	.102264	.083366
Urban resident	Yes=1, 0 otherwise	.2786649	.2945252
Household head gender	Male=1, 0 otherwise	.9344174	.9214733
Mother's age	Years	29.14311	29.29617
Improved water sources	Yes=1, 0 otherwise	.6553359	.6757395
Improved sanitation practices	Yes=1, 0 otherwise	.5715477	.6017022
Gender of the child	Male=1, 0 otherwise	.5138611	.5216076
Altitude of place of residence	Meters	325.1275	300.5842
Usage of mosquito nets	Yes=1, 0 otherwise	.6652138	.6322549
Age of the child	Years	30.0257	29.89384
Child is a twin	Yes=1, 0 otherwise	.0570783	.0241331
Mother's educational levels			
None	Yes=1, 0 otherwise	.4611254	.4362461
Primary	Yes=1, 0 otherwise	.1545751	.1423092
Secondary	Yes=1, 0 otherwise	.2868196	.314801
Tertiary	Yes=1, 0 otherwise	.0974798	.1066437
Births in the past 5 years	Number	1.791658	1.526023
Own a mobile phone	Yes=1, 0 otherwise	.5394846	.5748197
Total children	Number	4.262147	3.973311
Household's head age	Years	43.11179	43.13773
Wealth index	Composite indicator	-26349.88	-20467.72

Table 2 Mean of child mortality and survival across selected demographic variables

Variables	Average Dead Children	Percentage Alive Children
North Central	.2315634	.9810863
North East	.4773414	.9620438
North West	.8215136	.9465008
South East	.2083333	.994863
South South	.2397408	.9803371
South West	.1391941	.981203
Rural	.5077258	.9646465
Urban	.2713891	.9785671
No Education	.666996	.9580242
Primary	.5085066	.966932
Secondary	.2121993	.9801667
Tertiary	.1200000	.9810181
All	.4365827	.9687841

Table 2 further shows the distributions of child mortality and survival across selected demographic variables. It reveals that average number of dead children was highest in the North West zone with 0.822, while South West had the lowest value of 0.139. Women who were resident in rural areas had a higher average number of dead children with 0.507, as against 0.271 for urban residents. The women with no education had a higher average mortality of 0.667, as against 0.120 for those with tertiary education. Similarly, North West zone had the lowest child survival rate of 94.65%, while South East had the highest (99.49%). The children from rural areas had 96.46% survival rate, while those from urban areas had 97.86%. Child's survival rate among children whose mothers had no formal education was the lowest (96.69%), as against 98.10% for those with mothers who attained tertiary education.

Table 3 Determinants of child mortality (negative binomial regression) and survival (logit regression)

	Child Mortality (NBREG)		**Child Survival (Logit)**		
Variables	Coeff	z-stat	Coeff	Odds ratio	z-stat
Dwelling Characteristics& Wealth					
North East	.4296908***	3.50	-.8441968***	.4299025***	-3.83
North West	1.066941***	9.51	-.8339873***	.4343141***	-3.96

South East	-.0180727	-0.10	1.420923***	4.140939	2.74
South South	.0349559	0.24	-.2877871	.7499212	-0.91
South West	-.214499	-1.27	.1469957	1.158349	0.43
Urban residence	-.3625935***	-4.25	.607531***	1.835893***	3.17
Improved drinking water	.107572	1.61	-.0885613	.915247	-0.63
Improved sanitation	-.0471624	-0.66	-.1772003	.837612	-1.19
Altitude of residence	-.000371**	-2.30	.0003824	1.000382	1.14
Mosquito net usage	.1715777**	2.36	.0355724	1.036213	0.25
Mothers' Characteristics					
Head gender	.0553766	0.38	.0375186	1.038231	0.11
Mothers' age	.0679007***	15.06	.0500485***	1.051322***	4.07
Mother born twins	.6076846***	3.02	-	-	-
Education level of Mother					
Primary	.0453676	0.55	-.1005889	.9043048	-0.52
Secondary	-.4086559***	-3.95	.1156973	1.122656	0.51
Tertiary	-.7763053***	-4.50	-.0890547	.9147955	-0.25
Births in the past five years	.032957	0.69	-.4483745***	.6386655***	-4.46
Ownership of mobile phone	.0097721	0.14	-.4437012***	.6416571***	-2.75
Head age	-.0008999	-0.39	-.0037	.9265841	-0.78
Total child born	-	-	-.0762504**	.9963069**	-2.58
Child's characteristics					
Sex of the child	.0585781	0.87	-.3102565**	.7332588**	-2.46
Age of child	-.0003643	-0.16	.0018021	1.001804	0.53
Child is Twins	-	-	-.6750176***	.5091474***	-5.63
Wealth of households					
Wealth index	-2.44e-06***	-4.45	1.11e-06	1.000001	0.98
Constant	-3.450194***	-13.75	4.043795***	57.0424***	6.94
Lnalpha	.4836562				
Alpha	1.621994				
Number of observations	7222		10988		
Wald chi2(22)	1011.28***		203.90***		

Note: *** - statistically significant at 1 percent level; ** - statistically significant at 5 percent level

Table 3 shows the results of negative binomial regression (NBREG) and logit regression. The explanatory variables were examined for multicollinearity using the Variance Inflation Factor (VIF). These values were generally low (<2.00) for the two models, showing that multicollinearity was not a problem. The computed Wald Chi-Square statistics revealed that the stated hypotheses of no significant association between the selected characteristics of the mothers and the children in relation with child mortality and child survival cannot be accepted. The models therefore produced good fits for the data. Two of the regional dummy parameters – North East and North West – showed statistical significance in the child mortality model ($p<0.01$). In addition to these, South East region dummy parameter showed statistical significance in the child survival model ($p<0.01$). The NBREG results indicate that holding other variables constant, and when compared with mothers from the North Central region, the respondents from North East and North West had their logs of dead children increased by 0.4297 and 1.0669, respectively. In addition, the logit results showed that if other variables are held constant, and when compared with the children who resided in North Central region, the children from the North East and North West regions were 57.01% and 56.56% less likely to survive. In addition, those from the South East region are 314.09% more likely to survive, when compared with their counterparts from the North Central region.

The dummy parameters of urban residence in the two models also showed statistical significance ($p<0.01$). When compared with their rural counterparts, the log of dead children reduced by 0.363 for mothers from urban areas. Similarly, the children who were residing in urban areas had 83.59% more likelihood of surviving, when compared with their counterparts from rural areas. The altitude parameters in the NBREG model showed statistical significance ($p<0.05$). This implies that as altitude of place of mothers' residence increases by one meter, the log of dead children decreased by 0.0004. However, contrary to expectation, the mothers who were using mosquito nets had their log of dead children significantly increased by 0.1716 ($p<0.05$), when compared with those who were not using nets.

The parameters of mothers' age variable showed statistical significance ($p<0.01$) in the two models. In the NBREG, it implies that as the mothers' age increased by one year, the log of dead children increased by 0.0679. Also, the logit results indicate that as mothers' age increases by one year, the likelihood of child survival increases by 5.13%. The results further revealed that the mothers who gave birth to twins had their log of dead children significantly increased by 0.6077 ($p<0.01$), when compared with women with singletons.

Among the variables that captured some characteristics possessed by the children, gender dummy parameters show statistical significance ($p<0.05$) in the logit model. Male children were 26.67% less likely to survive, when compared with their female counterparts. Twin children were 49.09% less likely to survive than their counterparts who were not of multiple births.

Discussion

The results have shown the magnitude of child mortality, and determinants of child survival in Nigeria. The children who were born in the North-West and North-East regions had a lower probability of surviving. This agrees with the

findings from some previous studies [22,34,35]. Low child survival in northern Nigeria can be attributed to several factors, among which poverty is notable. Specifically, under-5 children are the foremost recipients of persistent economic deprivations in Nigeria, where northern regions disproportionately account for about 87% of poor households [36]. Economic situation in northern Nigeria has been adversely affected by growing insecurity that has subsumed many households into chronic poverty [37]. Similarly, urban children had a higher probability of surviving than their rural counterparts. This is in consonant with the findings of some previous studies [34, 35, 38]. Survival of urban children may have been promoted from biasness in the distribution of some basic health and social infrastructures and services that often favours urban centres.

The altitude of mother's residence reduced the total recorded deaths among children. This is contrary to the findings in some previous studies but in line with finding of Oyekale [27]. Literature emphasizes some pathways through which child's growth may be adversely influenced by their residences' altitudes. These are possibility of chronic hypoxia in high altitudes, soil fertility and nutrient depletion and exposure to some disease-causing pathogens [39]. Mohammed et al. [40] found that children in high altitudes had higher incidence of stunting, as compared with their lowland counterparts. Contrary to expectation, child mortality was higher in households that indicated under-5 children slept under mosquito net in the previous night. However, with mosquito being one of the major ways to prevent malaria among children, it is also important to note that children can be exposed to mosquito bites in other places within the household. More importantly, the use of mosquito net has been found to reduce malaria-related child mortality in rural Tanzania [41] and promote overall survival of children [42]. It should also be emphasized that child mortality may have resulted from other causes besides malaria, and the use of mosquito net as captured in the data did not probe into long-term compliance.

The results further showed that the number of dead children from a mother increased with their ages. This may be due to expected correlation between mothers' age and the number children born. However, as the age of the mothers increased, the chance of surviving increased. This is expected because children born to under-aged mothers are often with low birth weights, thereby reducing their chances of surviving. The finding is contrary to those of Friede et al. [43] and Tesema et al. [44], but in agreement with those of Noori et al. [45], Finlay et al. [46] and Finlay et al. [47]. Emphases have been placed on some factors that promote child mortality among young mothers. These include physical and biological unpreparedness for pregnancy, complications, inadequate access to antenatal care (ANC), stigmatization, poverty and increased economic vulnerability [48-50].

As expected, attainment of secondary and tertiary education by the mothers reduced the number of dead children. Educated mothers are expected to have the requisite money and expertise to properly take of children. They are also expected to understand the essence of timely utilisation of some healthcare services when the child is sick, and the role of adequate nutrition and vaccination in promoting child's health [51]. The results are in accordance with those of Adewusi and Nwokocha [52], Oyekale and Maselwa [30], Andriano and Monden [53], Gakidou et al. [54], Yaya et al. [21], Balaj et al. [17], Murarkar et al. [18], and Fenta and

Fenta [19]. The role of maternal fertility and child's spacing in explaining child's mortality was also evaluated. These results indicate that the number of births within past five years of data collection and total children born reduced the chance of child's survival. These findings are expected because short preceding birth intervals and high maternal fertility have been reported to promote child mortality [30,55].

Finally, the role of multiple births in explaining child's survival was explored and the results revealed that mother who gave birth to twins recorded a higher number of dead children. Similarly, the children who were born as twins also recorded a lower probability of surviving. These findings are expected and in accordance with those of Jahn et al. [56], Dejene and Girma [57] and Stock and Norman [58]. Mortality among twins can be promoted by a higher probability of being born with low weight due to a very high tendency of preterm delivery, resource constraints from parent and limitations from mothers to effectively breastfeed two children.

Conclusion

A proper understanding of the correlates of the rate of child mortality and survival is of fundamental importance in promoting achievement of some SDGs. This remains a pressing concern for many countries in SSA due to their notoriously high rate of child mortality, despite some drastic reduction in global incidences. In this study, focusing on the most populous country in Africa, some correlates of child's survival were analyzed and the results have highlighted some vital issues for policy interventions. Specifically, some regional differences exist in child mortality and survival in Nigeria. This emphasizes the need for region-differentiated and integrated approaches to address child's health outcomes in Nigeria. Specifically, there is the need to intensify efforts in reducing child mortality in the states in northern Nigeria and among residents in rural areas. Revitalization of rural health care facilities with functioning emergency response preparedness promises to address progress inequity in child survival among rural children and their urban counterparts. In addition, promotion of maternal education promises to reduce child mortality. There is the need for interventions to facilitate enrolment of girl child in education facilities and concerted efforts in promoting information on the dangers of teenage pregnancy and high fertility. Proper creation of awareness on the use of family planning can assist in reducing maternal fertility, which will impact on child survival. Finally, there is the need for public health interventions at the local, state, and national levels to assist economically vulnerable women with multiple foetuses right from the time of being detected. Such interventions can target enhancement of their access to medical services, counselling, and post-delivery financial assistances.

