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A Study on the Occurrence of Hand Dermatitis in Healthcare Workers during the COVID-19 Pandemic due to Enhanced Hand Hygiene

Abhishree B S, Kavitha R, Geetha A

Department of Pharmacology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka - India

Abstract

Hand hygiene measures have increased in the general population and among healthcare workers since the pandemic outbreak. However, enhanced hand hygiene can hurt the skin barrier leading to the development of hand dermatitis (HD). The study aimed to determine the occurrence of occupational-related contact dermatitis among healthcare workers. An observational, questionnaire-based cross-sectional study was conducted in 2021 amongst 257 Health Care Workers (HCWs) of a tertiary care hospital. The data were analyzed using Microsoft Excel for Windows. The frequency of hand washing had increased to > 5 times in 42% of the HCWs while hand sanitizer usage had increased to >5 times in 95% of them during the pandemic. The duration of glove usage had increased from 3% pre-pandemic to 91 % during the pandemic and the majority of them used latex gloves. Symptoms of hand dermatitis in HCWs had increased from 3% pre-pandemic to 84% during the pandemic. Less than 10 % of the study participants moisturized their hands after sanitization. The fact that over 84% of the HCWs developed HD during the pandemic can be attributed to preventive measures to reduce the transmission of the virus. Measures such as the use of moisturizers should be recommended to prevent the onset of occupational hand eczema. It is thus imperative to raise awareness of HD in India and intensive measures should be provided.

Keywords: COVID-19, hand dermatitis, hand eczema, health care workers, hand hygiene

Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS CoV-2) was first detected in Wuhan, China. Despite having attempted to curb the virus, it has spread globally and was declared a pandemic by World Health Organization (WHO). The virus is highly transmissible and primarily spreads through the respiratory tract, by respiratory secretions, droplets, via direct contact, and less commonly through fomites.[1]

Health Care Workers (HCWs) being the front-line workers of the SARS-CoV-19 outbreak response are exposed to the infection which puts them at risk of contracting the virus. Hand hygiene encompasses hand washing and hand sanitizer usage. Frequent hand hygiene and the use of protective gear such as gloves are recommended to prevent the transmission of the disease.

Corresponding Author: Abhishree B S. Department of Pharmacology, Bangalore Medical College and Research Institute, Bengaluru-560 002, Karnataka, India. Email: abhi.abhishree100@gmail.com
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Enhanced hand hygiene, duration of employment, wet work, and glove usage play a detrimental role in skin integrity and contributes to the development of Hand Dermatitis (HD). HCWs in particular are at risk of developing occupational dermatitis.[2] To mitigate the expected rise in HD from enhanced hand hygiene the American Contact Dermatitis Society (ACDS) recommends good hand hygiene techniques such as the application of moisturizer after hand sanitization.[3]

Occupational HD is one of the most common occupational diseases. Several studies worldwide have reported that occupational skin disease prevalence in HCWs is between 8 and 90%.[4-6] The symptoms of HD include itching, swelling, redness, burning, and scaling. Stringent hand hygiene measures result in the loss of surface lipids, leading to an increase in trans-epidermal water loss, and increasing the penetration of allergens and irritants resulting in HD.[3,7]

Despite the recognition of the problem, there is insufficient data on developing hand dermatitis in India during the COVID-19 pandemic. Therefore, the aim was to conduct a cross-sectional study to determine the occurrence of occupational-related HD among the HCWs.

Methods

This observational, questionnaire-based cross-sectional study was conducted in October 2021 amongst HCWs attached to Bangalore Medical College and Research Institute, Bengaluru, India. The hospital was a designated COVID-19 center with 3000 beds dedicated to COVID-19 patients. Around 4000 HCWs currently work in the hospital. However, HCWs working in the first week and second week of October 2021 formed the sample pool for the study.

The online questionnaire was distributed to 400 HCWs and the google form was kept open for 10 days to collect the responses. After obtaining institutional ethics committee clearance, informed consent was taken from HCWs over the google form before proceeding to answer the questions.

Study Population

The study population consisted of all frontline HCWs (doctors, nurses, and lab workers) who worked during the COVID-19 outbreak. All HCWs who had no contact with the patients or the patient's tissues and body fluids were excluded from the study. Participants who were not able to comprehend the google questionnaire were also excluded from the study. The sample size was calculated for an assumed prevalence of 19% with an absolute precision of 5% based on previous studies. [4-6] A minimum of 250 participants were required to find a statistically significant difference. The questionnaire was distributed to 400 HCWs of which 257 responded, hence the results are analyzed for 257 HCWs.

Questionnaire

A comprehensive literature review was done using search engines like Pubmed and Google Scholar and questions were identified from these articles.[5,8] The developed questionnaire was subjected to evaluation by a team of eight experts from different healthcare fields for their inputs, critical appraisal, face, and content validation. The subsequent version of the questionnaire was tested by conducting a pilot study on a sample of 60 HCWs to test the instrument's validity, resulting in modifying some questions to prevent misinterpretations. Further, construct validity was established by using factor analysis.

The questionnaire included demographic features (age, sex) and work-related questions (occupation), frequency of hand washing in a

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day pre and during the pandemic, frequency of using hand sanitizer a day pre and during the pandemic, type of hand sanitizer used, preference for the type of hand sanitization, moisturization of hands post hand disinfection, types of gloves used, duration of glove usage pre and during the pandemic, presence of symptoms of hand dermatitis pre and during the pandemic, symptoms associated with hand dermatitis (redness, itching, burning, scaling, and dryness) and treatment is taken for hand dermatitis.

Statistical Analysis

The data were analyzed using Microsoft Excel for Windows. Data were presented as percentages or ranges. For analyzing item responses to the questionnaire, descriptive statistics were applied. The association between two categorical variables was analyzed using the Chi-square test. A p-value of less than or equal to 0.05 was considered statistically significant. All the results are summarized as figures and tables.

Results and Discussion

The SARS-CoV-19 pandemic necessitated drastic changes in the healthcare system to protect frontline workers and patients. Frequent sanitization and use of personal protective equipment were recommended for all those working in the hospitals.

Two fifty-seven HCWs responded to the survey. The results from our study indicate that the majority of the participants belonged to the age group 20-39 years while the least belonged to the age group 50-59 years (Table 1). This is in line with the recommendations issued by WHO where older individuals are at a higher risk of developing severe COVID-19 illness and such HCWs should not be required to carry out high-risk tasks.[9] Of note, the majority of the HCWs during the pandemic reported features of HD with the most common presenting symptom being dryness followed by itchiness, scaling, burning, and redness (Figure 1).

Our data showed an increase in the frequency of hand washing and hand sanitizer usage to more than 5 times per day during the pandemic. The preferred method was using soap water followed by a hand sanitizer. There was an increase in the duration of glove usage to more than an hour with a majority of HCWs using latex gloves (Table 1). Among the HCWs who developed HD, the frequency of hand sanitizer usage was more than 5 times per day in the majority of them. The duration of glove usage for more than an hour was seen in most of the HCWs with HD ($p<0.05$). (Table 2)

The aforementioned measures of hand hygiene are to the international guidelines issued by WHO to prevent transmission of the virus.[8] The increase in symptoms of HD during the pandemic suggests a temporal link to the increased hand hygiene measures undertaken globally. Studies conducted in Ireland, Wuhan, and Hubei showed that the majority of the HCWs developed hand eczema during the pandemic.[2,10,11] In the study by Alluhayyan et al in Saudi Arabia 92% of HCWs developed dryness of hands followed by itchiness.[5]

Excessive hand sanitization using detergents impairs the hydrolipid barrier of the skin causing dryness and itching.[12] In a comparative study conducted by Erdem et al in Turkey, the frequency of hand washing had increased to over 10 times per day in the COVID group.[13] Excessive hand washing can remove essential oils from the surface of the skin. Washing hands immediately before or after using an alcohol-based hand rub could aggravate dermatitis as the alcohol in the hand rub can penetrate the sensory nerve endings of pre-irritated skin.[14]

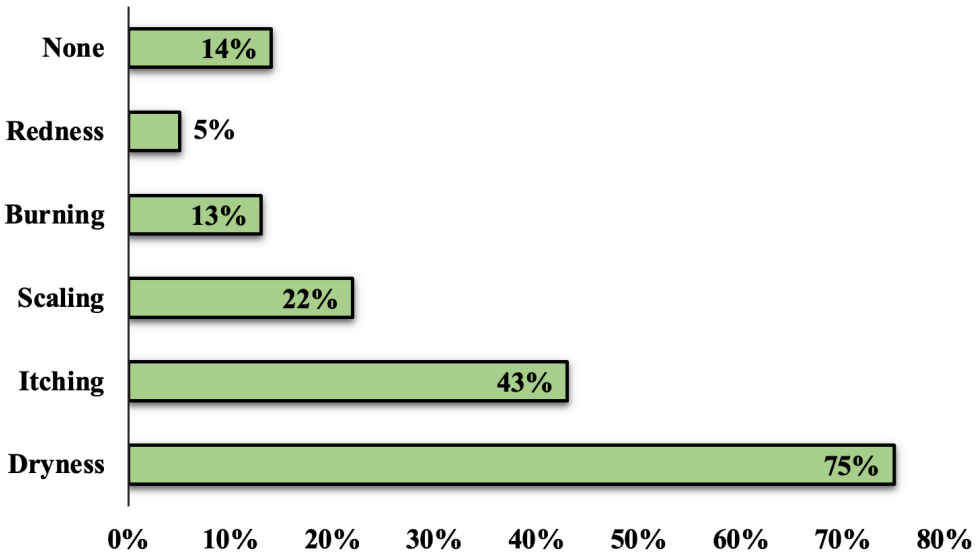

Figure 1. Presentation of Skin Changes in HCWs (Common Symptoms of Hand Dermatitis)

Repeated usage of hot water should be avoided to prevent the development of HD. A study by Hansen et al claims that individuals are at a high risk of developing HD due to an increase in usage and prolonged exposure to latex gloves.[15] Rubber gloves contain the chemicals 1,3-diphenyl guanidine and cetylpyridinium chloride that are known to cause HD.[16] In addition, long-term usage of gloves leads to occlusion and hyperhydration state of the epidermal layer of skin leading to the development of HD.[12] Hence, to lower the humidity, gloves should be changed frequently and applied only on dry hands.

The use of a moisturizer post handwash and sanitization is one of the most important skincare precautions recommended to prevent HD.[3,9] The UK and European guidelines recommend using a moisturizer similar to the guidance by ACDS which stresses the application of moisturizers before wearing the gloves.[3] Skin moisturizers protect from developing HD by trapping the water effectively and help in epithelial regeneration.[16] In the present study less than a quarter of HCWs used moisturizer after hand sanitization and many opined that a hand moisturizer dispenser is essential along with a sanitizer (Table 1).

The non-availability of a moisturizer, dearth of time due to an overburdened healthcare system during the pandemic, and lack of awareness regarding the effects of increased hand hygiene could be some of the reasons for the aggravation of HD. A study conducted by Kiely et al in Ireland during the COVID pandemic showed that over 45% of the participants denied using emollients after hand sanitization resulting in HD.[2] However, a study conducted in Germany by Reinholz et al showed an increase in the frequency of moisturizer application in most participants.[18]

The higher frequency of washing hands in our study, in contrast to a lower percentage of moisturizer application provides an imbalance that predisposes the front-line staff to an increased risk of HD. Hence, a standard therapeutic regimen should be framed and implemented to prevent and treat HD in developing countries like India.

Table 1. Comparison of Participant Characteristics by Gender (1)

		Total		Male		Female		p-value
		n	%	n	%	n	%	
N=257				76	29.57	181	70.43	NA
Age (Mean-35 years; Median- 34 years; SD: +/- 9 years)	20-29 years	78	30.4	17	6.60	61	23.80	<0.001
	30-39 years	101	39.3	26	10.12	75	29.18	
	40-49 years	49	19.1	15	5.84	34	13.26	
	50-59 years	29	11.3	18	7.00	11	4.3	
Occupation	Doctor	150	58.4	37	14.40	113	44	0.0553
	Nurses	63	24.5	20	7.78	43	16.72	
	Laboratory Technicians	44	17.1	19	7.40	25	9.70	
Major activity at work	Direct patient care	187	72.8	54	21.01	133	51.79	0.689
	Laboratory work	70	27.2	22	8.56	48	18.64	
Handwashing frequency per day before the pandemic	< 5 times	252	98.05	73	28.40	179	69.65	0.132
	5-10 times	5	1.82	3	1.16	2	0.66	
	>10 times	0	0	0	0	0	0	
Handwashing frequency per day during the pandemic	< 5 times	145	56.42	44	17.12	101	39.30	0.121
	5-10 times	96	37.35	24	9.34	72	28.01	
	>10 times	16	6.23	8	3.11	8	3.12	
Hand sanitizer usage per day before the pandemic	< 5 times	232	90.27	67	26.07	165	64.2	0.458
	5-10 times	24	9.34	8	3.11	16	6.23	
	>10 times	1	0.39	1	0.39	0	0	
Hand sanitizer usage per day during the pandemic	< 5 times	13	5.06	7	2.72	6	2.34	0.023
	5-10 times	114	44.36	39	15.18	75	29.18	
	>10 times	130	50.58	30	11.67	100	38.91	

Table 1. Comparison of Participant Characteristics by Gender (2)

		Total		Male		Female		p-value
		n	%	n	%	n	%	
N=257				76	29.57	181	70.43	NA
Preference for type of hand sanitization during the pandemic	Hand sanitizer	105	40.9	23	8.95	82	31.95	0.0579
	Soap and water	6	2.3	3	1.16	3	1.16	
	Both	146	56.8	50	1.95	96	54.85	
Type of hand sanitizer used often	Alcohol based	248	96.50	75	29.18	173	67.32	0.216
	Alcohol free	9	3.50	1	0.39	8	3.11	
Type of gloves used often	Latex	216	84	70	27.24	146	56.76	0.022
	Non latex	41	16	6	2.33	35	13.62	
Duration of glove usage before the pandemic	< 1 hour	249	96.89	74	28.79	175	68.09	0.773
	>1 hour	8	3.11	2	0.78	6	2.33	
Duration of glove usage during the pandemic	< 1 hour	23	8.95	9	3.50	14	5.45	0.292
	>1 hour	234	91.05	67	26.07	167	64.98	
Moisturisation of hands post sanitization	Yes	25	9.7	5	1.95	20	7.78	0.269
	No	232	90.3	71	27.63	161	62.65	

Table 1. Comparison of Participant Characteristics by Gender (3)

		Total		Male		Female		p-value
		n	%	n	%	n	%	
N=257				76	29.57	181	70.43	NA
Is a hand cream dispenser essential along with hand sanitizer at the hospital?	Yes	228	88.7	51	19.84	177	68.87	<0.001
	No	29	11.3	25	9.73	4	1.56	
Did you have symptoms of hand dermatitis before the pandemic?	Yes	8	3.11	1	0.39	7	2.72	.282
	No	249	96.89	75	29.18	174	67.70	
Did you have symptoms of hand dermatitis during the pandemic?	Yes	217	84.44	52	20.23	165	64.20	0.0002
	No	40	15.56	21	8.17	19	7.39	
Are you aware that hand dermatitis could alter the skin flora and result in frequent infection?	Yes	175	68.1	48	18.68	127	49.42	0.366
	No	82	31.9	27	10.51	55	21.40	

Table 2. Candidate Predictors in the Development of Hand Dermatitis during the Pandemic

N= 257		Have you noticed skin changes during COVID-19 pandemic?				p- value
		NO		YES		
		N	%	N	%	
Gender	Male	15	5.84%	61	23.74%	0.2318
	Female	25	9.73%	156	60.7%	
Age	20-29	8	3.11%	70	27.24%	0.445
	30-39	17	6.62%	84	32.68%	
	40-49	9	3.5%	40	15.56%	
	50-59	6	2.35%	23	8.95%	
Occupation	Doctor	24	9.34%	126	49.03%	0.724
	Nurses	8	3.11%	55	21.4%	
	Laboratory Technicians	8	3.11%	36	14%	
Major activity at work	Direct Patient Care	30	1.17%	157	61.09%	0.729
	Laboratory Work	10	3.89%	60	23.35%	
Handwashing frequency per day during the pandemic	< 5 times	27	10.51%	118	45.91%	0.213
	5-10 times	10	3.90%	86	33.46%	
	>10 times	3	1.17%	13	5.06%	
Hand sanitizer usage per day during the pandemic	< 5 times	6	2.34%	7	2.72%	0.0076
	5-10 times	16	6.23%	98	38.13%	
	>10 times	18	7%	112	43.58%	
Duration of glove usage during the pandemic	< 1 hour	7	2.72%	16	6.23%	0.039
	>1 hour	33	12.84%	201	78.21%	

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Our study shows that the majority of the HCWs did not seek treatment though they were aware that HD could alter the skin barrier and flora leading to frequent infections. Of particular concern, our study has observed that there is an inconsistency between the development of symptoms and uptake of treatment with less than 20% opting for over-the-counter (OTC) moisturizers and medicated treatments like corticosteroids or antiseptics (Table 3).

Topical corticosteroids and moisturizers act by reducing inflammation and have immunosuppressive effects.[19-21] With Eurasian countries witnessing a surge in new variant infections, COVID will likely be a recurrent problem, it is thus imperative to raise awareness of HD in India and intensive measures should be provided to prevent the development and progression of dermatitis.

The limitations of the present study include self-selection bias, where only HCWs having symptoms of HD are likely to complete the self-administered questionnaire. This was a monocentric study with a small number of participants, hence giving only a snapshot of the problem.

Conclusion

The majority of the HCWs during the pandemic developed HD which can be attributed to increased hygiene measures to reduce the transmission of the virus. Interestingly, HCWs were not able to follow the skincare routine that would prevent the development of HD. With a majority of the respondents reporting signs and symptoms of HD, we must be vigilant that there is no escalation of HD cases. The extent of skin damage reported by both our HCWs and those of international studies is of concern and appropriate implementation of the recommended guidelines is important to prevent the onset of occupational hand eczema.

Hand Hygiene task forces such as the Healthcare Infection Control Practices Advisory Committee (HICPAC), American Contact Dermatitis Society (ACDS), European Society of Contact Dermatitis (ESCD), and Centre for Disease Control (CDC), recommend the use of moisturizers after hand sanitization. Studies like these are indispensable to raise awareness of HD and elevating the importance of good skin care among the staff.

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Analysis of ADRs with Hypokalaemia for Severity, Preventability and Causality in a Tertiary Care Centre in South India

Najundappa S. Murthy,[1] Alikutty Safeera K,[2] Kuriakose Mabel EV,[2] Shivanna Basalingappa[3]

[1]Department of Pharmacology, Dr Chandramma Dayananda Sagar Institute of Medical Education and Resarch (CDSIMER), Devarakaggalahalli, Harohalli Hobali, Kanakapura Taluk, Ramanagara District, Karnataka, India.
[2]DM Wayanad Institue of Medical Sciences, Meppadi, Wayanad, Kerala - India
[3]Department of Pharmacology, Anna Medical College, Sans Saouci Road, Montagne Bianche, Mauritius.

Abstract

Hypokalemia is one of the most frequently seen electrolyte disturbances in clinical practice. Various drugs are known to induce hypokalemia, such as furosemide, thiazides, dicloxacillin, ampicillin, etc. This study aimed to assess hypokalemia adverse drug reactions (ADRs) for severity, preventability, and causality in a tertiary care centre in the southern part of India. It is a retrospective, cross-sectional study. Data collected at DMWIMS Medical College, India, as per the ongoing pharmacovigilance program of India from November 1st, 2016 to October 30th, 2017 (12 months period) was included for analysis in this study. The SADR form published by the Government of India under the PVPI program was used for collecting the data. In-patients who were on at least one medication and experienced hypokalemia ADRs with or without other symptoms or signs were included. Both primary suspected drugs and concomitantly prescribed drugs were analyzed. For the assessment of ADRs, modified Hartwig and Siegel assessment scales and plasma K^+ level criteria were used for severity, Schumock and Thornton criteria for preventability, the WHO-UMC scale, and Naranjo's algorithm for causality, respectively. Sixty hypokalemia ADRs were considered for analysis. Both genders were equally affected, with a mean age of 64.28 ± 3.02 years. Four groups of drugs were suspected to cause hypokalemia viz., anti-asthmatics (36.67%), diuretics (31.67%), antibiotics (18.33%), and antidiabetics (13.33 polypharmacy was reported in 43.33% of cases, with 4.40 ± 01.689 drugs prescribed on average. To summarize, hypokalemia is a preventable ADR and minor variations in serum K^+ levels can have a negative impact on patients' outcomes and mortality. FDC of Levosalbutamol with Ipratropium Bromide was the most common causative agent suspected of causing hypokalemia. Elderly patients receiving one or more drugs that are known to alter K+ levels, need close monitoring, and correction of hypokalemia should be done to improve prognosis. Further studies are required to understand the mechanisms involved in DDIs and DDiIs to derive preventive strategies.

