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EDITORIAL

The Osmani Medical Teachers Association Journal Volume 21 Number 1

The Pandemic's Digital Dilemma: Internet Addiction Among Children and Adolescents

The COVID-19 pandemic transformed the world overnight, redefining how we live, work, and interact. With lockdowns and school closures, the digital world became a lifeline, connecting us to education, social activities, and even mental health support. However, this increased reliance on the internet brought with it an unintended consequence: a surge in internet addiction, particularly among children and adolescents. As schools transitioned to virtual learning and social interactions moved online, screen time sky rocketed. For children and adolescents, the internet became not only a source of knowledge but also a critical social outlet. Yet, the boundaries between constructive use and harmful overuse began to blur. Many found themselves trapped in a cycle of prolonged online gaming, social media scrolling, and video streaming. Studies during the pandemic highlighted that screen time among children and adolescents increased by over 50%, with some youth spending upwards of 7-8 hours daily on non-academic activities.[1,2] The sudden shift created fertile ground for the emergence of internet addiction, a disorder characterized by an inability to control internet use, leading to significant impairment or distress.[3,4] Internet addiction in young people has far-reaching consequences. During the pandemic, social isolation and increased stress levels created a perfect storm for developing addictive behaviors. The dopamine-driven rewards of online games or social media became substitutes for real-world interactions and achievements, contributing to a sense of escapism. Prolonged internet use has been linked to anxiety, depression, and disrupted sleep patterns. For adolescents, whose brains are still developing, these effects can be particularly detrimental. Emotional regulation, impulse control, and social skills can be impaired, potentially leading to long-term challenges in mental health and behavior.[5] Moreover, academic performance often suffers, as children may struggle to prioritize schoolwork over the instant gratification offered by online activities. This imbalance creates a feedback loop: academic stress drives them to seek solace online, perpetuating the addictive behavior.[6]

More alarmingly, adults who are supposed to be the role model for change are themselves have internet addiction., approximately 1 in 10 adults are addicted to internet.[7]

Addressing internet addiction requires a multifaceted approach that involves parents, educators, and mental health professionals. Some key strategies to aid recovery can be establishing healthy boundaries, modelling positive behavior, promoting digital literary, encouraging real life social interaction and seeking professional help in need can be some key strategies to overcome this alarming issue.

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ORIGINAL ARTICLE

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Efficacy, Safety and Tolerability of Rivastigmine in Patients with Dementia: A 20 Weeks Trial

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Abstract

Dementia is a term used to describe a combination of symptoms that greatly interfere with memory, thinking, and social skills. Dementia frequently affects elderly people. The most common and widely used test for dementia is the MMSE test. This quasi-experimental study was done to observe the efficacy, safety and tolerability of Rivastigmine in dementia Patients. Total 104 patients with dementia from July 2017 until June 2018 attending at Sylhet MAG Osmani Medical College Hospital, Sylhet, were included in this study. Irrespective of sex, all patients with mild-to-moderate dementia received Rivastigmine 1.5 mg twice daily. At the end of the fourth, twelfth, and twentieth weeks, cognitive function was assessed using the MMSE (Mini–Mental State Examination) score. Monitoring and recording each adverse effect were part of assessments of safety and tolerability. In dementia patients, the MMSE score increases considerably over time ($p< 0.05$). As Rivastigmine treatment continued, the side effects subsided gradually ($p<0.05$). It can be concluded that the therapeutic dose of rivastigmine is efficient, well-tolerated in the treatment of dementia.

Keywords: *dementia, Rivastigmine, MMSE, efficacy, tolerability*

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Introduction

A group of symptoms that severely impair memory, reasoning, and social skills and significantly interfere with day-to-day functioning is referred to as dementia.[1] The most common causes of progressive dementia in older persons are Alzheimer's disease, but there are several other dementia-causing conditions as well, such as vascular dementia, Lewy body, frontotemporal dementia, and mixed dementia.[1,2] Other conditions associated with dementia are Huntington's disease, traumatic brain injury, parkinson's disease.[1] The clinical syndrome of dementia is brought on by neurodegeneration, is defined by a steady decline in mental capability and the ability to live independently.[2] Elderly persons are frequently affected; however it isn't a typical aspect of healthy aging.[2,3] Globally, an estimated 35.6 million people had dementia in 2010, and that number is anticipated to rise in the next 20 years.[3]

Degeneration of the cholinergic neurons reported in dementia results in a decrease in the cholinergic neurotransmission seen in the cerebral cortex and other parts of the brain.[4] As the cognitive functions were impaired, several neurological tests were carried out in clinical settings such as Ascertain Dementia 8 (AD8), Functional Activities Questionnaire (FAQ), mini-Cog, Mini-Mental State Exam (MMSE), Montreal Cognitive Assessment (MoCA), Neuropsychiatric Inventory Questionnaire (NPI-Q).[5]

The almost commonly acknowledged screening technique is the MMSE for mental illness.[6] The MMSE is made up of a number of brief cognitive probes that are administered exclusively to the patient. A value is considered from 1 (worst) to 30 (best) to represent the outcomes.[7] A score of less than 24 necessitates additional testing, which includes a more thorough cognitive assessment.[6]

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When the MMSE score is between 21 and 26, it indicates mild cognitive impairment; between 10 and 20, it indicates moderate cognitive impairment dementia; and below 10, it indicates severe cognitive impairment.[8]

The medications that have so far shown the highest efficacy in the treatment of cognitive impairment in clinical trials are acetylcholinesterase inhibitors (AChEIs), which can boost intrasynaptic cholinergic activity by preventing the breakdown of acetylcholine.[4,9] There are three well-known AChEIs: donepezil, rivastigmine, and galantamine. [9,10]

Among them, Rivastigmine is most frequently used by physicians. Although several studies observed the effectiveness and safety of Rivastigmine in dementia patients, no studies so far have observed such effectiveness and tolerability in Bangladesh.

Patients and Methods

This quasi-experimental study was carried out in the Departments of Pharmacology and Therapeutics in collaboration with the Departments of Neurology, Psychiatry, and Medicine from July 2017 until June 2018 at Sylhet MAG Osmani Medical College Hospital, Bangladesh. All mild-to-moderate dementia patients, irrespective of sex, who attended the outpatient departments of medicine, neurology, and psychiatry, meeting the requirements for inclusion criteria, were considered as the subject population. Convenient sampling methods were implied for data collection. Data were gathered in a pre-designed data sheet. Rivastigmine 1.5 mg was administered to these patients twice daily. The MMSE scale was used to measure cognitive function, with a score of baselines, at the end of the 4th, the 12th, and the 20th weeks. Assessments of safety and toleration include monitoring and documentation of each negative incident where any unfavorable symptoms, signs, or medical conditions. Over the course of the 20-week study period, the researchers maintained a positive rapport with the participants. Each patient is followed up with by telephone or by visiting the patient's place with a scheduled appointment to maintain a proper follow-up. Throughout the study period, 11 patients were dropped due to failure to maintain the study protocol. Finally, data from 104 patients were analyzed. All ethical issues were addressed duly.

Mean and standard deviation was used to express quantitative data. By using repeated measure ANOVA, a comparison between the before and after MMSE score measurement was done. Frequency and percentages were used to express the qualitative data. By utilizing SPSS version 25, statistical analysis was carried out. A p-value <0.05 was considered as statistically significant.

Results

Table I showed that among 104 patients, 34.6% were under 60 years and 65.4% patients were more than 60 years of age. The majority (56.7%) of patients were female, 68.3% were a non-smoker. Among the patients, 46.2% were hypertensive and 26.0% had diabetes mellitus. 57.7% of patients had vascular dementia and 42.3% had probable Alzheimer's disease.

Table II shows the effect of Rivastigmine on MMSE scores in the study population. At baseline, the MMSE score was 14.39, and at the end of the 20th week, the MMSE score was 21.05 ($p<0.05$).

Table III shows the adverse effects of Rivastigmine at different weeks of the trial. The adverse effects were significantly reduced ($p<0.05$) as the treatment continued.

Table 1: Particulars of the Patients (N=104)

Variables		Number (%)
Age (years)	60	36 (34.6%)
	>60	68 (65.4%)
Gender	Male	45 (43.3%)
	Female	59 (56.7%)
Smoking habit	Smoker	33 (31.7%)
	Non-smoker	71 (68.3%)
High blood pressure	Present	48 (46.2%)
	Absent	56 (53.8%)
Diabetes mellitus	Present	27 (26.0%)
	Absent	77 (74.0%)
Types of dementia	Vascular dementia	60 (57.7%)
	Probable AD	44 (42.3%)

Table II: Effect of Rivastigmine on MMSE Score (N=104)

Duration of Rivastigmine use	MMSE score (Mean ± SD)	p value
At Baseline	14.39 ± 2.95	p<0.001
At 4th week	16.37 ± 3.21	
At 12th week	19.95 ± 3.50	
At 20th week	21.05 ± 2.14	

Table III: Adverse Effect of Rivastigmine at Different Weeks (N=104)

Weeks	Adverse effect	Number (%)	p value
At 4th week	Nausea	12(11.5%)	<0.05
	Vomiting	3(2.9%)	
	Diarrhea	3(2.9%)	
	Dizziness	11(10.6%)	
	Hypersensitivity	0(0.0%)	
At 12th week	Nausea	3(2.9%)	
	Vomiting	0(0.0%)	
	Diarrhea	3(2.9%)	
	Dizziness	3(2.9%)	
	Hypersensitivity	0(0.0%)	
At 20th week	Nausea	3(2.88)	
	Vomiting	1(0.96)	
	Diarrhoea	0(0.0%)	
	Dizziness	0(0.0%)	
	Hypersensitivity	0(0.0%)	

Discussion

Dementia is used to describe a variety of symptoms linked to a mental deterioration that is severe enough to impair a person's ability to carry out daily tasks. Mental abilities besides memory that may be hampered include visual perception, thinking, and judgment, as well as communication and language skills. Additionally, motivation, social behavior, and emotional regulation may decline.[3]

This study's objective was to assess the safety and effectiveness of Rivastigmine for 20 weeks in mild to moderate dementia patients. At the onset of the study, the MMSE score of the subjects was 14.39. When the MMSE score was measured at the end of 4 weeks, it was 16.37. At the end of 12 weeks, the score was 19.95, and at the end of the study (20th week), the score was 21.05. The gradual increase of MMSE score in the patients treated with Rivastigmine indicates that the drug is well effective to dementia patients.

This outcome was consistent with research by Abolfazli et al. that indicated that Rivastigmine treatment led to a statistically significant improvement (p=0.007) in MMSE scores after six months of therapy. At the onset of the treatment, the MMSE score of the patients in their study was 20.03. After one month of treatment, the score was 20.8, and after 6 months, the score was 22.71.[11] Another study found almost similar findings. The MMSE showed improvement from baseline at weeks 12 and 24 for both cognitive and noncognitive symptoms. The MMSE score improved from 19.2 at the beginning to 21.9 in Week 24.[12]

Given that Rivastigmine has a rather short half-life, it must be used twice daily. In accordance with the labeling guideline, titration is necessary from 3 mg/day at a minimum to the effective dose range of 6-12 mg/day. In general, Rivastigmine is well tolerated at low dosages, but at larger levels, cholinergic side effects like nausea and vomiting have been documented.[8] The side effects gradually decreased as the Rivastigmine treatment continued in the current study. Nausea (11.5%), vomiting (2.9%), diarrhea (2.9%), and lightheadedness (10.6%) were the most commonly reported side effects in the fourth week of treatment. During the 12th week of treatment, nausea (2.9%), diarrhea (2.9%), and dizziness (2.9%) were noted as adverse side effects. At the end of the 20th week, 2.88% of patients complained of nausea, and 0.96% of patients complained of vomiting. The findings from this study suggested that after 20 week treatment, the use of Rivastigmine is well tolerated to the dementia patient. This study findings were nearly similar to Bullock et al.[13] They found that the adverse effect of rivastigmine is more prominent in the titration phase, but during the maintenance phase, the adverse effect is much less.[13]

Reduced levels of the neurotransmitter acetylcholine (ACh), which is correlated with the onset of disease symptoms, are caused by the degradation of cholinergic neurons in dementia. AChE is inhibited by Rivastigmine by binding to the catalytic site, where it is hydrolyzed.[14] Rivastigmine's exact mechanism is still unknown; however, it is hypothesized that it binds to and inactivates cholinesterase, such as acetylcholinesterase, blocking the hydrolysis of acetylcholine and

increasing the concentration of acetylcholine at cholinergic synapses. Rivastigmine has a rather high level of specificity for brain acetylcholinesterase in its anticholinesterase effect.[14,15]

Conclusion

The therapeutic dose of rivastigmine is effective, well tolerated and does not cause any unexpected side effects in the treatment of dementia.

Conflict of Interest

The authors declared that no conflicting interest exists.

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Contribution of authors

All the authors were equally involved in protocol preparation, data collection, data processing and manuscript writing.

