ISSN No. 2663-2314

Bangladesh Medical & Dental Council (BM&DC) Recognized Journal

Green Life Medical College Journal

Volume 7 Number 2 July 2022

Published in 2024

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Official Journal of
Green Life Medical College

Website: greenlife.edu.bd

ISSN No. 2663-2314

Bangladesh Medical & Dental Council (BM&DC) Recognized Journal

GREEN LIFE MEDICAL COLLEGE JOURNAL

Vol. 7, No. 2, July 2022

Published in 2024

Journal Committee

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ABOUT THE JOURNAL

Full Name of the Journal	:	Green Life Medical College Journal
Short Name	:	GMCJ
Nature of Publication	:	Bi-annual
Published From	:	Green Life Medical College
Accreditation	:	Recognized by Bangladesh Medical & Dental Council (BM&DC)
ISSN	:	2663-2314
Address	:	31 and 32, Bir Uttam K.M. Shafiullah Sarak, Dhanmondi, Dhaka-1205 Phone: 9612345-50 Ext. 1252

AIMS & SCOPE:

The Green Life Medical College Journal is an english language scientific papers dealing with clinical medicine, basic sciences, epidemiology, diagnostic, therapeutics, public helath and healthcare in relation to concerned specialities. It is an official journal of Green Life Medical College and is published bi-annually.

This Joural is recognized by Bangladesh Medical & Dental Council (BM&DC).

The Green Life Medical College Journal of Bangladesh intends to publish the highest quality material on all aspects of medical science. It includes articles related to original research findings, technical evaluations and reviews. In addition, it provides readers opinion regarding the articles published in the journal.

INSTRUCTION TO AUTHORS:

Papers:

The Green Life Medical College Journal (published bi-annually) accepts contributions from all branches of medical science which include original articles, review articles, case reports, and letter to the Editor.

The articles submitted are accepted on the condition that they must not have been published in whole or in part in any other journal and are subject to editorial revision. The editor preserves the right to make literary or other alterations which do not affect the substance of the contribution. It is a condition of acceptance that the copyright becomes vested in the journal and permission to republish must be obtained from the publisher. Authors must conform to the uniform requirements for manuscripts submitted to biomedical journals (JAMA 1997; 277: 927-34).

Legal considerations:

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Preparation of manuscript:

Each manuscript should indicate the title of the paper, and the name(s) and full address(es) of the author(s). Contributors should retain a copy in order to check proofs and in case of loss. Two hard copies of each manuscript (double-spaced) should be submitted. If a manuscript is accepted for publication in the GMCJ, the editor responsible for it and may request a soft copy (a CD or via internet) for the revision. Each paper will be reviewed for possible publication. The Editor may wish to see the raw data (electronic form) if necessary.

In preparing the manuscript, use double spacing throughout, including title, abstract, text, acknowledgement, references, table and legends for illustrations and font type and size 'Times New Roman 12'. Begin each of the following sections on a separate paper. Number pages consecutively.

The standard layout of a manuscript:

- Title page
- Abstract, including Keywords
- Introduction
- Methods
- Results
- Discussion
- Acknowledgements
- Funding
- List of references
- Tables & Figures
- Illustrations

The pages should be numbered in the bottom right-hand corner and the title page being page one, etc. Start each section on a separate page.

Title page:

A separate page which includes the title of the paper. Titles should be as short and concise as possible (containing not more than 50 characters). Titles should provide a

reasonable indication of the contents of the paper. This is important as some search engines use the title for searches. Titles in the form of a question, such as 'Is drinking frequent coffee a cause of pancreatic carcinoma?" may be acceptable.

The title page should include the name(s) and address(es) of all author(s). Details of the authors' qualifications and post (e.g., professor, consultant) are also required. An author's present address, if it differs from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers ([1, 2, 3] etc.) If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

Abstract:

The 'Abstract' will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Introduction/Background; Methods; Results; and Conclusions) for all Clinical Investigations and Laboratory Investigations. For Reviews and Case Reports, the abstract should not be structured. The Abstract should give a succinct account of the study or contents within 350 words. The results section should contain data. It is important that the results and conclusion given in the 'Abstract' are the same as in the whole article. References are not included in this section.

Keywords:

Three to six keywords should be included on the summary page under the heading Keywords. They should appear in alphabetical order and must be written in United Kingdom English spelling.

Introduction:

The recommended structures for this section are:

- Background to the study/Introduction
- What is known/unknown about it
- What research question / hypothesis you are interested in
- What objective(s) you are going to address

The introduction to a paper should not require more than about 300 words and have a maximum of 1.5 pages double-spaced. The introduction should give a concise account of the background of the problem and the object of the investigation. It should state what is known of the problem to be studied at the time the study was started. Previous work should be quoted here but only if it has direct bearing on the present problem. The final paragraph should clearly state the primary and, if applicable, secondary aims of the study.