Conflict of Interest

No conflict of interest in this study

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ORIGINAL ARTICLE

In-Vitro Susceptibility Testing of Dermatophytes Isolated in Delhi (India) Against Five Antifungal Drugs

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ARTICLE INFO

Article history:
Received :
March 1, 2024
Received in revised form:
September 29,2024
Accepted:
October 2, 2024

Keywords:
Dermatophytes, broth microdilution method, minimal inhibitory concentration, culture plates & antifungal drugs

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ABSTRACT

Background: Over the past few decades, cases of dermatophytosis have been on the rise. Recently, the introduction of newer, less toxic antifungal drugs has improved treatment options. However, the prolonged use of antifungals has led to the emergence of acquired resistance among strains that were previously susceptible, as well as an increase in infections caused by less common species. This scenario underscores the growing need for rapid and accurate antifungal susceptibility testing methods. In this study, antifungal susceptibility was assessed using the in-vitro micro broth dilution method, adhering to the CLSI M38-A guidelines

Methods: 60 clinical specimens were collected from Nail and skin of the patients of dermatophytosis from Delhi (India). Minimal inhibitory concentration (MIC) was performed in microtiter plates with U-bottom and incubated at 35° C. Reading were taken after 48 & 96 hrs of incubation for Trichophyton mentagrophytes and Trichophyton rubrum, against 5 antifungal drugs namely fluconazole, itraconazole (triazoles), griseofulvin, terbinafine and Luliconazole.

Results: Most of the dermatophytes had uniform patterns of susceptibility to the antifungal agents tested. Low MIC values as 0.03µg/mL were found for 33.3%, 31.6% and 15% of isolates for itraconazole and terbinafine, respectively.

Conclusion: In conclusion, it may be useful to undertake periodical screening programs to detect the antifungal susceptibility of newer antifungal agents.

Medical and Health Science Journal

Introduction

Dermatophytes, a group of keratinophilic filamentous fungi thriving on the keratin substrate are the etiological agents responsible for causing Dermatophytosis in human and animal worldwide. Dermatophytosis is a fungal infection of the skin, hair and nail caused as a result on colonization of the keratinized layers of the body by organisms belonging to the three genera namely Trichophyton, Microsporum and Epidermophyton. More predominant in the tropical and subtropical countries; especially in the developing countries like India where the hot climate and humid weather is favorable to the acquisition and maintenance of the disease.[1] The World Health Organization estimates global prevalence of Dermatophytosis to be approximately 20percent. The incidence of onychomycosis has been reported to be 0.5-5% in general population and it may be as high as 45 percent as detected in a five year study from North India. The reported prevalence of onychomycosis varies from 2% to 8% [2] worldwide and from 0.5% to 5% in India.[3]

Oral antifungal therapy such as triazoles (itraconazole, fluconazole), allylamine (terbinafine), griseofulvin and Luliconazole are current systemic treatment of choice for Dermatophytosis that do not respond to the tropical therapy.[4] Role of antifungal in reducing the fungal load to have the association of immune clearance the degree of clinically failure is 25-40%.[5] However, the relapse rate is upto 10 percent in toenail onychomycosis after cessation of therapy. The variable activity of these drugs leading to treatment failure can be attributed to poor patient compliance, infection with the new strain, lack of drug penetration into the nail, medication bioavailability, or drug interactions and resistance.[6-8] In-vitro antifungal susceptibility tests could help in optimizing the therapy and to select an effective antifungal agent for dermatophytosis.[9-10]

Therefore, the purpose of this study was to detect the in-vitro antifungal susceptibility testing of dermatophytes isolated from superficial skin and nail infections against antifungal agents like fluconazole, itraconazole, terbinafine, griseofulvin and luliconazole at a tertiary care hospital of North India using the broth micro dilution method (M38-A) according to CLSI standards (previously the NCCLS method).

Materials and Methods

Study group

The present study was conducted on 50 clinically diagnosed patients with dermatophytosis of skin and nail attending dermatology out patient centre of a tertiary care hospital, Delhi. The data from the patients were collected by supplying a data sheet regarding name, age, sex, address, occupation, family history, and socioeconomic background, duration of illness personal contact at home, work place/school and involvement of more than one site. The samples from patients were collected in aseptic conditions from infected areas by scraping such as skin, nail collected in the Mycology section of the department of Microbiology, GTB Hospitral, Delhi. Each clinical sample was mixed with a drop of 10% potassium hydroxide (KOH) and examined under a light microscope. Part of the specimen was then cultured on Sabouraud's dextrose agar (Hi-media) containing chloramphenicol (0.05 g/l), gentamicin (20 mg/l), and cycloheximide (0.5 g/l). The inoculated tubes were kept at 25°C to promote optimal fungal growth. Upon observing growth,

the causative organism was identified based on the unique morphology of the colony and the microscopic characteristics of the fungus observed on a Lacto Phenol Cotton Blue (LPCB) slide. These isolates were further analyzed for antifungal sensitivity.

Preparation Antifungal agents as per CLSI M-38 A -:

Antifungal drugs: Antifungal drugs fluconazole, itraconazole, terbinafine & griseofulvin, Luliconazole were obtained from Sigma Pvt. Ltd. Fluconazole was dissolved in sterile distilled water and all other drugs were dissolved in 100% Dimethyl Sulfoxide (Invitrogen) following the protocol of CLSI M – 38 A. Stock solutions of 1,000 µg/ ml were prepared for each drug and stored at -20°C till tests were performed. All the drugs were further diluted to two fold dilutions were performed. All working solution of drugs diluted in DMSO should always be prepared in tubes with the same solvent (DMSO) before transferring onto plates, whereas serial dilutions of water soluble drugs are prepared directly in Microtitre plate. The final concentrations ranged from 0.125 to 64 µg/mL for fluconazole, 0.03 to 16 µg/mL for,itraconazole and terbinafine, and 0.03 to 8 µg/mL for griseofulvin, Luliconzole 0.00625 to2 µg/mL.

Preparation of inoculum:- The MIC was performed according to CSLI (M38-A) modified method in a polysterene microtiter plates with U-bottom wells. Dermatophyte inoculum suspensions were prepared using seven-day-old sub-cultures grown on Sabouraud dextrose agar at 25°C. About 10 mL of normal saline was poured over the fungal colonies, and the surface was gently scraped with the tip of a sterile loop to produce the suspensions. After collecting the mixture of conidia and hyphal fragments, it was transferred into sterile tubes and allowed to settle for 15 to 20 minutes at room temperature. The optical density of these suspensions was measured at 530 nm, adjusted to a transmittance of 65 to 70% (equivalent to 1 to 4 X 10^6 cells/mL), and then diluted with RPMI 1640 medium and MOPS (4-Morpholinepropanesulfonic acid) from Sigma Chemical Co., St. Louis, Mo. A 1:50 dilution was made to achieve a final inoculum concentration of approximately 0.4 X 10^3 to 5 X 10^4 cells/mL. The density of the inoculum was confirmed through quantitative colony counts using a Colony Counter unit.

Test procedure (Susceptibility testing):- 100 µL RPMI & antifungal was distributed in all wells and 200 µL of RPMI was taken as growth control in the u-bottom microtitre plate . 100 µL of inoculum was added in each well except growth control well.Growth and sterility control wells also maintained for each assay and all the tests were performed in duplicate. MICs of quality-control ATCC strains of C. parapsilosis ATCC-22019 and C. krusei ATCC-6258 were also used. Plates were incubated for 96 hrs at 350C.MICs were based on the lowest drug dilution that inhibited at least 80% of growth compared with the control. Dermatophytes, MIC measurements were taken using a viewing mirror.

Endpoint determination

Visual assessments for endpoint determination were conducted every 24 hours for up to 96 hours, observing the growth in a control well without the drug. Minimum Inhibitory Concentrations (MICs) were evaluated in duplicate across three separate tests. The MIC was identified as the least concentration of the drug that prevented fungal growth. For azole medications, the MIC was

recognized as the concentration that achieved an 80% reduction in growth relative to the control. Growth sterility controls were included in each test. For Terbinafine, the MIC was the concentration that completely inhibited growth by 100%, whereas for Fluconazole, it was 50%. For Itraconazole and Griseofulvin, the MIC was determined as the concentration that visibly inhibited approximately 80% of fungal growth. MIC50 was determined by the concentration at which 50% of the isolates were inhibited, and MIC90 was noted at the concentration inhibiting 90% of the isolates. The MIC values were determined based on the extent of growth inhibition. Luliconazole MICs were defined according to the established MIC reports.

Statistical analysis:- MIC data were transformed to a normal distribution using the ANOVA was used to compare each antifungal agent vs. its MIC for each isolate . Differences in MIC values were analyzed using the Tukey test (a = 0.05). Mean geometric MIC values were determined for all the isolates tested, and the MIC values at which 50% and 90% of the isolates were inhibited (MIC50 and MIC90, respectively) were determined only for groups containing ‡T.R 15 & T.M 35 isolates. SAS using software (Version 6.12; SAS Institute, NC State University, Raleigh, NC, USA) . $P < 0.05$ was considered not significant.

Results

A total of 50 dermatophytes strains, including Trichophyton rubrum (n = 15), T. mentagrophytes (n = 35) from nail (35) and skin(15) were tested.

Table 1 Pattern of in-vitro activity of 5 antifungal against 50 clinical isolates of *T. rubrumand T. mentagrophytes* from dermatophytosis patients by micro dilution testing

SAMPLE S.no.	Samples	Species	Fluconazole Range (ug/ml)	Itraconazole Range (ug/ml)	Terbinafine Range (ug/ml)	Griseofulvin Range (ug/ml)	Luliconazole Range (ug/ml)
1	Nail	T.M	1	0.0313	0.125	0.0313	0.00005
2	Nail	T.R *	64	16	16	0.5	0.00005
3	Nail	T.M	64	0.625	0.25	0.125	0.00005
4	Nail	T.R *	1	0.5	0.625	0.625	0.00005
5	Nail	T.M	2	4	0.125	8	0.00005
6	Nail	T.R *	4	8	8	0.0313	0.00005
7	Nail	T.M	4	8	0.125	4	0.00005
8	Nail	T.M	8	0.5	0.125	0.25	0.00005
9	Nail	T.M	8	0.0313	0.5	0.5	0.00025
10	Nail	T.M	8	16	0.0313	0.5	0.00005
11	Nail	T.M	4	0.125	0.0625	0.125	0.00005
12	Nail	T.M	2	0.125	0.0313	0.125	0.00005
13	Nail	T.R *	64	4	0.125	0.625	0.00025

14	Nail	T.R *	1	8	0.625	0.0313	0.00005
15	Nail	T.M	64	0.5	8	16	0.00025
16	Skin	T.R *	128	0.0313	0.0313	0.0313	0.00005
17	Skin	T.M	8	0.5	0.125	0.25	0.00005
18	Skin	T.M	32	0.25	0.125	0.0313	0.00005
19	Skin	T.M	8	2	0.5	0.125	0.00005
20	Skin	T.R *	4	2	0.0313	4	0.00025
21	Skin	T.R *	2	0.0313	0.0313	0.125	0.00005
22	Skin	T.M	1	0.0313	0.0313	0.125	0.00005
23	Skin	T.M	32	0.0625	0.625	8	0.00025
24	Skin	T.M	1	0.0313	0.5	0.625	0.00005
25	Skin	T.M	0.5	0.625	0.0313	0.625	0.00005
26	Skin	T.M	0.5	0.125	0.0313	0.0313	0.00005
27	Skin	T.R *	0.5	4	0.125	0.0313	0.00005
28	Skin	T.R *	64	2	8	16	0.00025
29	Skin	T.R *	128	0.0313	0.125	0.125	0.00005
30	Skin	T.M	8	0.313	0.625	0.25	0.00005
31	Skin	T.M	1	0.0313	0.125	0.625	0.0012
32	Skin	T.M	1	0.5	0.125	0.125	0.00005
33	Skin	T.M	0.5	2	0.125	0.125	0.00005
34	Skin	T.R *	0.5	0.625	0.0313	0.5	0.0012
35	Skin	T.R *	1	0.125	0.0313	0.625	0.00005
36	Skin	T.M	1	0.125	0.125	0.125	0.00005
37	Skin	T.R*	2	0.125	0.0313	0.125	0.00005
38	Skin	T.M	1	0.0313	0.0313	0.5	0.0012
39	Skin	T.M	2	0.0313	0.0125	0.125	0.00005
40	Skin	T.M	1	0.0313	0.0313	0.0313	0.00005
41	Skin	T.R *	64	0.625	0.0313	0.125	0.00025
42	Skin	T.M	1	0.625	0.0625	0.0313	0.00005
43	Skin	T.M	1	0.0313	0.0313	0.0313	0.00005
44	Skin	T.M	2	0.0313	0.625	0.0625	0.00005
45	Skin	T.M	1	0.625	0.125	0.0313	0.00025
46	Skin	T.M	2	0.125	0.0313	0.625	0.00005
47	Skin	T.M	1	0.125	0.625	0.0313	0.00005
48	Skin	T.M	2	0.0313	0.625	0.0313	0.00025
49	Skin	T.M	1	0.0313	0.0313	0.0625	0.00005
50	Skin	T.M	2	0.0125	0.0313	0.0313	0.00005

Summarizes the MIC ranges, concentrations inhibiting 50% MIC50) and 90% (MIC90) of the isolates and Nail (15)& Skin(35) in T.R & T.M of the MICs against the five antifungal drugs against 50 strains of dermatophytes. The MIC ranges of Fluconazole, Itraconazole (triazoles), Terbinafine, Griseofulvin and Luliconazole for within the values standardized by CLSI document M-38-A.