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ORIGINAL ARTICLE

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Clinical Characteristics and Early Outcome of Children with COVID-19: Experience from a Tertiary Care Hospital of Bangladesh

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Abstract

COVID-19, caused by SARS-CoV-2, has spread around the world, posing an international public health disaster. Children are also affected by COVID-19. There is a scarcity of data regarding the effect of COVID-19 on pediatric population. So, the present study was undertaken to determine the clinical characteristics and early outcome of COVID-19 in children admitted into a tertiary care hospital of Bangladesh. This prospective observational study was conducted between July2020 and June 2021 at the Department of Pediatrics in Sylhet MAG Osmani Medical College Hospital. A total of 38 children admitted into the Pediatric Ward were confirmed as having COVID-19 by RTPCR. Subsequent laboratory tests such as CBC, Chest X-ray, Serum Ferritin and D-dimer were done. Majority of the children belongs to 1-5 year age group (50.0%). Mean age of the children with COVID-19 was 4.5 years. Among the study children 24 were male and 14 were female with a male-female ratio of 1.7:1. The chief presenting complaints were fever (100%), cough (63.2%), respiratory distress (60.2%) and convulsions (34.2%). The most common physical finding was crepitations in the lung fields (60.5%), which was followed by toxic appearance (52.1%), lethargy (42.1%), nasal flaring (26.3%) and chest indrawing (26.3%). Anemia was present in 39.5% children with COVID-19. Leukocyte count was normal in 52.3% children and 47.4% presented with leukocytosis. Majority of the children presented with normal platelet count (81.6%); only 13.2% had thrombocytosis. ESR was raised in only in 36.8% children and raised CRP was found in 18.4% children. Serum Ferritin and D-dimer were elevated in 5.3% and 7.9% children. Chest X-ray findings were normal in maximum patients (47.4%) which was followed by bilateral patchy opacity (28.9%)%, unilateral consolidation (15.8%), ground glass opacity (5.3%) and pleural effusion (2.6%). Associated co-morbidities were nephrotic syndrome in 3 (7.9%) cases, moderate acute malnutrition in 2 (5.3%) cases, Ventricular septal defect in 1 (2.6%) case and cerebral palsy with epilepsy in 1 (1.1%) case. Thirty three (86.8%) children were discharged after complete recovery, 2 (5.3%) were discharged on risk bond before complete recovery. Death rate was 5.3%. Children of all ages appeared susceptible to COVID-19, and there was a male preponderance. The main clinical features of COVID-19 in children were fever, cough, respiratory distress, convulsions and diagnosed as having pneumonia. Laboratory and radiology findings are mainly nonspecific. Outcome of COVID-19 in children was good with a low mortality rate.

Key Words: *COVID-19, children, Bangladesh.*

[OMTAJ 2022; 21 (1)]

Introduction

COVID-19, caused by SARS-CoV-2, has spread around the world, posing an international public health disaster.[1] SARS-CoV-2 is contagious to the majority of people, including children. The majority of children infected with COVID-19 present wit minor clinical symptoms unless they hav underlying co-morbidities or concomitan diseases.[2,3] In comparison to adults, experience fro nations recovering from big COVID-19 outbreak indicates that children seldom acquire severe c critical disease or die from the infection.[3-5]

In Bangladesh, it is difficult to estimate th COVID-19 infection in pediatric patients due t restraining from seeking medical help in mino illness and also due to low rate of testing. The late WHO report indicates that about 7-8 % are infecte in the pediatric age group with mortality rate o

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about 0.5-1%.[6] But infection in children was found rare among hospitalized COVID-19 patients in Bangladesh (4% below 15 years).[7]

Children of all ages can get COVID-19.[3,4] COVID-19 symptoms are identical in children and adults, but their frequency differs.[4,5] Although severe cases of COVID-19 in children, including fatal cases, have been reported, most children appear to have asymptomatic, mild, or moderate disease and recover within one to two weeks of disease onset.[8] Fever, cough, shortness of breath, vomiting, diarrhea, and exhaustion are all common symptoms of COVID-19 in children.[8,9]

The results of laboratory tests vary. Several common laboratory results are mentioned, including increased C-reactive protein, lactate dehydrogenase, D-dimers, procalcitonin, serum ferritin, erythrocyte sedimentation rate, creatine kinase, myocardial band, and serum aminotransferases. Other findings include leukopenia, leukocytosis, lymphocytosis, and lymphopenia.[9,10]

There is scarcity of data on COVID-19 infections in children, especially in Bangladesh. So, the present study was undertaken to determine the clinical characteristics and early outcome of COVID-19 in children admitted into Sylhet MAG Osmani Medical College Hospital.

Patients and Methods

This prospective observational study was conducted between July 2020 and June 2021 at the Department of Pediatrics in Sylhet MAG Osmani Medical College Hospital. Prior commencement of the study, permission was taken from the Institutional Review Board. All children aged 1 day to 12 years admitted into the Pediatric Ward were searched for COVID-19 infection. A detailed history was taken and thorough physical examination was done. Suspicion was based on common symptoms such as fever, cough, respiratory distress, headache, nausea, vomiting, diarrhea, abdominal pain, convulsions and so on. Following that, RTPCR was done on suspected covid patients. Only patients with positive RTPCR results were included in the study. Subsequent laboratory tests such as CBC, Chest X-ray, Serum Ferritin and D-dimer were done and recorded.

Data were collected in a pre-formed structured questionnaire which was prepared by 4 senior teachers of the department. Collected data included necessary socio-demographic and clinical information.

All the patients with COVID-19 were followed up by the investigators at least twice daily and treated according the guideline of Child Corona Unit (which was prepared following BPA Guideline). Patients were discharged after fulfilling the discharging criteria of the guideline. Early outcomes were recorded. Data analysis was performed by using Microsoft Excel version 16.16.21.

Results

A total of 38 children were confirmed as COVID-19 by RT-PCR and included in the study. Majority of the children belongs to 1-5 year age group (19, 50.0%) which was followed by 5-10 year age group (8, 21.0%). Mean age of the children with COVID-19 was 4.5 years (Table-I).

Male patients accounted for 24, while female patients accounted for 14 with a male-female ratio of 1.7:1 (Table-II).

Table I: Distribution of Patients According to Age (N=38)

Age Range	Number of children	Percentage
Neonate	3	7.9
1 month – 1 year	5	13.2
1-5 year	19	50.0
5-10 year	8	21.0
>10 year	3	7.9
Mean age	3.5 years	

Table-II: Distribution of Patients According to Gender (N=38)

Gender	Number	Percentage
Male	24	63.2
Female	14	36.8

Table-III shows the presenting complaints of the children with COVID-19 at the time of admission. The chief presenting complaints were fever (100%), cough (63.2%), respiratory distress (60.2%) and

convulsions (34.2%). Some patients were admitted with drowsiness, runny nose, poor feeding, fatigue, restlessness, malaise, unconsciousness, sore throat, vomiting, diarrhea and abdominal pain.

Table-III: Presenting Complaints of Children with COVID-19 on Admission (N=38)

Complaints	Frequency	Percentage
Fever	38	100
Cough	24	63.2
Respiratory distress	23	60.5
Convulsion	13	34.2
Drowsiness	12	31.6
Runny nose	8	21.1
Poor feeding	8	21.1
Fatigue	6	15.8
Restlessness	3	7.9
Nasal congestion	2	5.3
Sore throat	2	5.3
Malaise	2	5.3
Unconsciousness	5	13.2
Vomiting	2	5.3
Diarrhea	2	5.3
Abdominal pain	1	2.6
Confusion	1	2.6
Headache	1	2.6

Physical findings of the children with COVID-19 are shown in Table-IV. The most common physical finding was crepitations in the lung fields (60.5%), which was followed by toxic appearance (52.1%), lethargy (42.1%), nasal flaring (26.3%) and chest indrawing (26.3%).

Table-IV: Physical Findings of Children with COVID-19(N=38)

Findings	Frequency	Percentage
Toxic appearance	20	52.1
Lethargy	16	42.1
Pallor	2	5.3
Jaundice	1	2.6
Cyanosis	2	5.3
Dehydration	2	5.3
Nasal flaring	10	26.3
Suprasternal recession	2	5.3
Chest in drawing	10	26.3
Crepitations on lung field	23	60.5
Rhonchi on lung fields	2	5.3
Murmur in heart	2	5.3
Signs of meningeal irritation	2	5.3
Hypertonia	1	2.6

Regarding investigation findings (Table-V), anemia was present in 39.5% children with COVID-19. Leukocyte count was normal in 52.3% children, 47.4% presented with leukocytosis, no one with leucopenia. Majority of the children presented with normal platelet count (81.6%); only 13.2% had thrombocytosis. ESR was raised in only in 36.8% children and raised CRP was found in 18.4% children. Serum Ferritin and D-dimer were elevated in 5.3% and 7.9% children. Chest X-ray findings were normal in maximum patients (47.4%) which was followed by bilateral patchy opacity (28.9%)%, unilateral consolidation (15.8%), ground glass opacity (5.3%) and pleural effusion (2.6%).

Table-V: Laboratory Findings

Parameters	Number	Percentage
Hemoglobin		
<10gm/dl	15	39.5
>10gm/dl	23	60.5
Total leukocyte count		
Normal (4000-11000/mm^3)	20	52.3
Leukopenia (<4000/mm^3)	00	00.0
Leukocytosis (>11000/mm^3)	18	47.4
Platelet		
Normal (1,50,000-4,00,000/mm^3)	31	81.6
Thrombocytopenia (<1,50,000/mm^3)	01	2.6
Thrombocytosis (>4,00,000/mm^3)	05	13.2
ESR		
Normal	24	63.2
Elevated (>10 mm in 1sthr)	11	28.9
Extremely elevated (>100 mm in 1sthr)	03	7.9
CRP		
Normal	31	81.6
Positive (>10mg/L)	07	18.4
Ferritin		
Normal	36	94.7
Increased (>200ng/ml)	02	5.3
D dimer		
Normal	35	92.1
Elevated (>2.27 mg/L)	03	7.9
Chest X-ray		
Normal	18	47.4
Bilateral patchy opacity	11	28.9
Consolidation (Unilateral)	6	15.8
Ground-glass opacity	2	5.3
Pleural effusion	1	2.6

Among the 38 children 7 (18.4%) already had a pre-existing co-morbidity. Associated co-morbidities were nephrotic syndrome in 3 (7.9%) cases, then moderate acute malnutrition in 2 (5.3%) cases, Ventricular septal defect in 1 (2.6%) case and cerebral palsy with epilepsy in 1 (1.1%) case (Table-VI).

Table-VI: Presence of Co-morbidities among the Children with COVID-19

Pre existing Medical condition	Number	Percentage
Nephrotic Syndrome	3	7.9
Moderate Acute Malnutrition	2	5.3
Ventricular Septal Defect	1	2.6
Cerebral Palsy with Epilepsy	1	1.1

Outcome of the children with COVID-19 is shown in Table-VII. Thirty three (86.8%) children were discharged after complete recovery, 2 (5.3%) were discharged on risk bond before complete recovery. Death rate was 5.3%.

Table-VII: Outcome of Children with COVID-19 (N=38)

Outcome	Number	Percentage
Discharged with complete recovery	33	86.8
Absconded	01	2.6
Discharged on risk bond	02	5.3
Death	02	5.3

Discussion

COVID-19 appears to be more prevalent in adults than in children, with pediatric instances tending to be less frequent and less severe.

This study found that children of all ages were affected including 3 neonates. Majority of the children (50.0%) belongs to 1-5 year age group which was followed by 5-10 year age group (21.0%). Mean age of the children with COVID-19 was 4.5 years. A single center study[8] in Dhaka found that 85.8% of the COVID-19 positive cases belong to 1-3 year age group and the mean age was 33.86±46.34 months. Another multicenter study[9] involving 5 tertiary care hospitals in Dhaka also found that children of all ages were affected and 30.74% were <1 year of age, 25.68% were in 1-5 year age group, 21.34% belong to 6-10 year and 22.24% belong to 11-15 year age group. The difference in age with the present study may be due to the fact that the above mentioned two studies were conducted in different hospitals of Dhaka city. But the present study represents the findings of a tertiary care hospital from peripheral part of Bangladesh.

This study found that 63.2% children with COVID-19 were male and 36.8 percent female, with a boy to girl ratio of 1.7:1. Lu et al.[2] reported that 60.8% male and 39.2% female children were affected by COVID-19. Zheng et al.[10] also found, the boy to girl ratio was 1.27:1 among the hospitalized patients with COVID-19. The findings of these two studies are comparable to the present study.

The chief presenting complaints of the children with COVID-19 at the time of admission were fever (100%), cough (63.2%), respiratory distress (60.2%) and convulsions (34.2%). Vomiting and diarrhea were detected in 5.3 percent of study participants. Ferdous et al.[8] found that the major clinical symptoms were fever (85.7%), loose stool, vomiting and abdominal pain (42.9%), convulsion (28.6%), cough (21.4%) and breathing difficulty (14.3%). Hussain et al.[9] reported that the most common presenting symptoms were fever (94.92%), cough (79.69%), dyspnea (59.77%). The findings of these two studies from Bangladesh differ somewhat from the present study. But Zachariah et al.[11] in New York and Lu et al.[2] in China found nearly similar presenting complaints at the time of admission.

A good number of children presented with signs of respiratory insufficiency like nasal flaring (26.3%) and chest indrawing (26.3%) and crepitations in the lung fields (60.5%). Other common findings were toxic appearance (52.1%) and lethargy (42.1%). Ferdous et al.[8] and Hussain et al.[9] also reported that maximum of the children with COVID-19 had features of pneumonia and respiratory insufficiency. Zheng et al.[10] found that 68% children had features of pneumonia. Zachariah et al.[11] also found 64% children with respiratory problems.