Methods:

The title of this section should be 'Methods' - neither 'Materials and methods' nor Patients and methods'. The Methods section should give a clear but concise description of the process of the study. Subjects covered in this section should include:

- Ethics approval/license
- Patient/population
- Inclusion/exclusion criteria
- Conduct of the study
- Data handling
- Statistics
- Cognitive Task Analysis (CTA)

Ethical clearance:

Regardless of the country of origin, all clinical investigators describing human research must abide by the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association. This document can be found at: http://ohsr.od.nih.gov/guidelines/helsinki.html. Investigators are encouraged to read and follow the Declaration of Helsinki. Clinical studies that do not meet the Declaration of Helsinki criteria will be denied peer review. If any published research is subsequently found to be non-compliant to Declaration of Helsinki, it will be withdrawn or retracted. On the basis of the Declaration of Helsinki, the Green Life Medical Journal requires that all manuscripts reporting clinical research state in the first paragraph of the 'Methods' section that:

- The study was approved by the appropriate Ethical Authority or Committee.
- Written informed consent was obtained from all subjects, a legal surrogate, or the parents or legal guardians for minor subjects.

Human subjects should not be identifiable. Do not disclose patients' names, initials, hospital numbers, dates of birth or other protected healthcare information. If photographs of persons are to be used, either take permission from the person concerned or make the picture unidentifiable. Each figure should have a label pasted on its back indicating name of the author at the top of the figure. Keep copies of ethics approval and written informed consents. In unusual

circumstances the editors may request blinded copies of these documents to address questions about ethics approval and study conduct.

The methods must be described in sufficient detail to allow the investigation to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be stated in detail, but appropriate reference to the original should be cited. However, any modification of previously published methods should be described and reference given. Where the programme of research is complex such as might occur in a neurological study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation. In longitudinal studies (case-control and cohort) exposure and outcome should be defined in measurable terms. Any variables, used in the study, which do not have universal definition should be operationalised (described in such terms so that it lends itself to uniform measurement). Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Keyence VHX-6000 digital microscope). The manufacturer's town and country must be provided, in the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

Single case reports:
Single case reports of outstanding interest or clinical relevance, short technical notes and brief investigative studies are welcomed. However, length must not exceed 1500 words including an unstructured abstract of less than 200 words. The number of figures/tables must not be more than 4 and references more than 25.

Animal studies:
In the case of animal studies, it is the responsibility of the author to satisfy the board that no unnecessary suffering has been inflicted on the animal concerned. Therefore, studies that involve the use of animals must clearly indicate that ethical approval was obtained and state the Home Office License number or local equivalent.

Drugs:
When a drug is first mentioned, it should be given by the international non-proprietary name, followed by the chemical formula in parentheses if the structure is not-well known, and, if relevant, by the proprietary name with an initial capital letter. Dose and duration of the drug should be mentioned in sufficient details. If the drug is already in use (licensed by appropriate licensing authority), generic name of the drugs should preferably be used followed by proprietary name in brackets.

Present the result in sequence in the text, table and figures. Do not repeat all the data in the tables and/or figures in the text. Summarize the salient points. Mention the statistics used for statistical analysis as footnote under the tables or figures. Figures should be professionally drawn. Illustration can be photographed (Black and White glossy prints) and numbered.

Discussion:
Do not repeat the data in detail, already given in the results. Give implications of the findings, their strengths and limitations in comparison to other relevant studies. Avoid un-qualified statements and conclusions which are not supported by the data. Avoid claiming priority.

Conclusion:
Comments on the observation of the study and the conclusion derived from it. New hypothesis or implications of the study may be labeled as recommendations.

References:
References should be written in Vancouver style, numbered with arabic numerals in the order they appear in the text. The reference list should include all information, except for references with more than six authors, in which case give the first six names followed by et al.

Examples of correct forms of references:
Dorababu M, Prabha T, Priyambada S, Agrawal VK, Aryaa NC, Goel RK. Effect of Azadirachta indica on gastric ulceration and healing of bacopa monnierang in experimental NIDDM rats. *Indian J Exp. Biol 2004; 42: 389-397.*

Chapter in a book:
Hull CJ. Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. Acute Pain. London: Butterworths. 1985,1 55-79.

All manuscripts for publication should be addressed to the executive editor.

LETTER TO THE EDITOR:
Any reader can provide feedback regarding published articles by writing letter to editor. The reader can also share any opinion in relation to medical science.

Prof. Dr. ABM Bayezid Hossain
Editor-in-chief
Green Life Medical College Journal and
Principal
Green Life Medical College

ABOUT THE COLLEGE

INTRODUCTION

In 2005, about fifty distinguished physicians of the country started a hospital to give specialized care in the private sector. They named it Green Life Hospital and it turned out to be a great success. So in 2009, they decided to establish a medical college which will be a non-government, non-profit, self-financing project and will serve the humanity.

This College came into existence in 2009. The college commences its activities with the enrollment of 51 students in the 1st batch in 2010. Since inception, the college has undergone tremendous development and became a splendid centre for learning and development. At present we are enrolling 110 students each year. Among them, numbers of seats are reserved for overseas students.

We continue to evaluate and improve our programme to ensure the best medical education for the students. Our educational strategy is to create a conducive learning environment and to steer our students to acquire adequate knowledge, skills and temperament to practice medicine and be a competent health care professional group.

Green Life Medical College (GMC) is approved by the Ministry of Health and Family Welfare (MOHFW), Government of Bangladesh and Bangladesh Medical and Dental Council (BMDC) and affiliated to the University of Dhaka.

AIMS AND OBJECTIVES OF THE COLLEGE

Aims:

To create a diverse and vibrant graduate scholars in medical discipline and to create highly competent and committed physicians for the country.