Table 2 Activity of fluconazole, Itraconazole, Terbinafine,Griseofulvin and Luliconazole against dermatophytes by Minimum inhibitory concentrations (MICs) for tested antifungal drugs against a range

Antifungal drugs	**Break points**	**Species (no.)**	**R**	**SDD**	**S**	**MIC 50**	**MIC 90**	**GM**
Fluconazole	S≤ 8, SDD ≤ ≥64 R≥64	T.R 15 T.M 35	4 4	0 2	11 29	8	32	16.09
Itraconazole	S≤0.125, SDD ≤ ≥0.25-0.5 R≥1	T.R 15 T.M 35	7 5	2 3	6 27	0.125	1	1.68
Terbinafine	S≤0.125, SDD ≤ ≥0.25-0.5 R≥1	T.R 15 T.M 35	2 2	2 2	11 31	0.5	2	0.97
Griseofulvin	S≤0.125, SDD ≤ ≥0.25-0.5 R≥1	T.R 15 T.M 35	2 4	2 6	11 25	0.5	2	1.32
Luliconazole	S≤0.0005, SDD ≤ ≥0.0625-0.0125 R≥0.25	T.R 15 T.M 35	0 0	1 2	14 33	0.0005	0.016	0.00015

Antifungal activity against dermatophyte species

The he dermatophytes most frequently isolated were T. rubrum and T. mentagrophytes, as indicated in Table 1. Terbinafine demonstrated superior antifungal efficacy against these fungi, with geometric mean (GM) values of 0.014 for T. rubrum and 0.190 for T. mentagrophytes, as shown in Tables 2 and 3. Significant variations were observed in the MIC values of all antifungals tested against the dermatophytes on days 2 and 6, whereas the differences in MIC values between days 2 and 4 were not statistically significant ($P > 0.05$)

Table 3 Species V/S Drugs

Antifungal drugs	Break points	Species (no.)	R	SDD	S	MIC 50	MIC 90	GM
Fluconazole	S≤ 8, SDD ≤ ≥64 R≥64	T.R 15 T.M 35	4 4	0 2	11 29	8	32	16.09
Itraconazole	S≤0.125, SDD ≤ ≥0.25-0.5 R≥1	T.R 15 T.M 35	7 5	2 3	6 27	0.125	1	1.68
Terbinafine	S≤0.125, SDD ≤ ≥0.25-0.5 R≥1	T.R 15 T.M 35	2 2	2 2	11 31	0.5	2	0.97
Griseofulvin	S≤0.125, SDD ≤ ≥0.25-0.5 R≥1	T.R 15 T.M 35	2 4	2 6	11 25	0.5	2	1.32
Luliconazole	S≤0.0005, SDD ≤ ≥0.0625-0.0125 R≥0.25	T.R 15 T.M 35	0 0	1 2	14 33	0.0005	0.016	0.00015

Minimum inhibitory concentrations (MICs) for tested antifungal drugs against a range of organisms.

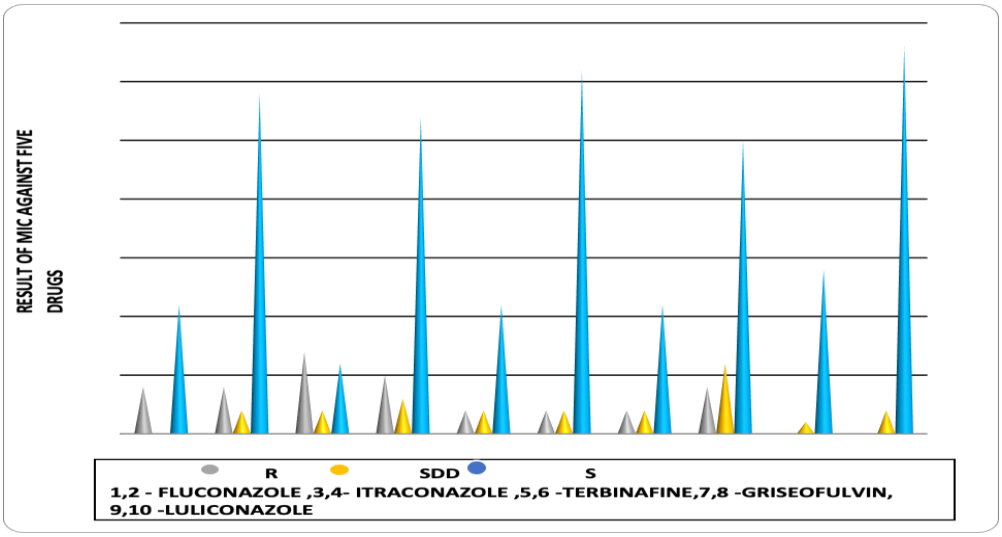

Figure 1 Bar chart for species v/s drugs

In case of fluconazole total 16 % cases resistant(R), 4 % cases susceptible but dose depended (SDD) & 80% cases are sensitive(S).Itraconazole- 24 % cases R,12% cases SDD & 64% S, Terbinafine – 8 % cases are R, 6 % SDD & 86 % cases are Sensitive . Griseofulvin - 12% R, 16% SDD & 72 % sensitive. Luliconazole – 6 % SDD & 94 % are sensitive.

Table 4 Total percentages of Resistant, SDD & Sensitive

Antifungal drugs	**Resistant % N = 50**	**Susceptible but dose depended (SDD)% N = 50**	**Sensitive % N = 50**
Fluconazole	16%	4%	80%
Itraconazole	24%	12%	64%
Terbinafine	8%	6%	86%
Griseofulvin	12%	16%	72%
Luliconazole	0%	6%	94%

Table 5 Percentage of resistant isolates

Antifungal drugs	**Species**	**Resistant % N = 50**	**Susceptible but dose depended (SDD)% N = 50**	**Sensitive % N = 50**
Fluconazole	T.R T.M	3.75%	4%	80%
Itraconazole	T.R T.M	24%	12%	64%
Terbinafine	T.R T.M	8%	6%	86%
Griseofulvin	T.R T.M	12%	16%	72%
Luliconazole	T.R T.M	0%	6%	94%

Note: I – Itraconazole, T –Terbinafine, G-Griseofulvin, L -Luliconazole

Discussion

Treating fungal infections is more challenging than treating bacterial infections due to the eukaryotic nature of fungal cells, which are structurally closer to human cells than bacteria. This similarity means that many antifungal drugs can also be toxic to humans.[11-12] Additionally, fungal cells possess a detoxification mechanism that can alter many antibiotics, often through hydroxylation.[13] Effective antifungal agents often work by removing sterols from the membrane or inhibiting their synthesis. Most target the production or function of ergosterol, a crucial element of the fungal cell membrane.[14-20]

Currently, there are no universally accepted thresholds (epidemiological cutoff values) to define susceptibility or resistance of dermatophyte strains to antifungals across various regions. [21-25] Therefore, our minimum inhibitory concentration (MIC) benchmarks for fluconazole, itraconazole, and griseofulvin are based on standardized reference methods and CLSI guidelines.[19] In our study, most antifungal drugs except fluconazole exhibited effective activity against dermatophytes, with itraconazole and terbinafine showing particularly low MIC values and geometric means, corroborating findings by other researchers who noted similar efficacy. These low MICs contribute to the promising treatment outcomes observed for dermatophytosis with these drugs.

Despite fluconazole displaying the highest MIC values among the tested antifungals, we found that T. rubrum strains, which often cause chronic, stubborn infections, were more responsive to this drug compared to T. mentagrophytes and M. canis strains, with geometric means of 7.60 for T. rubrum, 9.96 for M. canis, and 11.31 for T. mentagrophytes.[26-30] This observation aligns with findings by Fernández-Torres et al., who noted fluconazole's higher efficacy against T. rubrum than T. mentagrophytes.

Conclusion

In conclusion, it may be useful to undertake periodical screening programs to detect the antifungal susceptibility of newer antifungal agents. Our data on the antifungal susceptibility of dermatophyte isolates may contribute to a choice of antifungal treatment to ringworm infections. Terbinafine is considered as most potent drug. But still the efficacy of Terbinafine drug was totally dependent upon the variation of causative dermatophytic strains of particular tinea infections. We consider that our study on the antifungal susceptibility of dermatophytes can be beneficial for investigation of in vitro resistance of dermatophytic species, and for management of cases clinically unresponsive to treatment.

Conflict of Interest

The authors declare no potential conflicts of interest or competing interests. The authors received non-financial assistance or grants from public, private, or non-profit funding agencies.

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ORIGINAL ARTICLE

Antidepressant Effects of Mitragyna speciosa Korth Extract on Diabetic Rats

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ARTICLE INFO

Article history:
Received: May 30, 2024
Received in revised form:
October 5, 2024
Accepted:
October 19, 2024

Keywords:
Mitragynine, Diabetes Melitus, FST

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ABSTRACT

Background: Diabetes mellitus is most common associated with neurological complications, including depressive symptoms, so this study investigated whether *mitragyna* may provide benefits in reducing depressive symptoms in animal models of diabetes. This study aims to evaluate the effect of *mitragyna* as a potential antidepressant agent in animal models of diabetes mellitus using the Force Swimming Test (FST).
Methods: In this study, diabetes mellitus rats were induced by administering streptozotocin and then divided into four groups: control group (Control), Group Diabetes (DM), *Mitragyna* treatment group (DM+EMS 15mg) and (DM+EMS 30mg). After the treatment period, the rats were then tested with the FST, which is used to measure immobility behavior which can be used as an indicator of depressive symptoms.
Results: The results showed that the treatment group that received *mitragyna* showed shorter immobility times compared to the control group ($P<0.01$), indicating an increased active response in facing FST stressors.
Conclusion: These results indicate that *mitragyna* has potential as an antidepressant agent in reducing depressive *symptoms* in rats models of diabetes mellitus.

Medical And Health Science Journal
Available at http://journal2.unusa.ac.id/index.php/MHSJ ; DOI: 10.33086/mhsj.v7i02.5919
pISSN 2549-7588. eISSN 2549-75961

Introduction

Depression is a common mental disorder worldwide and can occur alongside other medical conditions, including diabetes.[1] Diabetes mellitus is a chronic disease characterized by high levels of glucose in the blood and significantly affected quality of life patient.[2] Diabetics have a higher risk of developing depression compared to the general population. Treatment of depression usually involves taking antidepressants, but these medications often have undesirable side effects. *Mitragyna speciosa Korth* (otherwise known as Kratom) is a plant from Southeast Asia and has been used traditionally as a herbal medicine to treat various health problems, including depression.[3] Several studies have demonstrated the potential of *Mitragyna speciosa* in treating symptoms of depression, but no studies have specifically explored its antidepressant effects in individuals suffering from diabetes.[4]

Force Swimming test (FST) is a method has been used in experimental study. FST used for evaluated behavioral and measure the level of depression in mouse. This test involves forcing rats to swim in a pool of water for a certain period of time and measuring their behavior during the swimming test.[5]

This study aims to evaluate the antidepressant effect of *Mitragyna speciosa Korth* extract on rats suffering from type 2 diabetes by testing the swimming method. Data from this study is expected to provide new insight into the potential use of *Mitragyna speciosa* as an alternative treatment for depression in individuals with underlying medical conditions such as diabetes.

Methods

This is a research experimental study, with the research design control group (Post Test Only Control Group Design), by taking measurements after the treatment is given.

Extraction and fractions methods

The extraction method used in this research is maceration. A total of 3 kg of dried *Mitragyna speciosa Korth* simplicia powder was extracted using 96% methanol solvent. Change the solvent every 1x24 hours and macerate for 7x24 hours. The maserate is concentrated using a rotary evaporator and water bath to obtain a thick extract.

Experimental animals

The experimental animals used were *Mus musculus* purchased from PUSVEPMA. A total of 20 male rats were separated according to research groups, namely control group (K), DM group, DM group and 15 mg dose of *Mitragyna speciosa Korth* extract (DM+EMS1), and DM group and 30 mg *Mitragyna speciosa Korth* extract (DM+MS2). Before testing, the rats were adapted (acclimatized) for one week in the UNUSA Faculty of Medicine Research Laboratory. Before treatment, the weight of the test animals was weighed and marked. The test animals used are those that comply with the criteria for the use of test animals and have passed the ethical review. Then, grouped according to treatment.

Streptozotocin induction

Streptozotocin (STZ) induction uses a dose of 75 mg/kg BW by injection via the intraperitoneal route for 3 consecutive days.

Forced Swimming Test (FST)

Forced Swim Test (FST) was carried out according to Yankelevitch-Yahav et al. (2015) with modifications. The test was carried out by placing rats in a tube filled with water at a certain depth so

that the rats's hind legs did not touch the bottom of the tube and their front legs could not hold on to the edge of the tube. The water temperature is adjusted to room temperature because water temperature that is too cold can trigger more active swimming behavior. The duration of forced swimming was 6 minutes and the time when the rats showed signs of immobility was recorded.