This study revealed anemia in 39.5% of children, which is consistent with the study by Tiwari's et

al.[12] Leukocyte count was normal in 52.3% children, 47.4% had leukocytosis, no one had leucopenia. Although maximum studies found leucopenia, Xia et al.[13] found 70% children with normal WBC count and 10% children with leukocytosis. The majority of cases (81.6%) in this study had normal platelet counts. Tiwari's et al.[12] found 81.8% children with normal platelet count. Liu et al.[14] and Korkmaz et al.[15] also support this finding.

ESR and CRP were raised in only in 36.8% and 18.4% children respectively. Wang et al.[16] found raised ESR in 14.7% children with COVID-19. Hussain et al.[9] reported raised CRP in 28.91% children with COVID-19. Xia et al.[13] found 35% children had raised CRP level. Serum Ferritin and D-dimer were elevated in 5.3% and 7.9% children. Abdelrazic et al.[17] found both these marker were raised in children with COVID-19. Liu et al.[14] and Korkmaz et al.[15] also found raised D-dimer level in children with COVID-19.

Chest X-ray findings were normal in maximum patients (47.4%) which was followed by bilateral patchy opacity (28.9%)%, unilateral consolidation (15.8%), ground glass opacity (5.3%) and pleural effusion (2.6%). Hussain et al.[9] found insignificant chest X-ray findings in 8.2%, ground glass opacity in 3.52%, local patchy shadow in 46.88% and bilateral patchy shadow in 28.52% cases. The chest X-ray findings by de Munain et al.[18] are almost similar with the present study where 53% chest X-rays were normal. A meta-analysis and systemic review including 129 studies from 31 countries comprising 10251 children found that 44.1% cases had radiological abnormalities; ground glass opacities (27.4%) were the most commonly reported abnormality. Other abnormalities included unilateral or bilateral patchy opacity, unilateral or bilateral consolidation and pleural effusion.[19]

The current study found that18.4% children already had a pre-existing co-morbidity which included nephrotic syndrome (7.9%), moderate acute malnutrition in (5.3%), Ventricular septal defect (2.6%) and cerebral palsy with epilepsy (1.1%). Xia et al.[13] found that 35% children had a previous history of congenital or acquired diseases. This finding may indicate that children with underlying diseases may be more susceptible to COVID 19 infection.

Among the 38 children with COVID-19, 86.8% children were discharged after complete recovery, 5.3% were discharged on risk bond before complete recovery and 5.3% died. Ferdous et al.[8] reported 100% recovery in their study, but Hussain et al.[9] found that the mortality rate was 4.52%.. Irfan et al.[19] found 3.6% death in their meta-analysis which is almost consistent with the present study.

This study was done in a tertiary care hospital situated in the North-East region of Bangladesh. Pediatric ICU is not established here. The sample size was small and all investigation facilities were not available. Outcome may be better if all facilities were available.

Conclusion

Children of all ages appeared susceptible to COVID-19, and there was a male preponderance. The main clinical features of COVID-19 in children were fever, cough, respiratory distress and convulsions. Majority of the children were diagnosed as having pneumonia. Laboratory and radiology findings were mainly nonspecific. Outcome of COVID-19 in children was good with a low mortality rate. Larger epidemiological and clinical cohort studies are needed to better understand possible implications of COVID-19 infection in children.

Conflict of interest

The authors have no potential conflicts of interest to disclose.

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RESEARCH ARTICLE

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p53 Immuno-expression and Its Association with Tumor Grade and Muscle-invasiveness of Urinary Bladder Carcinoma

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Abstract

Urinary bladder carcinoma is one of the threatening causes of human morbidity and mortality. Various molecular studies and prognostic biomarkers are helpful to assess the outcome of urinary bladder carcinoma. High expression of p53 may represent the aggressiveness of the disease and indicate poor prognosis. This cross-sectional study was conducted at the Department of Pathology, Sylhet MAG Osmani Medical College from September 2018 to July 2020 to observe the immune-expression of p53 in urinary bladder carcinoma and their association with tumor grade and muscle-invasiveness.Total 57transurethral resection (TURBT) samples of radiologically and clinically suspected bladder tumor cases diagnosed histopathologically were included in the study. Age of the study patients ranged from 35 to 80 years with a mean of 60.60 years ± 11.14 and male to female ratio was 4.7:1. There were 31 (54.4%) high grade and 26 (45.6%) low grade urinary bladder carcinomas on histopathological examination. Thirty (52.6%) cases were histopathologically muscle invasive bladder carcinoma (MIBC) and 27 (47.4%) cases were non-muscle invasive bladder carcinoma (NMIBC). Positive p53 expression was observed in 24 (77.4%) cases of highgrade carcinoma while only in 6 (23.1%) cases of low grade urinary bladder carcinoma. Positive p53 expression was seen in 22 (73.3%) cases of MIBC and 8 (29.6%) cases of NMIBC. Statistically significant association ($p<0.05$) was observed in histopathological grades and muscle invasiveness of UBC with p53 expression. The results of this study agree with the opinion that p53 immunomarker may provide additional prognostic information in urinary bladder carcinoma to stratify the highrisk patients.

Keywords: *urinary bladder carcinoma, MIBC, NMIBC, p53, immune-expressionIntroduction*

[OMTAJ 2021; 20 (2)]

Introduction

Urinary bladder cancer (UBC) is one of the most frequent malignant tumors in the urinary system.[1] It is the 7th most common cancer in men and the 17th in women.[2]

Worldwide newly diagnosed urinary bladder carcinoma cases are 5,73,278 (3% of all malignancies), among them 2.1% died.[3] In Bangladesh, newly diagnosed urinary bladder carcinoma cases are 1,626 (1.1% of all malignancies), among them 0.92% died. Prevalence of urinary bladder carcinoma in Bangladesh is 2.08%.[4]

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Urothelial carcinoma (UC) represents more than 90% of bladder cancer; other histological types include squamous cell carcinoma (2%) and adenocarcinoma (1.5%).[5] Bladder cancers can also be classi ed as non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC).[6]

The important factors in determining the prognosis of the bladder carcinoma are infiltrative pattern, histopathological grading, staging and tumor recurrence. However, these pathological variables are not conclusive to predict the prognosis. Newer molecular techniques are becoming day by day the important adjunct to predict the behavior of bladder carcinoma.[7]

The tumor suppressor gene TP53 had been shown potential biological and prognostic significance of urinary bladder carcinoma.[8] TP53 mutations cause

loss of normal p53 function and accumulated DNA damage may result in tumor development9. Mutated TP53 gene results in p53 protein accumulation in cells' nuclei; this accumulation is detectable with immunohistochemical methods.[10] Mutations of TP53 are more common in high-grade invasive urinary bladder cancers.[11] High expression of p53 protein is more common in advanced stage of urinary bladder carcinoma, which is a concern and should take proper measures after radical cystectomy.[12] Many studies had shown a definite correlation of p53 immunoexpression with histopathological grade and stage of UBC7.[13-15] The aim of this study was to observe theimmune-expression of p53 in urinary bladder carcinoma and their association with tumor grade and muscle-invasiveness.

Materials and Methods

This cross-sectional study was conducted at the Department of Pathology, Sylhet MAG Osmani Medical College from September 2018 to July 2020. Ethical clearance was obtained from the ethical committee of Sylhet MAG Osmani Medical College. Fifty-seven patients were selected following the enrolment criteria who later underwent trans-urethral resection of urinary bladder carcinoma at the Department of Urology, Sylhet MAG Osmani Medical College Hospital. These specimens were then processed and routine H&E stain was carried out to see the histologic type, tumor grade and muscle invasiveness. The paraffin blocks were then carried to the Armed Forces Institute of Pathology (AFIP), Dhaka for immunostaining of p53. Assessment of p53 immunohistochemical staining was done according to Wang et al.[13] Evaluation of immunostaining and scoring were performed by light microscopy. Only the nuclear staining was evaluated. At least 1000 tumor cells (x400 magnification) from the most immune-positive regions and the percentage of positive cells were calculated. Each slide was given a value composed of the sum of staining intensity and the proportion of the stained cells. This proportion was graded as follows: 0 for 0-10% of tumor cells stained, 1 for11–25% of cells stained, 2 for 26–50% of cells stained and 3 for >50% of cells stained. Staining intensity was graded as follows: 1 for light yellow, 2 for dark yellow and 3 for brown. The final score was as follows: 0 for insignificant expression (1-2), 1+ for weak expression (3), 2+for moderate expression (4) and 3+ for strong expression. Score 0 was considered negative and scores more than 0 such as (1+, 2+,3+) were considered positive for p53 expression.Statistical analysis of the results was obtained by using SPSS software version 23.

Results

Age of the study patients ranged from 35 to 80 years with a mean of 60.60 ± 11.14 with male to female ratio of 4.7:1. Male patients were predominant (82.5%) and female patients were 17.5%. Among the 57 urinary bladder carcinoma cases, 53 cases (93.0%) were histopathologically diagnosed as urothelial carcinoma. Adenocarcinoma and squamous cell carcinoma were 2 cases (3.5%) each. According to WHO grading system, 31 cases (54.4%) were histopathologically diagnosed as high grade and 26 cases (45.6%) as low grade. Thirty cases (52.6%) of bladder carcinoma were muscle invasive (MIBC) and 27 cases(47.4%) were non-muscle invasive (NMIBC).The relationship of high and low grades with muscle invasiveness of urinary bladder carcinoma were statistically significant ($p<0.001$) [Table I].

p53 expression was positive in 30 cases (52.6%) and negative in 27 cases (47.4%).Statistically significant association ($p<0.05$) was observed in histopathological grades and muscle invasiveness of UBC with p53 expression (Table:II, III).

Table I: Relationship between Histological Grade and Muscle Invasiveness (n=57)

Muscle-invasiveness	Histopathological grade		p value
	Low	High	
NMIBC	24 (92.3)	3 (9.7)	<0.001
MIBC	2 (7.7)	28 (90.3)	
Total	**26 (100.0)**	**31 (100.0)**	

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ORIGINAL ARTICLE

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Terminal QRS Distortion on Admission ECG as a Predictor of Left Ventricular Systolic Dysfunction in Patient with ST Elevation Myocardial Infraction

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Abstract

Coronary artery disease (CAD) becomes a major cause of death. CAD is an atherosclerosis process, which progressively develops into plaque that will lead to stenosis of coronary artery lumen. Several studies have found that Terminal QRS distortion is associated with left ventricular systolic dysfunction (LVEF) in acute ST elevation myocardial infarction (STEMI). The present study was done to find out the correlation of terminal QRS distortion with LVEF in acute STEMI. This cross-sectional observational study was conducted in the Department of Cardiology, Sylhet MAG Osmani Medical College Hospital, Sylhet, from 1st January 2019 to 31st December 2020. A total of 136 patients with acute STEMI were selected by consecutive sampling. Patients were divided into two groups, 68 with terminal QRS distortion (Group I) and 68 without distortion matched with site of infarction (Group II). Normal LV function was in 4.4% patients in group I and in 25% patients in group II. Mild LV dysfunction was in 38.2% patients in group I and in 61.7% patients in group II. Moderate LV dysfunction was in 57.4% patients in group I and in 11.8% patients in group II. Severe LV dysfunction was in 0% patients in group I and in 1.5% patients in group II. LV dysfunction was significantly different between these two groups ($p<0.001$). Terminal QRS distortion on admission ECG was associated with LV systolic dysfunction in patients with acute STEMI.

Key words: *terminal QRS distortion, LV systolic dysfunction, STEMI.*

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Introduction

Coronary artery disease is a global health problem reaching an epidemic proportion in both developed and developing countries and is the leading cause of mortality and morbidity worldwide.[1,2] By 2020 the world's population will grow to 7.8 billion and 32% of all deaths will be caused by coronary artery disease.[3]

The 12 leads electrocardiogram (ECG) is the most readily available noninvasive test by which in addition to diagnosis, we can also localize and assume the size of myocardial infarction. ST segment elevation is used to define subsets of patients who can benefit most from early thrombolysis.[4] A specific QRS morphology termed as terminal QRS distortion is independently associated with increased in hospital mortality.[5] Severe ischemia causes prolongation of conduction in either Purkinje fiver or myocardium in the ischemic zone cause change like terminal distortion.[6]

According to Birnbaum hypothesis absence of terminal QRS distortion on ECG of acute STEMI is a sign of myocardial protection either by collateral circulation or incomplete or intermittent occultation or preconditioning via medication.[7] Patients with terminal QRS distortion group have larger area at risk (AAR) larger infarct and worse LVEF.[8] Severity of ischemia can be categorized in three grades: Grade I: Tall T and no ST Segment elevation. Grade II: ST segment elevation without distortion. Grade III: ECG have terminal QRS distortion.

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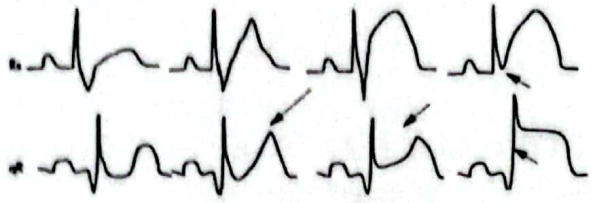

Fig. 1: *The grades of ischaemia*

(Source of figure-9)

However simple ECG reading can be good tool to predict severity of LV systolic dysfunction which can make decision to take further necessary action to benefit the patient general condition and outcome and referral to higher center for early intervention or medication.