Objectives:

- To provide an appropriate learning environment where medical students can acquire a sound theoretical knowledge and practical skills with empathetic attitude to the people.
- To carry out research in medical sciences to scale up the standard of medical education in the country.

LOCATION

The campus is located at 31 and 32, Bir Uttom K. M. Shafiullah Sarak (Green Road), Dhanmondi, Dhaka. The location is at the heart of the mega city Dhaka and is facilitated with very good communication networks.

The Medical College and the Hospital complexes have been raised in a multistoried fully air-conditioned building with an arrangement of approximately 500 patients. The building is equipped with state-of-the-art infrastructure, excellent with an out-patient department and adequate in-patient facilities.

EDITORIAL

Biochemical Advances: Changing the Paradigms of Health and Illness

Recent years have seen incredible advancements in biochemistry that go beyond the confines of conventional research, having a significant impact on our comprehension of health and illness. The goal of this editorial is to examine the important developments in biochemistry that are changing the field of medicine.

These discoveries, which range from deciphering complex biochemical pathways to developing ground-breaking therapeutic approaches, have the potential to completely transform the healthcare industry. The most recent discoveries and advancements that have potential for the advancement of medical science are covered in this conversation. As the study of biochemistry continues to uncover the molecular foundations of life, it is at the forefront of scientific research. There has been a notable increase in innovative research in recent years that goes beyond clarifying cellular principles to have a direct impact on medical procedures. This editorial explores the latest developments in biochemistry and their significant effects on maintaining health and managing illness.[1]

Molecular Insights into Diseases

1. Precision Medicine: The field has entered a new age with the combination of genomics, proteomics, and metabolomics. Comprehending individual differences at the molecular level facilitates tailored treatments, maximizing therapeutic results and reducing side effects.[2]
2. Immuno-Oncology: The development of immuno-therapies has been spurred by biochemical research, transforming the treatment of cancer. Immuno-modulatory drugs, such immune checkpoint inhibitors, use the body's defenses against cancer by stimulating the immune system, giving patients with incurable diseases fresh hope.[3]

Therapeutic Innovations

1. Gene Editing Technologies: Targeted genetic alterations have become possible with the development of CRISPR-Cas9 and other gene-editing techniques. This has potential applications in treating hereditary disorders, fixing genetic flaws, and possibly delaying the beginning of some illnesses.
2. RNA therapies: With the advancement of RNA interference (RNAi) and antisense oligonucleotide technology, the field of RNA therapies has grown. These methods present fresh opportunities for the treatment of various illnesses, such as viral infections and neurological diseases.[4]

This recent biochemistry advancements serve as an excellent example of how science may change the world. These accomplishments, which range from understanding the molecular causes of illnesses to developing novel treatment approaches, are essential to the development of more accurate and individualized healthcare in the future. The cooperative efforts of scientists, physicians, and industry stakeholders promise a new era of healthcare where the lines between health and sickness blur, bringing hope for better outcomes and a healthier society as biochemistry continues to change.

Journal of Green Life Med. Col. 2022; 7(2): 45

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ORIGINAL ARTICLE

Efficacy of Hypertonic Saline Solution in Children with Bronchiolitis: A Double Blind Control Trial

KHAYER MA[1*], MALEK A[2*], AHMED A[3], ALI MM[4]

Abstract

Introduction: *Airway edema and mucus plugging obstruct flow in the small airways, leading to hyperinflation, atelectasis and wheezing in children with acute viral bronchiolitis. Nebulized hypertonic saline (3% NaCl) solution may reduce these pathological changes and decrease airway obstruction and there by improve bronchiolitis. The objective of this study was to assess the effects of nebulized hypertonic saline (3% NaCl) solution in children with acute viral bronchiolitis.*

Methods: *It was a randomized, double blind controlled trial. The study was conducted in the department of pediatrics, MAG Osmani Medical College Hospital, Sylhet from January 2009 to December 2009.Ninety hospitalized children (mean ± SD age, 11.1±12.3 months) with viral bronchiolitis received inhalation of 3% NaCl solution (group-I), and 91 children with viral bronchiolitis received inhalation of salbutamol solution with normal saline (group-II). This therapy was repeated three times every hospitalization day until discharge; and recording of clinical variables were taken two times daily for 3 days.*

Results: *There was improvement in both groups after inhalation of either hypertonic saline solution (Group-I) or salbutamol solution with normal saline (Group-II) on the first, second and third days after hospital admission. Head nodding and nasal flaring were reduced all the patient of both groups after second day of hospitalization and variables were not statistically significant (P> 0.05). Chest indrawing, wheeze, respiratory rate and SpO2 (%) also improved in both groups and it was statistically significant in-group –II (P<0.05) after 2 days but after 3 days of hospitalization it was not statistically significant (p>0.05). Duration of hospital stay was 3.61±1.51 days in group-I and 3.16±1.22 days in group-II and it was not statistically significant (p>0.05).*

Conclusions: *We concluded that children hospitalized with viral bronchiolitis, nebulized hypertonic saline (3%NaCl) solution and nebulized salbutamol solution with normal saline had the same efficacy. There were no significant adverse effects observed. Since hypertonic saline solution is cost effective than salbutamol solution and no significant adverse events observed, it can be used in children with acute bronchiolitis. Hypertonic saline (3% NaCl) solution nebulization is effective and safe in children with acute bronchiolitis.*

Keywords: *Hypertonic Saline Solution, Salbutamol solution, Bronchiolitis*

Journal of Green Life Med. Col. 2022; 7(2): 47-53

Introduction:

Bronchiolitis is the most common lower respiratory tract infection in infants, occurring in a seasonal pattern, with highest incidence in the winter in temperate climates, and in the rainy season in warmer countries. It often occurs in epidemics and mostly in children < 24 months, with a peak incidence in infants < 6 months. Globally the annual incidence in the first year of life is about 11 cases/100 children. It is a common reason for attendance and admission to hospital. It accounted for around 3% (1.9 million) of emergency department visits in children below two years of age between 1992 and 2000 in the USA. Virtually all children become infected with RSV within 2 years after birth,[1] with 1% requiring hospitalization.