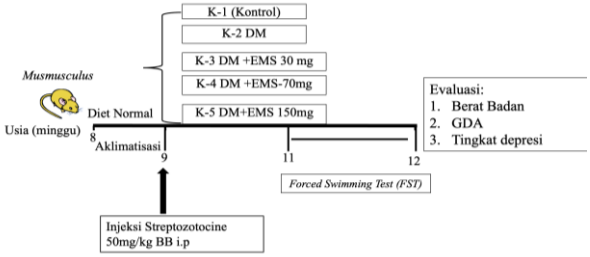

Figure 1. Design studies

Blood Glucose examination

After 14 days of treatment, blood glucose levels were evaluated.

Data Analysis

Research data are presented as mean ± standard error. By analyzing with the ANOVA test. If it does not meet the ANOVA test then use a non-parametric test, namely the Kruskal Wallis Test. Then proceed with the Mann-Whitney test.

Results

Effect of *Mitragynine* on immobility time Forced swim test (FST)

The forced swim test (FST) is a behavioral test commonly used in preclinical research to assess depression-like behavior and the potential antidepressant effects of a substance. Animals subjected to FST (usually rodents) are placed in a container filled with water so that they cannot escape. The time they spend immobile is considered an indicator of hopeless or depression-like behavior. *Mitragynine*, as one of the main active compounds in kratom, has been the subject of research to understand its effects on behavior and physiology.

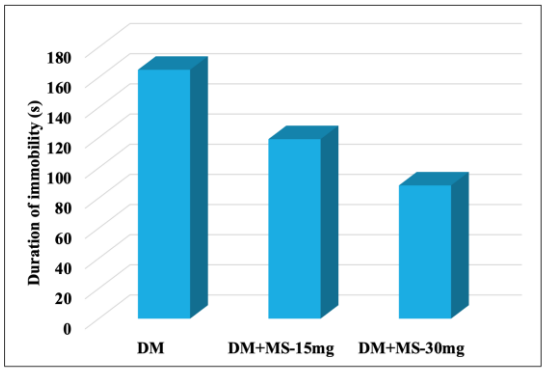

Figure 2. Effect of *Mitragynine* on FST immobility

This study showed that after 30 minutes of treatment, mitragynine significantly reduced ($P < 0.05$) the duration of immobility time at 15 mg/kg and 30 mg/kg respectively compared with the diabetes mellitus group.

Discussion

Comorbidity of diabetes and depression represents a significant clinical challenge, and new treatment options are needed. *Mitragynine*, which is one of the herbal plants that has potential as an antidepressant, is a promising candidate. The results of this study suggest that Mitragyna speciosa Korth, commonly known as kratom, exhibits significant antidepressant effects in diabetic rats, a finding that aligns with previous research demonstrating the psychotropic potential of kratom alkaloids (Singh et al., 2019).[9] Notably, the administration of kratom extract resulted in a marked improvement in the behavioral symptoms associated with depression in diabetic models, as evidenced by increased exploration in the open field test and a reduced immobility time in the

forced swim test (Hassan et al., 2017).[10] The findings of this study suggest that *Mitragyna speciosa* Korth, commonly known as kratom, has notable antidepressant effects in diabetic rats. These effects are particularly significant given the dual challenge of managing diabetes and depression concurrently. Kratom's efficacy could be attributed to its active alkaloids, such as mitragynine, which have been previously noted for their impact on mood regulation through interaction with opioid receptors (Singh et al., 2019).[9] The observed reduction in immobility time in the FST in diabetic rats treated with *Mitragynine* supports the hypothesis that *Mitragynine* may reduce depressive-like behavior in this population. These effects can be attributed to its interactions with various neurotransmitter systems.[6]

Behavioral assessments, including the open field test and the forced swim test, indicated improved activity levels and reduced signs of despair in rats after treatment with kratom extract. These behavioral changes are consistent with prior studies indicating the potential of kratom extracts in alleviating depressive symptoms through neurotransmitter modulation (Hassan et al., 2017).[10-12] Additionally, the observed improvement in glycemic control among the treated rats suggests a possible synergistic effect of kratom's antidiabetic properties, which could further enhance its antidepressant potential. [6,13]

The interaction between kratom's analgesic and antidepressant properties is particularly relevant in diabetic populations, where chronic pain is a prevalent and debilitating symptom.[14,15] The ability of kratom to address pain, a common comorbid condition, may contribute to its overall effectiveness in improving mood.[16,17,18] However, while the analgesic properties of kratom are well-documented, their direct contribution to its antidepressant effects warrants further investigation.

Despite these promising findings, the use of kratom is not without concerns. The potential for dependency and the variability in alkaloid content across different batches of kratom pose significant challenges. These factors complicate its clinical use and necessitate standardized production practices to ensure consistent therapeutic outcomes.[19]

The results showed that diabetic rats treated with *Mitragynine* exhibited significantly reduced immobility time in the FST compared with diabetic control rats. This suggests that *Mitragynine* may exert antidepressant-like effects in diabetic rats, potentially reducing the comorbidity of depression in diabetes.[7] *Mitragynine's* mechanism of action includes modulation of opioid receptors, adrenergic receptors, and serotonin receptors, all of which are involved in the pathophysiology of depression.[8] Further research is needed to elucidate the precise mechanism through which *Mitragynine* exerts its antidepressant effects in diabetic rats.

In light of these results, kratom presents a potential natural alternative for treating depression in diabetic patients. However, extensive clinical trials are necessary to fully understand its mechanisms, therapeutic potential, and safety profile. Future research should focus on the pharmacokinetics, long-term effects, and optimal dosing of kratom to establish its efficacy and safety in clinical settings.[20]

Conclusion

These results indicate that *Mitragyna* has potential as an antidepressant agent in reducing depressive *symptoms* in rats models of diabetes mellitus. This suggests that *Mitragynine* potentially reducing the comorbidity of depression by mechanism modulation of opioid receptors, adrenergic receptors, and serotonin receptors, all of which are involved in the pathophysiology of depression.

Limitations and Further Research

However, the study's limitations include a lack of comparison with non-diabetic rats and other standard antidepressants, which could provide additional insights into the specific antidepressant effects of mitragynine in the context of diabetes. Future research should also address the long-term effects and safety profile of mitragynine, especially given the chronic nature of diabetes and depression. Further pharmacokinetic and pharmacodynamic studies are necessary to explore how mitragynine interacts with other common medications in diabetic populations, which is critical for its potential use as an adjunct therapy. Additionally, transitioning from animal models to human clinical trials is essential to validate these findings and consider any translational implications.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

All authors are grateful to Desy for their expert technical assistance. Authors also thanks Research and Community Service Institute Universitas Nahdlaul Ulama Surabaya for the grant funds provided with contract number.....

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ORIGINAL ARTICLE

The Relationship between Body Mass Index and Blood Pressure Control in Hypertension Patients at the Sukawati I Community Health Center, Gianyar Regency

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ARTICLE INFO

Article history:
Received: June 25, 2023
Received in revised form;
September 29, 2024
Accepted:
October 19, 2024

Keywords:
Hypertension, BMI, Blood Pressure Control

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ABSTRACT

Background: Being overweight or obese is one of the factors that cause an increase in blood pressure. The bigger a person's body, the more blood is needed to supply nutrients and oxygen to other tissues and muscles. Bali Province, especially Gianyar Regency, has a relatively high number of hypertension sufferers. The highest estimate of hypertension sufferers is in the working area of the Sukawati I Public Health Center, with a prevalence of 8.55% of the total in Gianyar Regency of 17.35%. This research aims to determine the relationship between body mass index and blood pressure control in hypertensive patients at the Sukawati I Public Health Center, Gianyar Regency.

Methods: The research design used was analytic observational with a cross-sectional approach. The number of research subjects, namely 83 people, was taken by consecutive sampling technique. Data analysis will be carried out univariately and bivariate using the chi-square test method with a confidence level of 95% ($p < 0.05$).

Results: The results of the univariate analysis showed that the majority of study subjects were aged 51-60 years (60.2%), were female (66.3%), most had normal BMI (66.3%), and 66.3% of subjects with hypertension were classified as have controlled blood control. Based on the results of statistical tests, a value of $p = 0.003$ ($p < 0.05$) was obtained, which indicated a significant relationship between body mass index and blood pressure control in hypertensive patients at the Sukawati I Public Health Center, Gianyar Regency. **Conclusion:** The results of this study indicate that the increasing BMI status of hypertensive patients will tend to have uncontrolled blood pressure.

Medical And Health Science Journal
Available at http://journal2.unusa.ac.id/index.php/MHSJ ; DOI: 10.33086/mhsj.v7i02.4580
pISSN 2549-7588. eISSN 2549-75961

Introduction

Hypertension is a health problem that receives serious attention in every world. Hypertension is an important risk implication of cardiovascular diseases such as stroke, heart problems, kidney disease, and heart attacks[1]. Based on data from the World Health Organization (WHO), it is estimated that 1.28 billion adults aged 30 to 79 years in several countries suffer from high blood pressure[1]. Basic Health Research (Riskesdas) states that the high blood pressure level in Indonesia is 34.1%[2]. Riskesdas data for 2018 shows Bali Province has a hypertension prevalence rate of 30.97%. Data from Riskesdas for the Province of Bali in 2020 showed that Gianyar Regency had 89,603 cases of hypertension sufferers at the age of >15 years, but only 18,773 patients, or 21% received health services[3]. According to the Gianyar Regency health profile data for 2020, the highest incidence of hypertension is in the working areas of the Ubud I, Gianyar II, Sukawati II, and Sukawati I Health Centers[4]. The total estimation of hypertension sufferers in the working area of the Sukawati I Health Center is 10,872 people out of a total population of 127,050 people. In comparison, only 1,196 people have just received health services. The number of sufferers receiving this health service when compared to the public health centers with the other highest incidence of hypertension is still very far away. As a comparison, the working area of Ubud I, with the highest incidence of hypertension has an estimated number of hypertension sufferers of 4,811 people and those who have received health services totaling 3,160 people[4]. In this case, each working area of the public health centers must have an active role in capturing and providing health services to people with hypertension because hypertension is classified as one of the top 10 diseases and ranks 2nd[4].

Hypertension is a condition in the composition of the blood circulation which increases blood pressure above the standard limit, which is above 140/90 mmHg[5]. High blood pressure becomes very dangerous if the patient does not control blood pressure so that it is below 140/90 mmHg, because, in a long time it can cause various complications. The high incidence of hypertension is caused by risk factors that can be divided into two components: components that cannot be changed and those that can be changed. Components that cannot be altered consist of gender, race, age, and heredity. Components that can be changed include obesity, stress, smoking, lack of exercise, and hyperlipidemia[6]. The National Health and Nutrition Examination Survey III (NHANES III) says that the increase in hypertension in obese men is 42% and in women with obesity is 38%. Hypertension with obesity has a relationship as illustrated by increased plasma volume and cardiac output (output), hyperinsulinemia or insulin resistance, increased activity of sympathetic nerve structures, sodium retention, and dysregulation of salt regulating hormone. The blood that the body needs to carry nutrients and oxygen to all organs will increase with the increase in one's body size[6]. The assessment of whether a person is included in the obese category or not, which is often used is by using anthropometry. Anthropometric measurements consist of various methods, one of which is by measuring Body Mass Index (BMI)[7]. Previous research has suggested that there is a link between BMI and blood pressure in people with

hypertension, where respondents with obesity are more likely to have hypertension (91.3%) than non-obese respondents who have hypertension (58.2%)(8). The results of other studies also convey that a high prevalence rate of obesity will increase the prevalence rate of hypertension. In contrast, other studies suggest that there is no relevant link between BMI and the incidence of hypertension[9]. Based on the background above, researchers are very interested in getting the answer by carrying out scientific evidence through a study that focuses on finding out whether there is a relationship between body mass index and blood pressure control in hypertension sufferers who are at the Sukawati I Health Center, Gianyar Regency, Bali.

Methods

The method used in this study is an analytic observational survey with a cross-sectional method. This research was conducted at the Sukawati I Public Health Center, Sukawati District, Gianyar Regency from August to November 2022. The population was high blood pressure sufferers aged 18-60 years who routinely came for control and the number of samples taken was 83 people who met the criteria set has been determined. The primary data measured were blood pressure, weight, and height. The instrument used to measure blood pressure control utilizes a mercury tension meter with the Riester brand. Weight measurement uses a digital weight scale with the Onemed brand and a stature meter with the Onemed brand for height measurements. Furthermore, the data will be analyzed using the Chi-Square test with the SPSS program. This research was approved based on an ethical clearance letter from Udayana University issued on October 27, 2022.