Transthoracic echocardiography is the diagnostic tool of choice for evaluation of left ventricular (LV) systolic function, at the latest by the time of hospital discharge, is important to estimate prognosis, and echocardiography (as well as other imaging modalities) can provide this information.[10]

Terminal QRS distortion is characterized by emergence of j point e" 50% of the R wave in leads with qR configuration and/or disappearance of the S wave in leads with Rs configuration. The changes in the terminal portion of the QRS are believed to be caused by prolongation of the electrical conduction in either the Purkinje fibers or the myocardium in the ischemic zone and reflect severe ischemia.

Birnbaum hypothesized that absence of terminal QRS distortion on the ECG of patients presenting with acute STE myocardial infarction (STEMI) is a sign of myocardial protection by persistent perfusion (via collateral circulation or incomplete or intermittent epicardial artery occlusion) or preconditioning via ischemia or medications.[7]

Patients and Methods

This cross-sectional observational study was conducted from 1st January 2019 to 31st December 2020 in the Department of Cardiology, Sylhet MAG Osmani Medical College Hospital, Sylhet. All adult patients of STEMI admitted in Sylhet MAG Osmani Medical College Hospital, Sylhet within12 hours of onset of chest pain were enrolled in the study and patient with history of PCI, CABG, old myocardial infarction, Valvular heart diseas cardiomyopathy, arrhythmia were excluded fro the study. Total 136 patients with acute STE were selected by consecutive sampling. Patie were divided into two groups, 68 with termin QRS distortion (Group I) and 68 without distortio matched with site of infarction (Group II).

After admission of patient with chest pain suggestive of acute coronary syndrome were treated by standard treatment protocol. The diagnosis of ST elevated MI was made in patient who presented with retrosternal chest pain and duration of 20 minutes or more, with electrocardiographic (ECG) changes i.e. ST segment elevation 1mm in at least two adjacent limb leads, 2 mm ST segment elevation at least two contiguous precordial leads or new onset bundle branch block. Patient's data including age, sex, previous history of anginal chest pain, smoking, hypertension (HTN), diabetes mellitus (DM), family history of CAD and clinical findings on admission was taken.

STEMI was diagnosed when ECG show ST elevation of 0.1mv in two or more limb leads or 0.2 mv in two or more consecutive chest leads with increase in cardiac enzymes.

ECG was analyzed for presence of terminal QRS distortion. Terminal QRS distortion is characterized by emergence of j point e" 50% of the R wave in leads with qR configuration and/ or disappearance of the S wave in leads with Rs configuration.

The cases were divided into two groups, 68 patients with terminal QRS distortion were taken in group I and 68 patients without terminal QRS distortion matched with site of infarction were taken in group II. Group I again were subdivided into anterior MI and inferior MI, each having 34 patients. And group II again subdivided into anterior MI and inferior MI each having 34 patients. ECG was analyzed by three experienced physicians who were blinded to clinical data of the patients. Continuous ECG monitoring was done for first 24 hours in CCU and 12 lead ECG were repeated every 24 hours and when necessary.

Transthoracic Echocardiography were done and results of 2D, M-mode echocardiography such as left ventricular internal diameter in diastole

(LVIDd), left ventricular internal diameter in systole (LVIDs) and left ventricular ejection fraction (LVEF) was noted on day two. LVEF was measured by Teichholz method. Patients was monitored at CCU for at least 24 hours and then at ward till discharge or death. In this way 136 patients of Acute ST elevated MI were selected. All patients were managed according to the treatment protocol of the Department of Cardiology Sylhet MAG Osmani Medical College Hospital, Sylhet. Informed written consent was taken from each patient. Approval of study protocol was obtained from the Institutional Ethical Committee of Sylhet MAG Osmani Medical College, Sylhet before commencement of the study.

Data were tabulated, coded then analyzed using the computer program SPSS version 25.0. Qualitative data were expressed as percentage and frequency and difference between two groups were analyzed by chi-square test. Quantitative data were expressed as mean and standard deviation and difference between two groups were analyzed using t-test. Odd ratio was analyzed to assess the risk of imposed QRS distortion for left ventricular systolic dysfunction. A p-value of <0.05 was considered as statistically significant.

Results

A total 148 patients with first attack of STEMI were selected initially. Follow-up of the patients were carried out clinically and by ECG and echocardiography. Among them 7 did not give consent, 4 were discharged earlier on request of the patient, and 1 patient died. Finally, QRS distortion was observed in 136 patients with STEMI and they were grouped into two groups; (1) Group-A (n=68): STEMI with QRS distortion and (2) Group-B (n=68): STEMI without QRS distortion. Table I represents the demographic distribution of the participants of this study. Mean age was 52.99 years with SD 12.88. Most of the patient was within 46-55 years age (29.4%). Almost all of them was male (94.9%). Most of them was farmer (46.3%), earned more than 10000 taka per month (64%), could not complete SSC (58.1%).Table II depicts the prevalence of risk factors of ischemic heart disease among the patient of this study. Most of them had dyslipidemia (94.9%), family history of coronary artery disease (55.1%) and was smoker (84.6%), although few of them had diabetes (7.4%) and hypertension (33.1%).Table III represents the clinical properties of the participants. Mean time of chest pain, chest tightness and dyspnoea in group I were 7.15, 2.47 and 0.38 and in group II 5.68, 1.09, 0.29 respectively. Mean troponin was 57663.78 pg/ml in group I and 43952.99 (35160.79) mg/dl in group II and left ventricular EF 39.26 in group I and 46.3 in group II respectively. Table IV represents the association of demographic properties and risk factors with QRS distortion. Only chest tightness was found significant association with QRS distortion (p-value 0.04). Other factors were not significantly associated with QRS distortion. The association between various categories of LV function with QRS distortion was illustrated in table V. This association was found highly significant (p<0.001) in Chi-square test. Moderate LV dysfunction was noted in most of the patient who had QRS distortion (57.4%).

Table VI represents the correlation of LV ejection fraction, troponin, RBS and serum creatinine between two groups who had QRS distortion or not. As the p-value was <0.001, it indicated that there was highly significant correlation between QRS distortion and LV ejection faction. A weak correlation was also found between troponin and QRS distortion (p=0.03). There was no correlation found between RBS or serum creatinine and QRS distortion. Table VII represents the linear regression analysis of LVEF for QRS distortion. The R square value was 0.242 meaning 24% of LVEF change explained by QRS distortion. The p-value was less than 0.001 indicating that the regression was highly significant. In the table of co-efficient it was found that slope was 7.008. It indicated that QRS change contributed 7% of LVEF deterioration.

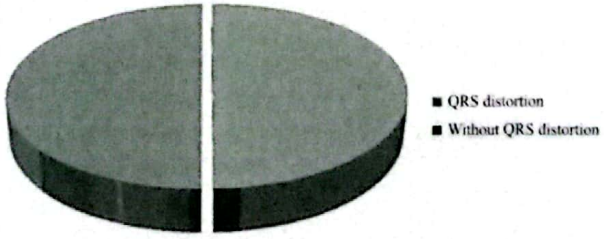

Figure- 1: Grouping of the Patients by QRS Distortion (n=136)

Table I: Demographic Properties of Participants

	Frequency	Percent
Age in years		
45	35	25.7
46-55	40	29.4
56-65	31	22.8
>65	30	22.1
Total (Mean±SD)	136 (52.99±12.88)	100.0
Sex		
Female	7	5.1
Male	129	94.9
Occupation		
Businessman	49	36.0
Farmer	63	46.3
Housewife	7	5.1
Service	17	12.5
Monthly income		
<Tk. 10,000	49	36.0
>Tk. 10,000	87	64.0
Education		
<SSC	79	58.1
>SSC	57	41.9

Table II: Risk Factors among the Patients

Diabetes			
	Yes	10	7.4%
	No	126	92.6%
Hypertension			
	Yes	45	33.1%
	No	91	66.9%
Dyslipidemia			
	Yes	7	5.1%
	No	129	94.9%
Smoking			
	Yes	115	84.6%
	No	21	15.4%
Family history			
	Yes	75	55.1%
	No	61	44.9%

Table III: Clinical Properties of Participants

	ST change: Distortion present Mean(SD)	ST change: Distortion absent Mean (SD)
Duration of chest pain (hours)	7.15 (3.08)	5.68 (2.79)
Duration of chest tightness (hours)	2.47 (3.55)	1.09 (2.42)
Duration of Dyspnoea (hours)	0.38 (1.93)	0.29 (1.54)
Pulse	72.53 (13.92)	72.99 (15.50)
SBP	119.93 (26.04)	120.60 (24.19)
DBP	71.25 (14.31))	74.41 (13.62)
JVP	7.09 (0.33)	7.07 (0.53)
Troponin (pg/ml)	57663.78 (37872.59)	43952.99 (35160.7
RBS (mg/dl)	131.25 (43.99)	119.54 (40.41)
S. Creatinine (mg/dl)	1.14 (0.39)	1.13 (0.50)
LVEF (%)	39.26 (5.50)	46.35 (7.05)

Table IV: Association of Demography and Risk Factors with ST Change Distortion

	ST change: Distortion present	ST change: Distortion absent	p-value
Age in years			0.734
45	15 (22.1)	20 (29.4)	
46-55	20 (29.4)	20 (29.4)	
56-65	16 (23.5)	15 (22.1)	
>65	17 (25)	13 (19.1)	
Mean ± SD	53.53 ±11.9	52.44± 13.9	
Sex			0.698
Male	65 (95.6)	64 (94.1)	
Female	3 (4.4)	4 (5.9)	
Chest tightness			0.040
Yes	26 (38.2)	15 (22.1)	
No	42 (61.8)	53 (77.9)	
Diabetes			0.189
No	61 (89.7)	65 (95.6)	
Yes	7 (10.3)	3 (4.4)	
Hypertension			0.202
Yes	26 (38.2)	19 (27.9)	
No	42 (61.8)	49 (72.1)	
Dyslipidemia			0.565
Yes	4 (5.9)	3 (4.4)	
No	64	65 (95.6)	
Smoking			0.812
Yes	10 (14.7)	11 (16.2)	
No	58 (85.8)	57 (83.8)	
Family history of CVD			0.121
Yes	42 (61.8)	33 (48.5)	
No	26 (38.2)	35 (51.5)	

Table V: ST Change Distortion and Severity of LV Dysfunction among the Participants

	ST change: Distortion present	ST change: Distortion absent	p-value
Normal LV function	3 (4.4)	17 (25)	<0.001
Mild LV dysfunction	26 (38.2)	42 (61.7)	
Moderate LV dysfunction	39 (57.4)	8 (11.8)	
Severe LV dysfunction	0 (0)	1 (1.5)	

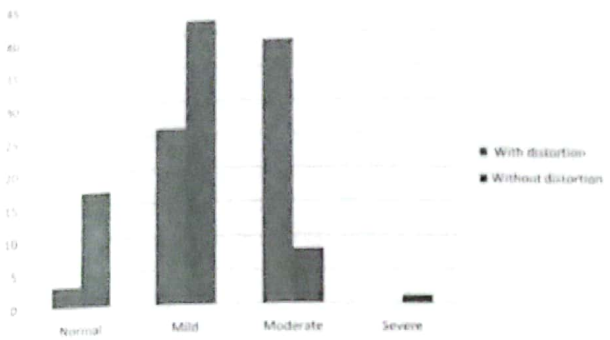

Figure-2: Relation between QRS distortion and severity of LV dysfunction

Table VI: Correlation between ST Change Distortion and LVEF

	t	p-value
LEVF	-6.537	<0.001
Troponin	2.188	<0.030
RBS	1.616	0.108
Serum creatinine	0.101	0.919

Table VII: Regression Analysis of LVEF for QRS Distortion

Model	Sum of squares	df	Mean square	F	p-value
Regression	1708.265	1	1708.265	42.732	<0.001
Residual	5356.765	134	39.976		
Total	7065.029	135			
R square 0.242					
Co-efficient a					
	B	t	p-value		
constant	39.265	51.210	<0.001		
ST change QRS distortion	7.088	6.537	<0.001		

Table VIII: Distribution LVEF According to QRS Distortion among the Anterior MI

	ST change: Distortion present	ST change: Distortion absent
	ECG: Anterior MI	ECG: Anterior MI
LVEF Mean (SD)	39% (5)	45 % (6)

Table IX: Distribution LVEF according to QRS distortion among the Inferior MI

	ST change: Distortion present	ST change: Distortion absent
	ECG: Inferior MI	ECG: Inferior MI
LVEF Mean (SD)	39% (8)	48% (8)

Discussion

In the present study, mean age was 53.53±11.9 years with QRS distortion group and 52.44±13. 9 years in without QRS distortion group. and there was no significant difference of age between these two groups (p=0.734). This result was in agreement with the study of Ahsan et al where they found that the mean age was 55.31± 11.81 years with QRS distortion group and 52.60±10.45 years in without QRS distortion group and there was no significant difference of age between these two groups (p=0.08).[9]