The incidence of ARI cases in Bangladesh is gradually increasing since the year 2001. The last nine year-wise total no. of ARI / pneumonia cases were 5,77,152(1999), 6,83,412(2000), 20,55,916(2001), 25,94,580(2002), 24,27,331(2003), 18,37,727(2004), and 15,87,690(2005),

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Received: 02.07.2019 **Accepted:** 06.07.2023

19,04,559(2006) and approx. 24,00,000(2007).[2] Among the important respiratory disorders - cough and cold 48%, bronchiolitis 21%, pneumonia 11.5%, asthma 8.0%, rhinitis 2%, sore throat 2%, acute otitis media 2% and infantile wheeze 2%.[3] There was first report of outbreak of RSV bronchiolitis in Bangladesh in the winter period of 2001-2002.[4] Recurrent wheeze or asthma is long-term sequelae after an attack of RSV bronchiolitis.[5-8] Nearly two thirds of the cost related to annual RSV epidemics is attributable to hospitalization.[1,9] Therefore, therapies that reduce hospital days could potentially reduce health care expenditures.

Infectious agents associated with acute bronchiolitis includes – Respiratory syncytial virus (RSV) >50%, Para influenza viruses 25%, Adenovirus 5%, Rhinoviruses 5%, Influenza viruses 5% and Enteroviruses 2%. RSV is transmitted by direct inoculation of large droplets or by self-inoculation and incubation period is 2-8 days. The susceptibility of young infants and young children to bronchiolitis is partly as a result of immunological immaturity and smaller airways.

Pathophysiologically, bronchiolitis is an infection of the bronchiolar epithelium, with subsequent profound submucosal and adventitial edema, increased secretion of mucus, peribronchiolar mononuclear infiltration and epithelial cell necrosis. These changes obstruct flow in the small airways, leading to hyperinflation, atelectasis and wheezing.[1,10,11] The complete plugging of some airways and partial plugging of others may lead to localize atelectasis of some units of lung parenchyma and over distention of other units. This patchwork of over distention and under distention is a common finding on chest radiographs in infants with bronchiolitis. The imbalance of ventilation and perfusion results in hypoxemia that is generally relieved by the administration of oxygen.

The goals of care for hospitalized children with acute bronchiolitis is to ensure adequate fluid intake, to provide a suitable thermal environment in which oxygen consumption will be minimized, and to administer oxygen in order to maintain adequate gas exchange.[10] Antiviral therapy with aerosolized ribavirin and symptomatic therapy with bronchodilators and corticosteroids are the available treatment options for RSV infections. Unfortunately, they produce only a modest short-term improvement in respiratory outcome, or have no effect at all.[12]

Most available data do not support the use of corticosteroids in the treatment of acute RSV bronchiolitis. Intravenous hydrocortisone followed by oral prednisone[13], intramuscular or oral dexamethasone[14, 15], and oral prednisolone[16] have yielded little or no benefit, except possibly in a select subgroup of patients.

Hypertonic saline solution, by absorbing water from the submucosa, can theoretically reverse some of the submucosal and adventitial edema and decrease the thickness and dryness of the mucosal plaque inside the bronchiolar lumen. It has been shown to increase mucociliary transit time in various situations: in vitro, in normal subjects, in patients with cystic fibrosis, and in patients with Sinonasal diseases.[17-26] So simply hypertonic saline solution nebulizations may improve clinical sign and symptoms and there by decrease hospital stay.[21,27,28] Thus it may be cost effective.

The commonest practice in our country is to treat hospitalized babies with acute bronchiolitis by inhalation of salbutamol solution diluted with normal saline solution, which does not reduce hospital stay.[29] We hypothesized that simply hypertonic saline solution inhalations may improve acute viral bronchiolitis by reducing submucosal and adventitial edema osmotically and allow to treat the infections with better results reducing hospitalizations, getting the patient better quicker and reducing the use of hospital resources. So if only hypertonic saline solution nebulization can improve bronchiolitis, it will be cheaper way to treatment.

Methods:

It was a randomized double blind controlled trial and was conducted in the inpatient department of Paediatrics at Sylhet MAG Osmani Medical College Hospital during February 2009 to December 2009. All the admitted bronchiolitis patients were enrolled. Systematic random sampling were done and every second case were enrolled. Patient with chronic lung disease, associated illness i.e., heart failure etc. associated complications i.e., pneumonia, pneumothorax etc., Congenital airway disease i.e., laryngomalacia, tracheomalacia etc. were excluded from enrolling as study baby. After randomization, the code number recorded in the questionnaire; and after intervention, daily follow up and monitoring recorded on the questionnaire.