Keywords: : Hypokalemia, Adverse Drug Reactions, Causality, Severity, Preventability, Pharmacovigilance

Corresponding Author: Shiva Murthy N . Department of Pharmacology, Dr Chandramma Dayananda Sagar Institute of Medical Education and Resarch (CDSIMER), Devarakaggalahalli, Harohalli Hobali, Kanakapura Taluk, Ramanagara District, Karnataka, India. Email: shivuindia@gmail.com
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Introduction

The physiological functions of many human cells, such as nerve cells, and skeletal and cardiac muscles, require homeostasis of intra- and extracellular potassium. About 98% of cation potassium (K^+) remain inside the cell (intracellular fluid (ICF)) and the remaining 2% is found in extracellular space (ECF). Normal plasma K^+ levels range from 3.5 to 5 mmol/L. Alteration in serum K^+ levels can have lethal consequences.[1-3]

Serum K^+ levels may be altered due to dietary deficiencies, underlying diseases that induce acid-base disturbances, changed tonicity of body fluids, excretion through sweat, the gastrointestinal tract, and the renal route. It is also altered by hormones such as aldosterone, insulin, catecholamines, etc. Coexisting hypomagnesemia promotes potassium wasting as it reduces the function of Sodium-Potassium Adenosine Tri-Phosphatase (Na^+-K^+ ATPase) pump.[1]

Various drugs are known to induce hypokalemia, such as furosemide, thiazides, dicloxacillin, ampicillin, amphotericin B, aminoglycosides, penicillin, salbutamol, formoterol, isoproterenol, pseudoephedrine, terbutaline, salmeterol, hydrocortisone, fludrocortisone, prednisone, insulin, and adrenocorticotrophic hormone (ACTH), etc.[1,3]

Hypokalemia is a frequently seen electrolyte disturbance in clinical practice. A serum K^+ level below 3.5 mmol/L is considered as hypokalemia. It can be graded as mild (> 3.0–3.5 mmol/L), moderate (2.5–3.0 mmol/L), and severe (< 2.5 mmol/L) hypokalemia. The severity of clinical signs and symptoms can vary from asymptomatic in mild cases to cramping, malaise, myalgia, and weakness in moderate hypokalemia. Severe cases may present with arrhythmias, paralysis, and electrocardiogram (ECG) changes like ST-segment depression, U-wave elevation, and T-wave inversion.[1-3]

Hypokalemia in elderly patients who are suffering from cardiovascular, hepatic, or renal diseases is bound to have higher mortality and morbidity. The severity of hypokalemia had a linear relationship with the development of ventricular arrhythmia in patients with myocardial infarction. Potassium levels below 4 mmol/L are an independent predictor of mortality in heart failure patients. Choline acetylase activity is reduced in hypokalemia, leading to a depletion of acetylcholine levels. These patients may experience decreased intestinal motility and even paralytic ileus due to reduced neuromuscular function. Hypokalemia may enhance ammonia genesis and worsen the symptoms of hepatic encephalopathy, which may precipitate hepatic coma.[1]

Epidemiology studies suggest that, irrespective of gender, up to 20% of hospitalized patients may have mild, 4-5% moderate (clinically significant), and 1% severe hypokalemia. Up to 50% trauma patients and 2.5% of elderly subjects aged ≥75 years are reported to have hypokalemia.[1,4,5,6] Approximately 80% of patients on diuretics and 0.9% of those receiving antimicrobial agents reported having hypokalemia. Drug disease interactions (DDIIs) and drug-drug interactions (DDIs) are expected to enhance the possibility of hypokalemia.[1,4,5]

Although a sufficient number of publications are available on hypokalemia worldwide, there are few studies in the Indian population. Rehan HS et al., and Mayee KR et al., published on drug-induced hypokalemia in hospitalised patients, and Kunder SK et al., reported with case series analysis.[3,6,7] Therefore, investigators of this study conducted this systematic analysis of drug-induced hypokalemia in inpatients

with the objective to "assess their severity, preventability, and causality in a tertiary care centre in the southern part of India."

Methods

Institutional ethics committee approval (Ref No. IEC/DMWIMS/July/2018-007) was obtained before the initiation of this study. It was a retrospective, cross-sectional study. The study lasted for 12 months, beginning on November 1st, 2016 and ending on October 30th, 2017. Data collected as per the ongoing Pharmacovigilance Program of India (PvPI) program was used for the study, and access was limited to investigators, and confidentiality of patient identifiers was maintained.

Doctors, nurses, and pharmacists (HCPs) were encouraged to report adverse drug reactions (ADRs) through awareness programmes organized regularly in the institute. All ADRs from inpatients (wards and ICUs) were collected using the Suspected ADRs Reporting (SADR) Form of PvPI8. The completed SADR forms were collected and analyzed by a team of pharmacologists and clinical pharmacists.

Inclusion Criteria

In-patients of both genders, irrespective of age, receiving at least one medication and having hypokalemia alone or any other concomitant sign or symptom as an ADR.

Exclusion Criteria

ADRs in patients treated on an outpatient basis. ADRs due to drug abuse; accidental poisoning; intentional self-harm; blood transfusion, or its products. Incomplete forms that do not have minimum requirements such as an identifiable patient, event, reporter, and drug were excluded from analysis.

Completed SADR forms were subjected to analysis under the following parameters: age, gender, weight, single/multiple events, presence/absence of polypharmacy, DDI, the severity of the ADRs based on plasma K+ levels1 and Modified Hartwig and Siegel's Severity Assessment Scale,[9] causality based on WHO-UMC causality categories,[10] Naranjo's algorithmic scale,[11] and preventability based on the Modified Schumock and Thornton Scale.[12] In addition, analysis was done on the primary suspected drug(s), concomitant medication(s), and their therapeutic area.

Statistical Analysis

The values were expressed in frequency, proportions, mean, and standard deviation (SD), as appropriate. The unpaired student t' test was used to compare age and body weight between male and female patients. It was also used to compare K+ values in patients with or without DDI. One-way Analysis of Variance (ANOVA) was used to compare K+ values between different therapeutic groups of primary suspected drugs. $p \leq 0.05$ was considered significant. GraphPad InStat 3 statistical software was used for statistical analysis. MS Word and MS Excel were used to generate tables as necessary.

Results and Discussion

During the study period, 60 hypokalemia ADRs were reported. All the hypokalemia reports were included for analysis in the study. This ADR was found in an equal number of males (n = 30) with a mean (±SD) age of 63.50 (±11.64) years and females (n = 30) with a mean (SD) age of 65.06 (±14.42) years. Twenty-one (21) patients were aged less than 60 years. The remaining 39 patients were all over the age of 60. The median age was 64 years; the minimum was 38 years, and the maximum was 88 years. The mean (±SD) body weight of male patients was 62.33 (±07.66) kg, and for female patients, it was 54.23 (±06.87) kg. (Table 1.)

Table 1. Details of Demographic Profile, Poly-Pharmacy, Associated Events of Patients with Hypokalemia

Sl No	Parameter	Sub parameter	n	Mean	SD	p value	Comment
1	Gender	Male	30	-	-	-	No comments
		Female	30	-	-		
2	Age	Male	30	63.50	11.64	0.6451	Statistical test used is "unpaired t test".
		Female	30	65.06	14.42		
3	Weight	Male	30	62.33	07.66	0.0001	
		Female	30	54.23	06.87		
4	Single event or Multiple events	Single event (Hypokalemia Only)	47	-	-	-	Concomitant ADRs (number of patients): Bleeding (1), Blurring of Vision (1), Constipation (2), Hyperglycemia (1), Hypoglycemia (2), Hypomagnesemia (1), Hyponatremia (2), Oral candidiasis (1), Rash (1), Hypotension (1) *, Thrombocytopenia (1) * * Same patient had 3 events at a time including hypokalemia
		Multiple Events (Hypokalemia + other symptoms/signs)	13				
5	Poly-pharmacy**	No	34	04.40	01.689	-	**Definition[13,16]: Using five or more medications in the same patient at a time
		Yes	26				
6	Drug-drug interaction***	Yes	37	2.8702	0.3447	0.5784	Serum K^+ levels compared using Statistical test "unpaired t test".
		No	23	2.9200	0.2687		***. Three patients' records did not have potassium values. 57 patient's data considered for mean/SD calculation.

Table 2. Primary Suspected Drugs that Caused Hypokalemia and Their Therapeutic Area

Sl No	Therapeutic Area of Drugs (Total %)	¥Plasma K^+ Levels Mean ± SD (n)	Names of Drugs	No of Patients (%) n = 60
1	Antibiotics (18.33 %)	2.74±0.43 (10) *¥	Piperacillin + Tazobactam,	09 (15.00%)
			Cefoperazone	01 (01.67%)
			Cefoperazone + Sulbactam	01 (01.67%)
2	Anti-diabetic (13.33 %)	2.91±0.15 (7) * ¥	Insulin	08 (13.33 %)
3	Diuretic (31.67 %)	2.90±0.34 (18) * ¥	Furosemide	13 (21.67 %)
			Hydrochlorothiazide	03 (05.00 %)
			Furosemide + Spironolactone	01 (01.67%)
			Spironolactone + Torsemide	01 (01.67%)
			Torsemide	01 (01.67%)
4	Anti-Asthmatics (36.67 %)	2.94±0.28 (22) ¥	Levosalbutamol + Ipratropium Bromide	16 (26.67 %)
			Salbutamol	04 (06.67 %)
			Levosalbutamol	02 (03.33%)

*one patient in each group did not had K^+ values, they were excluded from analysis.

¥Intergroup comparison of K^+ values with One-way Analysis of Variance (ANOVA) done and P=0.4431 (no significant difference noted).

Hypokalemia is common in community dwellers (2.5%) aged 55 years and older, in-patients (20%), and those admitted to the emergency department (39%). According to Liamis G et al., women may have twice the risk of hypokalemia as male patients.[5,14] Reports suggest that pediatric inpatients suffering from fever and needing critical care are expected to suffer from hypokalemia. A severe form of it may be seen in patients with diarrhea and severe malnutrition.[15] In our study, 65% (39/60) of the patients were in the over-60 age group. However, an equal number of male and female patients suffered from hypokalemia. Therefore, treating physicians should expect such electrolyte imbalances irrespective of age and gender while treating these patients.

Details of drugs that are suspected to cause hypokalemia are shown in Table 2. They are grouped under four therapeutic areas, namely: anti-asthmatics (36.67 %), diuretics (31.67 %), antibiotics (18.33 %), and anti-diabetics (13.33 %). Among anti-asthmatics, FDC of Levosalbutamol (β2 agonist) with Ipratropium Bromide (26.67 %) was the most frequently suspected cause of hypokalemia.

Table 3. Concomitant Medications and Their Frequency of Use in Patients with Hypokalemia ADRs

Sl No	Concomitant medication system	No of Patients n=60 (%)	Names of Drugs (frequency of use)
1	Drugs Affecting Gastrointestinal System	38 (63.33 %)	Pantoprazole (35), Ranitidine (3), Omeprazole (2), Ondansetron (2)
2	Antibiotics	26 (43.33%)	Piperacillin (8), Tazobactam (8), Amoxicillin (8), Clavulanic acid (7), Metronidazole (5), Sulbactam (5), Cefoperazone (4), Ceftriaxone (3), Azithromycin (2), Meropenem (2), Cefixime (1), Ciprofloxacin (1), Clotrimazole (1), Doxycycline (1), Nitrofurantoin (1), Oseltamivir (1)
3	Cardiovascular Drugs	17 (28.33 %)	Amlodipine (4), Aspirin (1), Bisoprolol (1), Digoxin (2), Hydralazine (1), Isosorbide Dinitrate (1), Ivabradine (2), Losartan (1), Metolazone (1), Moxonidine (1), Telmisartan (1), Verapamil (1)
4	Drugs Affecting Immune System	09 (15.00 %)	Hydrocortisone (6), Methyl Prednisolone (2), Dexamethasone (1)
5	Anti-Inflammatory, Analgesic, Anti-gout	07 (11.67 %)	Paracetamol (3), Aspirin (1), Diclofenac (1), Febuxostat (1), Tramadol (1), Allopurinol (1)
6	Drugs Affecting Respiratory System	07 (11.67 %)	Deriphyllin (5), Levosalbutamol (2), Budesonide (1), Ipratropium Bromide (1),
7	Anti-diabetics	06 (10.00 %)	Insulin (4), Metformin (2), Glimepiride (2), Insulin Aspart (1), Insulin Glargine (1)
8	Anti-coagulants	06 (10.00 %)	Clopidogrel (4), Aspirin (1), Enoxaparin (1), Acenocoumarol (1), Cilostazol (1)
9	Drugs Affecting Genital and Urinary tract	04 (06.67 %)	Prazosin (1), Sildenafil (1), Tamsulosin (1), Stanozolol (1)
10	Lipid Lowering Drugs	04 (06.67 %)	Atorvastatin (4)
11	Drugs Affecting Electrolyte Levels	04 (06.67 %)	Furosemide (2), Calcium Polystyrene Sulphonate, Potassium Chloride (1), Sodium Bicarbonate (1)
12	Thyroid Hormone	01 (1.67 %)	Levothyroxine (1)

Furosemide (21.67%), FDC of Piperacillin with Tazobactum (15.00%), and Insulin (13.33%) were the common drugs suspected from other therapeutic areas. As per Hsu E et al. and Veltri KT et al., beta-2 agonists and xanthines are known to produce hypokalemia due to an inward shift of potassium into the cells due to an effect on the membrane-bound Na+/K+-ATPase1,[17]. In contrast, corticosteroids increase renal potassium loss.[1] Furosemide and thiazides are kaliuretic diuretics and can worsen coexisting hypokalemia.[18]

Hypokalemia may be worsened in diabetic patients due to trans-cellular shifts after using high dosages of insulin.[19] Beta-lactam antibiotics are reported to produce hypokalemia through two mechanisms; first, they increase the transepithelial electronegativity by acting as nonabsorbable anions in the distal nephron. This leads to increased distal sodium delivery and potassium excretion; second, they are administered with large amounts of sodium, which can result in solute diuresis. This kind of solute diuresis can cause potassium excretion through the BK channels due to a high flow rate in the cortical collecting duct.[20,21]

According to the literature search, all 60 (100%) ADRs in this study were suspected to be caused by drugs that were already known to cause hypokalemia1.[3,7] Therefore, the majority of the ADRs could have been prevented if therapeutic drug monitoring (TDM) protocols had been implemented. Drugs used for treating GIT diseases (63.33%), infections (43.33%), CVS diseases (28.33%), and inflammation and immune diseases (15.00%) were the common concomitant medications prescribed, respectively, in descending order (Table 3).

Fifty-nine (98.33%) patients received more than one drug, and on an average patients received 4.40±01.689 drugs per patient. Polypharmacy was identified in 43.33% (26/60) of the cases. Further systematic studies are required to understand the mechanisms involved in the development of hypokalemia through DDI when more than one drug known to cause hypokalemia is used together

Two methods were applied for severity analysis (able No. 4). Both methods gave approximately similar results. Based on plasma K^+ levels[1] and the Modified Hartwig and Siegel's Severity Assessment Scale,[9] mild to moderate cases totaled 50 (83.33%) and 49 (81.66%) events, respectively. Forty-seven (78.33%) patients had a single event, i.e., non-symptomatic hypokalemia, and the remaining 13 patients (21.66%) had more than one sign or symptom. As per literature, patients with mild to moderate hypokalemia may not show any symptoms or may have some vague symptoms of systemic diseases like heart failure, ADRs of anti-asthmatics, or other electrolyte disturbances, e.g. sodium retention.[7]

Diuretics, such as hydrochlorothiazide, frequently cause mild hypokalemia at the start of treatment, which may resolve spontaneously depending on the underlying disease and severity.[1,5] According to Nasralla HA et al. and Lemieux G et al., 12% of hypokalemia patients may experience symptoms such as generalized weakness, muscle weakness, fatigue, and cramps, particularly those taking diuretics and steroids1.[5,7] ECG monitoring may detect changes like prominent U waves, flat T waves, and ST segment depression in hypokalemia. Digitalis intake in hypokalemia patients may induce palpitations and ventricular and supraventricular tachyarrhythmias. Monitoring the ECG will thus be beneficial in these patients.[14]

In our study, the majority of ADRs were considered to be possibly related to the primary suspected drugs. As per the WHO-UMC scale,

Table 4. Assessment of Severity of Hypokalemia

Sl No	Parameter		Based on plasma K^+ concentration*		Modified Hartwig and Siegel's Severity Assessment Scale
			No of Patients (%)	Mean (SD) In mmol/L	No of Patients (%)
1	ADR Severity$	Mild	30 (50.00%)	3.103 (0.1189)	02 (03.33%)
		Moderate	20 (33.33%)	2.795 (0.1791)	47 (78.33%)
		Severe	07 (11.66%)	2.228 (0.0951)	11 (18.33%)
2	Average of K^+ conc.	Lower Level Reported***	57**	2.887 (0.3185)	-
		Higher Level Reported ***	57**	3.768 (0.7209)	-

Note:

*Severity based on lowest recorded K^+ value in mmol/L: **a).** Mild = less than 3.6 and more than/ 3.0;

b). Moderate 2.5 to 3.0;

c). Severe less than 2.5.

**Three patients records did not have potassium values. 57 patient's data considered for mean/SD calculation.

***If only one value available, then same value was considered for both lower and higher level for calculation purposes.

$ According to definition of Serious Adverse Event (SAE)[22] 47 where SAEs were considered as SAEs, and remaining 13 were not.

The reasons for considering SAE: **a).** Hospitalization was prolonged in 43 cases;

b). Four patients had life threatening events.

43 (71.66%) events and, according to the Naranjo ADR probability scale, 40 (66.66%) events were considered possibly related. All 60 ADRs were considered to be definitely preventable. (Table 5). These results were considered to be similar to those reported in Mayee et al., study.[7]

Serum K^+ monitoring is part of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score or the Simplified Acute Physiology Score (SAPS). Both hypokalemia and hyperkalemia will cause the scores to rise. This indicates that patients admitted to the intensive care unit with abnormal potassium levels have a worse prognosis.[4] Abensur VL et al, reported that serum potassium disturbances are bound to increase mortality in patients with chronic diseases like diabetes mellitus, hypertension, ischemic heart diseases, congestive heart failure, and kidney failure. Both hyper- and hypokalemia are expected to worsen these patients' prognoses.[23]

Renal or non-renal loss of K^+ may lead to hypokalemia due to drug use of drug(s) or disturbance in homeostasis. Renal loss of K^+ occurs due to acidosis in the renal tubules,

hormonal disturbances regulating electrolytes, hypomagnesemia, starvation, dementia, and anorexia. Homeostasis may be disturbed due to a transient intracellular K^+ shift in metabolic alkalosis and inadequate dietary intake. Non-renal loss may occur in diarrhea, vomiting, excessive perspiration, and dehydration with subsequent secondary hyperaldosteronism. Procedures such as nasogastric suctioning, laxative use, hemo, and peritoneal dialysis can all cause hypokalemia.[14]

As discussed earlier, the majority of ADRs could have been prevented if therapeutic drug monitoring (TDM) protocols were implemented. This was again supported when preventability was assessed by applying the Modified Schumock and Thornton scale. Preventive strategies may include the use of a low-salt diet, but rich in potassium, magnesium, and chloride (either through foods enriched with these elements or through potassium chloride supplements); management of the underlying disease or elimination of the causative factor; discontinuation of laxatives; use of lower doses of drugs known to cause hypokalemia; and/or use of potassium-sparing drugs.[1,5] Joon-myoung K et al. used 6- and 12-lead ECGs to detect and monitor electrolyte imbalances in serum potassium, sodium, and calcium by integrating artificial intelligence (AI) and computer-triggered reminders (CTR).