In this study, 95.6% patients were male and 4.4% patients were female in QRS distortion group, 94.1% patients were male and 5.9% patients were female in without QRS distortion group, there was no significant difference of sex distribution between these two groups (p=0.698).This result was in agreement with the study of Rommel et al where they found that80% patients were male in QRS distortion group, 76% patients were male in without QRS distortion group, there was no significant difference of sex distribution between these two groups (p=0.39).[1]

In our study, 10.3% were diabetic in QRS distortion group, 4.4% patients were diabetic in without QRS distortion group, there was no significant difference of diabetic between these two groups (p=0.189). This result was in agreement with the study of Mulay et al where they found that 13% were diabetic in QRS distortion group, 10.9% patients were diabetic in without QRS distortion group, there was no significant difference of diabetic between these two groups (p=0.69).[4]

In the current study, 38.2% were hypertensive in QRS distortion group, 27.9% were hypertensive in without QRS distortion group, there was no significant difference of hypertension between these two groups (p=0.202).This result was in agreement with the study of Mulay et al, where they found that 15.9% were hypertensive in QRS distortion group, 25.2% % were hypertensive in without QRS distortion group, there was no significant difference of hypertension between these two groups (p=0.15).[4]

In the recent study, 14.7% were smoker in QRS

distortion group, 16.2% were smoker in without QRS distortion group, there was no significant difference of smoking status between these two groups (p=0.812).This result was in agreement with the study of Rommel et al where they found that 48% were smoker in QRS distortion group, 47% were smoker in without QRS distortion group, there was no significant difference of smoking status between these two groups (p=0.83).[11]

In our study, dyslipidemia was present in 5.9% in QRS distortion group, dyslipidemia was present in 4.4% in without QRS distortion group, there was no significant difference of dyslipidemia between these two groups (p=0.565). This result was in agreement with the study of Rommel et al where they found that dyslipidemia was present in 41% in QRS distortion group, dyslipidemia was present in 34%in without QRS distortion group, there was no significant difference of dyslipidemia between these two groups (p=0.12).[11]

In our study, 61.8% had family history of CVD in QRS distortion group and 48.5% had family history of CVD in without QRS distortion group, there was no significant difference of family history of CVD between these two groups (p=0.121).This result was in agreement with the study of Ahsan et al where they found that 22% had family history of CVD in QRS distortion group and 15 % had family history of CVD in without QRS distortion group, there was no significant difference of family history of CVD between these two groups (p=0.20).[9]

In this study, mild LV dysfunction was in 38.2% patients in QRS distortion group and in 61.7% patients in QRS non-distortion group. Moderate LV dysfunction was in 57.4% patients in QRS distortion group and in 11.8% patients in QRS non-distortion group. Severe LV dysfunction was in 0% patients in QRS distortion group and in 1.5% patients in QRS non-distortion group. LV dysfunction was significantly different between these two groups (p<0.001). This result was in agreement with the study of Ahsan et al[9] where they found that mean ejection fraction was significantly lower in group I (42.6 ± 5.4% vs 49.7 ± 5.3%, p=0.001). Mean ejection fraction was 40.4± 4.7% in terminal QRS distortion patients with anterior MI and 47.9± 5.9% in patients without terminal QRS distortion with anterior MI (p=0.001). Mean ejection fraction was 46.6± 6.4% in terminal QRS distortion patients with inferior MI and 53.9± 7.8% in patients without terminal QRS distortion patients with inferior MI (p=0.003).

Conclusion

It may be concluded that terminal QRS distortion on admission electrocardiogram is associated with left ventricular systolic dysfunction in patients with acute STEMI.

Conflict of Interests

The authors do not have any potential conflicts of interest, whether of a financial or another nature.

Source of Funding

Self

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ORIGINAL ARTICLE

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Patterns of Antimicrobial Use in the Intensive Care Unit of a Tertiary Care Hospital

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Abstract

Antimicrobials are readily prescribed in seriously ill patients, accounting for a substantial amount of total drugs administered in intensive care units (ICUs). The intent of this study was to demonstrate the pattern of antimicrobials utilize in an ICU. This retrospective cross-sectional study was conducted in Sylhet MAG Osmani Medical College Hospital, where medical records of 530 patients were reviewed that were admitted into the ICU from July 2020 to June 2021.The mean age of the patients was 53.41 (±9.58) years; males were 54.15% and females were 45.85% of the study population. Septicemia was the commonest emergency (36.23%). Antibiotic treatment was given to 498 patients (93.96%). Culture sensitivity test was done in 72.09% patients; blood sample was more frequently cultured (42.03%). A total of 412 (95.15%) of 433 samples yielded a positive culture report. Klebsiella made up 33.25% of the isolated organism. The average extent of antimicrobials given per patient was 2.50±1.40. Cephalosporin (38.79% of patients), Carbapenem (31.33%), and Penicillin (28.92%) were the most commonly given antimicrobial group. Ceftriaxone was once the most generally prescribed (37.34&) antimicrobial followed by Meropenem (27.71%), Amoxicillin plus Clavulanic acid (19.68%), and Piperacillin plus Tazobactum (9.24%). About half of the patients (50.80%) received multiple antibiotics. The most frequently used drug combination was Ceftriaxone and Metronidazole, that was given to 48.0% of the patients. Cephalosporin and Carbapenem are frequently utilized antimicrobial agents in ICU. However, due to the rise of resistance, physicians should be more aware of using these drugs.

Keywords: *intensive care unit, critically ill patient, antimicrobial agents, cephalosporins, carbapenem.*

[OMTAJ 2022; 21 (1)]

Introduction

Intensive care units (ICUs), moreover recognized as intensive treatment units or medical crisis units, are specialized places for patients with serious illnesses to get particular and tailored clinical management. As patients with complex infectious disorders are treated in the ICU, it can become a remarkable origin of transmittable organisms that can spread and cause nosocomial infections. Nosocomial infections are critical public health problem in today's healthcare structure and a major cause of mortality among hospitalized patients. ICU patients are more prone to have nosocomial infections than general ward patients.[1] Nosocomial diseases affect persons in both economically developed and developing nations.[2] While staying in ICU, patients have been prescribed various medications. Antimicrobial drugs are used to treat critical illness and prevent infections in critically sick patients with low immunity, higher sensitivity to pathogenic microorganisms, and various medical procedures (catheterization) or medical device use (ventilator).[3] Antimicrobial medicines are commonly provided to surgical patients admitted to the ICU to treat and prevent postoperative infections.[4]

The use of total antimicrobial agents (AMA) in

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ICUs is ten times higher than in normal hospital wards.5 Because various academics have expressed worry about AMAs' improper and irrational use, evaluating and monitoring the prescription pattern of AMAs is critical. Furthermore, the emergence of medication resistance has been a topic of discussion.6 By 2050, the estimated 700,000 individuals who expire every year because of drug-resistant diseases will have risen to 10 million.[7] The evolution of resistance is aided by indiscriminate and inappropriate antimicrobial use, a lack of laboratory facilities, and notification.

Despite this, according to World Health Organization (WHO) about 50 percent of antimicrobial drugs are misused over the world.[8] Inappropriate antibiotic usage involves incorrect antimicrobial selection, and poor antimicrobial use, such as inadequate doses, short duration, minor intervals, and unsuitable routes.[9] Improving the use of AMA is a critical public health and patient safety problem and a national priority.[10,11] In light of this, the current study examined the usage of antimicrobial drugs in patients in ICU of a tertiary referral center in Sylhet, Bangladesh.

Materials and Methods

This hospital based retrospective cross-sectional study was carried out from July 2020 to June 2021 at Department of Pharmacology and Therapeutics of Sylhet Women's Medical College in collaboration with Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh. The data of all adult patients (18 years and above) received antimicrobial therapy were collected from the ICU of Sylhet MAG Osmani Medical College Hospital; data from the pregnant women and lactating mother were excluded from this study. Patient's hospital admission and treatment files were checked thoroughly. General data of the patients included patient's age, gender, diagnosis, risk factors for infection due to MDR pathogens; infection related data included duration of ICU stay, date of diagnosis of infection, number of the patient received an antibiotic, source of infection (nosocomial or community-acquired), and microbiological documentation; and data regarding antibiotic used included total amount of drugs used per patient, the total amount of antimicrobials consumed per patient, more than one antibiotic (concurrent or sequential), antibiotic treatment of the current illness (type and duration of antibiotic consumption).

Nosocomial infection also referred to as healthcare-associated infection (HAI) that was absent during admission but acquired during the process of receiving health care within 48 hours of admission to a hospital. Unless the patients were moved straight from another hospital or discharged within the 30 days before the present admission, infections arising within 2 days of arrival to the hospital were suggested as community-acquired. A patient who received two or more antibiotics simultaneously was said to be using them concurrently. When the first antibiotic was stopped and then a second antibiotic was started, this was known as sequential usage. Clinical microbiology protocols were followed for bacterial identification. The disc diffusion technique was used to identify antibiotic sensitivity and resistance by using several antibiotic discs. A zone of inhibition was used to track the sensitivity.

Institutional ethical approval was taken before commencement of the research. However, data were taken from the treatment sheet only. None of the treatment protocol was modified by the researchers during the period of the study.

Categorical data was expressed in frequencies and percentages, and numerical data was provided as mean (± Standard Deviation). Descriptive statistics were used; data analysis was done using Microsoft Excel Worksheet.

Results

A total of 530 case papers of ICU were analyzed. The mean age of the patients was 53.41±9.58 years and within the range from 19 years to 84 years. A maximum of 42% (222) cases were above 60 years, and minimum cases belonged to the age group of 19–32 years, i.e., 68 (12.8%) patients. 287 (54.15%) cases were male, and 243 (45.85%) were female.

Majority of the cases,192 (36.23%), were suffering from septicemia. Other disorders included cardiovascular problems (136 patients, or 25.66%), difficult acute abdomen (44 patients, or 8.30%), and unintentional accidents (34 patients, or 6.42%). Other minor health complications were discovered in 124 (23.39%) of the individuals.

In 213 (40.19%) of the 530 patients, risk factors for infections caused by multidrug-resistant organisms were found. The most prevalent risk factors reported in this study were past antibiotic therapy and previous hospitalization (both within the last three months) in 156 (73.24%) and 145 (68.08%) individuals, respectively. Continued immunosuppressive sickness or therapy (27.69%), home wound care (12.21%), and hemodialysis within one month were other common risk factors (2.82%). (Table I)

Table I: Risk Factors for Infection Due to MDR Organisms.

Risk factors	N	%
Antimicrobial therapy in the preceding three months	156	73.24%
Hospitalization for 48 hours in the preceding three months	145	68.08%
Ongoing immunosuppressive illness or therapy	59	27.69%
Home wound care	26	12.21%
Hemodialysis within one month	6	2.82%
Intravenous antibiotic therapy or chemotherapy at home	4	1.88%

The average period of staying in the ICU was six days (ranging from 0 to 9 days). AMAs were given to 498 (93.96%) of the 530 patients. Nosocomial infection was observed in 265 (53.21%) patients, the rest were the patients of community-acquired infection. In 359 (72.09%) of the patients, an antibiotic culture and sensitivity test was done. Before initiating antibiotic medication, 433 samples for bacterial culture were collected from 359 individuals. Blood samples (42.03%), urine samples (31.41%), respiratory samples (13.40%), stool samples (5.77%), peritoneal samples (2.77%), and samples from other sites were all cultured samples (4.62%). A total of 412 (95.15%) of 433 samples yielded a positive culture report. The most common isolates were ESBL-producing Enterobacteriaceae, primarily Klebsiella pneumo niae (33.25%), E. coli (19.91%), and Pseudomonas (16.02%), followed by Acinobacter spp. (15.05%), Staphylococcus aureus (12.86%) and miscellaneous species (2.91 %) (Table II).

Table II: Infection Profile of the Patients

Parameters	N	%
Number of patients received antibiotics (n = 530)	498	93.96%
Origin of infections (n = 498)		
1. Nosocomial / Hospital-acquired infection	265	53.21%
2. Community-acquired infection	233	46.79%
Culture and sensitivity preformed (n = 498)	359	72.09%
Total samples for culture taken	433	
Culture sites (n = 433)		
1. Blood sample	182	42.03%
2. Urine sample	136	31.41%
3. Respiratory sample	58	13.40%
4. Stool sample	25	5.77%
5. Peritoneal sample	12	2.77%
6. Others	20	4.62%
Total positive culture report (n = 433)	412	95.15%
Clinical isolates for positive reports (n = 412)		
1. Klebsiellapneumoniae	137	33.25%
2. E. coli	82	19.91%
3. Pseudomonas	66	16.02%
4. Acinobacter spp.	62	15.05%
5. Staphylococcus aureus	53	12.86%
6. Others	12	2.91%

During the study period, antibiotics were prescribed as empirical therapy, culture-directed therapy, clinically documented therapy, and failure of prior antimicrobial therapy. During the current hospitalization, 51.41% of patients (256/498) received empirical therapy. Cephalosporins (Ceftriaxone, Ceftazidime, Cefepime) were used empirically in 57.03% of cases, Carbapenems (Imipenem, Meropenem) in 28.91% of cases, Vancomycin in 23.83% of cases, Piperacillin-Tazobactam in 23.05% of cases, and Metronidazole in 14.84% of cases.