Hypertonic saline solution (x1) with hypertonic saline (x2) solution (0.05 ml/kg/dose) (total 3 ml) in nebulization group-1 was administered via compressor nebulizers 8 hourly. The same amounts of normal saline (x6) with salbutamol solution (x5) (0.05 ml/kg/dose) nebulization were given in the control group (group-II) in the same way. The standard treatments of acute bronchiolitis (humidified O2, correction of dehydration, fluid and nutrition, antibiotic) were given to both groups.

Sample size was calculated by statcalc module of EPI_logo soft ware of CDC, Altanta, WHO, where the following formula has been used:

$N=\{(Zá+Zß)^{2*} 2(Sd)\}/(Difference)^2$

Considering outcome variable: disappearance of chest indrawing

Mean duration in 4 days (96 hours)

Minimum expected difference = 8 hours

Considering 95% confidence internal and power 80%,

Cases required = 79 in each group

So, total cases required in two groups (3% NaCl soln. and salbutamol soln. with normal saline) = 79x2=158

Considering 10% cases to be non responsive and 5% absconded and DORB, total cases to be included into the study = 158+16+8=182

Informed consent were taken from parents or legal guardians. Beforehand ethical permission were taken from the ethical committee of Sylhet MAG Osmani Medical College and Hospital.

Results:

The age of the patient was ranging from 1-24 months with mean age of 11.1±12.3 in group-I and age ranging from 1-24 months with mean age of 9.3±6.1 in group-II. The mean age of the patient in both group-I&II were not vary statistically significant (p>0.05).

Table I

Age distribution of the patients

Age in month	Group I (n=90)		Group II (n=91)		P value
	n	%	n	%	
1- 11	68	75.6	65	71.4	
12 - 24	22	24.4	26	28.6	
Mean±SD	11.1	±12.3	9.3	±6.1	0.190^{NS}
Range (min-max)	(1.8	-74)	(1	-24)	

NS= not significant, P value reached from unpaired 't' test

Runny nose were present in 94.4% in group-I, 95.6% in group-II (p=0.719); in 100% of group-I and 97.8% in group-II (p=0.157); wheeze were present in 100% of group-I and 97.8% in group-II (p=0.157); fever in 73.3% of group-I and 81.3% in group-II (p=0.199); feeding difficulty in 32.2% of group-I and 16.5% in group-II (p=0.013). The difference between two groups in relation to clinical parameters did not vary statistically significant except feeding difficulty, which is statistically significant (p<0.05).

Table II

Distribution of patient according to clinical presentation

Clinical information	Group I (n=90)		Group II (n=91)		P value
	n	%	n	%	
Runny nose	85	94.4	87	95.6	0.719^{NS}
Cough	90	100	89	97.8	0.157^{NS}
Wheeze	90	100	89	97.8	0.157^{NS}
Fever	66	73.3	74	81.3	0.199^{NS}
Feeding difficulty	29	32.2	15	16.5	0.013^{S}

S= Significant, NS= not significant,
P value reached from chi square test

Nasal flaring were present in 15 (16.7%) patient in group-I and 10 (11%) patient in group-II; head nodding were present in 25 (27.8) patient in group-I and 21 (23.1%) patient in group-II; chest indrawing were present in 81 (90%) patient in group-I and 81 (89%) patient in group-II; cyanosis were present in 3 (3.3%) patient in group-I and 5 (5.5%) patient in group-II. Wheezes were present in 90 (100%) patient in group-I and 89 (97.8%) patient in group-II. The difference between the two groups in relation to physical findings during admission did not vary statistically significant (p>0.05).

Table III

Distribution of patient according to Physical findings during admission

	Group I (n=90)		Group II (n=91)		P value
	n	%	n	%	
Nasal Flaring	15	16.7	10	11.0	0.268^{NS}
Head nodding	25	27.8	21	23.1	0.467^{NS}
Chest indrawing	90	100	91	100	0.828^{NS}
Cyanosis	3	3.3	5	5.5	0.479^{NS}
Wheeze	90	100.0	89	97.8	0.251^{NS}

NS= not significant
P value reached from chi square test

Mean respiratory rate in group-I were 57/min. and 53.3/min. in group-II; mean heart rate in group-I were 140.3/min and group-II were 140.2/min. these parameters in two groups did not vary statistically significant (p>0.05).

Table IV

Distribution of patient according to respiratory rate and heart rate during hospitalization

	Group I (n=90) Mean ±SD	Group II (n=91) Mean ±SD	P value
Respiratory rate/min	57.8 ±11.3	53.3 ±11.4	0.09^{NS}
Range (min-max)	(36 -92)	(30 -96)	
Heart rate/min	140.3 ±17.3	140.2±19.2	0.948^{NS}
Range (min-max)	(96 -180)	(100 -180)	

NS= not significant

P value reached from unpaired 't' test

Seventy eight (86.7%) patient in group-I and 82 (90.1%) patient in group-II had vesicular with prolonged expiration and 100% patient of both group were bilateral creps and ronchi. Auscultatory findings in two groups did not vary statistically significant (p>0.05).