Similarly, AI and CTR tools can be used to prevent hypokalemia induced by DDIs and DDIIs.[24-26] Integration of hospital information management systems to include clinical pharmacologists in the internal referral systems may help the hospitals to utilize their services related to TDM, causality assessment, prescription auditing, and DDI/DDIIs predictions to prevent severe forms of ADRs.

Advantages and Limitations of the Study

This is the first study published on this subject from Kerala, south India. Therefore, this study adds important value to the existing knowledge on hypokalemia. As mentioned in the methodology section, ADRs experienced by outpatients, those due to OTC medication intake, and domestic medication consumption were excluded from the analysis. Our study is a retrospective cross-sectional study based on the available 12-month data. All the available cases formed the basis for analysis. An exact sample size was not calculated for this study. Therefore, we accept this as a limitation of this study.

Conclusion

Hypokalemia is a preventable ADR, and minor variations in serum K^+ levels can adversely affect the patient's outcome and may also increase mortality. In our study, four groups of drugs, such as β2 agonists, diuretics, antibiotics, and anti-diabetics, were suspected as the causative agents of hypokalemia. Any patient receiving drugs originating from one of these groups needs monitoring of serum K^+ levels, especially in those patients who are suffering from diseases known to have altered electrolyte levels. In such cases, close monitoring should be implemented, and suitable management and prevention strategies should be considered. Further studies are required to understand the mechanisms involved in DDIs and DDIIs and derive better preventive strategies.

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Table 5. Assessment of Causality and Preventability of Hypokalemia

Sl No	Causality Assessment				Preventability Assessment	
	WHO-UMC scale	n=60	Naranjo ADR probability scale	n=60	Preventable (and its reasons) or Not preventable (based on Schumock and Thornton preventability assessment scale)	n=60
1	Certain	03	Definite	0	**1.** Definitely preventable	60
2	Probable	14	Probable	20	**a.** Was there a known treatment for the Adverse Drug Reaction? *	60
3	Possible	43	Possible	40	**b.** Was required Therapeutic drug monitoring or other necessary laboratory tests not performed? *	49
4	Unlikely	00	doubtful	00	**c.** Were preventative measures not prescribed or administered to the patient? *	18
5	Conditional / Unclassified	00	-	-	**2.** Not preventable	00
6	Unassessable / Unclassifiable	0	-	-	*More than one reason attributed for preventable events	

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Conflict of Interest
None declared

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Correlation of Polypharmacy and Comorbidity with NIHSS Status in Ischemic Stroke Patient

Firdha A. Wardhani[1,2]
[1]Faculty of Pharmacy, Gadjah Mada University. Yogyakarta - Indonesia
[2]Faculty of Pharmacy, dr. Soebandi University. Jember District, East Java - Indonesia

Abstract

Drug-related problems are a common problem among stroke patients due to comorbidities resulting from the complex management of stroke treatment leading to polypharmacy management. Studies show that 90% of stroke patients have drug-related problems (DRPs). However, there is limited information on the impact of comorbidities as risk factors for DRP prevalence and unfavorable prognosis in patients with ischemic stroke. This study aimed to determine the risk factors for DRP and clinical outcomes as modifiable comorbidities in ischemic stroke patients admitted to a tertiary hospital between January 2020 and October 2021 were indeed significant influences. The study was conducted retrospectively using a cross-sectional analysis of patient's medical records. The study found no significant association between the presence of comorbidities and polypharmacy in patients with the incidence of DRP, although we found that the DRPs occurrence was found more in a patient with comorbidities and polypharmacy. Diabetes mellitus was found to have a significant association with no improvement in NIHSS scores in ischemic stroke patients. We found that diabetes mellitus patient had an increased risk of non-improvement NIHSS score 2,987 times compared to patients without diabetes mellitus. The second increased risk was the presence of comorbid hypertension (OR 1.352), the third was the occurrence of polypharmacy (OR 1,175), and the fourth was dyslipidemia (OR 1.138).

Keywords: Comorbid, DRPs, ischemic stroke, NIHSS

Introduction

Stroke is defined as a sudden onset of focal neurological deficit that persists for at least 24 hours. Stroke can be classified as ischemic or hemorrhagic and is diagnosed by a doctor after a patient has undergone a CT (Computed Tomography) scan or MRI (Magnetic Resonance Imaging).

Age, sex, race, family history; and comorbidities such as hypertension, atrial fibrillation, cardiovascular disease, diabetes, dyslipidemia, obesity; and other factors like smoking, alcohol, postmenopausal hormone therapy, and lifestyle factors such as diet are a few of stroke risk factors.[1–3]

Stroke is not only the major cause of death, but also one of the leading causes of disability worldwide.[4] Studies have shown that most ischemic stroke patients have cognitive and functional abnormalities, of which 60.44% have cognitive impairment and 37.37% have moderate-to-complete category-dependent functional impairment.[5]

Corresponding Author: Firdha Aprillia Wardhani, Master of Clinical Pharmacy, Faculty of Pharmacy, Gadjah Mada University. Yogyakarta - Indonesia. Email : firdhaaprillia@mail.ugm.ac.id
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Ischemic stroke is a complex disease affected by many factors. Stroke patients often receive multiple medications in their treatment management.[6,7] According to research, each additional drug increases a patient's risk of DRPs (Drug-Related Problems) by 7%.[3] Therefore, stroke patients are much more likely to develop DRPs than patients with other diseases that do not require multidrug therapy. Approximately 90.2% of stroke patients had DRPs, with 2,015 DRPs per patient.[8]

However, there was limited information regarding the effect of comorbidity and polypharmacy as both a risk factor for DRPs prevalence and worse outcomes in an ischemic stroke patient. This research was conducted to see whether modifiable comorbidities and polypharmacy indeed had a significant impact as a risk factor for DRPs and clinical outcomes, using NIHSS (National Institution of Health Stroke Scales) as a sensitive parameter to detect the clinical outcome in hospitalized ischemic stroke patients.

Methods

This study was retrospectively conducted with a cross-sectional analysis of ischemic stroke patients admitted to a tertiary hospital in Yogyakarta, Indonesia from January 2020 to October 2021. Using medical records as a data source, we included adult patients (> 18 years old) diagnosed with ischemic stroke, and NIHSS analyzed both when patient admitted and discharged. Subjects would be excluded if they had length of stay less than 2 days or had incompletion of medical record. The data extracted from the medical records were age, gender, length of hospital stay, medication regimen, route of administration, laboratory data, and the clinical status of patients as subjective data.

DRP was analyzed using local guidelines from PERDOSSI (Perhipunan Dokter Saraf Indonesia-Indonesian Neurologist Association) and PNPK (Pedoman Nasional Pelayanan Kedokteran-National Guidelines for Medical Services), as well as international guidelines widely used by the AHA (American Heart Association), ASA (American Stroke Association), ESC (European Society of Cardiology), and the NICE (National Institute for Health and Care Excellence). Drug interactions were checked and analyzed using Lexicomp's Drug Interaction Checker, with at least risk modified D with alternative therapy as patient's management, or X with a contraindication. Patients were categorized as improved based on a reduced NIHSS score of at least 2 points, and unimproved if the discharged NIHSS score was reduced by less than 2 points, stay at the same value as admission, or death.

Statistical Analysis

Mean ± SD were used to described the continuous variables and percentages were used to count the categorical variables. Demographic characteristics, such as gender and age, were compared between comorbidity groups using the Chi-square test. To discover the association between comorbidities with both DRPs prevalence and clinical outcome using NIHSS, we performed multivariate binary logistic regression. The feasibility of the model is tested using Hosmer and Lemeshow test.

Results and Discussion

A total of 111 ischemic stroke patients were included. The characteristic of patients with comorbidities is summarized in Table 1. We found no significant difference in the age group between patients with comorbidities diabetes mellitus and dyslipidemia group; and gender with comorbidities dyslipidemia and hypertension. There was unsignificant difference in the age group with diabetes and dyslipidemia; sex with dyslipidemia and

hypertension. Notably, hypertensives were older (51 vs 23, p<0,05), and more women than men were diabetic (29 vs 13, p<0,05).

This result is following research that has been done, which states that the prevalence of hypertension is significantly associated with older age 9. Based on the National Diabetes Statistics Report by the CDC (Centers for Disease Control and Prevention) and data from the International Diabetic Federation, shows that the prevalence of diabetes mellitus in men is greater than in women.[10,11] Meanwhile, data by Riskesdas (Riset Kesehatan Dasar-Basic Health Research) Indonesia shows that in 2018 the prevalence of diabetes mellitus in women was higher than in men (1.78% vs. 1.21%), which has increased since 2013 (1.7% vs. 1.4%). In the last 5 years, the prevalence of diabetes mellitus in women has shown an increase, while the prevalence in men has decreased.[12]

As shown in Table 1, the average age of the participants was 62.11 years old, that were considered elderly patients. The previous studies have also shown that age is one of the risk factors for ischemic stroke prevalence.[13-14] The presence of comorbidities in patients is a risk factor for ischemic stroke, meanwhile the most common aging change in older adult is stiffness of the arteries, causing hypertension. Total cholesterol and LDL (Low-Density Lipoprotein) showed an increasing trend with age. Those two factors combined produce an increased risk in the occurrence of ischemic stroke in older adult.[15,16]
The average length of stay was 7 days, 47.7% of patients had improved NIHSS scores at discharge, and the remainder (52.3%) were classified as not improving. Patients were categorized as improved based on a reduced NIHSS score of at least 2 points, and unimproved if the discharged NIHSS score was reduced by less than 2 points, stay at the same value as admission, or death.

Drug-Related Problems
The occurrence of DRPs in 111 patients observed was 88,3%, with the most common DRPs observed were "patient needs additional therapy" with 74,8%, followed by "dosage too low" (48,6%), "ineffective drug therapy" (33,3%), and "adverse drug reaction" (9,9%) respectively. This finding is supported by previous research, in which "patients need additional drugs" and "dosages too low" were the most commonly found DRPs in patient.[17]

Conditions where patients require additional therapy are mostly found in patients with diabetes mellitus with hyperglycemia that has not been controlled until the patient is discharged from the hospital. While the condition where the patient received less effective therapy was when the patient

Table 1. Demographic Characteristic of Patients

Characteristic	Overall	Diabetes Mellitus (n=42)	*P*	Dyslipidemia (n=43)	*P*	Hypertension (n=74)	*P*
Age group	62,11 ± 14,048 (29-92)						
Geriatric	66 (59,5)	29	0,160	27	0,711	51	**0,008**
Non-geriatric	45 (40,5)	13		16		23	
Gender							
Woman	60 (54,1)	29	**0,023**	24	0,920	41	0,840
Man	51 (45,9)	13		19		33	

We bold the value that statistically significant
We presented the variables as n (%) in nominal data; mean ± SD in continuous data

received antihypertensive therapy within 24 hours, when the patient's neurological condition was not yet stable. The condition in which the patient receives drug therapy with a dose that is too low is in a condition where the patient receives antihypertensives in a stable condition, with blood pressure until discharge from the hospital is still above the target of therapy. And lastly, the type of unwanted effect due to therapy that is most commonly found in patients is the occurrence of liver injury due to drugs.

Clinical Outcome

We found that 53 (47,7%) patients in this study had a reduced NIHSS score of at least 2 points and were categorized as improved patients when discharged, and 58 (52,3%) patients were categorized as unimproved. (Table 2).

DRPs that are often found in patients with diabetes mellitus in this study are hyperglycemic conditions of patients who have not been controlled, either using insulin or oral antidiabetic. Based on the PERKENI (Perhimpunan Endokrinologi Indonesia-Indonesian Endocrinologist Association) Insulin Therapy Guidelines, ischemic stroke conditions are included in non-diabetic emergencies, where insulin is recommended.[18]

Initiation of insulin can be done using prandial insulin 5 – 10 IU/8 hours or a combination of basal and prandial based on the recommendations of the ADA (American Diabetic Association) and ACCE (American Association of Clinical Endocrinology), with dose adjustment depending on the patient's blood glucose.[19,20]

The presence of high blood pressure, with the ineffective therapy; or the presence of a decrease in blood pressure in patients without an indication of a decrease in blood pressure, are the types of DRPs found in patients with hypertension. Although lowering blood pressure is recommended in post-acute stroke patients, excessive blood pressure reduction is associated with worsening NIHSS scores.

The study showed that patients with very high SBP (Systolic Blood Pressure) (SBP 211 mmHg) or low SBP 110 mmHg, were significantly associated with worsening NIHSS scores ($p=0.003$).[21] Based on PNPK Stroke, AHA/ASA, and ESO, blood pressure reduction is recommended immediately if there are comorbidities such as acute coronary syndrome, acute heart failure, aortic dissection, intracerebral hemorrhage, or preeclampsia or eclampsia. However, if there are no comorbidities, then the blood pressure is reduced by about 15% in the first 24 hours if the patient's blood pressure is > 220/120 mmHg.[22–24]

Table 2. Association between Comorbidities and the Incidence of DRPs

Comorbidity	DRPs (n=98)	Without DRPs (n=13)	P value
Polypharmacy	90 (81)	12 (10,9)	0,913
Diabetes mellitus	38 (34,2)	4 (3,6)	0,498
Hypertension	64 (57,6)	10 (9)	0,410
Dyslipidemia	37 (33,3)	6 (5,4)	0,544

We bold the value that statistically significant
We presented the variables as n (%) in nominal data; mean ± SD in continuous data

ESO explains that optimal blood pressure is different in patients with ischemic stroke who do not meet the eligibility for reperfusion therapy, where lowering blood pressure can reduce the risk of hemorrhagic transformation and edema, but high blood pressure has benefits in maintaining cerebral blood flow when the autoregulation process is imbalanced with the presence of ischemic stroke. Thus, both European (ESO) and American (AHA/ASA) guidelines do not recommend reducing blood pressure in ischemic stroke patients for at least 24 hours, unless the patient's blood pressure is extreme (> 220/120 mmHg), and certain comorbidities have been described. previously.[24]

Inadequate lowering lipid profile in dyslipidemia patients, especially LDL-c is a problem found in patients with dyslipidemia. According to the AHA/ASA, one of the clinical conditions of ASCVD (Atherosclerotic Cardiovascular Disease) is stroke, and in patients aged 75 years it is recommended to use a high-intensity statin with a target for LDL-c reduction of 50%, or use a moderate-intensity statin if high-intensity therapy is contraindicated or produces significant undesirable effects. In patients >75 years of age, initiation of moderate-high intensity statins is recommended.[23]

Polypharmacy was found in 102 patients (91,9%), with the average medicine used in each patient being 9,98 medicines. This founding is aligned with our hypothesis that ischemic stroke patients have more chance to be treated in polypharmacy management, and one of the causes is the existence of comorbidities that are often followed or diagnosed before the acute stroke onset. It was also proven with the similar proportion between polypharmacy and comorbidities occurrence in this study, that show comorbidities are also found in most patients, to be exact in 83,8% of patients.

This study found no significant relationship between the presence of comorbidities in patients with the incidence of DRPs. However as shown in Table 2, the occurrence of DRPs was found more in a patient with polypharmacy and comorbidities. A study with a larger population is needed to define a more significant relationship between polypharmacy and comorbidities, with DRPs occurrence in an ischemic stroke patient.

Correlation of Comorbidities and Polypharmacy with NIHSS Improvement

In this study, it was found that all comorbidities contributed to the occurrence of non-improved outcomes, which was indicated by no decrease in the NIHSS score. A significant risk was found in the presence of comorbid diabetes mellitus in these patients. Diabetes mellitus was found to have a significant association with no improvement in NIHSS scores in ischemic stroke patients. In diabetes mellitus patients, there is an increased risk of non-improvement NIHSS score 2,987 times compared to patients without diabetes mellitus. The second increased risk was the presence of comorbid hypertension (OR 1.361, 95% CI 0.598-3.095, p-value = 0.463), and the third was dyslipidemia (OR 1.125, 95% CI 0.505-2.502, p-value 0.774). (Table 3).

This is reciprocal with a previous study, in which patients with hyperglycemic diabetes were significantly associated with increased NIHSS scores. The literature states that hyperglycemia during acute stroke, both in patients with or without a history of diabetes mellitus, is significantly associated with higher mortality, a longer length of stay, and reduced chances of recovery.[25].

Another study also stated that persistent hyperglycemic conditions were significantly correlated with increased mortality at 30 days in patients with ischemic stroke.[26]

Table 3. Correlation between Comorbidities with NIHSS Improvement

Comorbidity	Improvement (n=53)	No improvement (n=58)	P value	OR (95% CI)
Diabetes mellitus	13 (11,7)	29 (26,1)	**0,009**	2,960 (1,304-6,720)
Hypertension	33 (29,7)	41 (38,9)	0,474	1,352 (0,593-3,082)
Dyslipidemia	19 (17,1)	24 (21,6)	0,754	1,138 (0,508-2,548)

Statistically significant values are given in bold
Variables are presented as n (%) in nominal data; mean ± SD in continuous data

Table 4. Correlation between Polypharmacy with NIHSS Improvement

Condition	Improvement (n=53)	No improvement (n=58)	P value	OR (95% CI)
Polypharmacy	48 (43,2)	54 (48,6)	0,825	1,175 (0,280 4,929)

Statistically significant values are given in bold
Variables are presented as n (%) in nominal data; mean ± SD in continuous data

Hyperglycemia patients had a higher NIHSS (14.9 vs 7.8, p=0.000), higher mortality (65.9 vs 5, p<0.001), and a longer LoS (12.5 vs.3,p<0.001) compared to normoglycemia.[27] The presence of high glucose exposure in hyperglycemic patients associated with mitochondrial dysfunction, inflammation, and oxidative stress that triggers endothelial apoptosis, and has the potential to increase infarct volume, decrease recanalization, and increase the risk of ischemic stroke transformation into hemorrhagic stroke.[26]

The association between comorbid hypertension and NIHSS scores is also consistent with studies showing that blood pressure correlates with clinical outcomes in ischemic stroke patients. The study found that higher post-stroke blood pressure in patients (blood pressure 48 hours post-onset), was significantly associated with decreased neurologic improvement and increased neurological and functional deterioration.[28] The presence of hypertension in these patients was also associated with a significantly increased risk of stroke recurrence.[29,30]

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The association between comorbid dyslipidemia and clinical outcome in ischemic stroke patients is supported by several studies showing that LDL-c levels in dyslipidemia patients have an association with an increase in NIHSS scores. The study found that an increase in LDL-c was significantly correlated with an increase in NIHSS (p=0.033), and when compared with patients with low LDL-c values, there was an increased risk of an increase in stroke severity based on NIHSS data, as much as 2.9-fold (95% CI 1.48-5.74)31. The study found a correlation between LDL and HDL ratios and patients' NIHSS outcomes, where the LDL and HDL ratios could predict 31% of patients' NIHSS outcomes32. Another study found that the presence of LDL-c levels independently predicted NIHSS values (OR 1.537, 95% CI 0.134-2.878, p=0.042), with the mean LDL-c levels in patients with mortality outcomes being significantly higher than in patients without mortality (1.04 vs 0.88, p=0.017).[33]

This study has limitations, including the study design in this study which was cross-sectional which identified an association but not a causal relationship. Although we found no significant association, polypharmacy also contributed to the risk of unimproved NIHSS score in a patient with ischemic stroke (OR

1,175) (Table 4). Studies have found that the increase in drug number has been associated with negative outcomes in health, including a more frequent hospitalization and DRPs occurrence.[34–37] However, it should be noted that both unnecessary drugs and patient needs for additional therapy, are included in DRPs. When indeed polypharmacy increased the risk of DRPs occurrence, and as known, the DRPs occurrence contributed to the unimproved clinical outcome; reducing the necessary medication is not an alternative. If treatment is needed by the patient, then reducing the amount of medication received by the patient is not an option, in order to reduce polypharmacy. Polypharmacy does not always mean that the therapy received by the patient is irrational, but clinical pharmacy needs to ensure that the polypharmacy received by the patient is rational and does not cause problems, which we refer to as DRPs.