Results

Characteristics of Respondents

Based on the research that has been done, it shows that the sufferers of high blood pressure at the Sukawati I Health Center, Sukawati District, Gianyar Regency mainly occur in the female sex, namely 55 people (66.3%). The age distribution of the study subjects showed that high blood pressure sufferers at the Sukawati I Health Center, Sukawati District, Gianyar Regency mostly occurred in the age range of 51-60 years, namely 50 people (60.2%).

Table 1. Distribution of Gender and Age of Study Subjects

Variable	Total (n), (%)
Gender	
Man	28 (33,7)
Woman	55 (66,7)
Age	
18-30 Years	2 (2,4)
31-40 Years	6 (7,2)
41-50 Years	25 (30,1)
51-60 Years	50 (60,2)

Source: Research Data, 2022

The distribution of the study subjects' body mass index showed that most people with high blood pressure at the Sukawati I Public Health Center, Sukawati District, Gianyar Regency had a normal BMI, namely 55 people (66.3%).

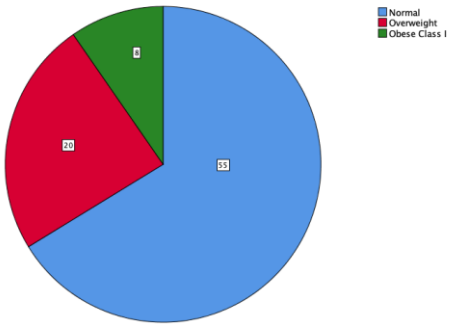

Figure 1. Distribution of Body Mass Index of Study Subjects

The distribution of blood pressure control in the study subjects showed that 55 people (66.3%) had controlled blood pressure at the Sukawati I Public Health Center, Sukawati District, Gianyar Regency.

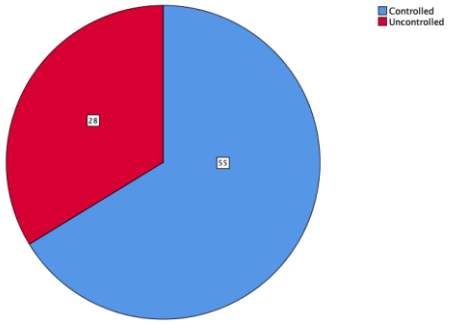

Figure 2. Distribution of Blood Pressure Control of Study Subjects

Correlation Test Between Body Mass Index And Blood Pressure Control

Based on the analysis that has been done, it shows that most of the study subjects with normal body mass index have controlled blood pressure, namely 40 people (72.7%). Most study subjects with overweight body mass index had controlled blood pressure, namely 14 people (70%). While study subjects with obesity body mass index I mostly had uncontrolled blood pressure, namely seven people (87.5%).

Based on the analysis that has been carried out, a p-value of 0.003 is significant at the 95% confidence level, which is substantial or there is a relationship between body mass index and blood pressure control in hypertension sufferers at the Sukawati I Health Center, Gianyar Regency. Hypertensive patients with obesity body mass index status tend to have uncontrolled blood pressure compared to hypertensive patients with normal body mass index status and are overweight.

Table 2. Correlation Test Between Body Mass Index and Blood Pressure Control

BMI	Hypertension		p
	Controlled n (%)	Uncontrolled n (%)	
Normal	40 (72,7)	15 (27,3)	
Overweight	14 (70)	6 (30)	0,003 *
Obese class I	1 (12,5)	7 (87,5)	

*statistically meaningful

Discussion

Prevalence Of Controlled And Uncontrolled Hypertension

Based on the research that has been done, it shows that the prevalence of blood pressure control in people with high blood pressure at the Sukawati I Public Health Center, Sukawati District, Gianyar Regency has controlled blood pressure, namely 55 people (66.3%).

This is in line with research conducted by Almira in 2013. In this study, out of 128 respondents, it was found that the number of respondents who had controlled blood pressure was more than those who had uncontrolled blood pressure. This is caused by respondents who have paid attention to a healthier lifestyle in terms of food intake, physical activity, not smoking, and taking antihypertensive drugs regularly. This dramatically impacts blood pressure

in people with hypertension because many other factors can affect blood pressure, such as salt intake, level of stress experienced, physical activity, and body mass index[10].

This study is also in line with research conducted by Jayanti et al. in 2013, which found that more people with hypertension have controlled blood pressure. This is caused by increased patient knowledge about the various causes and risk factors for hypertension, which indirectly impact better behavior in controlling blood pressure so that blood pressure remains under control. Patient knowledge about hypertension also affects patient adherence in carrying out treatment. Patients with good knowledge about hypertension will adhere to treatment, where treatment is an essential factor in controlling blood pressure in people with hypertension. Along with increasing knowledge about hypertension, people with hypertension can better manage their condition so that sufferers have controlled blood pressure[11].

Research conducted by Awan in 2018 also found that the average hypertension sufferer has controlled blood pressure. Most of the respondents in Awan's study had an age range of 46-55 years (37.23%). The older a person is, the wiser they are in making decisions, the more experience they gain, and the more things they do so that they increase their knowledge, especially information about the condition of hypertension. Age affects one's mindset, and mindset influences one's behavior. Age will be an indicator in every decision that refers to each experience[12].

This differs from research by Budi and Mahalul in 2016, which found that people with hypertension tend to have uncontrolled blood pressure. This can be caused by the habit of people with hypertension who consume coffee and salt. Coffee contains caffeine which has a competitive antagonistic effect on adenosine receptors. Adenosine is a neuromodulator that influences several functions in the central nervous system. This impacts vasoconstriction and increases total peripheral resistance, increasing blood pressure. Excessive salt consumption causes a buildup of fluid in the body because it will attract fluids outside the cells so they don't come out, increasing blood volume and pressure[13].

Donghao et al. also obtained a different study in 2018. In this study, it was found that hypertension sufferers had uncontrolled blood pressure. This study found that hypertensive patients who had taken medication but did not control their blood pressure had an increased risk of all causes and death from Cardiovascular Disease (CVD) compared to normotensive adults. The results of this study are related to several risk factors. High-risk factors with the majority of subjects in this group is found to be older, black race, obesity, diabetes, and low educational status. Patient non-adherence to hypertension drugs (for example, inadequate doses or wrong types of antihypertensive medications) can also increase the risk of death in hypertensive patients undergoing treatment but with uncontrolled blood pressure[14].

Body Mass Index Of Hypertension Patients

In this study, the distribution of the body mass index of the research subjects showed that most of the people with high blood pressure at the Sukawati I Public Health Center, Sukawati District, Gianyar Regency had a normal BMI, namely 55 people (66.3%).

This research is supported by Yoel et al. in 2017, which found that hypertension sufferers based on

BMI were in the normal category. This can be caused by less physical activity. Lack of physical activity is a risk factor for hypertension. People with less physical activity tend to have a higher heart rate, so the heart muscle must work harder with each contraction. The stronger and more frequently the heart muscle pumps, the greater the pressure on the arteries[15].

This is also supported by research conducted by Angelia in 2019 which found that people with hypertension tend to have normal BMI status. Patients with hypertension are not only influenced by BMI status but can also be influenced by other factors such as age. With the increasing age of a person, the incidence of high blood pressure (hypertension) will be higher. This is because in old age, there are structural and functional changes in the peripheral vascular system, which are responsible for changes in blood pressure that occur in old age[16].

A different study was obtained by Agnes and Evelin in 2020, which found that more people with hypertension were in the obese BMI category. Obesity results in increased deposition of fatty acids in the heart muscle, which impacts left ventricular dysfunction and changes the hormone regulatory system, namely the renin-angiotensin system. This results in salt retention and increased blood pressure. Apart from body fat in general, the accumulation of abdominal fat (high waist circumference) is a cause of hypertension[17].

A different thing was also found by Ikhya et al. in 2018 most hypertension sufferers were in the obesity category. There is a role in the inflammatory process in hypertension, which is produced from fat cells, which causes them to become sensitive to lipolysis and have higher levels of inflammatory cytokines. If this process continues, it will develop into more severe hypertension and result in end-organ damage[18].

The Relationship Between Body Mass Index And Blood Pressure Control

According to the bivariate analysis using the Chi-Square test with a p-value of 0.003 it means that at the 95% confidence level it is stated to be significant or it means that there is a relationship between body mass index and blood pressure control in hypertension sufferers at the Sukawati I Health Center, Gianyar Regency. Body mass index has a significant impact on the incidence of hypertension. An increase in BMI value will be followed by a rise in blood pressure, which indicates that the higher a person's BMI value, the higher the chance of developing hypertension[19].

In this study, respondents who were obese tended to have uncontrolled blood pressure. This aligns with research by Ebrahim and Smith, who tested eight experimental people who were examined to see the effect of weight loss on blood pressure. After experimenting, it was concluded that weight gain is associated with increased blood pressure. Meanwhile, weight loss results in a decrease in blood pressure. The reduction in blood pressure was in the range of 5.2 mmHg both systolic and diastolic for various levels of weight loss[19].

A study conducted by Hammami et al. found that patients with uncontrolled blood pressure tend to be obese and have a higher BMI. Among patients who are overweight or obese, there is a correlation between the prevalence of uncontrolled blood pressure and the severity of obesity (71.5% in overweight people, 74.8% in moderately obese patients, and 79.4% in severely obese patients)[20].

Research conducted by Erika Maryani et al. also found that people with hypertension tend to be obese. The results showed that out of 84 respondents, 47 respondents were obese, 30 of them suffered from hypertension and 17 respondents did not suffer from hypertension. Meanwhile, of the 37 respondents who were not obese, 12 of them suffered from hypertension and 25 respondents did not suffer from hypertension. This research also aligns with Hasanah et al. which states that hypertension and obesity are interconnected because the more extensive a person's body, the more blood is needed to supply oxygen and nutrients to body tissues. The leading causes of hypertension in obesity are related to increased body volume, cardiac output, and decreased systemic vascular resistance[20].

Being overweight and obese are one of the characteristics of people with hypertension. Heart function in people with obesity conditions must work harder to pump blood throughout the body. Losing weight strongly correlates with reducing blood pressure in obese individuals. The pumping power of the heart and circulation of blood volume in obese patients with hypertension is higher than in hypertensive patients with average weight. The pathophysiology focuses on three main things: autonomic disorders, insulin resistance, and structural and functional abnormalities of blood vessels[8].

This differs from a study by Almira which found no relationship between blood pressure control and body mass index in hypertension sufferers. Based on the theory, body mass index is related to hypertension, but other factors impact increasing blood pressure. BMI status has no relationship with the incidence of hypertension caused by other influencing factors such as sodium intake. Respondents have normal BMI but have excessive sodium intake, which can cause blood pressure to increase[10]. Research conducted by Kaizhi et al. also found something different, namely that there was no relationship between BMI and hypertension. People with obesity are more willing to have their physical condition checked so that the disease can be detected and treated earlier, and they are also more compliant with doctors' treatment plans. The increase in the sympathetic system is also in line with the results of cross-tabulations between obesity and stress events, namely it was found that stress events were more common in older adults who were not obese. Sympathetic nerve activity that regulates nerve and hormone function can cause an increase in heart rate, narrowing of the arteries and increased retention of water and sodium[10].

Conclusion

Based on the analysis and discussion above, it can be concluded that most hypertension sufferers at the Sukawati I Public Health Center, Sukawati District, Gianyar Regency, have controlled blood pressure and a normal BMI. There is a relationship between body mass index and blood pressure control in hypertensive patients at the Sukawati I Public Health Center, Gianyar Regency. Hypertensive patients with obesity body mass index status tend to have uncontrolled blood pressure compared to hypertensive patients with normal body mass index status and are overweight.

Conflict of Interest

No conflict of interest in this study

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CASE STUDY

Navigating the Uncommon: Case Report of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Successfully Managed with Implantable Cardioverter Defibrillator (ICD)

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ARTICLE INFO

Article history:
Received: February 8,2024
Received in revised form:
June 9, 2024
Accepted:
October 20, 2024

Keywords:
Arrhythmogenic right ventricular cardiomyopathy,
Implantable cardioverter defibrillator,
Sudden cardiac death

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare genetic disorder known for its role in sudden cardiac death and primarily affects the right ventricle, leading to ventricular arrhythmias (VA). In a documented case, a 35-year-old patient experienced palpitations, and the detection of epsilon waves in the right precordial leads on an electrocardiogram (ECG) raised suspicions of ARVC. Further diagnostic tests, including a 24-hour Holter monitor showing over 500 ventricular extrasystoles and a cardiac MRI indicating right ventricular dyskinesia with transmural late gadolinium enhancement in the apical right ventricle, supported this suspicion. Additionally, an electrophysiologic study captured spontaneous polymorphic ventricular tachycardia and induction ventricle fibrillation, underscoring the need for an implantable cardioverter defibrillator. This case emphasizes the importance of recognizing ECG anomalies, timely further investigation, and appropriate therapeutic measures in managing ARVC, highlighting the vital role of combining cardiac, electrophysiological, and imaging assessments in the risk stratification and management of ARVC.