Table V

Distribution of patients according to auscultatory findings in lungs on admission

Breath Sound	Group I (n=90) n	%	Group II (n=91) n	%	P value
Vesicular					
Right	12	13.3	9	9.9	1.000^{NS}
Left	12	13.3	9	9.9	
Bronchial					
Right	0	0.0	0	0.0	-
Left	0	0.0	0	0.0	
Vesicular with prolong expiration					
Right	78	86.7	82	90.1	1.000^{NS}
Left	78	86.7	82	90.1	
Added Sound					
Ronchi					
Right	90	100.0	91	100.0	1.000^{NS}
Left	90	100.0	91	100.0	
Crepitation					
Right	90	100.0	91	100.0	1.000^{NS}
Left	90	100.0	91	100.0	

NS= not significant

P value reached from chi square test

SpO2 (%) on admission in group-I were 94.7?5.3 and group-II 93.9?7.6; between two groups oxygen saturation level did not vary statistically significant (p>0.05).

Table VI

Distribution of patient according to oxygen saturation level on admission

	Group I (n=90) Mean ±SD	Group II (n=91) Mean±SD	P value
SpO_2 (%)	94.7 ±5.3	93.9 ±7.6	0.508^{NS}
Range (min-max)	(64.0 -100)	(63.0-100)	

NS= not significant

P value reached from unpaired 't' test

Thirty three patient in group-I and 36 pateint in group-II required oxygen inhalation after hospitalization and the mean duration of oxygen inhalation were 18±10.3 hours in group-I and 16±12.1hours in group-II. The duration of oxygen inhalation in two groups were not statistically significant (p>0.05).

Table VII

Oxygen inhalation

	Group I (n=90) Mean±SD	Group II (n=91) Mean±SD	P value
Oxygen inhalation	33 36.7	36 39.6	0.688^{NS}
Duration time (hrs)			
Mean±SD	18 ±10.3	16 ±12.1	

NS= not significant

P value reached from chi square test

Mean duration (days) of hospital stay in group-I were 3.61±1.51 and in group-II were 3.16±1.22. The difference between days of hospitalization in 2 groups did not vary statistically significant (p>0.05).

Table VIII

Duration of hospital stay

	Group I (n=90) Mean±SD	Group II (n=91) Mean±SD	P value
Out come days	3.61 ±1.51	3.16 ±1.22	0.069^{NS}
Range (min-max)	(1 -7)	(1 -7)	

NS= not significant

P value reached from unpaired 't' test

Head nodding and nasal flaring were improved in 2 groups 100% after 48 hours; but there were no statistically significant variation (p> 0.05) of clinical improvement between 2 groups. Chest indrawing improved statistically significant after 28 hours of nebulization in group-II (p<0.05) and wheeze also improved most of the patients after 72 hours but it was significantly improved in group-I patient after 12 hours (p<0.0.5).

Table IX
Comparison of clinical improvement after 72 hours of admission

Follow up	Group I (n=90)		Group II (n=91)		P value
(Symptoms)	n	%	n	%	
Head nodding					
Day-1	25	27.8	21	23.1	
	20	22.2	16	17.6	0.516^{NS}
Day-2	14	15.6	12	13.2	0.519^{NS}
	13	14.4	10	11.0	0.440^{NS}
Day-3	0	0.0	0	0.0	-
	0	0.0	0	0.0	-
Nasal Flaring					
Day-1	15	16.7	10	11.0	
	9	10.0	5	5.5	0.466^{NS}
Day-2	0	0.0	0	0.0	-
	0	0.0	0	0.0	-
Day-3	0	0.0	0	0.0	-
Chest indrawing					
Day-1	90	100.0	91	100.0	
	52	57.8	53	58.2	0.949^{NS}
Day-2	20	22.2	27	29.7	0.198^{NS}
	13	14.4	16	17.6	0.688^{NS}
Day-3	13	14.4	11	12.1	0.036^{S}
	9	10.0	4	4.4	0.107^{NS}
Wheeze					
Day-1	90	100.0	91	100.0	
	72	80.0	81	89.0	0.036^{S}
Day-2	50	55.6	64	70.3	0.175^{NS}
	33	36.7	39	42.9	0.578^{NS}
Day-3	21	23.3	23	25.3	0.685^{NS}
	12	13.3	15	16.5	0.582^{NS}

Note: 0.864, 0.174, 0.608
S= significant, NS= not significant
P value reached from chi square test

All patient in group-I and Group-II had improved respiratory rate (breath/min.). Improvement was significant in group-II after 48 hours of nebulization (p<0.05). Oxygen saturation in both groups also improved and after 24 hours, the improvement was statistically significant in group-II (p<0.05). But after that, improvement of respiratory rate and oxygen saturation was not statistically significant.

Table X
Comparison between two groups by improvement of respiratory rate and SpO_2 (%)

	Group I (n=90) Mean ±SD	Group II (n=91) Mean±SD	P value
Respiratory rate/min			
Day-1	57.8±11.3	53.3±11.4	0.038^{NS}
	54.0±10.8	51.3±10.9	0.118^{NS}
Day-2	50.5±12.5	47.1±11.6	0.070^{NS}
	49.1±11.1	44.2±11.4	0.009^{S}
Day-3	49.2±12.8	41.7±10.0	0.001^{S}
	47.3±10.9	43.3±14.4	0.125^{NS}
SpO2 (%)			
Day-1	94.7±5.4	94.0±7.3	0.534^{NS}
	95.6±5.2	97.3±3.6	0.034^{S}
Day-2	95.6±10.3	97.3±3.8	0.206^{NS}
	98.2±2.4	98.4±2.7	0.739^{NS}
Day-3	97.5±3.9	97.1±8.1	0.774^{NS}
	98.9±1.8	98.9±2.2	0.999^{NS}

S= significant, NS= not significant
P value reached from unpaired 't' test

All patients of group-I and group-II had improved by the treatment, which did not vary statistically significant (p>0.05)

Table XI
Distribution of clinical outcome

	Group I (n=90)		Group II (n=91)		P value
	n	%	n	%	
Improved	90	100.0	91	100.0	1.000^{NS}
DORB	0	0.0	0	0.0	

NS=not significant
P value reached from chi square test.