Clinical pharmacists need to be more vigilant when finding patients with polypharmacy and comorbidities. Supervision and monitoring of therapy also need to be more stringent, to ensure that DRPs do not occur in these patients. A combined approach with skill integration from different health care professionals, especially from both clinicians and clinical pharmacies are needed to address medical complexity in an ischemic stroke patient, and eventually brought a positive effect on the patient's health outcomes.

Conclusion

This study found no significant relationship between the presence of comorbidities in patients with the incidence of DRPs, but all comorbidities contributed to the occurrence of non-improved outcomes, which was indicated by no decrease in the NIHSS score. A significant risk was found in the presence of comorbid diabetes mellitus in these patients. Diabetes mellitus was found to have a significant association with no improvement in NIHSS scores in ischemic stroke patients.

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Conflict of Interest

None declared.

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Evaluating the Knowledge, Attitude, and Perception of Medical Interns Regarding Contraception in a Tertiary Care Centre

Usha NS,[1] Sabari Anandh JV,[2] Afzal Khan AK,[1] Swapna R. Nayaka[1]

[1]Department of Pharmacology, MVJ Medical College and Research Hospital, Kolathur P.O, Hoskote, Karnataka, India
[2]Department of Pharmacology, Arunai Medical College, Velu Nagar, Mathur, Tiruvannamalai, Tamilnadu, India

Abstract

Maternal mortality is one of the significant burdens requiring appropriate measures including family planning methods to control post-partum morbidity and mortality. The early age of marriage among women is accompanied by early pregnancies also contributes to maternal mortality. Knowledge about contraceptive usage could prevent such incidences. This study aimed to evaluate the knowledge, attitude, and perception regarding contraceptives among medical interns in our college. This cross-sectional questionnaire study was done on 60 house surgeons (interns), at MVJ Medical College and Research Hospital, Hoskote, using a validated questionnaire that consisted of 22 questions, including MCQs and case scenarios to assess their knowledge, perception, and attitude about contraceptive methods. Data were analyzed in the form of percentages. Among 60 interns, 36 were females, and the majority of students were from urban backgrounds. About 73.3% of interns had adequate knowledge about various contraceptive methods and their usage. The interns have a perception that illiteracy, lack of awareness and social, and religious values are major hurdles for contraceptive usage and have an attitude that doctors are most suitable to give information regarding contraceptive methods. Considering medical interns as future physicians and their responsible role in counseling about contraceptive usage in effective family planning, they need to have a positive attitude with fair knowledge and perception about the contraceptive methods which can be achieved by educating them early in their academic carrier

Keywords: Maternal mortality, Contraception, Family Planning, Interns

Corresponding Author: Swapna R Nayaka. Department of Pharmacology, MVJ Medical College and Research Hospital. Kolathur PO, Hoskote- 562114, Karnataka, India. Email: drsappy.chinni@gmail.com
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Introduction

Contraception is the act of preventing pregnancy intentionally by using various medications, devices, sexual practices, and surgical procedures. Contraception gives a woman control over her reproductive health and the capacity to plan her family.[1] India is one of the most highly populated countries, maternal mortality is a remarkable problem for decades hence there is always an unmet need for family planning. Maternal mortality refers to deaths that occur as a result of problems during pregnancy or childbirth. According to United Nations' inter-agency estimates, the global maternal mortality ratio fell by 38% from 2000 to 2017 — from 342 to 211 deaths per 100,000 live births.[2]

According to the recently issued Sample Registration System (SRS), 2015-2017 bulletin for MMR, India's MMR has fallen from 130 per 1 lakh live births in 2014-2016 to 122 per 1 lakh live births in 2015-2017.[3] Unsafe abortion is one of the primary causes of death among women who become pregnant unintentionally due to a lack of contraceptive knowledge which can be prevented by comprehensive sex education.[2]

"Every woman has a right to have a planned parenthood." Contraception is used not just to prevent unexpected births, but also to improve their own and their families' health.[4] Increased access to contraception is associated with a reduction in mother and infant mortality, however, the greatest barrier for women to acquire appropriate and safe contraception is a lack of qualified healthcare practitioners and personnel.[5]

In India today women have access to the latest safe and affordable methods of contraception which are available in all public health sectors. To give women credible information, healthcare personnel must have adequate knowledge of contraceptive methods and counseling training skills.[6] In addition, research conducted in India found that only 58% of young women use contraceptive methods.[7] The competence of healthcare professionals in contraceptive methods is one of the major barriers that need to be addressed to increase the adoption of contraceptive methods.[6]

The medical interns are future physicians and considering their role as contraceptive counselors, limited information is available about their opinion on contraceptive methods, use, and counseling. The present study may enable curriculum designers some new ideas for improving medical education courses in contraceptive counseling to lower maternal mortality. Our study aims to evaluate the knowledge, attitude, and perceptions about contraceptive methods and counseling techniques among medical interns in our college.

Methods

The cross-sectional questionnaire study was carried out among 60 interns, at MVJ Medical College and Research Hospital, Hoskote, Karnataka, India after obtaining Institutional ethical committee clearance (Approval no: MVJMC&RH/Adm/ECM/2019-20) and informed consent. The content and relevance of the questionnaire were evaluated by topic specialists before the study. The final questionnaire contained 22 questions which included multiple choice questions (MCQs) to assess the knowledge regarding different contraceptive methods and case scenarios to assess their perception and attitude about contraceptive methods.

This questionnaire was distributed among the interns and the responses were collected during the study period between August 2019 and February 2020. All the medical interns during the study period were eligible for inclusion

into the study. The interns who rejected the consent were excluded from the study.

Informed consent was obtained from the interns, to utilize their data for research purposes and they were asked to complete the questionnaire anonymously. Students' sociodemographic features, their awareness about modern contraceptives, their attitudes toward the use of modern contraceptives, and contraception behavior were all gathered. The descriptive data collected was collected and analyzed in the form of percentages.

Results and Discussion

This study included 60 medical interns to evaluate the knowledge, attitude, and perceptions about contraceptive methods and counseling techniques in a tertiary care hospital and teaching center. Among them 40% were males and 60 % were females. All the respondents were unmarried, and the majority of participants were from urban (73%) backgrounds, belonging to the Hindu (88%) religion. Homogeneity among study participants' demographics was also observed in a previously reported similar study.[6] Table 1 shows the demographic data from the study participant.

The majority of the medical interns reported that sexual and reproductive health was included in their curriculum (86.7%) and were educated about contraceptive methods (93.3%) as well. Most of the interns had adequate knowledge regarding contraceptive usage, effectiveness, and limitations. About 73.3% of interns had proper knowledge about different contraceptive methods and their application based on various clinical conditions. Case scenarios were used to assess how they applied their knowledge in clinical practice. (Figure 1)

Figure 2 shows the study respondents have a perception that illiteracy (26.7%), lack of awareness (30%) and social, and religious values (20%) are major hurdles for contraceptive usage. Interns believe that traditional values are a major hurdle for sex education (70%) and old contraceptive methods are not safe (70%), although contraceptives are easily accessible (90%). Furthermore, they have an attitude that doctors are most suitable (73.3%) to give information regarding contraceptive methods (Figure 3) and they had an opinion that contraceptives should be made available to all age groups irrespective of marital status (Table 2).

Table 1. Demographic Data of the Study Participant

Demographic characteristics	Number (n=60)	Percentage (%)
Gender		
Male	24	40
Female	36	60
Religion		
Hindu	53	88
Muslim	3	5
Christian	2	4
Sikh	0	0
Others	2	3
Place of upbringing		
Urban	44	73
Rural	16	27

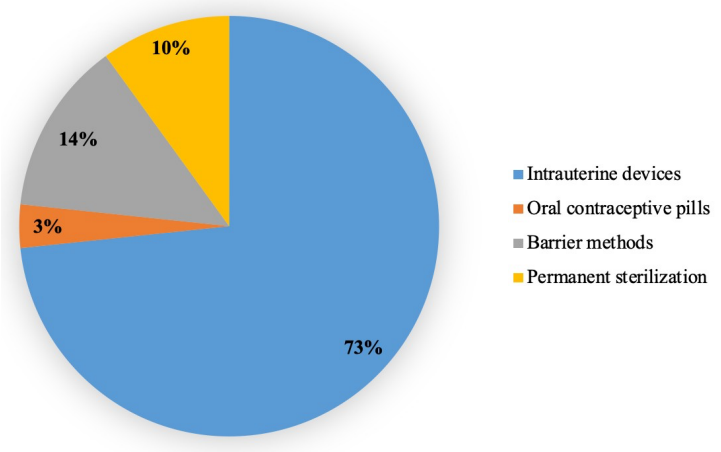

Figure 1. Knowledge about Choosing the Contraceptive Method

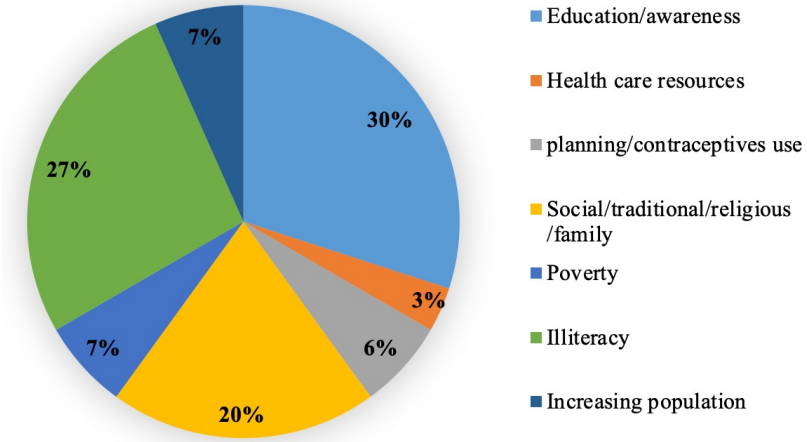

Figure 2. Special Problems within Reproductive Health

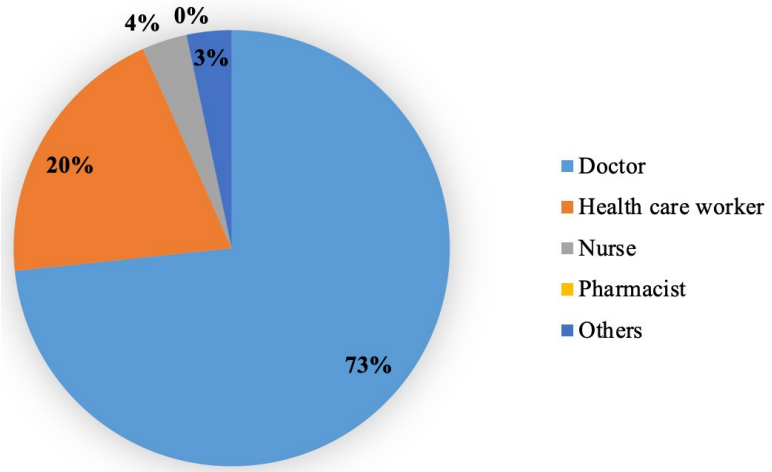

Figure 3. . Source of Information about Contraceptive

Table 2. Knowledge, Attitude, and Perception regarding Contraceptive Methods among Interns (1)

	KNOWLEDGE ABOUT CONTRACEPTION AMONG MEDICAL INTERNS	Number (n)	Percentage (%)
1.	Was sexual and reproductive health included in your curriculum?		
	Yes	52	86.7
	No	8	13.3
2	Contraceptive methods have been taught in your teaching curriculum?		
	Yes	56	93.3
	No	4	6.7
3	Have you had clinical practice in abortion care services during your training?		
	Yes	22	36.7
	No	38	63.3
4	Contraceptive pill might cause cancer		
	Agree	24	40
	Disagree	28	46.7
	Neither agree nor disagree	8	13.3
5	Contraceptive pill can cause infertility		
	Agree	12	20
	Disagree	38	63.3
	Neither agree nor disagree	10	16.7
6	Condoms protect against STD/HIV		
	Agree	60	100
	Disagree	0	0
	Neither agree nor disagree	0	0
7	Do you know about methods of emergency contraception?		
	Yes	52	86.7
	No	8	13.3
8	Situations in which EC pills to be taken to prevent unwanted pregnancy?		
	Forceful intercourse	2	3.3
	Condom damage	2	3.3
	Missed OCP	0	0
	Unsafe intercourse	0	0
	All	52	86.7
	Don't know	2	3.3
9	Emergency contraceptive pill can be used several times a month		
	Agree	8	13.4
	Disagree	48	80
	Neither agree nor disagree	4	6.7

n total=60

Table 2. Knowledge, Attitude, and Perception regarding Contraceptive Methods among Interns (2)

	KNOWLEDGE ABOUT CONTRACEPTION AMONG MEDICAL INTERNS	Number (n)	Percentage (%)
10	When should EC pill be taken?		
	Anytime	0	0
	During intercourse	0	0
	Within 24hrs of intercourse	14	23.3
	Within 72hrs of intercourse	44	73.3
	I don't know	2	3.3
11	Does the EC pill also protect against some sexually transmitted diseases?		
	Yes	6	10
	No	46	76.7
	I don't know	8	13.3
12	Menstrual irregularity is common side effect of EC.		
	Yes	58	96.7
	No	2	3.3
13	A 31-year-old mother of 5mths old baby is not interested in having another child for at least several years. She is frightened of injections and her husband does not like to use condoms. She has heard that contraceptive pills are easy to use and effective; she'd like to give them a try. You conduct some basic screening and obtain the following information: BP 140/90; she smokes 6–8 cigarettes a day, you observe mild varicosities on both lower legs. Which contraceptive method do your advice to her?		
	Intrauterine devices	44	73.3
	Oral contraceptive pills	2	3.3
	Barrier methods	8	13.3
	Permanent sterilization	6	10
14	A young lady 25yrs old who was regularly taking oral contraceptives, was diagnosed with Pulmonary Tuberculosis and is advised to take Anti-tubercular regimen including Rifampicin. What do you suggest for this patient?		
	Continue same oral contraceptive pills	6	10
	Stop Anti-tubercular therapy	0	0
	Alternative methods of contraception	44	73.3
	Reduce the dose of OCPs	10	16.7

n total=60

Table 2. Knowledge, Attitude, and Perception regarding Contraceptive Methods among Interns (3)

	PERCEPTION ABOUT CONTRACEPTION AMONG MEDICAL INTERNS	Number (n)	Percentage (%)
15	What do you think are the special problems within reproductive health today in India?		
	Education/ awareness	18	30
	Health care resources	2	3.3
	Planning/ contraceptive use	4	6.7
	Social/traditional/religious/family	12	20
	Poverty	4	6.7
	Illiteracy	16	26.7
	Increasing population	4	6.7
16	Contraceptive pills are inconvenient to use		
	Agree	12	20
	Disagree	20	33.3
	Neither agree nor disagree	28	46.7
17	Traditional values are barriers for sex education in India		
	Agree	42	70
	Disagree	8	13.3
	Neither agree nor disagree	10	16.7
18	Traditional contraceptive methods (safe periods, withdrawal) are the best methods		
	Agree	8	13.3
	Disagree	42	70
	Neither agree nor disagree	10	16.7
19	Contraceptives are easily accessible?		
	Yes	54	90
	No	6	10
	ATTITUDE ABOUT CONTRACEPTION AMONG MEDICAL INTERNS	Number (n)	Percentage (%)
20	Contraceptive information should be only for married couples		
	Agree	60	100
	Disagree	0	0
	Neither agree nor disagree	0	0
21	Who do you think is most suitable to give information on contraceptive methods?		
	Doctor	44	73.3
	Health worker	12	20
	Nurse	2	3.3
	Pharmacist	0	0
	Other	2	3.3
22	Should it be available to women over 18yrs only?		
	Yes	24	40
	No	36	60

n total=60

In 1952, India became the first country in the developing world to initiate the National Although we have a long history of promoting family planning, the number of women with an unmet need for contraceptive methods is higher than anywhere else in the world due to our rich cultural and traditional values. These are incorporated in all aspects of our practices, which is also reflected in our family planning methods, where still female sterilization is a preferred mode of family planning.[8]

The majority of participants in our study remembered that they have received basic education about contraception, still few interns (20%) believe contraceptive usage can lead to infertility and the findings are similar to a study done on medical students about contraception.[6] Although abortion is legalized in our country under the medical termination of pregnancy Act 1971, the incidence of unsafe abortions has increased. Many respondents (63.3%) have less clinical expertise in abortion care services, which is particularly needed to deliver healthcare to rural populations.

Interns were asked questions about emergency contraceptives in this study. Many components of emergency contraceptives were observed to be familiar among 85% of interns when compared to a similar study done by Patni MM et al. in which 40-70% of medical students were unfamiliar with the same and about 43.3% of interns knew about it in a study by Giri et al.[9,10] In our study, 73.3% of students had good awareness about emergency contraceptives to be taken within 72 hours of intercourse, in comparison with Giri et al. who found that 88.3% of medical students knew the proper time to use emergency contraception, 11.3% in Baiden et al. and 5.7% in a Kongnyuy et al. in university students.[10-12]

About 86.7% of interns were aware of indications for emergency contraceptive use like forceful intercourse, condom damage, missed oral contraceptive pills (OCP), and unsafe intercourse and 76.7% of them knew that emergency contraception (EC) doesn't protect against sexually transmitted diseases (STD's) which are significantly high compared to other studies (63.4%) done on medical undergraduates.[13] A large proportion of the interns (96.7%) believed that the use of EC will cause irregular menses. Similarly, to this, Shiferaw et al. also showed that EC will affect the periods. But in contrast, Tajure et al. observed that according to the majority of the participants (50.2%), EC didn't have any effect on the next menstrual cycle.[13-15]

In this context, other studies revealed that depending on whether the EC was administered well before, close to, or well after the anticipated ovulation for that cycle, incident intermenstrual bleeding, as well as substantial changes in menstrual cycle duration, menstrual period length, and menstrual appearance, varied. The preponderance of these alterations vanished over the cycle that followed. In a considerable number of users, emergency contraception is linked to severe but temporary changes in menstrual cycles.[16,17]

Based on the case scenarios given to assess their knowledge about contraceptive methods, 73.3% of interns were able to analyze and select an apt contraceptive method for the given cases. The problems faced in reproductive healthcare in India according to the respondents are lack of education, a lack of understanding regarding contraceptive techniques (30%), and illiteracy (26.7%), these findings are consistent with prior research that has indicated that a higher level of education among women is linked to increased contraceptive use.[18]

The Indian traditions contribute to the perception of sex-related matters as taboo, preventing young people from seeking

counseling on sexual health and the use of contraceptive techniques, as evidenced by interns' responses and other studies.[19,20]

The majority of the participants in our study had an opinion that details of contraceptive methods should be conveyed to only married couples, whereas in a similar study by Hogmark et al., only a few students had the same perception.[6] Doctors, health workers, nurses, and pharmacists play a role in providing contraceptive information and awareness in society, but 73.3% of respondents think only doctors are more suitable for it.

Conclusion

India, the 2nd populous country in the world, demands effective family planning strategies to reduce MMR and improve the reproductive health of females. In our study, interns have a positive attitude with fair knowledge and perception about contraceptives, which is very important for their future practice as they play a major role in the healthcare sector. Hence interns should be trained and timely updated about new contraceptive methods for the benefit of the community.

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Conflict of Interest

None declared

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Prescribing Pattern of Antifungal Drugs in a Tertiary Care Teaching Hospital in Western India

Parth Patel,[1] Akanksha Prajapati,[1] Sumit Patel,[1] Vipul Chaudhary,[1] Vasu Rathod[2]

[1]Department of Pharmacology, GCS Medical College, Hospital and Research Centre, Ahmadabad, India
[2]Department of Community Medicine, GCS Medical College, Hospital and Research Centre, Ahmadabad, India

Abstract

Fungal infections are prevalent in a tropical country like India. Pharmacotherapy of fungal disease has been revolutionized by the introduction of relatively less toxic oral drugs, combination therapy, and new formulations of older agents. However, data regarding antifungal drug usage patterns in India must be more present. Hence, this study was planned to study the prescribing pattern and to compare the cost of antifungal drugs in patients attending a tertiary care teaching hospital. It was a cross-sectional, observational study carried out at GCS Hospital, Ahmedabad, from April 2021 to Sept 2021. Prescriptions of 130 patients were collected and analyzed using Microsoft Excel version 2013. A total of 213 antifungal drugs were prescribed to 130 patients. Most patients, 81 (62.3%) were from the 18-40 age group. Combined antifungal treatment (Oral + Topical) was prescribed in 77(59.2%). The most common class of antifungal drugs was imidazole 107(50.23%), and clotrimazole was the most familiar drug. The most common indication for antifungal therapy was tinea cruris (45.38%). An average of 3.75 drugs were prescribed per prescription, of which 1.63 were antifungal drugs. Combined treatment of oral and topical antifungal drugs was common in dermatological practice. However, the cost of the treatment can be reduced by prescribing generic drugs.