Medical and Health Science Journal

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an uncommon hereditary cardiomyopathy. The incidence rate of ARVC is estimated to be between 1 in 2500 and 1 in 5000 individuals.[1] Prompt implementation of pharmacotherapy and device therapy may aid in mitigating the risk of arrhythmic events or sudden cardiac death (SCD). It's always interesting to find relatively uncommon diseases with common symptoms, especially when they appear with diagnosis challenges. Here, we provide a case of a young adult who had common complaints of palpitations, which were identified as ARVC and required implanted cardioverter defibrillator (ICD) therapy.

Case

A 35-year-old man with palpitations came into the cardiology clinic. The palpitation has been occurring intermittently for the past twelve months.

There was no medical history, either personal or familial, of unexplained syncope or cardiac arrest. The electrocardiogram (ECG) during his visit revealed epsilon waves in the right precordial leads (**Figure 1**). The results of an echocardiography examination revealed a slightly dilated right ventricle (RV) and right atrium (RA); the remaining cardiac chamber measurements are within normal ranges. An ARVC was suspected, and the patient was recommended to be hospitalized for further investigation and treatment. A holter monitoring was initiated, which revealed a persistent premature ventricular contraction (PVC) rate exceeding 500 over the course of twenty-four hours. Further investigation using a cardiac MRI (CMRI) revealed dyskinesia in the RV and transmural late gadolinium enhancement (LGE) in the apical RV.

An electrophysiology study (EPS) was arranged for the patient. Regardless of the induced ventricle fibrillation (VF), a spontaneous polymorphic ventricular tachycardia (VT) was seen during EPS. These data validated the ARVC diagnosis and indicated the need for implanted cardioverter defibrillators. A dual-chamber implantable cardioverter defibrillator (ICD) was successfully implanted, with no adverse events. Subsequently, the patient was released with a prescription once daily 5mg of bisoprolol.

Discussion

ARVC is a hereditary heart condition characterized by abnormal heart rhythms in the presence of functional and structural abnormalities of the right ventricle. These abnormalities are caused by the partial or complete replacement of heart muscle cells with fatty and fibrous tissue.[2] However, diagnosing ARVC is difficult since it presents with diverse and nonspecific symptoms. This condition is responsible for causing sudden mortality in 30% of young people and 5% of those under the age of 65.[3]

Study found that around 67% of persons diagnosed with ARVC have palpitations, whereas 32% experience syncope, 27% experience unusual chest pain, 6% experience RV failure, and 6% may not

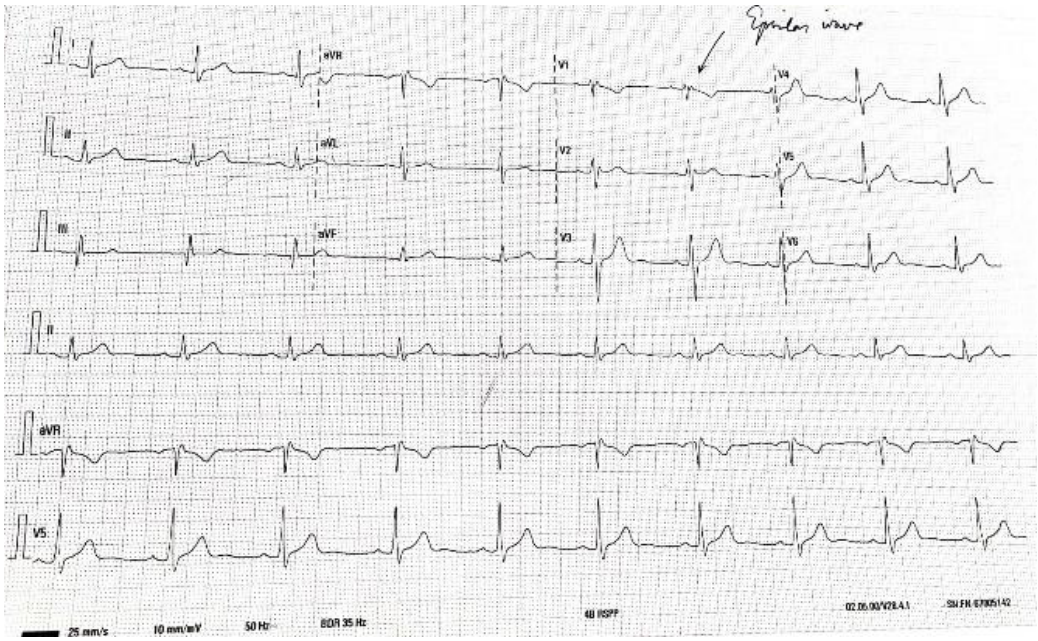

Figure 1. Epsilon waves in the right precordial leads

exhibit any symptoms.[4] In the first phase, known as the "subclinical" stage, there are hidden alterations in both function and structure. However, it is important to note that SCD might still present as the first symptom during this stage. The second phase is characterized by "overt electrical" manifestations, including the presence of RV arrhythmias and the identification of both structural as well as functional abnormality seen in ECG examination. The third stage is characterized by "right-ventricle dysfunction" when there is significant impairment of the right ventricle, while the left ventricle remains unaffected. The fourth stage, known as "biventricular or late," is characterized by substantial impairment of both the RV and left ventricle (LV).[5] ARVC is known to have a strong association with physical activity and may manifest at an early stage, with more severe symptoms seen in individuals who participate in competitive sports. A research conducted by Ruwald et al. found that performing competitive sports increases the incidence of ventricular tachyarrhythmias and SCD by two times compared to participating in recreational sport.[6] Thus, ARVC has been identified as the cause of sudden unexplained death in 11-22% of young athletes.[7]

Making an accurate diagnosis of ARVC is challenging and constantly improving. The criteria have been revised in 1994, 2010, and most recently in 2020, known as the 2020 International criteria or "Padua criteria," which are established by combining several diagnostic criteria. A definite diagnosis of ARVC requires two major, one major with two minor, or four minor criteria from different categories; a borderline diagnosis requires one major with one minor, or three minor criteria, and a possible diagnosis requires one major or two minor criteria from different categories. The primary novelty of the 2020 International criteria was the use of LGE to CMRI tissue characterization data for the identification of fibrofatty) myocardial replacement in both ventricles, which serves as the foundational diagnosis in our case. [8]

Nearly 90% of individuals diagnosed with ARVC have an abnormality on the ECG. Prolonged S-wave upstroke > 55 ms in V1–V3 (90%–95%) is one of the most prevalent findings, and in half of patients presenting with VT, it is followed by an inverted T wave on precordial leads (V1–V3). Furthermore, 30–33% of individuals with ARVC may have an epsilon wave, or depolarization anomaly, which is characterized as a unique wave at the end of the QRS complex.[4] A Holter monitor may reveal non-sustained ventricular tachycardia (NSVT) with varying morphologies. Research using 24-hour Holter monitoring has shown that the majority of patients with ARVC have numerous premature ventricular contractions (PVCs), either occurring isolated or in coupled, exceeding 500 PVCs during 24 hours. Various studies have shown that these premature PVCs and NSVTs are associated with an increased risk of ventricular arrhythmias (VA) and SCD. [9] Moreover, EPS may be used as a diagnostic tool to identify for inducible VT. EPS is a substantial diagnostic test used to differentiate between ARVC and idiopathic right ventricular outflow tract tachycardia. EPS may also give significant information for assessing the risk and making treatment decisions in patients with ARVC. [10]The occurrence of NSVT ($p < 0.001$), inducibility at EPS ($p = 0.005$), and a Holter with frequent PVC ($p = 0.024$) were shown to be significant indicators of effective ICD treatment in a retrospective investigation of 84 patients who

received an ICD for primary prevention. [11] Echocardiography can detect localized RV wall motion abnormalities, increased RV dimension (particularly at the RV outflow tract), and decreased RV ejection fraction (EF). With the advent of new technologies, CMRI has played an important role in diagnosing ARVC. CMRI may detect global or localized ventricular dilation, dysfunction, intramyocardial fat, aneurysmatic dilation, and fibrosis.[12]

Our patient's diagnosis of ARVC is confirmed by the presence of one major criterion and two minor criteria. These include the identification of right ventricular dyskinesia and transmural LGE in the apical right ventricle on CMRI, the presence of epsilon waves in the right precordial leads on electrocardiogram ECG, and the occurrence of frequent ventricular extrasystoles (>500 per 24 hours) on 24-hour Holter monitoring.

Patients with ARVC can present with a broad range of symptoms or they may continue to be asymptomatic. Hence, the treatment approach must be tailored to the patient's specific needs, taking into account their clinical symptoms, risk assessment, and the preferences of both the patient and clinician. Individuals diagnosed with ARVC who have encountered a sustained ventricular arrhythmia are at significant risk of having recurrent sustained VT and VF (or VFL, characterized by a cycle duration of 240 milliseconds or less).[13] During an EPS, the inducibility of sustained VT is another indicator of electric instability. Inducibility during EPS has been discovered as a risk marker in individuals with ARVC who have had an ICD according to studies. [9] These supports a recommendation for ICD implantation in our patient, with a spontaneous polymorphic ventricular VT was found regardless of the induction VF in our EPS.

Several studies have also shown that ICD treatment is an effective strategy for both primary and secondary prevention of SCD in individuals with ARVC. Individuals diagnosed with ARVC often have a youthful age and are anticipated to have a long lifespan when using the implanted device and leads. According to research, the death rates for both cardiac and noncardiac causes after implanting an ICD in individuals with ARVC are low. The cardiac mortality rate per year was 0.9%, whereas the noncardiac mortality rate per year was 0.8%. However, ICD treatment has potential risks in individuals with ARVC. One common issue that occurred was difficult ICD lead installation (18.4%). Lead displacement (3.3%), infection (1.4%), and lead malfunction (9.8%), were other issues associated with ICDs.[14]

Conclusion

The first manifestation of ARVC ranges from being without symptoms to SCD. Consequently, timely identification of the condition is crucial for preventing further mortality. Recognizing the potential ECG findings of ARVC is crucial in determining the need for additional investigations and the implementation of necessary therapies. Evaluating clinical, and cardiac imaging characteristics is crucial for diagnosing and determining the risk level of individuals with ARVC. We successfully delivered accurate diagnosis and treatment, therefore preventing the potentially life-threatening consequences. EPS and Holter monitoring may serve as diagnostic tools to assess the need for implantable cardioverter-

defibrillator (ICD) placement as a therapeutic strategy for patients with ARVC.

Conflicts of Interest

The author started there is no conflict of interest

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CASE REPORT

Atypical Presentation of Multiple Myeloma: from Heart Failure to Multiple Myeloma

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ARTICLE INFO

Article history:
Received : June 19, 2024
Received in revised form:
September 29, 2024
Accepted:
October 20, 2024

Keywords:
Multiple myeloma, cardiac amyloidosis, systemic amyloidosis, heart failure, AL amyloidosis

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ABSTRACT

Multiple myeloma (MM) is a hematological malignancy commonly associated with bone pain, hypercalcemia, and renal failure. However, its presentation can occasionally mimic other medical conditions, which may delay diagnosis. This case report describes a patient who was initially diagnosed and treated for heart failure but was later found to have MM, highlighting the importance of considering MM in the differential diagnosis of heart failure.

A 56-year-old lady presented with recurrent episodes of shortness of breath, orthopnea, paroxysmal nocturnal dypsnea and bilateral lower limb swelling which she had been treated for decompensated heart failure with optimal therapy. She denied any family history of cardiovascular disease personal history of underlying medical condition and was a non-smoker. This patient was diagnosed with multiple myeloma and probability of concomitant cardiac amyloidosis and commenced on bortezomib, thalidomide and dexamethasone (VTD) regime and standard optimal therapy of heart failure but her condition deteriorated. After a few days of starting chemotherapy, patient demised despite all the resuscitative effort. Multiple myeloma is common hematological malignancy with its distinct clinical features of "CRAB", however, more attention and alertness should also be exercised by clinicians as to be able to diagnose it early.

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Introduction

Multiple myeloma (MM) is the second most common hematological malignancy (after Non Hodgkin Lymphoma), accounts for incidence of 10%.[1] Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by the proliferation of malignant plasma cells within the bone marrow and the presence of a monoclonal protein in the blood or urine. Commonly presenting symptoms of MM include bone pain, renal impairment, hypercalcemia, and anemia, which form part of the CRAB criteria used to diagnose the disease.[2] However, MM can occasionally present in less typical ways, complicating its diagnosis and management. MM is an immunoglobulin-producing tumour of plasma cells. It is uncommon for MM to present initially as progressive heart failure, with common presentations include anaemia, recurrent infections, bone lesions, and renal failure. On the other hand, amyloidosis is a

systemic infiltrative disease characterized by the extracellular deposition of amyloid proteins at various organs; cardiac, renal, and skin among others. AL amyloidosis (ALA) is a sub-type that is commonly related to monoclonal gammopathy of unknown significant (MGUS), multiple myeloma and Waldenström macroglobulinemia. The development of ALA estimated to be 10-15% in MM patients.[3,4] The abnormal plasma cells from the above plasma cell disorders secret large number of light chains, which then gets deposited to organs, forming amyloid proteins.