Table III: Patients Antimicrobial Prescription Data (n=498)

Parameters	N	%
Types of indication-		
1. Empirical Therapy	256	51.41%
2. Culture directed treatment	139	27.91%
3. Clinically documented infection	87	17.47%
4. Failure with prior antibiotic treatment	16	3.21%

Cephalosporin was the most commonly prescribed antimicrobial drug group, with 193 (38.79%) patients receiving it, followed by Carbapenem (156, 31.33%), Penicillin (144, 28.92%), Aminoglycosides (98, 19.68%), Fluroquinolone (92, 18.47%), and antiamebic drug (85, 17.07%) during the study days (Fig. 1). Ceftriaxone was the most commonly given antimicrobial medicine, with 186 (37.34%) patients receiving it. Meropenem was given to 138 patients (27.71%). In 98 (19.68%) and 46 (9.24%) patients, combination of Amoxicillin plus Clavulanic acid and Piperacillin plus Tazobactum was utilized respectively. Antibiotics such as Amikacin, Moxifloxacin, and Metronidazole were being used in 98 (19.68%), 86 (17.27%), and 85 (17.07%) patients, respectively. Other antibiotics included Ciprofloxacin and several Cephalosporin generations, such as Cefuroxime (with or without Clavulanic acid), Ceftazidime, and Cefepime, which were given to 18 (4.82%) patients (Fig. 2).

Antimicrobial medicines were prescribed on average 2.50±1.40 times per patient. Antibiotics were not given to 32 of the patients. The remaining 498 patients received two or more antibiotics simultaneously or sequentially, with 245 (49.20%) receiving one antibiotic and 253 (50.80%) receiving two or more antibiotics simultaneously or sequentially. One hundred and fifty-three patients (30.72%) received two antibiotics, 63 (12.65%) received three antibiotics, 22 (4.42%) patients received four medications, and 15 (3.01%) patients received five antibiotics (Fig. 3). The most common combination was Ceftriaxone and Metronidazole, given to 121 individuals (48.0%).

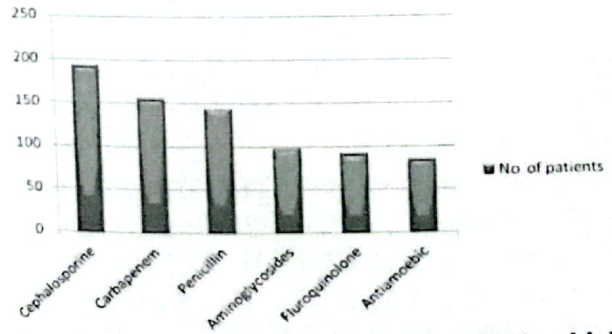

Figure 1: Most Commonly Used Antimicrobial Drug Groups in ICU

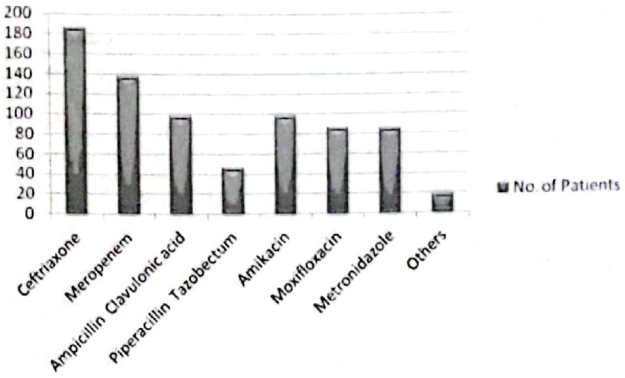

Figure 2: Commonly Prescribed Antimicrobial Drugs Used in ICU

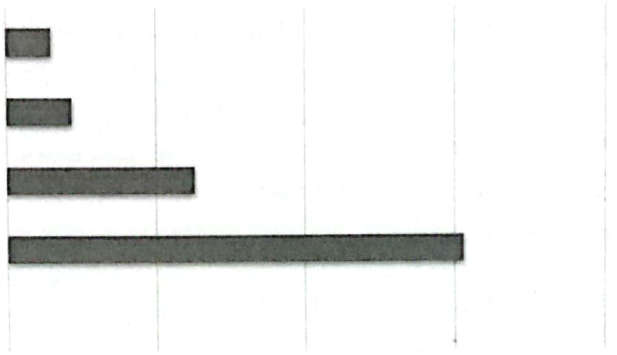

Figure 3: Number of Antibiotic Given to Each Patient in ICU

The minimal range of antibiotic therapy was one day, and the maximum was 14 days (Fig. 4). There were 15% of patients who received antibiotic therapy up to 3 days. Maximum patients (58%) received antibiotics from 4 days to 10 days. And 27% of patients received antibiotics for more than ten days.

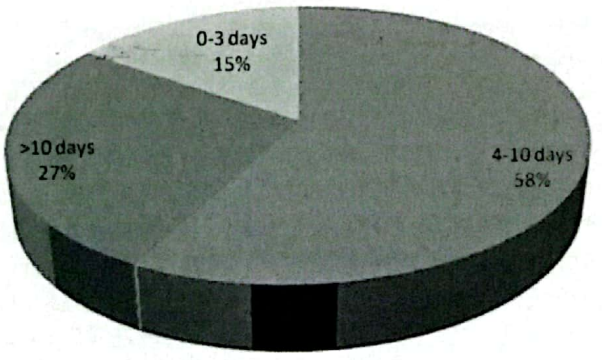

Figure 4: Duration of Antimicrobial Therapy in Days.

Discussion

Total 530 cases admitted in the ICU of a tertiary referral center were assessed. In the present study, ratio between male and female was 1.18:1, the male was 287 (54.15%), and the female was 243 (45.85%), which is similar to male 61.04% and female 38.95% of other studies.[12,13] In ICU, maximum cases were above 60 years, i.e. elderly patients. This could be because of cardiovascular disease and other co-morbid conditions like diabetes, hypertension, etc. are common in such populations. Pandiamunian et al.[14] and Williams et al.[15] also found older adults in their studies. Average age of patients was about 53 years. Studies done previously in India and Nepal had observed average age of patients of approximately 50 years. [16,17]

Greater number of the cases were admitted because of septicemia 192 (36.23%), cardiovascular emergencies 136 (25.66%), complicated acute abdomen 44 (8.30%), whereas in other studies most common indication was postoperative complications followed by sepsis.[3,13] Prior antibiotic therapy is a predisposing factor for the development of MDR-bacteria. This study observed that 40.19% of patients had minimum one predisposing factor for infection caused by multidrug resistant pathogens, specially hospitalization for 48 hours in the preceding three months and antimicrobial therapy in the initial three months, similar to another published report.[18] A study observed that the possibility of developing hospital-acquired infection was 9.1 times greater among patients admitted to the ICU than those admitted to general wards.[19] In a study conducted by Crucio in Latin America, the frequency of hospital-acquired infection in ICU was 46.5%, whereas in our study the rate was 53.21%.[20]

Antibiotic therapy is based on susceptibility testing of microorganisms isolated from urine or blood or infected tissues. Pathogen-directed treatment could be a means to decrease antibiotic use and improve patients' outcomes. In this study, antibiotic susceptibility testing was performed in 72.09% of patients, where positive rate is 95.15%; nevertheless, 27.91% of the patients received a culture-directed treatment. The most frequent sample processed was the blood sample (42.03%), followed by the urinary sample (31.41%). These findings are correlated with the results of Curcio.[20] The most commonly isolated microorganism was klebsiellapneumoniae (33.25%), wherein in another study, pseudomonas aeroginosa was the most commonly isolated microorganism.[21,22]

The average period of staying in the ICU was 6±2 days. Some studies, conducted in ICUs of India, Nepal, and the USA, the average length of stay in ICU was 6.22, 4.0, and 5.2 days respectively.[23,24]

Prevalence of antimicrobials consumption in ICUs has been reported elsewhere. In South Africa and Ghana, 75% and 71% of ICU patients were prescribed antibiotics, respectively.[3] In this study, 93.96% of the patient consumed antibiotics during their ICU stay, consistent with John et al.[18] and Mahendra et al.[25] But, the prevalence of AMAs utilization was not consistent with some previous studies conducted in Turkeyand Nepal,where they notified that 57.5% and 30% of the ICU patients were prescribed antibiotics, respectively.[17,26] These dissimilarities were maybe because of different topographic regions of study and various groups of population.

Since ICU patients are at high risk for developing infections, different necessary steps are generally taken to control the transmission of infection.[27] Initiating empirical therapy in ICU patients was related to reducing the frequency of nosocomial infections.[28] Hence several authors suggest using broad-spectrum AMAs for the empirical therapy for these severe infections.

In our study, 51.41% of the patients went through empirical therapy during the course of current treatment, where broad-spectrum cephalosporins were prescribed to 57.03% of the patients. These findings are in close relationship with the previous studies. [12,17,25]

In terms of antibiotic prescription during the study period, the more common prescribed groups were Cephalosporin group 193 (38.79%) followed by Carbapenem group 156 (31.33%). Penicillin group was given to 144 (28.92%) patients and Aminoglycoside group to 98 (19.68%) patients. On reviewing related studies, we found that Penicillin,

1st generation Cephalosporins and Quinolones were more frequently prescribed AMAs in Pakistan. Consequently, a study conducted in Brazil, where Cephalosporins, Aminoglycosides, and Fluoroquinolones were the frequently prescribed antimicrobial in ICU.[29,30]

The most frequently prescribed antimicrobial drug was Ceftriaxone 186 (37.34%), followed by Meropenem 138 (27.71%) and Amoxicillin plus Clavulonic acid 98 (19.68%), which was contrary to a study in India, which shows the antimicrobial agent with maximum consumption was Metronidazole (24.04%), followed by Ceftriaxone (17.23%) and Amoxicillin plus Clavulonic acid (11.16%).3

Although Cephalosporins and Carbapenems are commonly considered drugs for treating severe infections due to Gram-negative organisms, there are evidence in development of Cephalosporins and Carbapenem-resistant pathogens in the whole world.[20] Several studies from Dhaka City reported a variation in resistance pattern against Cephalosporins at different times. In 2015, Yasmeen et al. reported about 68% resistance against Cefixime and about 30% against Ceftriaxone. A research conducted in the northern part of Bangladesh showed that Cephalosporin resistance had risen more than 70%.[31] A study conducted by Andrew Stewardson and colleagues illustrated that Carbapenem-resistant enterobacteriaceae (CRE) infections raised the mortality rate in low-economic and middle-economic countries.[32] van Duin and Doi demonstrated that, Carbapenem-resistance by Klebsiella Pneumoniae Carbapenemase (KPC) is very frequent in South Asian countries, including Bangladesh.[33] In our study, 50.80% patients took more than one AMA. A South India study revealed that 57.8% of patients were given more than one antimicrobial agents.[18] In an average, each patient was prescribed 2.50±1.40 AMAs, which is related to some studies where the average number of prescribed antimicrobial drugs was 2.97and 3.36, respectively.[3,11]

We have observed a wide use of more than one antibiotic simultaneously. Most of these can be considered as rational – for example, the most common combination was Ceftriaxone and Metronidazole because of their different spectrum of action, and this combination is a sensible choice for diseases like abdominal sepsis.

Conclusion

The study provides an important conclusion about using antimicrobials in ICU of SOMCH. Antimicrobials like Ceftriaxone and Carbapenem were regularly used. For various reasons, the prescribing practices discovered in our study appear to be justified: (i) Nearly half of the infections were nosocomial, meaning MDR-microorganisms caused them. (ii) Other than Ceftriaxone and Carbapenem, almost 70% of the patients had prior antibiotic medication during their current hospitalization. ICU doctors believe that extending the antibacterial spectrum of previously given medicines is a good idea. (iii) Our patients had a high prevalence of ESBL-producing enterobacteriaceae. Carbapenem is the medication of choice against ESBL-producing enterobacteriaceae because it is resistant to their hydrolyzing action. (iv) To reduce the mortality of critically ill patients, a novel method is to start broad-spectrum antibiotic medication as soon as feasible after acquiring essential microbiologic samples, ideally within the first hour. We anticipate that our current study will spark interest in further studies with more artistic figure to confirm or refute our findings.

Conflict of Interest

None declared.

Funding

Not applicable for this study.

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ORIGINAL ARTICLE

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Comparison of Effects of Vitamin E and Mefenamic Acid on Pain in Medical Students with Primary Dysmenorrhea

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in primary dysmenorrhea. Vitamin E has been suggested as a possible treatment for primary dysmenorrhea in several studies. The objective of the study was to compare the efficacy of Vitamin E and Mefenamic acid in primary dysmenorrhoea. This quasi-experimental study was performed among 80 female medical students with primary dysmenorrhea. They were randomly assigned into group A and group-B; and were prescribed Vitamin E (400 units/day in every 12 hourly) and Mefenamic acid (250 mg/day in every 12 hourly) respectively for 5 days in each cycle for 3 consecutive cycles. Pain was measured using visual analogue scale (VAS) and duration by using Cox Menstrual Symptom Scale (CMSS). VAS score was significantly decreased in group-A (7.40 ± 0.98 versus 3.70 ± 0.72; p<0.001) and Group-B (7.05 ± 0.75 versus 3.52 ± 0.55; p<0.001); without significantly different between groups at baseline (p=0.077) and at 3rd cycle of treatment (p=0.228). The percentage reduction of VAS at 3rd cycle (49.60% versus 49.51%; p=0.968) did not differ significantly. CMSS score significantly decreased in group-A (3.88 ± 0.40 versus 1.25 ± 0.44; p<0.001) and group-B (3.95 ± 0.22 versus 1.35 ± 0.48; p<0.001) without significantly different between groups at baseline (p=0.306) and at 3rd cycle of treatment (p=0.335). The percentage reduction of CMSS score at 3rd cycle (67.50% versus 65.83%; p=0.520) did not differ significantly. Adverse effects were significantly fewer in group-A compared to group-B (20.0% versus 42.5%, p=0.030). It can be concluded that Vitamin E is effective in primary dysmenorrhea similar to Mefenamic acid and has lesser side effects.