Keywords: Antifungal Drugs; Cost Comparison; Prescribing Pattern

Introduction

Fungal infections are very common in tropical countries like India due to hot and humid weather, lack of hygiene awareness, etc. These infections range from superficial skin infections to systemic diseases.[1] Common antifungal drugs available in Indian markets are imidazole, triazole, allylamine, hydroxypyridone, antimetabolite, etc.[2] Because of the high safety profile of triazoles, they are extensively used nowadays.[3] However, data regarding antifungal drug usage patterns in India is particularly lacking.

Fungal infections usually occur in an immunocompromised state (critically ill, advanced age, use of immunosuppressive drugs) or due to opportunistic exposure to the fungus. Superficial fungal infections are not that serious but are associated with

Corresponding Author: Parth Patel. Department of Pharmacology, GCS Medical College, Hospital and Research Centre, Ahmadabad, India. Email: parth181995patel@gmail.com
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a significant decrease in quality of life and social stigma. In addition, they can be very uncomfortable, contagious, or may become invasive.[4] Invasive fungal infections are more associated with considerable morbidity and mortality. Therefore, appropriate antifungal drugs are very important to treat the condition and prevent the complications of fungal infections.[5]

Vast varieties of systemic and topical antifungal drugs are available in the market. Amphotericin B, fluconazole, itraconazole, capsofungin, griseofulvin and terbinafine are commonly used systemic antifungal drugs in India. Antifungal drugs like clotrimazole, ketoconazole, miconazole, terbinafine, ciclopirox, luliconazole, and eberconazole are available in topical preparations.[6]

Antifungal drugs are commonly prescribed for cutaneous fungal infections, ear fungal infections, gynecological conditions, and systemic infections like candidiasis.[7] Among these antifungal drugs are most commonly prescribed in dermatological conditions as combination therapy of systemic and topical antifungal agents.[5] Antifungal drugs are available in various dosage forms like tablets, capsules, injections, creams, lotions, powder, shampoo, ear drops, etc.[1]

Fixed-Dose Combinations of antifungal drugs with antimicrobials, corticosteroids, and local anesthetic drugs are also prescribed in some conditions.[8] Prescribing the branded antifungal drug is very common in most clinics. However, expensive brand drugs may increase the patients' financial burden because most fungal infections are chronic and require long-term treatment regimens.[7] Hence this study aims to evaluate the prescription pattern of antifungal drugs in various departments of a tertiary care teaching hospital.

Methods

An observational cross-sectional study was conducted at GCS Hospital from April 2021 to September 2021. Patients of any gender over 18 years of age coming to the outpatient department or admitted to the hospital were enrolled in the study. Data were collected from various departments (Dermatology, obstetrics, gynecology, medicine, and otorhinolaryngology) of the hospital daily. Data collection was done only after obtaining informed consent from the patient.

The necessary data were collected from the patients, including the age, gender, diagnosis, dosage, route of administration, name of the drug, dosage form, and cost of the antifungal drug. Before starting the study, ethical approval was obtained from the institutional ethics committee.

Data were analyzed using descriptive statistics. The frequency with percentage was used to summarize the patient's demographic details, indications, and prescribing pattern of antifungal drugs. Analysis of the data was carried out by using Microsoft Excel version 2013 and SPSS. A per-day cost comparison was analyzed by the Kruskal Wallis test

Results and Discussion

In our study, a total of 130 patients were enrolled. It has been found that in our study 62% of the patients from the age group of 18-40 years which is similar to the results of the study on prescribing patterns of antifungal drugs in dermatology conducted by Naaz et al. where they had 71% of patients in the age group of 21-40 years.[5] It may be due to adults being more conscious about their skincare. (Table 1)

Table 1. Demographic Data of the Study Participant

Characteristics	n (%)
Age (in years)	
18-40	81 (62.3%)
41-60	29 (22.3%)
>60	20 (15.4%)
Total	130
Sex	
Female	74 (57.00%)
Male	56 (43.00%)
Total	130

Table 2. Details on Prescribing Indicators

Indicators	Number
The total number of prescriptions analysed	130
Total number of drugs prescribed	488
Total number of antifungal drugs prescribed	213
Total number of concomitant drugs prescribed	275
The average number of drugs prescribed per prescription	3.75
The average number of antifungal drugs prescribed per prescription	1.63
The average number of oral antifungal drugs prescribed per prescription	0.73
The average number of injectable antifungal drugs prescribed per prescription	0.04
The average number of topical antifungal drugs prescribed per prescription	0.81
The average number of antihistaminic drugs prescribed per prescription	0.78
Percentage of antifungal drugs with fixed-dose combinations	14/213(6.57%)
Percentage of antifungal drugs prescribed by generic name	10/213(7.69%)
Percentage of antifungal drugs prescribed from WHO EML*	96/213(45.07%)
Percentage of antifungal drugs prescribed from NLEM**	87/213(40.84%)

* WHO model list of essential medicines, 22nd List, 2021

** National list of essential medicines, India, 3rd edition 2015

Table 3. Per day Cost Comparison between Single, Oral + Topical, and FDCs Antifungal Drugs

Antifungal drug treatment modalities	Median Cost (INR)	Kruskal Wallis Test value	P-value (Kruskal Wallis test)	Post hoc test (for comparison within groups)	P-value (post hoc test)
1. Single	15.8			Single and Oral + Topical	0.002
2. Oral+ Topical	33.9	12.79	0.002	Single and FDCs	0.004
3. FDCs	39.8			Oral+Topical and FDCs	0.356

Regarding prescribing indicators, as shown in Table 2, the 130 prescriptions contained 488 drugs. Out of these, 213 drugs were antifungal. The most common concomitant drugs were antihistaminic drugs. The average number of drugs per prescription was 3.75 and the average number of antifungal drugs per prescription was 1.63. The percentage of antifungal medicines prescribed by brand name was 92.31%. The percentage of antifungal drugs prescribed from the WHO Essential Medicine List and National List of Essential Medicine was 45.07% and 40.84%, respectively.

As mentioned in Table 3, the Kruskal Wallis test was applied to check the median cost comparison between single antifungal drugs, the combination of oral and topical antifungal drugs, and FDCs having antifungal drugs. In addition, a post hoc test was applied to check the statistically significant difference in the per-day cost within these three groups.

The P-value for the Kruskal Wallis test was 0.002, suggesting a statistically significant difference in median cost between these three groups. The post hoc test indicates a statistically significant difference in per day cost between single antifungal drugs and oral+topical antifungal drug treatment (P-value 0.002). There was also a statistically significant difference in per day cost between single antifungal drugs and FDCs (P-value 0.004). But the difference in per day cost between oral+topical antifungal drug treatment and FDCs was not statistically significant (P-value 0.356).

Medicine prescribing has a vital role in the health care system. Time-to-time evaluation of prescriptions is very much important for proper drug utilization, checking the cost burden of the treatment, and patient compliance.[5] The prescription reflects the overall attitude of the prescribing physicians along with their knowledge of the disease process and the pharmaco-therapeutic approach for the disease or condition.[9] The present study assessed the antifungal drug prescribing pattern and antifungal drug utilization trends in various departments at a tertiary care hospital in Ahmedabad.

In this study average number of drugs per prescription was 3.75. Bansal et al conducted a study in which an average of 3.68 drugs were prescribed per prescription.[3] A study on drug utilization patterns in the dermatology outpatient department conducted by Patil et al. showed an average of 3.27 drugs per prescription.[9] Polypharmacy promotes undesirable drug interactions and irrational drug prescribing, increasing the incidence of side effects and economic burden to patients. So, this was the point of our concern and we wanted to check on it.

We found that the average number of antifungal drugs prescribed per prescription was 1.63, and the average number of topical antifungal drugs prescribed per prescription was 0.81 in this study. In another study on the prescription pattern of antifungal drugs in dermatology conducted by Parvathy G at al. average of 2 antifungal drugs were prescribed per prescription, out of which 1.10 were topical antifungal drugs.[10]

Antihistaminics were the most commonly prescribed concomitant drugs in this study. The most probable reason for the maximum use of antihistaminic drugs could be due to itching associated with many fungal infections.[11] Generic drug prescription is considered the most rational and economical method of prescribing.[5] But here, most of the drugs were prescribed by brand name. (92.31%).

This study observed the usage pattern of antifungals, and the results found that most antifungal drugs were prescribed topically than orally. This is because topical drugs have the least side effects and easy application. In our study, 59% of patients received combined topical and oral antifungal drug treatment (Figure 1).

A study on the prescription pattern of antifungal drugs in dermatology conducted by Parvathy G et al. showed that 79.6% of patients received combined treatment of topical and oral antifungal drugs10. Most fungal infections can be managed with topical therapy alone; however, in an attempt to increase the cure rate, topical and systemic (oral) medications are often combined

Our study documented that creams were the most common dosage forms compared to other dosage forms (Figure 2). This was similar to the study's results on prescribing patterns of antifungal drugs in dermatology conducted by Naaz R et al.[5]

Moreover, most commonly prescribed antifungal drug was clotrimazole (30.05%) followed by itraconazole (21.13%). (Figure 3). A study on drug utilization patterns and cost-utility analysis of antifungal drugs conducted by Ali M et al. also reported Clotrimazole as the most commonly prescribed antifungal drug.[12]. Similar studies on prescribing patterns of antifungal medications conducted by Al Balushi et al. and Manohar M et al. fluconazole was the most commonly prescribed antifungal drug followed by nystatin.[13,14] This result difference is due to resistance development to older antifungal drugs like fluconazole.[15,16]

Tinea cruris was the common and seen in 45.38% of the patients followed by tinea corporis, which was seen in 23.85% of the patients. (Figure 4). A study on drug prescribing patterns of antifungal drugs for local fungal infections conducted by Bansal et al. also reported a similar observation as tinea cruris (41.50%) followed by tinea corporis (38.20%) as the most common fungal disease.[3]

Antifungal drugs were also prescribed to prevent fungal infections in covid-19 infected patients. An observational study on antifungal prophylaxis for prevention of COVID-19-associated pulmonary aspergillosis in critically ill patients conducted by Hatzl et al. showed that antifungal prophylaxis was associated with significantly reduced Covid-19-associated fungal infection incidence.[17]

This study prescribed a fixed-dose combination of antifungal drugs with corticosteroids and antibiotics. The most probable reason for using corticosteroids could be due to inflammation associated with some fungal infections.[18] (Figure 1). Superficial fungal infections are among general practitioners' most commonly managed skin problems. Although evidence shows combination antifungal/corticosteroid topicals are more expensive and less effective than single-agent antifungals, practitioners continue prescribing combination agents.

Per day cost comparison of single antifungal drug therapy with combined therapy of oral + topical antifungal drugs and with FDCs having antifungal drug showed statistically significant difference. But there was no statistically significant difference in per day cost of combined therapy of oral + topical antifungal drugs and FDCs having antifungal drugs. The higher cost of antifungal drugs was observed due to the use of combined therapy of oral + topical antifungal drugs, FDCs having antifungal drugs, newer antifungal drugs like itraconazole, and eberconazole, and also due to most of the drugs were prescribed by brand name.[19,20] However, we did not analyze the rationality of the antifungal drugs.

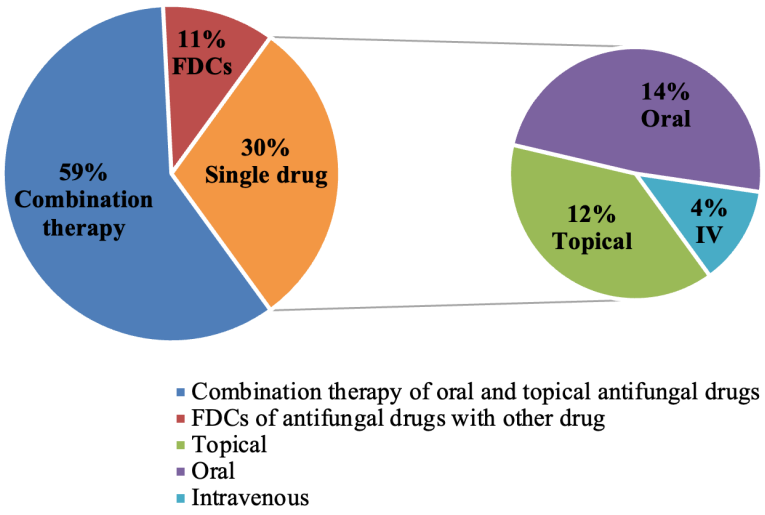

Figure 1. Antifungal Treatment Modalities

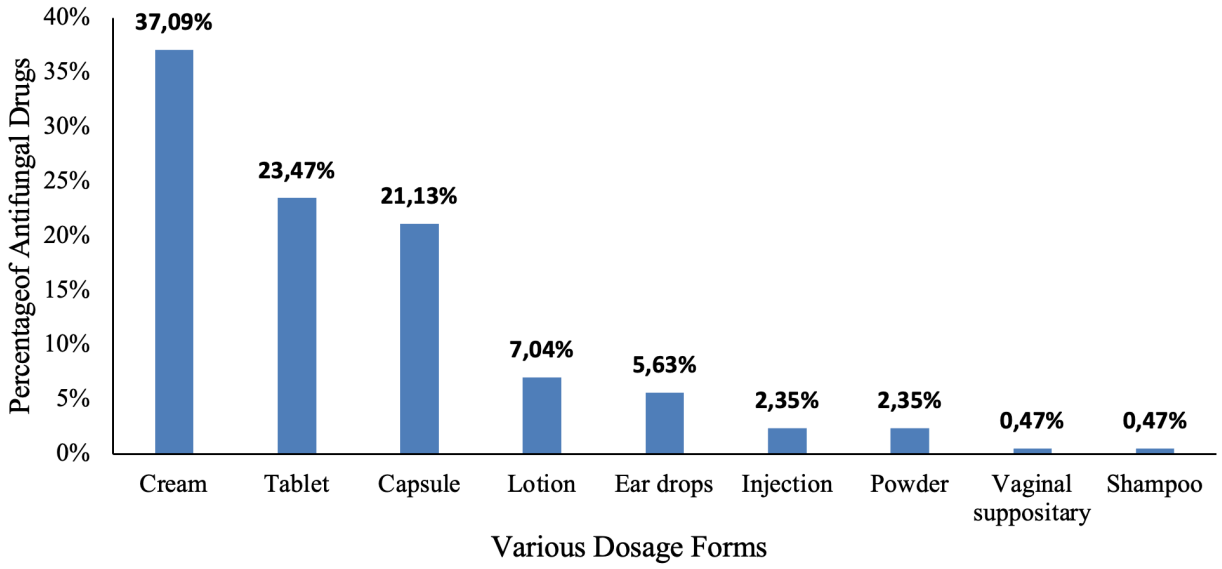

Figure 2. Dosage Forms of Antifungal Drugs Prescribed during the Study

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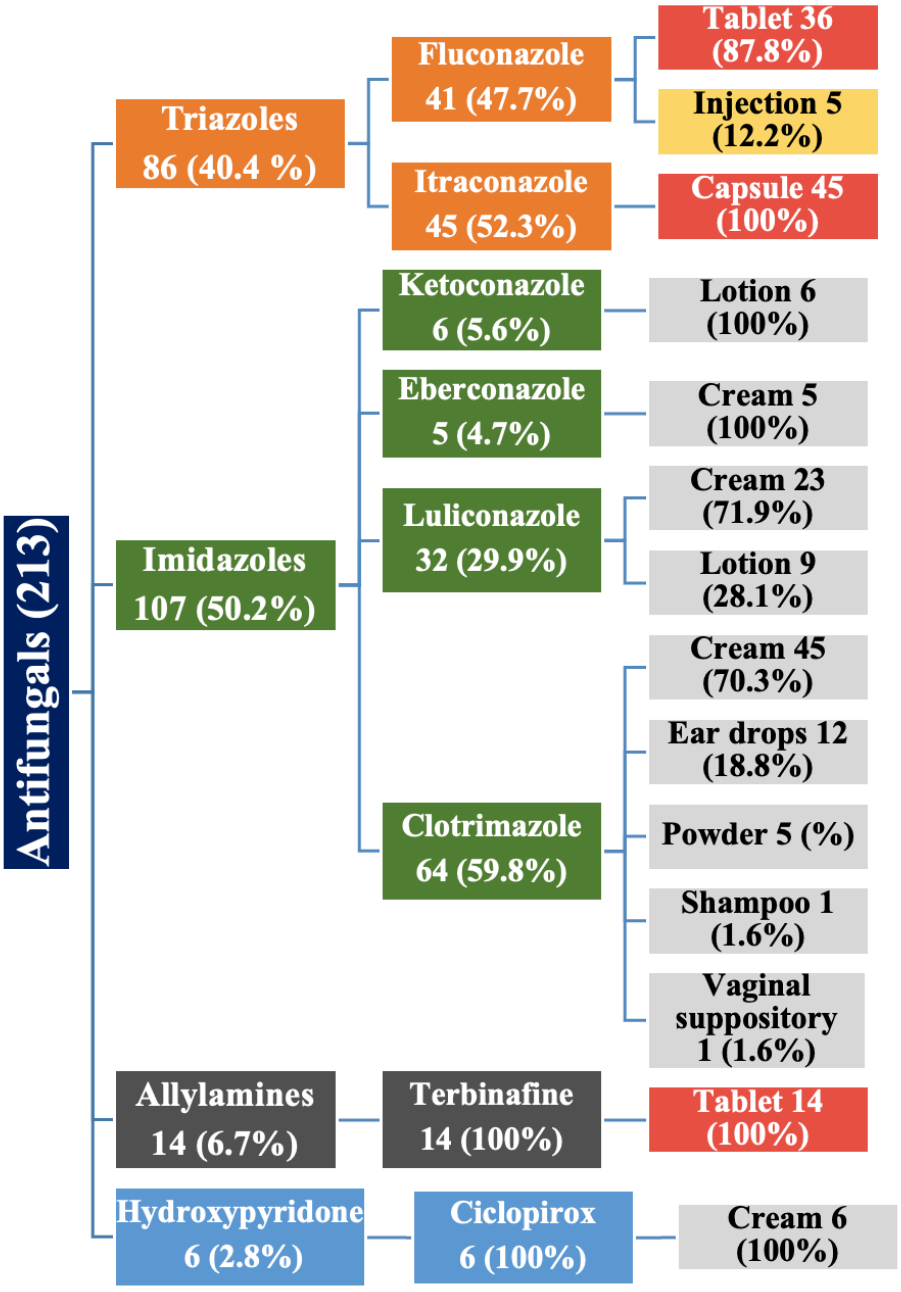

Figure 3. Antifungals Drugs Utilization according to Classification, Generic Name, and Formulation of Drugs

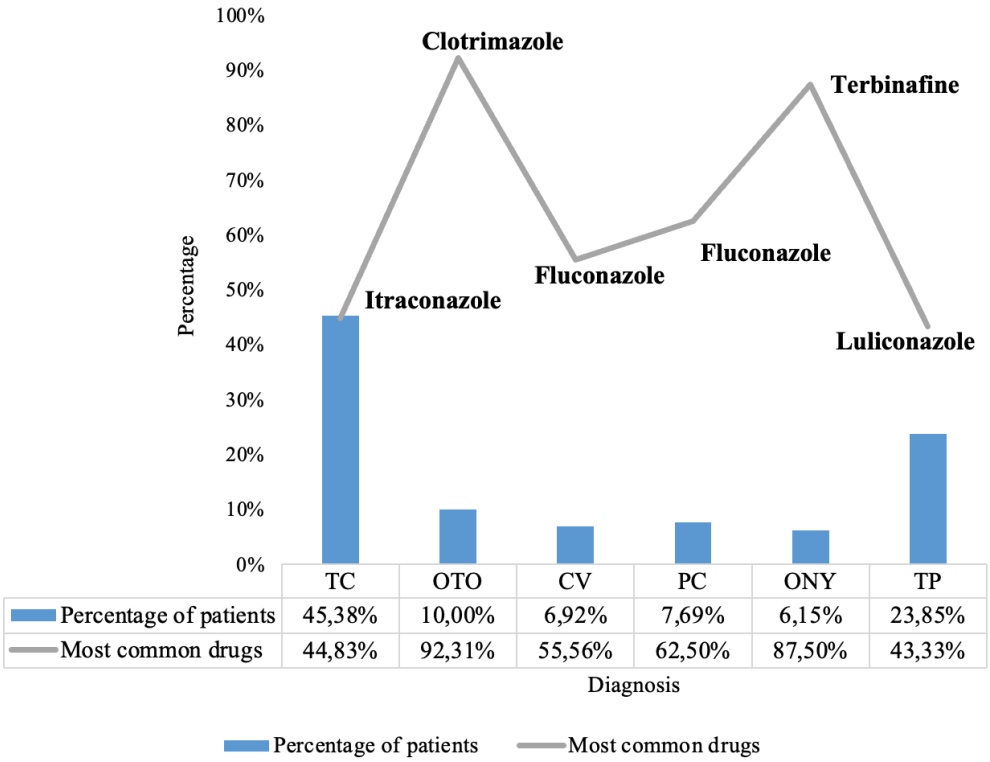

Figure 4. Distribution of Patients According to Diagnosis and Most Common Drug Given for that Condition.