Heart failure is a rare presentation of MM and is not typically associated with the initial diagnosis of this plasma cell dyscrasia. Cardiac involvement in MM usually occurs due to secondary amyloidosis (AL amyloidosis) where amyloid fibrils deposit in the cardiac tissue, leading to restrictive cardiomyopathy and heart failure.[5] Recognizing this link is crucial as it significantly influences both prognosis and treatment choices.

Whilst cardiac amyloidosis is the commonest cause of restrictive cardiomyopathy; delay in diagnosis is common with delay in treatment initiation. This can be overcome with a high degree of suspicion based on the clinical history and laboratory investigations. Management of cardiac amyloidosis with multiple myeloma requires a multidisciplinary team. Once heart failure occurs, the median survival is less than six months in untreated patients and is the most common cause of death. This case report details the diagnostic challenge of a patient who initially presented with signs and symptoms suggestive of heart failure, which on thorough investigation, was attributed to undiagnosed multiple myeloma complicated by cardiac amyloidosis. The atypical presentation emphasizes the need for a high index of suspicion and comprehensive diagnostic approach in patients with unexplained heart failure, particularly in the absence of common cardiac pathology risk factors.

Case Report

A 56-year-old lady presented with recurrent episodes of shortness of breath, orthopnea, paroxysmal nocturnal dypsnea and bilateral lower limb swelling which she had been treated for decompensated heart failure with optimal therapy. She denied any family history of cardiovascular disease personal history of underlying medical condition and was a non-smoker.

Laboratory tests showed anemia with hemoglobin (Hb) of 7.5 g/dl, elevated total protein of 96 g/L, renal impairment (creatinine clearance to 31 ml /min/1.73m2) and normocalcemia of 2.45mmol/L. Cardiac parameters revealed elevated troponin I of 67.9 and pro brain natriuretic peptide (pro BNP) of 4505 . Electrocardiogram (ECG) recorded sinus rhythm, with absence of low voltage QRS complex, and echocardiography showed evidenced of heart failure preserved ejection fraction (Left ventricular ejection fraction 50-60% with grade 3 diastolic dysfunction) with an additional finding of ‘granular sparkling’ appearance on myocardium. There was presence of moderate rouleux formation peripheral blood film. Bone marrow aspiration and trephine biopsy analysis showed 44% mature plasma cell infiltration, CD 138+, CD38+, with aberrant expression of CD56.

This patient was diagnosed with multiple myeloma and probability of concomitant cardiac amyloidosis and commenced on bortezomib, thalidomide and dexamethasone (VTD) regime and standard optimal therapy of heart failure but her

condition deteriorated. After a few days of starting chemotherapy, patient demised despite all the resuscitative effort.

Transthoracic Echo

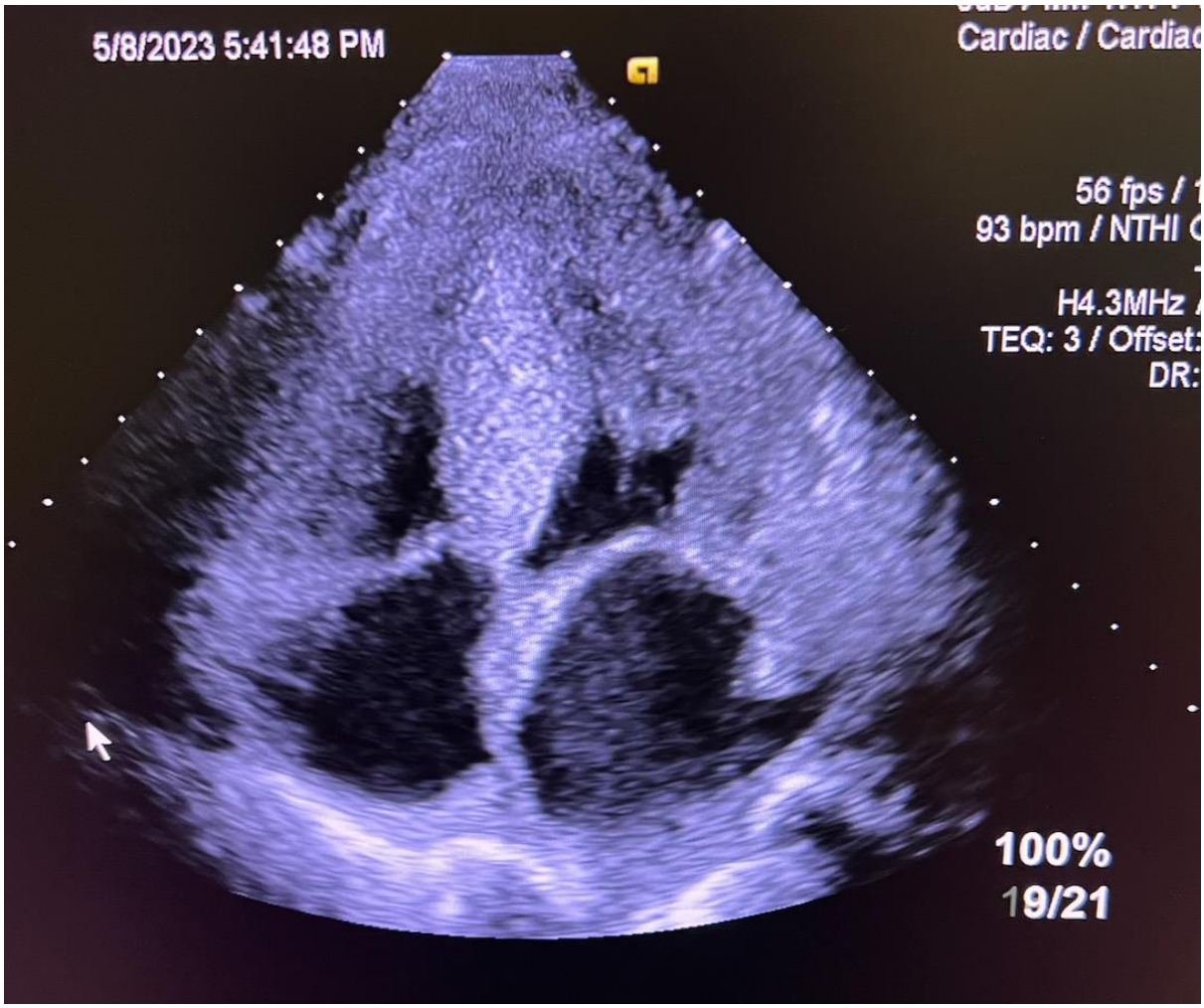

Figure 1 Patient transthoracic echo showing evidence starry sky appearance which suggestive of cardiac amyloidosis.

Bone Marrow Biopsy

HPE - Biopsy				
HPE				
Specimen # HPE				P230001280
Request details				HPE - Diagnostic Biopsy
Topography				
Request status				Request validated & printed
Summary report				Trephine biopsy: Consistent with Plasma cell Myeloma.

Figure 2 Result of patient bone marrow biopsy consistent with plasma cell myeloma

Discussion

This case illustrated an active multiple myeloma in a patient presenting with recurrence episode of decompensated heart failure. MM is part of plasma cell neoplasm with presence of monoclonal gammopathy. On the other hand, amyloidosis is a rare disorder characterized by extracellular deposition of light chain protein, called amyloids. ALA is the most common type of systemic amyloidosis. Approximately 10-15% of MM patients will develop ALA due to abnormal plasma cells produce light chain proteins which then deposited to become amyloid.[3,4] MM diagnosis can be made with either presence of clonal plasma cell proliferation in bone marrow >10%, or evidence of bony or extramedullary plasmacytoma, and any of the following myeloma-defining events (serum involve: uninvolved free light chain > 100, ≥ 1 focal bony lesions on imaging with size ≥ 5mm) or "CRAB" features (hypercalcemia, renal impairment, anemia and osteolytic bone lesions).[6] These classic symptoms are often clear indicators that prompt further diagnostic investigation into possible MM. However, when MM presents atypically, as in the case of heart failure without these traditional signs, the diagnosis can be markedly delayed, complicating and potentially worsening patient outcomes (Rajkumar et al., 2016).[2] In this case, due to the rarity of its presentation with further supported by investigation findings, the likelihood of cardiac amyloidosis as co-existing condition is entertained. Cardiac involvement in MM is primarily due to amyloid deposition, which results in restrictive cardiomyopathy—a condition often misdiagnosed due to its non-specific clinical presentation.[2,8]

Cardiac amyloidosis may manifest with progressive heart failure, with presence of "red flag" signs and symptoms (skin bruises, macroglossia, carpal tunnel syndrome, heart failure) are essential to raise suspicion of concomitant presence of MM.[5,8,9] In cardiac amyloidosis, disproportionately high N-terminal pro-B-type natriuretic peptide (NT-pro BNP), persistently raise troponin, low QRS complex on ECG, in addition to certain objective criteria on cardiac imaging helps to evoke cardiac amyloidosis. Diagnosis can be made either with the need for invasive (tissue biopsy for histopathological examination) or non-invasive (echocardiogram, cardiac magnetic resonance imaging, serum and urine electrophoresis, serum free light chain).[10] This depends on types of amyloid deposition though no impact on overall treatment management. More than 98% of cardiac amyloidosis consists of either light chain deposition, AL or transthyretin (ATTR). Biopsy proven AL deposition for AL cardiac amyloidosis is mandatory where else, non-invasive investigations are adequate for diagnosis in relation to ATTR.[11] Early diagnosis of MM, particularly in cases with atypical presentations such as unexplained heart failure, requires a high index of suspicion and may necessitate an integrated approach involving hematological, biochemical, and imaging studies. In cases like this, serum and urine electrophoresis, coupled with bone marrow biopsy, can be pivotal in uncovering the underlying MM.[12]

Illustrated by this case, given the atypical presentation with progressive heart failure without clinical improvement despite adequate optimal therapy, a second look of other probable diagnosis need to be considered. Diagnosis of MM is made by the evidence seen from initial investigations;

rouleaux formation on peripheral blood film, raised total protein, anemia and renal impairment. This is further supported by presence of 44% mature plasma cell infiltration in bone marrow.

A high index of clinical suspicion is required to diagnose cardiac amyloidosis. In addition to MM, the progressive heart failure with elevated pro BNP and troponin levels, presence of grade 3 diastolic dysfunction and 'granular sparkling' appearance on myocardium from echocardiogram makes the constellation of signs and symptoms highly suggestive of cardiac amyloidosis. Further confirmation with myocardial biopsy or cardiac magnetic resonance imaging (MRI) are not feasible in the context of this case, due to the hemodynamic instability of involved patient.[13]

Prognosis for MM associated with amyloidosis is grim in comparison to MM or amyloidosis alone. Furthermore, the extend of cardiac involvement in amyloidosis alone impacts negatively on disease survival. The parameters include granular sparkling appearance, diastolic relaxation abnormalities on echocardiogram, elevated troponin and pro BNP level (≥8500pg/mL) among others. Besides these, bone marrow plasma clonal size and level of free light chain (FLC) at the time of diagnosis also carries weight on poorer prognosis.[5,14,15] A retrospective study looking at effects of ALA with MM on prognosis shows that, the presence cardiac amyloidosis related to shorter overall survival, and pro BNP level ≥ 700pg/mL is an individual poor prognostic factor. This study also noted higher pro BNP level among ALA with MM, then in ALA alone.[3,16,17] These findings are supported by another study which shows in ALA with MM population, besides having higher pro BNP level, it was also reported to have higher FLC and larger bone marrow plasma clonal size. Poorer survival noted in ALA with MM and pro BNP appears to be a significant independent factor that negatively impact overall survival (≥8500pg/mL).[9,18,19] In this case, once MM was diagnosed, targeted therapy for MM, along with supportive measures for heart failure, was initiated, which is crucial for improving quality of life and extending survival.[20]

In this case, though the diagnosis of co-existing cardiac amyloidosis with MM was likely but not certain, there were poor prognosis factors present that negatively impact the overall survival; granular sparkling appearance, diastolic relaxation abnormalities on echocardiogram, high pro BNP (4505 pg/mL) and troponin levels. Despite initiation of MM-related therapy and optimization of heart failure therapy, patient still succumbed to her illness.

Conclusion

Multiple myeloma is common hematological malignancy with its distinct clinical features of "CRAB", however, more attention and alertness should also be exercised by clinicians as to be able to diagnose it early. As MM and systemic AL amyloidosis tends to co-exist, high index of suspicion is necessary, especially when cardiac involvement is seen in myeloma patients at any point throughout the course of illness. Due to its poorer prognosis, delay in diagnosis will delay in delivering focus directed therapy which subsequently affects the survival.