Key words: *Vitamin E, primary dysmenorrhea, Mefenamic acid*

[OMTAJ 2022; 21 (1)]

Introduction

Dysmenorrhea is defined as painful menstrual cramps of uterine origin, and considered as one of the most common gynecological disorders among females of childbearing age.[1] Primary dysmenorrhea (PD) is a painful menstrual cramping of the uterus without identifiable organic pathology that affects as many as 85% of women, 20% of whom describe their pain as severe. The initial onset of primary dysmenorrhoea is usually shortly after menarche, 6–12 months after ovulatory cycles begin.[2] It is one of the most common complaints in both young and adult females.[3] Dysmenorrheic pain has a clear and cyclic pattern, which is typically severe during the first day of menses and lasts up to 72 hours.[4] Despite its high prevalence and impact on daily activities, it is often inadequately treated and even disregarded, given that, many young females prefer to suffer silently, without seeking medical advice. Females consider PD as an embarrassment and a taboo, and also perceive the pain as an inevitable response to menstruation, that should be tolerated.[1-5]

The etiology of primary dysmenorrhea has been the source of considerable debate. Current understanding is that it is caused by an excessive or imbalanced amount of prostanoids (hormone-like substances including prostaglandin) released from

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the endometrium during menstruation. These cause the uterus to contract frequently and dysrhythmically, with reduced local blood flow and hyper sensitisation of the peripheral nerves.[6,7]

NSAIDs including aspirin, naproxen, ibuprofen and mefenamic acid relieve primary dysmenorrhea mainly by suppressing the production of endometrial prostaglandins, thus alleviating cramps and restoring normal uterine activity. Mefenamic acid is a conventional and non-selective NSAID. It is easily accessible over the counter and is widely used by most local adolescents and adults for dysmenorrhea. The dosage is 500mg to be taken orally three times/day after meal.[8] Besides their beneficial effects, they may also cause side effects including heartburn, blurred vision, dizziness, headache, constipation, diarrhea, fatigue, dysuria, drowsiness, anorexia, nausea, skin acne, vomiting and gastrointestinal bleeding.[9]

Vitamin E inhibits the release of arachidonic acid and the conversion of arachidonic acid to prostaglandins via an action on the enzymes phospholipase A2 and cyclooxygenase. Activation of phospholipase A2 is considered to be regulated by protein kinase C and the increase in the concentration of intracellular calcium.[10] It could also increase internal opioids and cause pain relief.[11] Vitamin E at a dose of 400 units per day for 5 days has a role in significant reduction of severity of pain in the treatment of dysmenorrhea in several studies.[10-13] Moreover, it has no toxic effects even after ingestion of 300 mg/day for 23 years.[14] Safari et al.[15] showed that Vitamin E has a significant effect on dysmenorrhea, equal to Mefenamic acid, which is a well-known medication for the treatment of dysmenorrhea. This study was designed to observe and compare the effectiveness of Vitamin E and Mefenamic acid in the treatment of primary dysmenorrhoea.

Patients and Methods

This quasi-experimental study was conducted in the Department of Pharmacology and Therapeutics, Sylhet MAG Osmani Medical College, Sylhet between July 2018 and June 2019. Eighty unmarried female medical students of Sylhet MAG Osmani Medical College, Sylhet with primary dysmenorrhea and moderate to unbearable pain during menstruation (baseline VAS score 4cm or above) were included. Patients with asthma, peptic ulcer disease, cholecystitis, pelvic inflammatory disease, previous history of abdominal or pelvic surgery; and those were using other medications like sedative, anxiolytic, antidepressant, hormone preparation, antihistamine were excluded.

Informed written consent was obtained from the participants after detailed explanation of the procedure and purpose of the study. The clinical histories and clinical examination were performed thoroughly. All the findings, previous history and investigations were recorded.

The diagnosis of primary dysmenorrhea was made based on having characteristics of pain and ruling out any history of pelvic disorders. The characteristics of pain in primary dysmenorrhea are supra-pubic cramps which appeared in first two years of menarche, begin a few hours or just after the onset of menstruation, and last 48–72 hours.[16] Diagnosis was confirmed by a Gynecologist.

After sample selection, the participants were given a form about their menstrual cycle and were provided an instruction on how to fill out the form. In order to assess pain severity, a 10 cm visual analog scale (VAS) was applied, which is a standard pain assessment tool.[17] The pain VAS is usually a horizontal line, 10 cm in length, defined by descriptive words of "no pain" (score of 0) and "very severe pain" (score of 10). Participants were asked to put a mark on the line that they felt represented the most severe pain that experienced during menstruation. The pain score was determined by measuring the distance between the score of 0 and the participants' mark in centimeters using a ruler. According to the 10-point VAS, mild dysmenorrhea was defined as score of 0-3, moderate as score of 4-6 and severe as score of 7-10.[16] The participants whose mean score of pain severity were less than 4 (based on VAS) were excluded from the study.

Duration of pain was measured from the onset of uterine cramps until they ended. CMSS was applied for the assessment of pain duration. Based on Cox Menstrual Symptom Scale (CMSS) score, pain

duration was categorized as follows: score 0: no pain; score 1: 0.5 hours of pain; score 2: 0.5-1 hours of pain; score 3:>1 hour of pain; score 4: >1 day of pain.[11] The participants were asked to record the longest duration of menstrual pain in the first three days of menstruation on special forms, based on CMSS score.

Those who met the inclusion criteria were taken as sample. In this way 80 patients with dysmenorrhea were selected. They were divided randomly in group-A (Vitamin E) and group-B (Mefenamic acid) each consisting 40 patients. The patients of Group-A were prescribed Vitamin E 400 units/day every 12 hourly for 5 days (5 days in a month, from two days before the menstruation until the first three days) and the Group-B received 250 mg Mefenamic acid every 12 hourly for 5 days (5 days in a month, from two days before the menstruation until the first three days).

As soon as the treatment started, they were asked to record their most severe pain during menstrual period using VAS and its duration in the first three using CMSS. The participants were also asked if they were taken any analgesics for their pain; if so, the name and dosage of the medication were recorded in the treatment form. Any drug related adverse effects were noted in each follow up visit.

All the collected data were compiled and analyzed using SPSS version 22.0. Quantitative data were expressed as mean and standard deviation and comparison was done between groups by unpaired't' test and after effect in same group by repeated measure ANOVA test. Qualitative data were expressed in frequency and percentage and comparison was done using Chi-Square test or Fisher's Exact test. A probability value (p) of less than 0.05 was considered as statistically significant. Ethical issues were addressed duly. Approval was taken from the Ethical Review Board of Sylhet MAG Osmani Medical College.

Results

The mean age of Vitamin E treated group was 20.40 ± 1.46 years and Mefenamic acid treated group was 20.15 ± 1.49 years; the difference was not significant (p=0.452).

VAS score was significantly decreased from baseline to end of treatment at 3rd cycle (7.40 ± 0.98 versus 3.70 ± 0.72; p<0.001) and (7.05 ± 0.75 versus 3.52 ± 0.55; p<0.001) respectively in Vitamin E and Mefenamic acid treated group. But VAS score did not differ significantly between two treatment groups before initiation of treatment (p=0.077) and at 3rd cycle of treatment (p=0.228) (Figure-1). The percentage reduction of VAS was 49.60% and 49.51% at 3rd cycle in Vitamin E and Mefenamic acid treated group respectively that did not differ significanlyt (p=0.968) (Table-I).

The CMSS score significantly decreased from baseline to end of treatment at 3rd cycle (3.88 ± 0.40 versus 1.25 ± 0.44; p<0.001) and (3.95 ± 0.22 versus 1.35 ± 0.48; p<0.001) respectively in Vitamin E and Mefenamic acid treated group; difference was not significant at baseline (p=0.306) and after 3rd cycle of treatment (p=0.335) (Figure-2). The percentage reduction of CMSS score was 67.50% and 65.83% at 3rd cycle of treatment in Vitamin E and Mefenamic acid treated group respectively; difference was not significant (p=0.520) (Table-II).

Adverse effects were significantly fewer in Vitamin E treated group in respect to Mefenamic acid treated group (20.0% versus 42.5%, p=0.030) (Table-III). Adverse effects reported were mild and no discontinuation was needed.

Table–I: Percentage Reduction VAS Score Estimated after 1st, 2nd and 3rd Cycle

Group	Percentage reduction of VAS score (mean)			p-value
	At 1st cycle	At 2nd cycle	At 3rd cycle	
Vitamin E group (n=40)	14.50	32.06	49.60	p<0.001
Mefenamic acid group (n=40)	15.81	32.16	49.51	p<0.001
p-value	p=0.555	p=0.955	p=0.968	

Table–II: Percentage Change in CMSS Estimated after 1st, 2nd and 3rd Cycle

Group	Percentage changes of CMSS (mean)			p-value
	At 1st cycle	At 2nd cycle	At 3rd cycle	
Vitamin E group (n=40)	18.96	47.08	67.50	p<0.001
Mefenamic acid group (n=40)	22.08	46.88	65.83	p<0.001
p-value	p=0.320	p=0.959	p=0.520	

...e III: Distribution of Patients by Adverse Effects

Adverse effects	Study group		p-value
	Group-A (n=40)	Group-B (n=40)	
...usea and or vomiting	5 (12.5%)	11 (27.5%)	p=0.094
Heart burn	0 (0.0%)	9 (22.5%)	p=0.002
Dizziness	3 (7.5%)	1 (2.5%)	p=0.615
Total	8 (20.0%)	17 (42.5%)	p=0.030

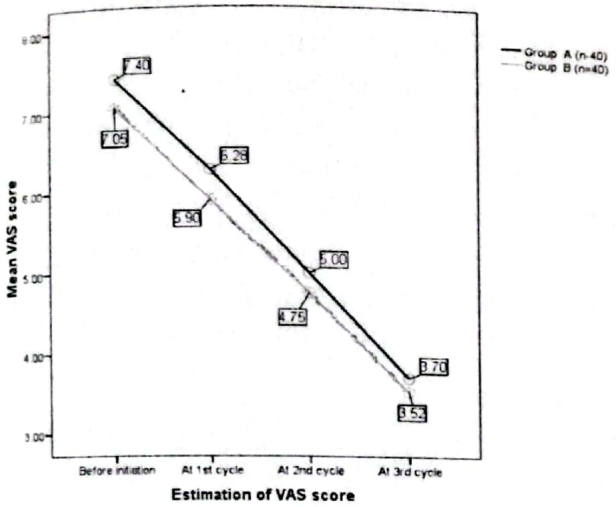

Figure-1: Comparison of VAS Score Estimated before Initiation of Treatment and after 1st, 2nd and 3rd Cycle of Treatment

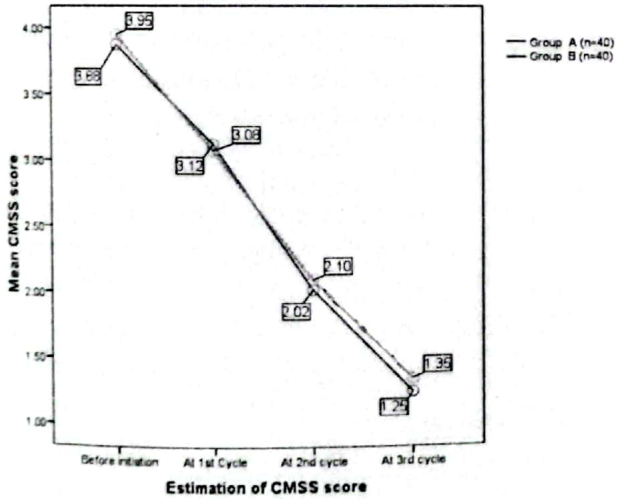

Figure-2: Comparison of the CMSS Score Estimated before Initiation of Treatment and after 1st, 2nd and 3rd Cycle of Treatment

Discussion

Primary dysmenorrhea explains the lower abdominal pain that is occurred during menstruation in young women without pelvic pathology.[18] The most widely accepted explanation for the pathogenesis of primary dysmenorrhea is the overproduction of uterine prostaglandins (PGs).[1] Therefore, the current most common pharmacological treatment for dysmenorrhea is non-steroidal anti-inflammatory drugs (NSAIDs) like Mefenamic acid.[19,20] Vitamin E inhibits the release of arachidonic acid and the conversion of arachidonic acid to PG.[12] Several studies reported that treatment with vitamin E therapy daily significantly reduced the severity of pain in primary dysmenorrhea.[10,11,21] A single study compared the effect Mefenamic acid and Vitamin E in the treatment of dysmenorrhea with similar efficacy.[15]

In this study the age of the patients was 20.40 ± 1.46 years in Vitamin E treated group and 20.15 ± 1.49 years in Mefenamic acid treated group; difference was not significant (p=0.452). Similar mean age of primary dysmenorrhea was reported in several studies.[21-23]

The reduction of VAS score at the end of treatment was significant in Vitamin E and Mefenamic acid treated patients without statistically significant difference between two groups before initiation of treatment and third cycle of treatment. Therefore, efficacy of Vitamin E and Mefenamic acid in pain reduction in both groups were similar. Nayeban et al.[10] found that the pain intensity was significantly reduced after vitamin E treatment (p<0.001) in primary dysmenorrhea. Several other studies also found the reduction of pain intensity with Vitamin E on dysmenorrhea.[12,13] Shirvani et al.[24] found that the pain intensity was significantly reduced in primary dysmenorrhea after treatment with Mefenamic acid (p<0.05). Farahani et al.[9] also found that the comparison of variations of pain pretreatment and post-treatment in the Mefenamic acid group (p<0.001).