Discussion:

The study included 182 bronchiolitis patient after fulfillment of inclusion criteria. Children were randomized in two groups by systemic random sampling and after randomization, in group-I were 91 and in group-II were also 91 patient. But in group-I, after first dose of inhalation one patient deteriorated and it was excluded from the study. After randomization, Group-I patient taken nebulization of hypertonic saline solution and group-II patient taken nebulization of salbutamol solution with normal saline and after nebulization, clinical variables were recoded two times daily for 3 days for each patient separately in a preformed questionnaire.

Bronchiolitis commonly affects children below 2 years of age and all children become infected with RSV within 2 years after birth, with 1% requiring hospitalization.[1] Males (68.9% in group-I and 68.1% in group-II) are more affected than female. Mean age of the patients in this study were 11.1 month (±12.3 SD) and 9.3 month (±6.1SD) in group-I and II respectively. The clinical presentation of the patient in this study were cough, respiratory distress, fast breathing, chest indrawing and wheeze which were almost similar that observed by Kabir et al.[29]

The length of hospital stay was defined an important outcome to measure the efficacy of nebulized hypertonic saline among inpatients with viral bronchiolitis. In our study, the mean duration of hospitalization in group-I and group-II were similar. The same result were found by Zhang L-2008.[31] The pooled results from this clinical trial demonstrated that the mean length of reduction in both groups were not statistically significant (table-VIII). Given the high prevalence of viral bronchiolitis in infants and the tremendous burden of this illness related to hospitalization, this may potentially have a positive economic impact since hypertonic saline solution is cheaper than salbutamol solution.

This study demonstrated a significantly better improvement in clinical variables like head nodding, nasal flaring (Table-IX) in both groups and the improvement in both groups were not statistically significant($p>0.05$). Improvement of chest indrawing and wheeze within 2 days were statistically significant ($p<0.05$) but after 72 hours the improvement were not statistically significant ($p>0.05$) (Table-IX). No significant differences were demonstrated for the preinhalation clinical variables.[12,17]

SpO2 measurement by pulse oxymeter was one of the most reliable way to detect hypoxia in this study. The mean time required SpO2 to become normal for both group was 12 hours by the aid of oxygen inhalation and nebulization (Table-VI) and it was statistically significant ($p<0.05$). But after 3 days of hospitalization, the improvement in both were not statistically significant ($p>0.05$).

The beneficial effect of any drug should be weighed against its side effects. The potential side effects, principally acute bronchospasm, remain a concern with nebulized hypertonic saline. This review included 90 children receiving 3% saline in repeated doses and no significant adverse events were reported. Similar observation were found by Wark and MC Donald [18] and others [19-24] who found no reports of bronchospasm in 143 reviewed patients with relatively severe cystic fibrosis treated with hypertonic saline solution inhalations.

The inhalation therapy was administrated via compressor nebulizers in all the patient. Theoretically, there are some differences in the physical properties of aerosols produced by compressor nebulizers and ultrasonic nebulizers, which may affect their therapeutical efficacies. On the one hand, ultrasonic nebulizers induce sputum more efficiently than compressor nebulizers. On the other hand, compressor nebulizers generate aerosols with smaller aerodynamic mass median diameter which may more easily reach smaller bronchi and bronchioles[31]. This review could not provide direct evidence regarding the impact of the physical properties of aerosols generated by different types of nebulizers, on the efficacy of inhaled hypertonic saline in infants with viral bonchiolitis. However, at least one trial (Tal-2006) demonstrated that both compressor nebulizers and ultrasonic nebulizers are an efficient method of delivery of hypertonic saline in these patients.

The delivery interval of nebulization in this study was 8 hours. The delivery interval of nebulized hypertonic saline was eight hours in different trials [32,33] but more frequent deliveries were administrated in one trial.[34] No significant difference was observed between the studies, regarding effect sizes of treatment with 3% saline inhalation delivered at different intervals, on the reduction of length of hospital stay.

Conclusion:

We concluded that children hospitalized with viral bronchiolitis, nebulized hypertonic saline (3%NaCl) solution and nebulized salbutamol solution with normal saline had the same efficacy. Nebulized hypertonic saline solution had improved the symptoms and sign and reduced the duration of hospital stay. There were no significant adverse affects observed. Since hypertonic saline solution is cost effective than salbutamol solution and no significant adverse events observed, it can be used in children with acute bronchiolitis. Hypertonic saline (3% NaCl) solution nebulization is effective and safe in children with acute bronchiolitis.