TC=Tinea cruris, OTO=Otomycosis, CV=Candidial vulvovaginitis, PC=Prevention of fungal infection in covid, ONY= Onychomycosis, and TP= Tinea Corporis.

Clinical decision-making was complex for each patient, so it was difficult to check the rationality of prescribing antifungal drugs.

Conclusions

Among various departments of the hospital, antifungal drugs were most commonly used in the dermatology department for cutaneous fungal infections. Combined treatment of oral and topical antifungal drugs was frequently observed in dermatological practice. The use of newer antifungal agents like eberconazole and luliconazole is increased. We can reduce the cost of antifungal therapy by prescribing a single antifungal drug instead of combined therapy or FDCs unnecessarily. The use of generic drugs must be initiated so that there will be some reduction in the cost of treatment. Future studies may check the rationality of the antifungal drugs which was not done in our study. They may use cost-effective analysis instead of direct cost comparison.

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Conflict of Interest

None declared.

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Impact of Antidepressant Treatment on Heart Rate Variability in Patients with Depression - A Cross Sectional Study

Raghav M V*, Geetha A, Praveen Panchaksharimath, Nivetha Raj

Department of Pharmacology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

Abstract

Heart rate variability (HRV) is a non-invasive index of cardiac autonomic regulation. HRV is reduced in depression, which indicates decreased Autonomic Nervous System flexibility. It is associated with an increase in the frequency of cardiac co-morbidities. Depression medications usually take six months for complete remission, but no data on patients on antidepressants for more than six months. Therefore, it becomes necessary to determine if anti-depressants have a better impact on HRV. The current study focused on analyzing the correction of HRV parameters after six months of antidepressant therapy. A cross-sectional study was conducted from February to September 2021 at the AFT lab inpatients. They were recruited from the Psychiatry department, Victoria Hospital, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India. The sample size was calculated to be 40 (20 Patients and 20 Healthy controls). AFT was done on all participants using Power Lab equipment and analyzed using Lab Chart 8 software. Heart rate variability parameters (AFT results) were analyzed using statistical software. The results with a p-value of >0.05% were considered statistically significant and taken up for the study. 55% of the patients with depression in our study were in the age group of 18-25 years, and the mean Ham-D (Hamilton Depression Rating Scale) score was found to be 9.8. There is a reduction in autonomic function flexibility among patients who are on antidepressants when compared to healthy controls, even after six months of treatment. No conclusion could arrive on the class of antidepressant which was more beneficial owing to its effect on autonomic functions. Hence, randomized controlled studies comparing various classes of antidepressants to assess efficacy in reducing autonomic complications of depression should be taken up.

Keywords: Autonomic Nervous System, Depressive Disorder, Anti-depressive agents

Introduction

Depression may be described as sadness, loss, or anger that interferes with a person's everyday activities. Depression is a chronic illness with an annual prevalence of 5.25%.[1] In addition, there are multiple consequences of untreated depression.[2] Thus, choosing a treatment modality that adequately addresses all effects of depression is critical.

HRV (resting heart rate variability) is a critical indicator for mental health and cardiovascular outcomes. Autonomic neuropathy, a prevalent and underdiagnosed consequence of common medical diseases discovered by evaluating autonomic reflexes, has a reduced resting HRV.[3,4] Heart rate variability parameters can indirectly assess autonomic nervous system

Corresponding Author: Raghav M V. Department of Pharmacology, BMCRI. Bangalore Medical College and Research Institute, Fort, K R Road, Chamarajpet, Bengaluru – India. Email: raghav.m.ram@gmail.com
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tone.[5] Cardiac reflex tests are gold standard diagnostic tests for cardiovascular autonomic dysfunction, but heart rate variability analysis is an easy and reliable alternative.[6,7]

Reduced heart rate variability is a marker of decreased parasympathetic system activity, such as a reduced capacity to respond to microenvironmental changes in the autonomic system.[8] Patients with depression show decreased HRV before antidepressant treatment.[9] Decreased HRV indicates a risk of increased cardiovascular accidents owing to autonomic dysfunction. Therefore, the symptoms have to be treated adequately and on time. The severity of depression also plays a role in determining HRV, such that the higher the depressive symptoms, the lesser the HRV.[10,11]

Studies have shown that Tricyclic antidepressants (TCA) and Selective Serotonin Reuptake Inhibitors (SSRI) prescribed for depression tend to have more effect on the heart rate and its variability compared to other classes of antidepressants.[12] However, there is a paucity of evidence on the level of autonomic function recovery after prolonged treatment of depression. Our study tried to compare and analyze the heart rate variability of patients on antidepressants for more than six months and healthy controls. The goal was to identify if there were any lacunae in the recovery of autonomic flexibility. The objective of the current study was to assess recovery of autonomic function after six months of antidepressant therapy.

Methods

A cross-sectional study during the study period (February to September 2021) in AFT lab in the Victoria Hospital attached to Bangalore Medical College and Research Institute, Bengaluru, and patients were recruited from the Psychiatry department in the hospitals attached to Bangalore Medical College and Research Institute, Bengaluru. Institutional Ethics Committee Clearance was obtained (Reference number – BMCRI/PS/210/2019-2020 dated 29.01.2020), and informed consent was obtained from all the study participants.

The sample size was calculated using the RMSSD (Root Mean Square of successive RR interval differences) values for healthy controls and patients with depression as per the study by Hartmann R et al.[13] An α was taken to be 0.05 and β was taken to be 0.1, which lead to a sample size of 36. It was then rounded off to the next multiple of ten, and the final sample size was 40 (20 Patients and 20 Healthy controls).

Age and gender were analyzed using percentages, and a Chi-square test was performed to assess the comparability between groups. In addition, Mann Whitney U test was used to determine the difference between the two groups.

Following are the participant eligibility criteria
Inclusion Criteria

1. Patients of either sex aged between 18-60 years.
2. Patients willing to give written informed consent
3. Patients on antidepressant medications for more than six months fulfilling the criteria of ICD-10 (International Classification of Diseases -10, WHO)

Exclusion Criteria

1. Patients with suicidal ideation
2. Pregnant and lactating women
3. Patients with ECG abnormalities
4. Patients with Psychotic depression, Bipolar disorder, Schizophrenia
5. Presence of epilepsy, mental retardation, mental disorders other than depression
6. Patients on drug treatment which can affect HRV

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Out-patients in the Department of Psychiatry fulfilling the inclusion/exclusion criteria were enrolled in the study. Patient demographic details, clinical evaluation, disease characteristics, and treatment were recorded in the study proforma.

AFT was done on all the patients using Power Lab equipment and analyzed using Lab Chart 8 software. Instructions given were as follows - participant should withhold coffee and nicotine at least 3-4 hours for at least 8 hours before testing, should not have food at least 2 hours before the test, and if possible, sympathomimetic/ sympatholytic drugs should be stopped for 24-48 hours before testing and anticholinergic for 48 hours.[5] The subject was seated down for 30 min in a quiet room with neutral temperature and humidity, and the patient's pulse rate and blood pressure were recorded.

The AFT procedure followed was also described as follows. The patient was made to lie in a supine position, the chest area was exposed to all the metal, and magnetic objects were removed. ECG leads were attached to the participant, and instructed to keep their eyes open and not fall asleep.

Baseline Blood Pressure (BP) was recorded before the start of each procedure, and 5 minutes of rest in between each procedure so that the BP goes to the baseline. The recording was taken for a minimum duration of 20 minutes. The first five minutes were empirically omitted from the analysis. HRV analysis was performed every 5 min intervals starting from 5 min. One 5 min segment for analysis was selected with the least number of outliers and no limb or chest movements leading to artifacts.

Results and Discussion

A total of 40 study participants underwent HRV analysis. The mean age was 25.85 and 23.68 years in the antidepressant arm and healthy control arm, respectively. 70% of the patients had a Ham-D (Hamilton Depression Rating Scale) of 8-16. A ham-D score of less than 7 indicates the patient has remission (no depressive symptoms), and a score of 8-16 indicates (mild depression). 60% of the patients had been under treatment for depression for more than a year.

Moreover, age and sex distribution was also depicted in Table 1. A chi-square test was performed to assess the comparability between the two groups. The Chi-square value was found to be 0.5169, but the p-value was not significant at a 95% confidence interval.

The usual discussion may not be possible because of the lack of similar studies in the past. Though there are studies on HRV and major depression, none of them measure the impact of antidepressants on HRV. One study by Hartmann et al. does measure but only takes readings at the end of 2 weeks of antidepressant treatment.[13] Antidepressants take at least to show improvement in depressive symptoms, but it may take around six months for complete remission.[14] Therefore, we have compared participants with more than six months of treatment with antidepressant therapy, which was not done before. Hence, ours is a novel study and a first of its kind.

There are two issues with a head-to-head comparison of AFT studies: device calibration and non-uniform units. Most devices are calibrated using a minimum of 100 human participants at that particular center. Differences can be based on the device brand, build, and the sample population considered.
The parameters measured are SDDN (Standard deviation of NN intervals), RMSSD

Table 1. Demographic Parameters of the Study Subjects

		Antidepressant Arm	Healthy Control Arm	Total
Age	< 25 years	11	10	21
	> 25 years	9	10	19
Gender	Males	13	11	24
	Females	7	9	16

Table 2. Heart Rate Variability Parameters

	Antidepressant - Mean (SD)	Healthy Control - Mean (SD)	P value
Heart rate (bpm)	77.31 (9.13)	80.83 (21.7)	0.79
SDDN (in ms)	84.94 (10.25)	133.83 (38.13)	<0.001*
RMSSD (in ms)	50.46 (5.48)	31.23 (12)	<0.001*
LF (in ms^2)	990.17 (423.7)	1116.48 (398)	0.42
HF (in ms^2)	1351.7 (350)	920.2 (219)	<0.001*
LF:HF ratio	0.80 (0.46)	0.97 (0.41)	0.17

* P-value <0.05 was considered statistically significant

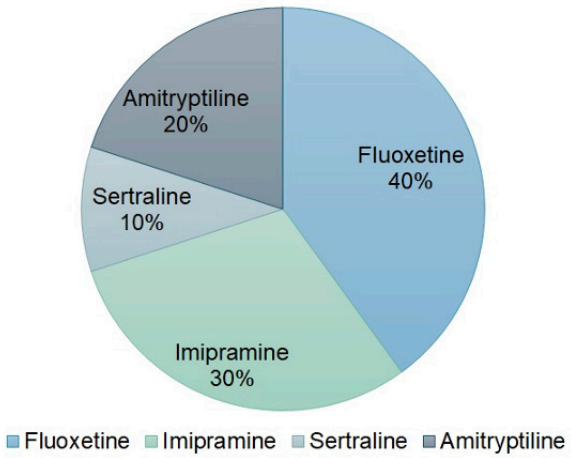

Figure 1. Antidepressants prescribed for ≥ 6 months for Major Depressive Disorder

(Root Mean Square of successive RR interval differences), LF (Relative power of the low-frequency band), HF (Relative power of the high-frequency band), and HF:LF ratio (ratio of LF to HF). SDDN and RMSSD are measured in milliseconds, whereas HF and LF are measured using four units (Percentage, Millisecond squared, Normal Units, and Hertz).

Our study clearly demonstrates that though antidepressants tend to bring HRV back to normal, the damage to autonomic function cannot be completely reversed. There is a statistically significant difference between SDDN, RMSSD, and HF values between a healthy adult and a patient with depression on antidepressants for more than six months, as depicted in Table 2.

A study by Hartmann et al. measuring the effect of antidepressants in patients before treatment and two weeks after treatment show normalization of HRV parameters and improvement of symptom severity of depression in correspondence to an increase in HRV parameter values. SDDN and RMSSD values were 50.46 versus 48.03 (Healthy versus depression) and 41.547 versus 28.872 (Healthy versus depression), respectively. This study shows a significant difference in HRV between healthy adults and depressed patients not on treatment, and our study states that there is a statistically significant difference in HRV between healthy adults and patients on antidepressants for six months.[13]

There is a link between depression and alterations in autonomic cardiac control.[15] Autonomic function influences depression risk rather than the other way around.[16] The administration of antidepressant medications may help to minimize the correlation between depression severity and cardiovascular health.[17] Therefore, in the management of depression, autonomic symptoms should be taken into account.[18]

Depression severity and the concomitant risk of mortality due to cardiac and vascular complications are clearly evident. Therefore, in some populations, depression may be the only marker of an underlying cardiovascular disease.[19] In addition, our study sheds light on diagnosing autonomic dysfunction in patients with depression with no other clinical suspicion. Altered mood states are often associated with multiple physical dysfunctions, most of which are attributed to a central biological substrate leading to depression. For example, it is seen that depression promotes vagal withdrawal leading to a reduction of heart rate variability indices.[20]

Although there is a clear understanding of how depression causes autonomic dysfunction, scarce studies are in the direction of how it can be reversed. Exercise, customized physiotherapy, and pressure stockings are non-specific treatment options for autonomic dysfunction.

Treatment with steroids, immunosuppressants, and intravenous immunoglobulins should be speculated if an immune mechanism is speculated.[21] Treatment of autonomic dysfunction though being beyond the scope of our current study, has to be augmented with antidepressants for depression.

The strengths of the current study were cheaper and easier to conduct due to the cross-sectional study. In addition, healthy controls were used to prevent errors due to device calibration. However, the limitations were as follows - small sample size, data before starting antidepressant treatment, and HRV on follow-up visits would have given a more precise answer to our research question.

In addition, to determine which antidepressant helped improve autonomic functions, a randomized controlled design would have been better. Most of the studies measured HRV parameters only after a month of treatment. Therefore, a randomized controlled trial can be taken up in the future involving only newly diagnosed patients with baseline HRV variables and HRV changes with the drug prescribed at multiple follow-up visits. If more research findings support that HRV is not reverted despite antidepressant therapy, an effort should be made to supplement antidepressant therapy with specific treatment for autonomic dysfunction.

Conclusion

There is a reduction in autonomic function flexibility among patients who are on antidepressants for more than 6 months when compared to healthy controls. Statistically significant evidence was obtained that RMSSD and HF were more markedly affected. No conclusion could arrive on the class of antidepressants and their effect on autonomic functions.

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None

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Pharmacogenomic Considerations In Propofol: A Review

Ziske Maritska, [1]*Tri U. Pratiwi,[2] Muhammad J. Aldwin,[2]
Clinton F.M Sitanggang,[2] Ferdy Rahadiyan[2]

[1]Department Of Biology Medicine, Faculty Of Medicine, Universitas Sriwijaya, Palembang, Indonesia
[2]Department Of Anesthesiology And Reanimation, Faculty Of Medicine,
Universitas Sriwijaya, Palembang, Indonesia

Abstract

Pharmacogenomics is one of the pivotal fields of science in the era of precision medicine. It helps provide an understanding of what causes the differences in terms of pharmacokinetics and pharmacodynamics of a particular drug in patients. Hence, this leads to better efficacy. This branch of medicine also applies to sedative drugs in the anesthesia field, one of which is propofol. Changes in propofol pharmacokinetics and pharmacodynamics properties might lead to toxicity and inadequate sedation. This review wishes to better understand how pharmacogenomics is applied in anesthesia, especially in propofol, one of its most commonly used medications.

Keywords: Pharmacogenomics, Anesthesia, Sedative, Propofol

Introduction

Pharmacogenomics is significant in current practice since it explains how genes affect how our body responds to certain medications.1 Pharmacogenomics will help identify which drug and dose will work better for individuals. The field of genetics, including pharmacogenomics, has improved significantly after the human genome.[2] A genome is all of the genes in an organism, and genomics is the branch of medicine that studies the genome related to hereditary. Pharmacogenomics is the branch of medicine focusing on how the genome affects how the body responds to the medication.[3]

The pharmacology of a drug can be observed in its pharmacodynamics (the impact of medication on the body) and pharmacokinetics (the body's reaction to drugs). Changes in hereditary material can make significant changes in pharmacodynamics and pharmacokinetics.[3] One of the leading issues in pharmacogenomics is the incidence of adverse events and the differences in drug responses that signal heterogeneity in pharmacology. This phenomenon also applies to anesthesia, with various adverse events and differences in drug efficacy between patients. The contributing factors to this diversity were age, sex, race, body weight, comorbidities, simultaneous medication use, and individual genetic makeup.[2]

In anesthesia, pharmacogenomics plays a part during the preoperative assessment by the anesthesiologist since it offers the chance for a customized sedative arrangement.[4]

Corresponding Author: Ziske Maritska. Department of Biology Medicine. Faculty of Medicine, Universitas Sriwijaya Palembang, Indonesia. Email: ziske_maritska@unsri.ac.id
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Patients can be grouped into phenotypic types based on the level of enzymatic activity: broad metabolizers (typical action), super quick metabolizers (expanded action), average metabolizers (decreased action), and low metabolizers (almost no enzymatic movement).[5] General anesthetics are commonly conducted in anesthesia, with many considerations, including consciousness, sensory system, blood pressure, respiratory, and pain.[6] As pharmacogenomics researches emerge, hereditary condition and genetic factors are now being considered when choosing anesthetic agents, based on the trials to improve drug distribution.[4,7] This literature review wishes to briefly explain pharmacogenomics consideration in propofol.