Conflicts of Interest

The author started there is no conflict of interest

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CASE REPORT

Unraveling Anesthetic Challenges of A Patient with Dilated Cardiomyopathy Posted for Lower Limb Amputation Surgery - A Case Report

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ARTICLE INFO

Article history:
Received: July 03, 2024
Received in revised form;
September 29, 2024
Accepted:
October 20, 2024

Keywords:
dilated cardiomyopathy, general anesthesia, peripheral vascular disease, low ejection fraction.

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ABSTRACT

This case report details the anesthetic management of a 64-year-old male with dilated cardiomyopathy (DCM) and a significantly reduced ejection fraction, undergoing lower limb amputation for peripheral arterial disease. Managing anesthesia in such patients poses considerable challenges due to the complexities associated with congestive heart failure. The successful administration of general anesthesia in this case can be attributed to a rigorous preoperative assessment and a meticulously devised anesthetic plan. The systematic approach included careful monitoring, fluid management, and the use of specific anesthetic agents that minimize cardiovascular stress, thereby ensuring an uneventful anesthetic course. This report emphasizes the importance of strategic planning and expert execution in the anesthesia management of patients with severe cardiomyopathy undergoing major surgical procedures.

Medical and Health Science Journal

Introduction

Dilated cardiomyopathy is a disease that affects primarily the myocardium. In dilated cardiomyopathy, a part of the myocardium is dilated without any obvious cause. The ventricular systolic pumping function of heart is impaired, leading to progressive cardiac enlargement and hypertrophy called remodeling. The incidence of dilated cardiomyopathy is reported to be 5-8/100,000 per year, more commonly found in men compared to women, generally between 20-60 years of age.[1,2,3] It is the third most common cause of heart failure worldwide and has a high incidence of sudden cardiac death.[4,5] Managing patients with dilated cardiomyopathy and reduced systolic function presents significant challenges during anesthesia, often resulting in high mortality rates. Maintaining cardiovascular stability and achieving optimal hemodynamic parameters can be challenging in such cases. Here, we present a successful case of anesthesia management for a patient with dilated cardiomyopathy and a low ejection fraction who underwent lower limb amputation.

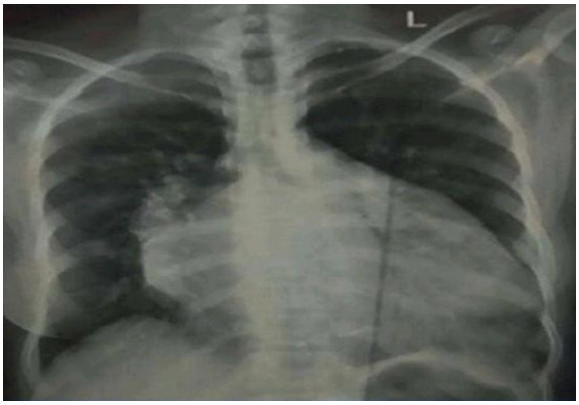

Figure 1- Chest X-ray showing massive cardiomegaly.

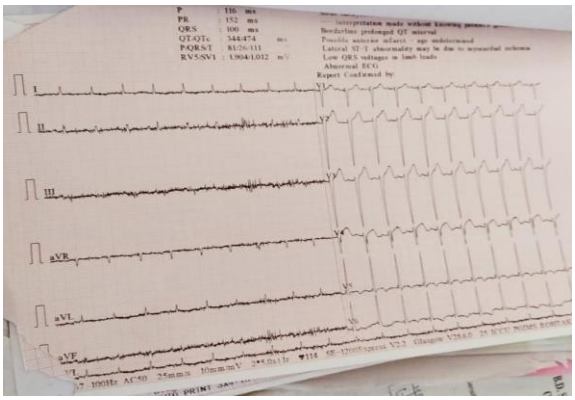

Figure 2: ECG showing sinus tachycardia, ST segment coving in V2-V5 , T wave inversion in V4-V6 and poor progression of R wave.

Case Report

A 64-year male patient with a history of type 2 diabetes mellitus, hypertension and coronary artery disease was referred to our institute for lower limb amputation. He was diagnosed with dilated cardiomyopathy. He had history of dyspnea (NYHA II), but no history of nocturnal dyspnea, orthopnea and palpitations. On physical examination, there were no signs of congestive heart failure, e.g., raised JVP, ankle edema, or hepatomegaly. His heart rate was 90/min and his blood pressure was 130/70 mmHg. A 2D echo showed dilated cardiomyopathy, depressed left ventricular systolic dysfunction (EF 10%), mild MR, dilated LA/LV, and a severely hypokinetic left ventricle. X-ray of the chest showed cardiomegaly. ECG showed sinus tachycardia, ST segment coving in V2-V5 , T wave inversion in V4-V6 and poor progression of R wave. His hemoglobin was 12gm/dl, and all biochemical markers were within normal limit. He was on treatment tab Ecosprin 75mg, Atorvastatin 20mg, Lasilactone 20/50 mg, Metoprolol 25mg, Ramipril 2mg, Dapaglifazone 100mg and Cilastozole 100mg. Patient was known diabetic for two years having blood sugar within normal limit. Cardiologist consultation was requested for patient's management, who advised continuing the above drugs. Patients and his relatives were explained about anesthetic risks and a high-risk consent was obtained.

General anesthesia was planned for the amputation of the lower limb. All emergency drugs and defibrillator were kept ready. The patient was monitored with standard American society of Anesthesiologists (ASA) monitors including electrocardiogram, noninvasive blood pressure and pulse oximetry. With all aseptic precautions, an arterial line was inserted for invasive BP monitoring. To maintain stable hemodynamics, anesthesia was induced with inj. Midazolam 1mg iv , inj. Fentanyl 160 micrograms, and inj. Etomidate 12mg iv. After checking ventilation, inj. vecuronium 6mg iv stat given. I-gel of size 4 was inserted and fixed after confirming air entry and adequate chest rise. Maintenance was done on oxygen+air+ sevoflurane. Intraoperatively, saturation was maintained at 98-99%, heart rate between 80-90/min and blood pressure 120-130 systolic, whereas diastolic between 70-80 mmHg. Blood loss was minimal. The patient received 800 mL crystalloid over 40 minutes. The patient remained hemodynamically stable throughout procedure. Other drugs given were tramadol 100 mg slow iv for analgesia, inj paracetamol 1gm iv,

and inj. dexamethasone 8 mg iv to allay postoperative nausea and vomiting. Inj.hydrocort 100 mg iv stat, in between budecort puffs (6-8 puffs), given for poor chest condition. Neuromuscular blockade was reversed with inj. glycopyrrolate 0.4mg and inj. neostigmine 2.5 mg iv, and inj. Esmolol 25 mg iv stat given to blunt sympathetic stimulation at extubation. Patient was shifted to ICU for post operative monitoring. After observing 24 hrs. in the ICU, patient was shifted to the ward.

Discussion

Dilated cardiomyopathy (DCM) presents unique challenges in anesthetic management due to its association with decreased ejection fraction and an increased risk of congestive heart failure. Patients with DCM are particularly vulnerable to changes in volume status and myocardial stress, which can precipitate acute heart failure during surgery (Smith et al., 2021).[6] The anesthetic management of patients with dilated cardiomyopathy (DCM) undergoing surgery presents unique challenges, particularly due to the associated cardiac dysfunction and the high risk of perioperative morbidity and mortality. DCM often results in a decreased ejection fraction, leading to reduced cardiac output and the potential for congestive heart failure under stress, such as surgery (Smith et al., 2021).[6]

In the context of our 64-year-old patient undergoing lower limb amputation, the complexities were significantly heightened due to the underlying peripheral arterial disease, which itself complicates anesthetic choice and patient stability (Jones and Brown, 2022).[7] Patients with severe systolic dysfunction are at an increased risk of perioperative morbidity and mortality. In this case, the anesthetic management plan was focused on minimizing the risks associated with anesthesia in a patient with an EF of less than 10%. The use of balanced anesthesia with etomidate and sevoflurane allowed for a smooth induction and maintenance of anesthesia while minimizing the impact on cardiac function. The administration of general anesthesia in DCM patients requires careful selection of agents that minimize myocardial depression. Studies have suggested that the use of etomidate and ketamine might be preferred due to their lower impact on myocardial function compared to other induction agents (White and Gupta, 2020).[8] In our case, the induction was managed with etomidate, supported by the findings of Patel et al. (2019)[9] who reported reduced hemodynamic perturbations with this agent in cardiomyopathy patients. Patients with DCM are especially susceptible to fluid shifts and hemodynamic instabilities during surgery. Anesthetic strategy must, therefore, be meticulously planned to avoid exacerbating the patient's condition. The use of general anesthesia in this context needs to be carefully balanced. Volatile anesthetics, though commonly used, can depress myocardial function and should be administered with caution (Johnson & Roberts, 2020). Intravenous agents that preserve myocardial function, such as etomidate or ketamine, might be preferred to minimize cardiac depression (Brown & Beattie, 2019). Intraoperative management focused on maintaining hemodynamic stability. The use of invasive monitoring techniques such as arterial lines and central venous pressure monitoring are crucial in these patients to provide real-time data on blood pressure and heart function, facilitating immediate adjustments in fluid therapy and vasopressor support (Kim and Lee, 2021).[10]

According to Zhang et al. (2020),[11] the precise control of volume status and avoidance of fluid overload are essential to prevent exacerbation of heart failure in DCM patients during surgery. Postoperative care for DCM patients should include careful monitoring in a high-acuity setting, such as an intensive care unit, to promptly address potential complications such as arrhythmias, significant fluid shifts, and acute heart failure episodes (Clark and Thompson, 2021).[12] In our case, the patient's postoperative course was uneventful, underscoring the efficacy of our anesthetic and perioperative management strategy. This case highlights the importance of a tailored anesthetic regimen that considers the pathophysiological alterations in DCM. Advanced planning and interdisciplinary collaboration are crucial to manage these high-risk patients effectively, as echoed by the guidelines proposed by Green et al. (2022)[13] for surgical interventions in patients with severe cardiomyopathies. Patients with DCM are especially susceptible to fluid shifts and hemodynamic instabilities during surgery. Anesthetic strategy must, therefore, be meticulously planned to avoid exacerbating the patient's condition. The use of general anesthesia in this context needs to be carefully balanced. Volatile anesthetics, though commonly used, can depress myocardial function and should be administered with caution.[14] Intravenous agents that preserve myocardial function, such as etomidate or ketamine, might be preferred to minimize cardiac depression.[15] Invasive monitoring techniques such as arterial and central venous pressure monitoring can be crucial for managing unstable patients with DCM. These monitoring tools assist in real-time optimization of preload, afterload, and myocardial contractility during the operative period. Moreover, the management of these patients does not conclude with the end of the surgery; postoperative care is equally critical. Ensuring adequate analgesia while avoiding respiratory depression is vital to prevent unnecessary strain on cardiac function.[16]

Patients with poor ejection fraction may deteriorate from induction of anesthesia until extubation and the postoperative period, so early recognition and immediate intervention of hemodynamic instability with appropriate vasoactive or inotropic medication is required. Ventricular arrhythmias may also occur which are life-threatening, so all emergency drugs such as lignocaine and amiodarone should be kept ready.[17] As patients are on diuretics from pre-operative period, they tend to be dehydrated, which can cause intraoperative hypotension. Preloading is not possible in these patients as it may lead to congestive heart failure, so adequate fluid management is important in these patients. Also, blood products should be made arranged prior to expecting blood loss. Arrhythmias can also occur when patients are on diuretics due to decreased magnesium or potassium, so one should be watchful for dyselectrolemia. Most of the aesthetic drugs are cardio depressant therefore selection of drugs that have minimal cardio-depressant, therefore, selection of drugs that have minimal cardio-depressant effect is of the utmost importance. Etomidate is the ideal induction agent for these patients, as propofol and thiopentone have depressant effects on the heart.[18] The predictors of poor prognosis in our patient were depressed left ventricular systolic function (EF 10%), mild MR, grade IV DDF. Also, the patient was a known case of hypertension, for above reasons, condition was explained to the patients as well as attendants and high risk consent was obtained. Patient's hemodynamic status was carefully monitored and

guided fluid was given. Postoperative management was focused on maintaining a stable hemodynamic status, avoiding fluid overload, and optimizing the patient's cardiopulmonary function. The patient's successful recovery highlights the importance of a multidisciplinary approach to the management of patients with severe systolic dysfunction undergoing major surgical procedures. We monitored this patient in ICU as post operative management requires intensive monitoring like intraoperative period until the patient is stabilized.

Conclusion

Anaesthetic management in patients with dilated cardiomyopathy patient with very low ejection fraction is challenging for the anaesthesiologist. So careful and intense hemodynamic monitoring and slow and judicious titration of anesthetic drugs is of prime importance.

Conflicts of Interest

The author started there is no conflict of interest

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