This study also showed the percentage improvement of VAS score was 49.60% at third cycle of treatment with vitamin E and the percentage improvement of VAS score was 49.51% at third cycle of treatment with Mefenamic acid; difference between two groups was not significant (p=0.968). In a study by Vilvapriya and Vinodhini,[10] showed that there was significant difference in percent of reduction of pain of 57.8 in Vitamin E group at the end of treatment. Other

available studies did not show the percent reduction of pain in Mefenamic acid.

In this study the CMSS score was decreased significantly in both Vitamin E and Mefenamic acid treated patients without significant difference before initiation of treatment and end of treatment of treatment. In a study by Vilvapriya and Vinodhini,[10] found that there was a significant difference between the pre and post-treatment periods in terms of pain duration by CMSS score (p=0.514 and p=0.027, respectively) in Vitamin E group. Nayeban et al.[11] also found that the mean of pain duration was significantly lower after the treatment with vitamin E treated patients (p<0.001).

This study also showed the percentage in CMSS in Vitamin E treated group and Mefenamic acid treated group were 67.50% and 65.83% respectively at the end of treatment without significant difference (p=0.520). Vilvapriya and Vinodhini,[10] showed that there was significant difference in percent of reduction of duration of pain in Vitamin E group at the end of treatment. Other available studies did not show the percent reduction of pain in mefenamic acid.

Safari et al.[15] showed that Vitamin E has a significant effect on dysmenorrhea, equal to Mefenamic acid, which is a well-known medication for the treatment of dysmenorrhea; the results are similar to the findings of the present study. One study shows that Mefenamic acid is a suitable drug for the treatment of primary dysmenorrhea, especially in those suffering from moderate pain.25 In another study, Mefenamic acid has been proposed as a dominant treatment for dysmenorrhea.[26] The probable mechanism of Vitamin E in dysmenorrhea could inhibit arachidonic acid release and its conversion to prostaglandin. It could also increase internal opioids and pain relief.[11,13] The analgesic effect of Mefenamic acid remains relevant for some gynecological disorders, although considerable competition from other NSAIDs,[27] and different studies showed the efficacy of this drug in dysmenorrhea. NSAIDs decrease the menstrual pain by decreasing intrauterine pressure and lowering prostaglandin F2 levels in menstrual fluid.[28-30]

In this study 20.0% patients experienced different types of adverse effects in Vitamin E treated group and 42.5% patients in Mefenamic acid treated group. Adverse effects were significantly fewer in Vitamin E compared to Mefenamic acid treated group (p=0.030). Adverse effects were mild and no discontinuation was noted. The recorded adverse effects were heart burn (0.0% vs 22.5%) which was significantly fewer in Vitamin E treated group in respect to Mefenamic acid treated group (p=0.002); while nausea and or vomiting (12.5% vs 27.5%, p=0.094) and dizziness (7.5% versus 2.5%; p=0.615) did not differ significantly between two treatment groups. Masoumi et al.[25] reported that adverse effects of Mefenamic acid were nausea (15%), vomiting (1.5%) and diarrhea (10.2%).

Conclusion

It can be conclude that Vitamin E is effective in primary dysmenorrhea in female medical students similar to Mefenamic acid. With regard to safety of Vitamin E, it is effective and safe option for the treatment of dysmenorrhea since fewer side effects are seen with Vitamin E. However, a double-blind, placebo-controlled, randomized clinical trial involving multicenter, large scale and long-term period should be conducted to evaluate the effect of Vitamin E on primary dysmenorrhea.

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Conflict of Interest

No conflict of interest exists.

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CASE REPORT

The Osmani Medical Teachers Association Journal Volume 21 Number 1

Tuberous Sclerosis with Pulmonary Tuberculosis in a 10 Year-Old Boy: A Case Report

Mamunur Rashid[1], Jannatul Ferdous Tonny[1], Satyajit Bhattacharjee[2], Md. Benzamin[3]

Summary

Tuberous sclerosis (TS) is an autosomal dominant rare genetic disorder. Mutations on Tuberous Sclerosis Complex 1 (TSC1) or Tuberous Sclerosis Complex 2 (TSC2) gene is responsible for development of hamartomas involving many organs, such as brain, heart, kidneys, skin, lungs, and liver. This case report is about an 10 years old boy presented with prolong fever, cough, low vision, poor IQ and history of convulsion, which was diagnosed as Tuberous sclerosis (TS) with Pulmonary Tuberculosis.

Keywords: *tuberous sclerosis, genetic disorder, hamartomas, pulmonary tuberculosis.*

[OMTAJ 2022; 21 (1)]

Introduction

Tuberous sclerosis, also known as tuberous sclerosis complex (TSC), is an autosomal dominant, multisystem neurocutaneous disorder. It was initially described in the 19th century by Virchow and Von Recklinghausen.[1] This condition has a prevalence of one in 6000 to 10,000 live birth, affecting both sexes in live birth.[2] TSC occurs due to the deletion, rearrangement and inactivating mutation of tumor suppressor genes TSC1 or TSC[2], that lead to abnormal proteins hamartin and tuberin.[3] The complex hamartin/tuberin is crucial for inhibiting the tumor growth via mTOR pathway. In TSC patients, alterations in these proteins lead to a permanent activation of the mTOR pathway, causing the development of nonmalignant tumors (hamartomas) that can occur in various organs, including the brain, kidneys, lungs, skin, eyes, and heart.[3]

Case Report

A10-year-old boy from low-socioeconomic background, presented with low-grade fever, cough for 45days, along with respiratory distress for last 20 days. He had history of close contact with a tuberculosis patient (his sister) three months back. He had history of recurrent generalized tonic-clonic seizures (GTCS) since the age of three years, which was irregularly treated with antiepileptic drug without proper evaluation. There was no history of seizure in family members. However his parents had skin nodules over the face along with a hypopigmented macule over the trunk. Before admission, he had received multiple antibiotics for fever and cough. On examination, patient was conscious but irritable, febrile (100°f), pale, anicteric. There was no clubbing, cyanosis, pedal edema, lymphadenopathy. Skin survey revealed multiple hyperpigmented papule over the nasolabial region (adenoma sebaceum, figure 1) and hypopigmented macule over the trunk. On oral cavity, gingival angiofibroma was observed and dental enamel pit (figure 2). Anthropometrically he was underweight (BMI 13 kg/m2). He was unable to communicate adequately, disoriented to place and person. His vision was impaired. Features of consolidation was present on right lower chest with decreased air entry in the left lung. On investigation, complete blood count revealed hemoglobin level 8.9 gm/dL, other parameters were within normal range. Chest x-ray showed left sided collapse with significant tracheal shift to the left, and right sided consolidation (figure 3). HRCT of chest indicated-collapse and consolidation of left lung with emphysematous bullae at the apical segment. (ii) right sided consolidation and (iii) left sided pleural thickening. The Mantoux test was positive (11 mm), USG of whole abdomen revealed

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features consistent with angiomyolipoma in both kidneys. EEG record indicated generalized seizure disorder. The CT scan of brain revealed multiple calcifications in both basal ganglia and in both periventricular region (figure 4). IQ testing showed severe mental retardation with an IQ 59. Ophthalmoscopy revealed retinal hamartomas in both eyes, accompanied by vision impairment. During the hospital course, this boy was treated with several antibiotics but consolidation was not improved. So based on history, clinical findings and investigations, we diagnosed this case as Tuberous sclerosis (TS) with Pulmonary Tuberculosis. We treated him with anti-tubercular chemotherapy and sodium valproate. One month after starting treatment, his fever, respiratory distress and convulsion improved.

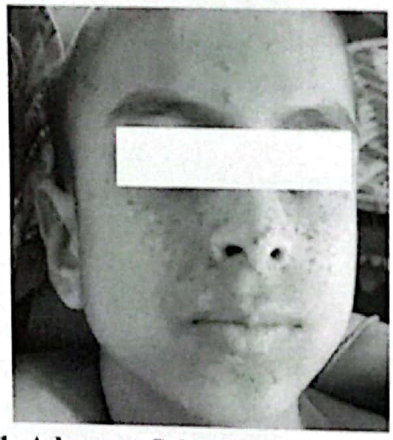

Figure 1: Adenoma Sebaceum

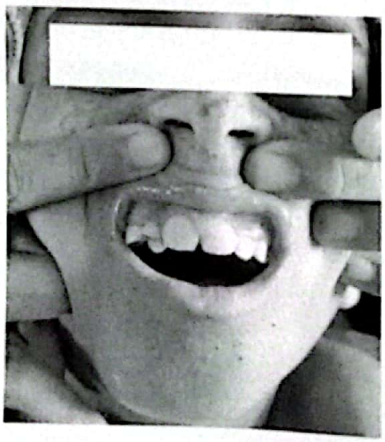

Figure 2: gingival angiofibroma and dental enamel pits

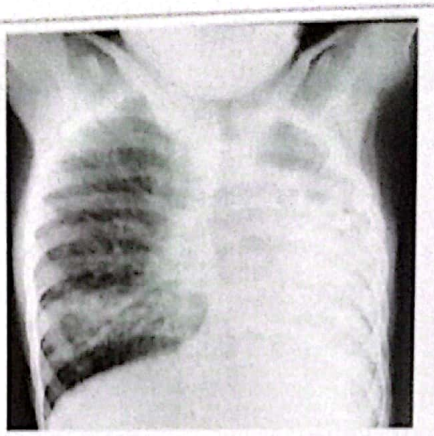

Figure 3: left sided collapse and right sided consolidation

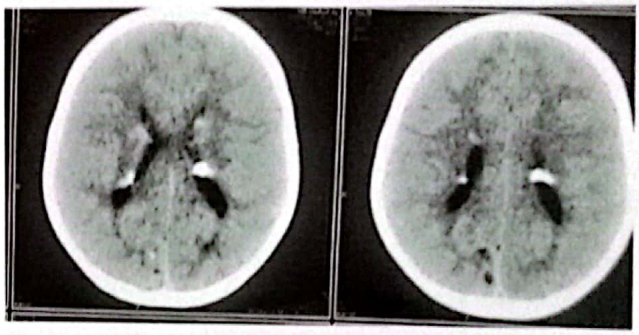

Figure 4: Calcification in both basal ganglia and in both periventricular region.

Discussion

Diagnostic criteria for tuberous sclerosis were first established in 1998, which was later modified in the second International Tuberous Sclerosis Complex Consensus Conference held in Washington, at 2012.[4] The definitive diagnosis is defined by the presence of two major criteria or one major and two minor criteria. A probable diagnosis can be made with one major criteria with two or more minor criteria.

Clinical criteria for the diagnosis of tuberous sclerosis complex

Major Criteria	Minor Criteria
1. Hypomelanotic macules (≥3, at least 5mm in diameter)	1. "Confetti" skin lesions
2. Angiofibromas (≥3) or fibrous cephalic plaque	2. Dental enamel pits (≥3)
3. Ungual fibromas (≥2)	3. Intraoral fibroma (≥2)
4. Shagreen patch	4. Retinal achromic patch
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Cortical dysplasia	6. Nonrenal hamartomas
7. Subependymal nodules	
8. Subependymal giant cell astrocytoma	
9. Cardiac rhabdomyoma	
10. Lymphangioleiomyomatosis	
11. Angiomyolipomas (≥2)	

Our patient had four major criteria like multiple angiofibromas (figure 1), multiple retinal hamartomas, subependymal nodules (figure 4), angiomyolipomas. Also had 3 minor criteria like hypopigmented macule over the trunk (Confetti" skin lesions), intraoral fibroma and dental enamel pits (figure 2). In TSC patients, cellular immunity is not affected and no reports on higher incidence of respiratory infections (including tuberculosis) among those patients. But changes in the parenchymal structure (e.g. the presence of bronchiectasis or bronchial cysts) favour the colonisation with mycobacteria.[5] Our patient had multiple air spaces in the lungs, which could favour mycobacterial infection. Tuberous sclerosis complex affects multiple organ systems so a multidisciplinary team of medical professionals is required. We consulted with dermatologist and the pediatric neurologist for symptomatic treatment. We managed him with sodium valproate as anti-convulsant. Patient should be monitored for ophthalmic, brain and renal complications and if need, surgery should be done.[5]

Conclusion

Tuberous sclerosis complex diagnosis is mainly clinical and cuteneous manifestations guide the physician to reach diagnosis.

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INFORMATION FOR THE CONTRIBUTORS

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