Propofol

Propofol as an Intravenous Anesthetics

Propofol is quite possibly regularly utilized intravenous anesthesia drugs. It works using the GABA-A receptor, that no inclination in a certain subunit. CYP2B6 protein hydroxylates Propofol and further O-glucuronidation by UGT1A9. In the auxiliary course, 4-hydroxypropofolis is created by CYP2C9 which is additionally used by the proteins DT-diaphorase (NQ01) and sulphotransferase or formed. Propofol infusion disorder, asystole, and Bradycardia are unfavorable impacts of propofol; however, it isn't clear if they are possibly portioned subordinate or, on the other hand, assuming hereditary variables influencing propofol attitude and impacts assume a part.[8]

Propofol as an Intravenous Induction Drug

Propofol is the enlistment of general sedation that might include the assistance of inhibitory neurotransmission interceded by GABA-A receptor restriction. Propofol allosterically builds restricting liking of GABA for the GABA receptor. This receptor, as recently noted, is coupled to a chloride channel, and the actuation of the receptor prompts hyperpolarization of the nerve layer.[9]

Propofol isn't water-soluble, but a fluid arrangement is accessible for intravenous administration as an oil-in-water emulsion. This mixing will frequently cause pain during infusion that can be diminished by earlier infusion of lidocaine or less really by blending lidocaine 9 There is a significant individual vulnerability to propofol. Its cause can be connected with hereditary polymorphism. There is a change in our gene related to propofol use, specifically a change in the 5HT2A gene.[8] Because of propofol's quick beginning and fast recuperation, it is a generally expected sedative medication for acceptance and upkeep. In any case, propofol administration isn't suggested for basically sick youngsters. As of late, the calming impact of propofol has been thought of.[8]

Ongoing investigations and research has zeroed in on the differential impacts on the proteome of intravenous versus inhalational specialists. Distributions have shown that propofol and unstable sedatives produce proteomic changes that are discoverable in the research facility.[3] Higher propofol openness will occur within 1 hour from the beginning of the mixture without dose change in these patients hence showing the meaning of this specific polymorphism for portion change to get ideal sedation and avoid unfriendly impacts.[6]

The Use of Pharmacogenomics in Perioperative Medication

Perioperative medications and sedation-related circumstances can be ordered, given information acquired from hereditary arrangements and variations. Malignant Hyperthermia (MH) is an autosomal predominant condition. Strange calcium homeostasis causes hypermetabolism,

hypoxia, hypercapnia, and hyperthermia in this condition. One potential explanation for changes in the ryanodine receptor quality (RYR1) in 70% of cases and transformations in the CACNA1S quality in 1% of the populace is recommended. Unstable sedatives or suxamethonium trigger MH; so thus, dantrolene (a skeletal muscle relaxant that lessens the arrival of calcium from the sarcoplasmic reticulum) is kept in the working room and recuperation area.[8]

For patients associated with having encountered MH, a muscle biopsy is prescribed to test the contracture condition. In this test, constriction is a positive outcome. Patients with positive or obscure effects ought to get MH-safe sedation for example, intravenous sedation. Powerful testing diminishes the MH death rate. Propofol infusion disorder (PRIS) is a model that could be an objective for pharmacogenomic research. PRIS starts with the presence of metabolic acidosis, rhabdomyolysis, and arrhythmias. Arrhythmias brought about by long haul (>48 hours) and high portion (>4 mg/kg/hour) of propofol. In patients who have had PRIS, a comprehension of the specific etiology of the genotype is vital. Screening given this pharmacogenomic information can successfully lessen the occurrence of PRIS. Individual hereditary profiles permit deciding treatment regimens for them in light of their pharmacokinetic genotype.[8]

Pharmacokinetics (PK) of Propofol

Absorption

Propofol is more appropriate to use intravenously and is not good enough to be taken orally because of its taste. The low oral metabolism caused by the first entry of metabolism impact and the high liver extraction rate of about 90% makes it unsuitable for use by routes other than intravenous. Several researchers have tried to expand propofol's oral bioavailability, one of which is by using nanoparticle assay.[10]

Distribution

Propofol is broadly engaged with the proteins in the plasma, for example, albumin, and red blood cells, after intravenous organization. The free division is, as it were 1.2–1.7%. Almost 50% of propofol is bound to the erythrocytes, and numerous clinical Pharmacokinetic examiners degree entirety concentrations instead of plasma propofol concentrations.[10,11] When propofol causes rapid loss of consciousness in one cycle, it can cross the blood-brain barrier.

Cardiac output is very important in patient induction, especially in the speed of induction and implantation. The proportion of free propofol in CSF is about 31%, of which 1% goes into plasma. The balance between brain and blood concentrations occurred after 30 minutes, with the proportion of propofol as much as 0.01 – 0.02. Propofol is safe to use in cesarean section because the placenta exchange is relatively fast and extensive, in neonates, the concentration will be removed, so there is no need to worry about its effects because it will not last long in neonates. The proportion of mother to fetus is about 0.7 to 0.8.[10]

In a rapid initial distribution, the clinical effect will also be shorter because the time given is relatively short after a single bolus administration. The volume distribution of propofol into the large-capacity compartment will be slow due to its high lipid solubility. Therefore, a large volume of distribution of 3-4 times the total body volume is produced, although there is no obesity factor. The redistribution of this drug is slow due to an imbalance between metabolism and excretion. However, clinically the effect is still above other hypnotic intravenous medicines.[10]

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In some cases, reducing this drug's dose is quite beneficial compared to other types of hypnotics. An infusion of about three hours can decrease by nearly eighty percent for fifty minutes; on the other hand, an infusion of a long duration of almost half a day can increase by about three hours.[10,12]

Metabolism

Conjugated propofol will become propofol glucuronide, almost seventy percent, which is facilitated by UDP glucuronosyltransferase. 4 - hydroxypropyl is the hydroxylation product of nearly thirty percent of propofol. Various isoforms of cytochrome P450 interact in propofol metabolism, with CYP2C9 first and CYP2B6 being the lowest. The result of this conjugation of propofol can provide a hypnotic effect compared to its main metabolite.[10]

Hepatic perfusion and hepatic blood flow will affect propofol levels; the lower the flow, the lower the metabolism. The efficiency of this drug metabolism is almost Ninety percent in the liver. The clearance process is higher than the blood flow to the liver, which is 2.2 liters per minute. Reductions that occur outside the hepatic process are up to forty percent, for example, in the kidneys, with a ratio of sixty to seventy percent, or equivalent to one-third of the total metabolism. If it enters the small intestine, the extraction reaches twenty-five percent. On the other hand, lung involvement is still temporary, releasing propofol from returning to circulation.[10]

Elimination and Excretion

The process of elimination of propofol can be found in the urine after five days almost 90%. Only a small part (<1%) was found intact, the metabolites would be found in a green color change in the urine. On inhalation, propofol is also excreted in minimal amounts. However, there was no difference in concentration between the plasma and the expired concentration. Measurement of concentration in the breath can use a spectrometer from exhaled air.[10]

Pharmacodynamic (PD) of Propofol

Central Nervous System

The hypnotic effect of this drug is the result of the potentiation of the neurotransmitter GABA inhibitors. Postsynaptic hyperpolarization and inhibition of neuronal depolarization result from binding to the b-subunit of postsynaptic GABAA but also influence this effect. If given a high concentration, it will directly open the activation channel; if the concentration is low, there will be chloride potentiation by the influence of GABA.[10,13]

Cardiovascular System

The main effect on the cardiovascular system is decreased cardiac output and a systemic down in blood pressure. However, this happens depending on the dose, and even in the sedative dose can still occur. In geriatrics, this is partly mediated by a critical diminish in sympathetic tone with changes in vascular resistance while being decreased. Cardiovascular depressant effects may occur, inhibiting the bare reflection of the physiological response.[14]

Hepatorenal System

Liver function is not affected much by this drug, although its metabolism and excretion are very extensive in the liver. High hepatic arteries and the presence of portal venous flow affect hepatic perfusion. Therefore we must maintain cardiac output to maintain liver and kidney perfusion. This is done so that there is no impaired function of the kidneys and liver. Cloudy urine is slightly greenish is the effect of the phenol green chromophore, after which uric acid excretion will occur in the urine, resulting in cloudy urine.[11]

Pharmacogenomics can influence the use of anesthetic drugs, which can result in adverse

drug events, overdose, and even death. In the use of anesthetic drugs, two types of events are the main focus of the adverse drug event, namely prolonged apnea and malignant hyperthermia.[15]

Propofol is often used as an induction and maintenance agent in anesthesia. Propofol is metabolized by CYP2B6 by extrahepatic cytochrome, CYP2C9, and UGT1A9. However, the CYP2B6 enzyme has been the most studied of the metabolic processes of propofol in several pharmacogenomic studies. CYP2B6*4 showed a significant difference in the process of elimination of propofol. In patients with CYP2B6*6, the T allele represents the need for a lower dose when undergoing general anesthesia. In the UGT1A9 gene, polymorphism also affects glucuronidase (propofol metabolism) and increases the risk of adverse reactions.[16]

The use of propofol in deep sedation inhibits the stress response, resulting in hypotension, sometimes brain tissue damage, complications due to sedation, and even worsening for the patient. If used under light sedation, or inadequate anesthesia, it can lead to tachycardia, hypertension, or worse; the patient is conscious during the operation. Propofol is also influenced pharmacodynamically by gene variants at the gamma-aminobutyric acid (GABAA) receptor target (GABRE).[17]

The effect of propofol on each individual generally has the same response, but in certain individuals, its use causes different symptoms or ADEs. This is partly influenced by the genetic composition of the individual. According to Awad et al., 2019[7] in patients with the CYP2B6*4 allele, it describes a decrease in drug clearance so it is suspected that there will be an increase in drug toxicity even with the usual dose. In a study by Luzon et al., 2018 in assessing nitric oxide synthase (NOS3), it was found that an increase and a decrease in average blood pressure and nitrite level occurred in patients with the CT + TT and ba + aa genotypes. A significant decrease in heart rate occurred in carriers of the ba + aa genotype. In carriers, the TT genotype resulted in a higher nitrate level increase than the GT and GG genotypes.[18]

Pavlovic et al., 2020, conducted a study on polymorphisms of the genes UGT1A9, CYP2B6, and CYP2C9 with propofol pharmacokinetics in children. As a result of metabolism by UGT1A9, the TT genotype required a higher dose of propofol than the CT genotype. The same data are shown from the metabolic process of CYP2B6, the dose required for patients with the GG genotype is greater than in patients with the GT+TT genotype.[16,20]

According to Zhang et al., 2017, who examined the propofol-remifentanil combination with MDR1 gene polymorphism in pediatric tonsillectomy surgery, the results of MDR1 1236C>T genotype CT+TT required a longer time than children with the CC genotype, at induction, recovery time. exhalation, eye-opening, and extubation. the same thing showed that patients with genotype TT require large doses of propofol and remifentanil because decreased of transport function by P-GP patients with TT genotype, which made propofol and remifentanil accumulate in the liver.[21]

Conclusion

Individuals will have different responses on medication, and it also happens in anesthesia medication, such as propofol. The number of doses, cleaning time, and side effects of propofol is determined by each individual's genetics.

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Conflict of Interest
None declared.

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REVIEW ARTICLE

Benefits of Probiotics in Autism Spectrum Disorders: A Meta-Analysis of Randomized Controlled Trials

Sharanabasayyaswamy B. Hiremath[1]* and Srinivas L. Devendrappa[2]

[1]Department of Pharmacology, Kodagu Institute of Medical Sciences, Madikeri, Karnataka
[2]Department of Pharmacology, Jagadguru Jayadeva Murugarajendra Medical College, Davangere, Karnataka

Abstract

Using probiotics as a pharmaceutical intervention is based on the fact that dysbiosis affects many people with autism spectrum disorders (ASD). This study aimed to quantify various probiotics' overall and individualized benefits in treating ASD. Randomized or cross-over trials comparing the efficacy of placebo or active control vs. probiotics in patients of any age diagnosed with ASD based on DSM IV/V criteria were considered under inclusion cri- teria. An electronic database search in PUBMED and Cochrane Library was conducted using MeSH search terms "probiotics" AND "Autism." Mean change in the total score of clinical parameters used to assess ASD symptom severity was the primary outcome measure analyzed. All the outcome measures were estimated by calculating the Standardized Mean Difference (SMD) values and their 95% Confidence Intervals (CI), considering the different clinical parameters used to assess the change in ASD symptoms in identified clinical tri- als. An insignificant decrease in the total score value of primary outcome measure by -0.14 (SMD: 0.14, 95% CI:-0.45 to 0.17) in patients treated with probiotics was observed. The quantity of decrease remained insignificant in subgroup analyses also. Observed insignifi- cant clinical benefits of probiotics in ASD patients could be due to the presence of gastroin- testinal symptoms as co-morbidity. We hypothesize that intolerance to dietary components is responsible for gastrointestinal symptoms and inflammation. Perhaps probiotics are still beneficial in ASD patients without gastrointestinal symptoms, while their combination with prebiotics is effective in patients with gastrointestinal symptoms.

Keywords: Probiotics, ASD, Autism.

Introduction

Autism spectrum disorder (ASD) is a spectrum of neurological and developmental disorders diagnosed primarily by the presence of impaired social interaction, social communication, and stereotypical behaviors.[1-3] It includes autistic disorder, Asperger's syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS), Rett's disorder, and childhood disintegrative disorder.[1,2] Increased screening, awareness, and changing diagnostic criteria have been attributed to its increased incidence rate.[1-3] The unclear etiology and pathogenesis of ASD have been due to the complex interplay of multiple genetic and environmental factors.[1,2]

Corresponding author: Sharanabasayyaswamy B. Hiremath. Department of Pharmacology. Kodagu Institute of Medical Sciences, Madikeri, Karnataka, India. Email: dr.sharan83@yahoo.com
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The involvement of multiple genes, the presence of multiple genetic deficits in ASD patients, the higher incidence in twins and male gender, the variation in clinical manifestations, and the association with other genetic disorders all support the genetic basis as a major etiological agent responsible for its pathogenesis. Early diagnosis and intervention with non-pharmacological behavior therapy is the treatment of choice for ASD.[3-4] However, it is costly and requires significant time and resources.[3-5] Thus, adopting behavioral therapy as a universal treatment strategy is unacceptable in all countries.[3-4]

Risperidone and aripiprazole are the only drugs approved by the FDA to treat irritability and disruptive symptoms of ASD.[2,5] Their selective efficacy on disruptive symptoms, minimal efficacy on core ASD symptoms, and high incidence of ADRs necessitate the development of better pharmacological agents.[3-5]

Using probiotics as a pharmaceutical intervention is based on the fact that dysbiosis or altered gastrointestinal microbial flora affects many people with ASD.[6] Dysbiosis has been attributed to leaky gut epithelium, systemic inflammation, and thus altered neurotransmitter signaling in the brain.[6] Results of clinical trials analyzing the benefits of probiotics in ASD are insignificant and inconclusive.[7–14]

The insignificant reduction is not only of ASD symptoms but also of the severity of gastrointestinal symptoms in ASD patients.[9,12] However, these trials are either pilot or small-scale trials, and the authors of these trials opine on the need for large-scale trials. Results of a meta-analysis study also do not support the benefits and use of probiotics for ASD.[15]

Moreover, this meta-analysis study included either a few trials or low-quality trials testing the efficacy of probiotics and prebiotics plus probiotics. Hence, there is no clarity on the actual benefits of probiotics alone in ASD. In addition, there is a lack of consistency in the type of probiotics used in individual clinical trials and meta-analysis studies published so far. Consequently, there was a need to analyze the efficacy of probiotics alone and by including recently published clinical trials. We also felt the need for subgroup analysis based on the type of probiotic agent used. Hence, the present meta-analysis was conducted to quantify the overall and individual benefits of various probiotics in reducing ASD symptoms.

Methods

The study is being reported by PRISMA statement consisting of a 27-item checklist and a 4-phase flow diagram.

Protocol and Registration

Protocol not registered and does not exist

Inclusion and Exclusion Criteria

Articles included in this study were restricted to randomized or cross-over trials. Only those trials comparing the efficacy of placebo or active control vs. any probiotic agent in patients of any age diagnosed with ASD based on DSM IV/V criteria were considered under inclusion criteria. The exclusion criterias adopted were: trials published with incomplete data required for statistical analysis, trials published in a language other than English, and trials published as abstracts. No restriction was applied based on phase, sample size used in the trials, or the year of publication. We didn't plan to contact the corresponding authors to access missing or other required data.

Information Source and Literature Search

A literature search in PUBMED and Cochrane Library was conducted using MeSH search terms "probiotics" AND "Autism". We limited electronic database searches to articles published or available online up to 19th May 2022 without restriction on the beginning or oldest year of publication. An additional manual search of some relevant articles was also conducted to identify any missed trials by reviewing their references. Two authors were independently involved in conducting both electronic database and manual searches.

Study Selection, Data Collection Process, and Data Items Collected

Both authors independently went through the standard process of article selection and data collection of all required data in a prior designed data extraction sheet. The screening process for the eligible articles was conducted by going through the titles and abstracts of all articles retrieved from the literature search. Potential articles selected by this method were then screened in their full-text form for the availability of required data on population, intervention, comparator, and outcome apart from trial design and other parameters to assess their eligibility for inclusion as per preset eligibility criteria.

Trials meeting all eligibility criteria were selected, and data on baseline demographic, clinical data, characteristic study data, intervention and data required to estimate outcome measures were collected by both authors individually. The mean change (baseline-final) and standard deviation (SD) values of any clinical parameter used to assess changes in ASD symptoms were extracted to compare efficacy. Those trials which did not report SD values were excluded from quantitative analysis. However, for those trials publishing baseline (day 0) and final (day 90) values, we used a mathematical formula to calculate SD values from baseline and final mean values. The following formula was used to calculate mean change SD value: square root of (baseline SD^2 + final SD^2 + 2 × 0.6 × baseline SD × final SD).[16] Differences in opinions between the authors on the trial selection and data extracted/calculated were resolved after achieving consensus between the authors, and then the final data extraction sheet was prepared.

Risk of Bias Assessment

Assessment of the risk of bias within the individual trials was independently done by two authors using the Cochrane Collaboration tool.[17] Discrepancies in the allotting level of bias in the individual trials were sorted after arriving at a consensus between the authors. Publication bias was analyzed by the funnel plot method. A funnel plot is a scatter plot of the effect size measures of individual trials plotted along the horizontal axis against the effect size measure of the study (meta-analysis) along the vertical axis. An asymmetrical funnel plot implies the possibility of publication bias or systematic difference between larger and smaller trials.

Summary Measures

The primary outcome measure analyzed was the mean change in the total score of any clinical parameters/scales used to assess ASD severity. The mean change in individual clinical parameters or scales used to assess the severity of ASD were the secondary outcome measures analyzed. The other secondary outcome measures analyzed were the mean change in individual ABC (Aberrant Behavior Checklist) sub-scores and the gastrointestinal Symptoms Severity Index (GSI).

Subgroup Analysis

Subgroup meta-analysis is conducted by including identical trials; identical based

on either type of probiotic used or baseline demographic or clinical features was planned. This was done to ascertain that the meta-analysis results that included all trials did not differ significantly and thus are not sensitive or vary significantly with variation in intervention, baseline demographic, or clinical features of patients.

Synthesis of Results and Statistical Methods
Various clinical parameters/scales were used to assess the effect of probiotics on the severity of ASD in our included trials. Hence, we estimated the efficacy of probiotics in reducing ASD severity by calculating the Standardized Mean Difference (SMD) values of these parameters/scales. An efficacy analysis by including only those trials publishing identical clinical parameter/scale was also done by estimating risk difference (RD) values. The mantel-Haenszel method and both fixed and random effect models were used in the analysis by Revman 5.4.1 software.

Apart from subgroup analysis, the sensitivity of the results was analyzed by comparing the results of the fixed effect model and the random effect model. The lack of significant variation in the results analyzed by the fixed effect model and the random effect model indicated that the effect size measured is robust. Heterogeneity between the included trials was analyzed using the Cochrane Q test for heterogeneity and the I^2 test. A chi-square test with a P value of 0.10 and an I^2 test value of > 50% was considered an indicator of significant heterogeneity.

Results and Discussion
Five randomized controlled trials were eligible and included in the quantitative synthesis of the meta-analysis.[9–13] However, there was a lack of uniformity in the clinical parameters/ scales used to assess the severity of ASD and the benefits of probiotics on ASD symptoms. Therefore, we preferred and included ABC or SRS (Social Responsiveness Scale) or ADOS (Autism Diagnostic Observation Schedule) scores for estimating standardized mean difference values to assess the efficacy of all probiotics used in all included trials in reducing ASD severity. (Figure 1)

Table 1 shows the baseline demographic, clinical features, and characteristics of individual trials included in the analysis. Of the five included trials, probiotic *L.Plantarum* was used in two trials, and a combination of eight propbiotic preparation was used in the other two trials. The remaining trials varied significantly regarding the use of Bovine Clostrum Product (BCP) in combination with the probiotic preparation *B.Infantis*.

The forest plot in Figure 2 shows the results of SMD analyzing the overall efficacy of all probiotics using total scores of any clinical parameters or scores used to assess the severity of ASD. The reduction in the severity of total ASD score was small (SMD: -0.14) and insignificant (95% CI -0.45 to 0.17). Quantities of reduction in total scores of individual clinical parameters/ scores considered under secondary outcomes measures were also insignificant and as follows: total ABC score (RD:2.64, 95% CI: -8.19 to 13.47, N=114, n=3), total SRS score (RD:-3.65, 95% CI: -8.36 to 1.05, N=118, n=3) and total CBCL score (RD:1.51, 95% CI: -6.25 to 9.28, N=134, n=2).

The efficacy of probiotics on individual ABC scale sub-scores were also insignificant and as follows: ABC-Irritability (RD:0.33, 95% CI: -4.63 to 5.3, N=63, n=3), ABC-Stereotype (RD:0.84, 95% CI: -1.39 to 3.08, N=63, n=3), ABC-Lethargy (RD:1.69, 95% CI: -1.46 to 4.84, N=63, n=3).

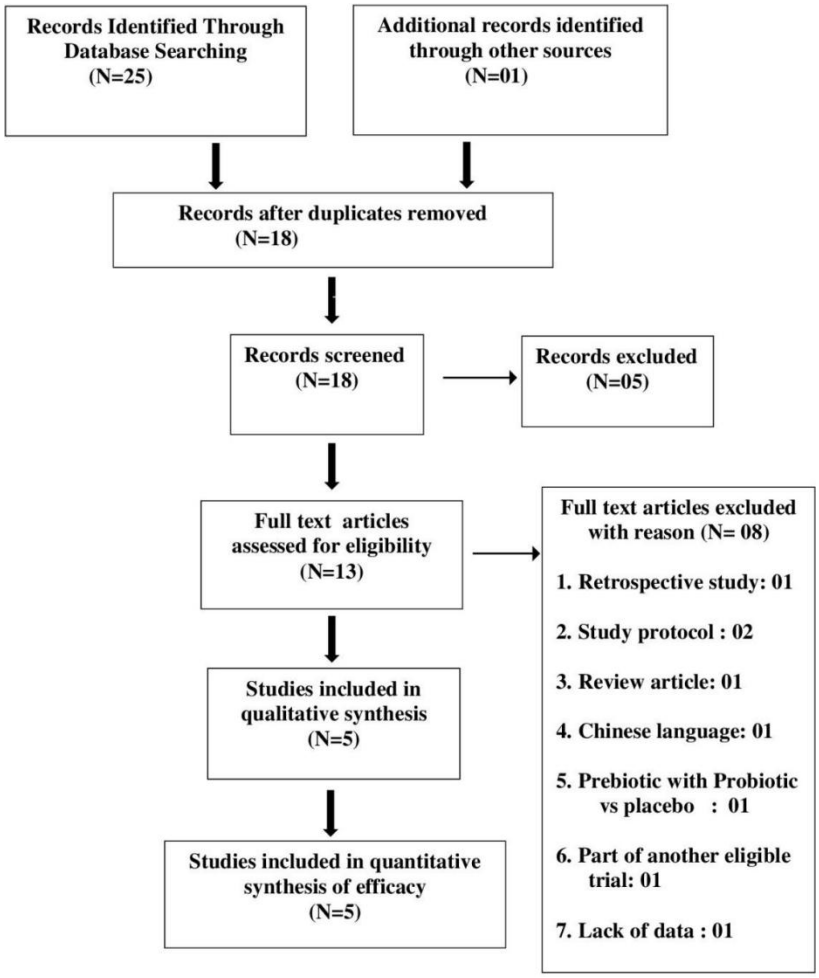

Figure 1. Showing Literature Search Results and Study Attrition Diagram

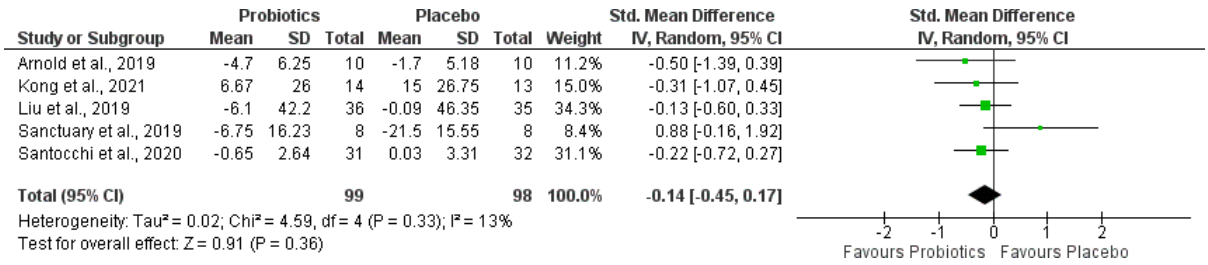

Figure 2. Forest Plot Showing SMD of Overall Benefits of Probiotics

ABC-Hyper activity (RD:1.65, 95% CI: -2.51 to 5.81, N=63, n=3), ABC-Inappropriate speech (RD:-0.60, 95% CI: -2.35 to 1.15, N=47, n=2). Individual estimation of efficacy about two other parameters, total ADOS score and total Vineland Adaptive Behavior Scales-II (VABS II) score, was not possible due to a lack of sufficient data. Additional analysis on the benefits of probiotics in reducing gastrointestinal symptom severity Index (6-GSI) was also not possible for the same reason.

Subgroup analysis was conducted by including those trials using identical probiotic agents. This analysis was done for the outcome measures: total ABC score and SRS score. We estimated the efficacy of two probiotic preparations, *L. plantarum* (PS128) and VISBIOME (a probiotic preparation containing eight probiotic species, mostly *Lactobacillus* and *Bifidobacterium*), in two subgroup analyses. There was no statistically significant change in SMD values of total ABC score after including VISBIOME preparation (SMD: -0.29, 95% CI: -0.72 to 0.14, n = 2, N =83). To assess the efficacy of L.Plantarum (PS128), we calculated RD values rather than SMD value. There was no significant reduction in ASD severity when L.Plantarum (PS128) was used as a probiotic preparation in total ABC score (RD: -7.21, 95% CI: -21.54 to 7.12, n = 2, N = 98) as well as total SRS score (RD: -8.22, 95% CI: -21.5 to 5.07, n = 2, N = 98).

Subgroup analysis after excluding the trial by Sanctuary et al., which included both prebiotic and probiotic preparations in the control group, was conducted. The result of this subgroup analysis on the total ABC score was also insignificant (SMD: -0.23, 95% CI: -0.52 to 0.06, n = 4, N = 181). Similarly, the result of subgroup analysis, including long-duration treatment (> 2 months) trials on total ABC score, also remained insignificant (SMD: -0.25, 95% CI: -0.66 to 0.17, n = 2, N = 90). Due to a lack of data, subgroup analysis based on patient age (less than and more than 7 years of age) and the presence or absence of gastrointestinal symptoms was not possible. Nevertheless, study results appear robust since there was no significant variation in effect measures analyzed by random and fixed effect models.

There was no evidence of publication bias in any of the outcome measures analyzed. There was evidence of heterogeneity between the trials only in two secondary outcome measures: ABC-Irritability and ABC-hyperactivity.

Results of our study suggest that probiotics are ineffective in reducing gastrointestinal and ASD symptom severity, irrespective of the type of probiotic preparations used and their duration of treatment. There was no significant reduction in any of the major sub-scores or symptoms of ASD. An interesting observation is their insignificant effectiveness in relieving gastrointestinal symptoms. Consequently, it is unfair to ascertain the ineffectiveness of probiotics in ASD for the heterogeneous demographic and clinical factors of patients included in our study.

There are significant results between patients' age range, varying treatment duration, type of probiotic tested, and inclusion of ASD patients with and without gastrointestinal symptoms. The influence of the duration of treatment and type of probiotic tested was insignificant in subgroup analysis. Patients' age and gastrointestinal symptoms significantly influence probiotic efficacy and appear to be strong confounding factors.[10,12]

Table 1. Baseline Demographic and Clinical Features of Included Trials (1)

Study	Arnold et al., 2019 (Cross over trial)		Liu et al., 2019		Sanctuary et al., 2019 (Cross over trial)
	Placebo (N=4)	Probiotics (N=6)	Placebo (N=35)	Probiotics (N=36)	(N = 8)
Age (Yrs):	8.76±1.18	8.83±2.80	9.91±2.33	10.11±2.34	6.8 ± 2.4
Male (%):	83.3	25	100	100	87.5
Baseline					
ABC:	NA	NA	17±9.31*	15.81±8.39*	NA
SRS:	87.0±4.76	82.17 ±7.85	135.8±26.04	138.8±24.19	NA
ADOS:	NA	NA	NA	NA	NA
VABS II:	NA	NA	NA	NA	NA
CBCL:	NA	NA	50.6±25.91	49.63±25.4	NA
GSI:	NA	NA	NA	NA	NA
Design:	R, UB, CO, PC, Pilot		R, DB, PG, PC		R, DB, CO, PC
Duration:	8 weeks		4 weeks		5 weeks
Country:	USA		Taiwan		USA
Sites:	Single		Single		Single
Probiotics:	VISBIOME		*L.Plantarum* (PS128)		*B.Infantis* ± BCP
Bias risk					
RSG:	UR		LR		LR
AC:	UR		LR		LR
BPP:	UR		LR		LR
BOA:	UR		UR		UR
IOD:	LR		LR		LR

ABC:Aberrant Behavior Checklist, SRS: Social Responsiveness Scale,ADOS:Autism Diagnostic Observation Schedule, VABS II: Vineland Adaptive Behavior Scales-II, CBCL:Child Behavior Checklist, GSI: gastrointestinal severity index, R: Randomized, UB: Un-blinded, CO: Cross Over, PC: Placebo-controlled, PG: Parallel Group, VISBIOME: (Probiotic preparation containing eight probiotic species, mostly Lactobacillus and Bifidobacterium), *ABC-Taiwan version, BCP: Bovine Colostrum Product, RSG: Random Sequence Generation, AC: Allocation Concealment, BPP: Blinding of Participants and Personnel, BOA: Blinding of Outcome Assessment, IOD: Incomplete Outcome Data, SR: Selective Reporting, UR: Unclear Risk, HR: High Risk, LR: Low Risk, N/A: Not Available, All values are in mean±SD

Table 1. Baseline Demographic and Clinical Features of Included Trials (2)

Study	Santocchi et al., 2020		Kong et al., 2021	
	Placebo (N=32)	Probiotics (N=31)	Placebo (N=17)	Probiotics (N=18)
Age (Yrs):	4.09±0.97	4.29±1.22	10.7±4.76	9.85±4.91
Male (%):	84.4	77.4	64.7	83.3
Baseline	NA	NA	278±34.8	272± 0.2
ABC:	NA	NA	83.0±12.1	82.3±11.5
SRS:	6.97±1.91	6.84±1.39	NA	NA
ADOS:	57±16.7	63.87±22.1	NA	NA
VABS II:	62.8±10.9	60.9±9.94	NA	NA
CBCL:	1.38±1.45	2.06±2.14	NA	NA
6-GSI:	NA	NA	NA	NA
Design:	R, DB, PG, PC		R, DB, PG, PC	
Duration:	6 months		16 weeks	
Country:	Italy		USA	
Sites:	Single		Single	
Probiotics:	VISBIOME		*L.Plantarum* (PS128)	
Bias risk:				
RSG	LR		LR	
AC	LR		LR	
BP	LR		LR	
BOA	LR		LR	
IOD	LR		LR	

ABC: Aberrant Behavior Checklist, SRS: Social Responsiveness Scale, ADOS: Autism Diagnostic Observation Schedule, VABS II: Vineland Adaptive Behavior Scales-II, CBCL:Child Behavior Checklist, GSI: gastrointestinal severity index, R: Randomized, UB: Un-blinded, PC: Placebo-controlled, PG: Parallel Group, VISBIOME: (Probiotic preparation containing eight probiotic species, mostly Lactobacillus and Bifidobacterium), RSG: Random Sequence Generation, AC: Allocation Concealment, BPP: Blinding of Participants and Personnel, BOA: Blinding of Outcome Assessment, IOD: Incomplete Outcome Data, SR: Selec- tive Reporting, UR: Unclear Risk, HR: High Risk, LR: Low Risk, N/A: Not Available, All values are in mean±SD

Due to a lack of sufficient data, the influence of these factors could not be assessed in subgroup analysis. It is imperative to rule out these two factors' influence to ascertain probiotics' ineffectiveness in ASD. Observed insignificant clinical benefits of probiotics in ASD patients could be due to the presence of gastrointestinal symptoms as a co-morbidity. Based on a clinical trial results, we believe that probiotics could be effective in a subgroup of ASD patients without gastrointestinal symptoms.[12]

Dysbiosis, or altered gastrointestinal microbial flora, is attributed to consequent leaky gut epithelium, inflammation, and altered neurotransmitter and biochemical levels apart from gastrointestinal symptoms.[6,20] Apart from its significant impact on brain function, dysbiosis is framed as the pathological basis for various systemic, psychological, and neurological disorders.[18-21] Restoration of favorable gastrointestinal microbial flora has proven clinically beneficial in these disorders.[19] A large proportion of ASD patients present with dysbiosis or gastrointestinal symptoms.[6,20] However, restoration of gastrointestinal microbial flora by probiotics failed to reduce ASD symptoms, especially in the subgroup of patients with gastrointestinal symptoms. The reasons for this failure and whether the association between ASD and dysbiosis is a coincidence or comorbidity is quite intriguing.

ASD aetiology and pathogenesis is a complex interplay of genetic and environmental factors, and dysbiosis is unlikely to be the single most important contributor. In addition, dysbiosis is not a co-feature in all ASD patients. Gastrointestinal symptoms in ASD patients do not correlate with the type of microbial flora colonizing their gut.[12]

Since restoring balanced microbial flora with probiotics was ineffective in reducing gastrointestinal symptoms in all ASD patients, the association of ASD appears to be not with dysbiosis but with gastrointestinal symptoms. "gastrointestinal symptoms" are a frequent co-morbidity in ASD patients.[19-21] It has been correlated with increased severity of ASD symptoms, especially irritability and social skill impairment.[20] Consequently, the ineffectiveness of probiotics in a subgroup of ASD patients with gastrointestinal symptoms is anticipatory and exploratory. There is also a lacuna in understanding the reasons for the co-morbid presentation of gastrointestinal symptoms in ASD.

We hypothesize that intolerance to dietary components is responsible for gastrointestinal symptoms and inflammation. Clinical symptoms and pathological changes of leaky gut epithelium, inflammation, and altered gastrointestinal microbial flora in ASD patients with gastrointestinal symptoms are identical to gluten intolerance.[20,22] Significant clinical benefits observed with interventions preventing exposure to intolerant dietary components or alleviating gut inflammation strengthen our hypothesis.

These clinical benefits were evident from nascent clinical trials employing four intervention strategies:

1. Prebiotics (Bimuno-galactooligosaccharide, B-GOS) plus gluten/casein exclusion diet
2. Prebiotics plus immune factors such as BCP (bovine colostrum product, an immune factor and prebiotic preparation)
3. Probiotic plus prebiotic preparation
4. Synbiotic 2000 (anti-inflammatory fibres and probiotic preparation).[7,12,23,24]

The success of the first strategy could be due to prevention of exposure to intolerant

dietary components (gluten/casein). While the gastrointestinal inflammation is reduced in the other three strategies.[7,12] In a trial analyzing the benefits of BCP, despite no change in the gastrointestinal microbial flora, there was a significant reduction in inflammation with a reduction in ASD and gastrointestinal symptoms.[12] It is unclear whether BCP preparation has direct anti-inflammatory properties and is responsible for gastrointestinal anti-inflammatory action. However, there was a significant reduction in inflammatory biomarkers in patients receiving BCP.

In the third strategy, adopting anti-inflammatory fibers and probiotics (Synbiotic 2000), apart from clinical benefits, favorable gastrointestinal microbial flora was restored along with a significant reduction in inflammation.[23] Nevertheless, the results of these trials demonstrate the significance of preventing or reducing gastrointestinal inflammation in alleviating gastrointestinal and, thus, ASD symptoms severity. There appears to be no significance in restoration of normal or good gastrointestinal microbial flora in ASD patients with gastrointestinal symptoms.

Quite interesting is the inclusion of probiotics and or prebiotics in all four strategies. Both probiotics and prebiotics have direct anti-inflammatory effects and other indirect beneficial effects that reduce gastrointestinal inflammation.[25,26] This could be the mechanism behind significant clinical benefits observed in the fourth strategy adapting supplementation of combined probiotic and prebiotic preparations.[24] Perhaps this combination is synergistic and significantly enhances their anti-inflammatory efficacy, sufficient to reduce gut inflammation. Additional evidence from clinical and animal studies supports the anti-inflammatory action of this combination to be beneficial in relieving chronic gut inflammation and ASD symptoms, respectively.[26,27]

Variable reductions in the quality and quantity of gastrointestinal or ASD symptoms were evident in these four strategies. Excluding intolerant dietary components (gluten, casein) has extrapolated to improved gastrointestinal symptoms but not ASD symptoms. Adding a prebiotic preparation to it has significantly improved the social behaviour domain of ASD. Combining prebiotics (FOS) with probiotics improved the language and speech domains of ASD symptoms.

The Synbiotic 2000 preparation significantly decreased the severity of stereotypical behaviors. Among the four interventions, BCP improved the most in the ASD domains of stereotypical behavior, irritability, and hyperactivity. Quite interestingly, benefits were the opposite in the group receiving a combination of probiotics plus BCP, which had a significant reduction only in the social behaviour domain. Hence, a strategy to combine these interventions to gain maximum benefits may not be beneficial. Probiotics alone have improved the social interaction domain, but only in a subgroup of ASD patients without gastrointestinal symptoms.[12] Hence, probiotics like prebiotics could also be beneficial in patients with gastrointestinal symptoms when combined with additional specific anti-inflammatory action agent. Overall, the reduction in core symptoms of ASD by these interventions further strengthens the significance of the gut-brain axis in ASD.

The involvement of hundreds of genes and multiple genetic deficits in patients of ASD support a strong genetic basis of its etiopathogenesis.[1,2] There is a complex interplay of genetic and environmental factors behind the etiology and pathogenesis of ASD.[1,2] Higher incidence in twins and male

gender, variation in clinical manifestations and its concurrence with other genetic disorders strengthens the genetic basis of its etiopathogenesis. Intolerance to dietary components could be one such strong environmental factor.

The presence of gastrointestinal symptoms enhances the severity of ASD symptoms.[20] Hence, relieving gastrointestinal symptoms' severity extrapolates into a reduction in the actual severity of ASD needs to be clarified. Heterogeneity in etiology and pathogenesis, variation in clinical manifestation, and coincidence of other co-morbid illnesses with ASD have led to inter-individual variations in response and inconsistency in the efficacy of both non-pharmacological and pharmacological interventions employed for ASD treatment.[2–5] Perhaps this could be another factor responsible for the insignificant effects of probiotics in patients with gastrointestinal symptoms.

The need to assess the efficacy of any intervention used in ASD based on the patients' individual genetic and phenotypic traits is also relevant for probiotics.[4] In addition, the effects of other non-genetic traits which are predictors of response to pharmacological interventions, especially age and gender, also need to be identified. Future trials analyzing the efficacy of any intervention need to be stratified based on these confounding factors. We didn't have sufficient data to conduct a network meta-analysis to compare the efficacy of prebiotic and probiotic-based interventions indirectly. Hence, the inclusion of a single standard clinical parameter to assess the efficacy and severity of ASD will be beneficial in comparing them.

The major drawback of our study is the exclusion of two randomized clinical trials, one due to publication in Chinese and the other due to the need for more sufficient data.[8,28] The influence of excluding them on our results could be altogether different. In addition, the inclusion of few trials and a small patient population in overall and subgroup analysis limits the strength of our evidence. However, the inclusion of more trials and conducting subgroup analysis are our major strengths compared to a previously published meta-analysis. We also highlighted the benefits of probiotics and other interventions in ASD patients with and without gastrointestinal symptoms.

Conclusion

The observed insignificant clinical benefits of probiotics in ASD patients could be due to the presence of gastrointestinal symptoms as a co-morbidity. We hypothesize that intolerance to dietary components is responsible for gastrointestinal symptoms and inflammation. Perhaps probiotics are still beneficial in ASD patients without gastrointestinal symptoms, while their combination with prebiotics is effective in patients with gastrointestinal symptoms. Prebiotic or probiotic-based combination intervention strategies aimed at preventing or reducing gut inflammation appear to be beneficial in ASD patients with gastrointestinal symptoms.

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Conflict of interest

None

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