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ORIGINAL ARTICLE

Evaluation of the Result of Selected Unstable Intertrochanteric Fracture Treated by Trochanter Stabilizing Plate (TSP)

ASHRAF Z[1], HAQ Z[2]

Abstract

Introduction: *Treatment of intertrochanteric fractures continue to be a challenge for Orthopaedic surgeons. A sliding screw device, has many advantages, but its use in unstable trochanteric fractures has been reportedly associated with collapse and medialization of femoral shaft. What has not received adequate attention is the trochanteric stabilizing plate (TSP), an add-on plate that extends proximally from the side-plate and provides a lateral buttress to the greater trochanterer. The purpose of this study was to evaluate the result of selected unstable intertrochanteric fracture of AO type of 31-A2.2, 2.3 and 3.3 treated by TSP.*

Methods: *This was a prospective observational study, carried out in National institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Dhaka from July 2014 to June 2016. After fulfilling inclusion and exclusion criteria a total of 20 cases treated with TSP superimposed on the regular DHS analysed.*

Results: *Out of 20 cases, 13 were male and 7 were female. Mean age 62.05 years (SD 12.59). Sedentary working job were the prominent occupation. Left side was involved in 55% cases. Maximum of 45% cases had ASA stage II. Abbreviated mental test score mean was 9.55. Mean interval between injury & operation was 9.1 days. Mean operation duration was 101.75 minutes. Lateralization of the greater trochanter and lag screw cut-out was successfully prevented in all fractures. Average lag screw sliding was 5.25 mm. All fractures had healed within 17 weeks. More than 10° varus deformity observed in 2 cases, but functional outcome was fair. One patient had persistent hip pain needed re-operation, followed by full gain of function. One patient had superficial wound infection, which was improved conservatively. Two patients died of unrelated to operation after radiological union. Hip functional results were satisfactory in 85% of patients and unsatisfactory in 15% according to the Salvati-Wilson score.*

Conclusion: *In selected unstable intertrochanteric fractures with small or missing lateral cortical buttress, the addition of a TSP to the DHS effectively supports the unstable greater trochanter fragment and can prevent lateralization, screw cut-out and limb shortening and can improve the outcome of surgery.*

Keywords: *Unstable intertrochanteric fracture, Trochanter stabilizing plate, Dynamic Hip Screw*

Journal of Green Life Med. Col. 2022; 7(2): 54-60

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Received: 25.04.2024 **Accepted:** 06.07.2024

Introduction:

Intertrochanteric fracture (ITF) which is a common fracture, has higher union rates, but functional outcomes is not satisfactory without surgery in adults.[1-4] Operative treatments of these fractures are challenging for all Orthopaedic surgeons. There are considerable varieties of implants employed to achieve pre-fracture functional status of patients as meaningful level as possible. This diversity of fixation devices available for treatment of ITF

demonstrate difficulties encountered in the actual treatment.[5]

Two most widely used type of fixation of ITF are intramedullary nailing and screw with plate fixation. Nails have advantage of preventing excessive sliding and medialization of shaft, lower implant failure rate, makes no dissection at fracture site.[6] However, they usually cost more, associated with iatrogenic abductor injury, complicated with femoral shaft fractures below the implant and the technique is more difficult than DHS.[7,8]

On the other hand, Dynamic Hip Screw (DHS), which is a sliding screw with side plate, became standard fixation device for most of the ITF. This system has advantages such as controlled telescoping & impaction and short operation time. Failure rates as low as 5% have been reported.[9,10] But unstable intertrochanteric fractures lack the posteromedial buttress, lateral buttress, or both. Therefore, after stabilization with DHS, these fractures have tendency to have significant medial displacement of the shaft with lateral dislocation of greater trochanter fragment, due to excessive sliding of screw within the barrel, and a higher incidence of screw cut-out, and failure rates of 5-12%.[5,9,11]

To solve this problem the AO introduced the trochanteric stabilization plate (TSP).[7] This TSP which is a modular extension of DHS that is mounted on the lateral femoral wall to stabilize greater trochanter. showed similar biomechanical and clinical stability comparable to nailing, while retaining advantages of DHS. Encouraging results have been reported in few small series.[1,9] The purpose of this study was to evaluate the result of selected unstable intertrochanteric fracture of AO type of 31-A2.2, 2.3 and 3.3 treated by Trochanter Stabilizing Plate (TSP).

Methods:

This was a prospective observational study, carried out in National institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Dhaka from July 2014 to June 2016. Patient who got admitted with radiologically proven cases of intertrochanteric fracture that meet the eligibility criteria were taken into study population. Inclusion criteria were Unstable trochanteric fracture AO type 31-A2.2, 2.3 and 3.3., age 18 years and above, all gender, close fracture and fracture less than 3 weeks old. Exclusion criteria were age below 18 years, history of previous surgery in proximal femur, AO type 31-A1, A3-3.1 & 3.2 fracture, open fracture, sign of infection, unstable medical illness that increase risk of morbidity or mortality and dementia.

A stable fracture has been defined as that has no post-fixation displacement. And an unstable fracture has been defined as fracture which has tending to collapse with axial loading after appropriate reduction and fixation.[12] AO type 31-A2.2 & 31-A2.3 and 31-A3.3– these fractures lack posteromedial buttress, lateral buttress, or both.[9] The lag screw sliding distance defined as radiological difference between the lag screw length on anteroposterior (A-P) view taken immediately after operation and 6 months after the operation.[1] Radiological union of fracture defined when fracture line could barely be visible because of callus and sclerosis in plain x-ray and clinically when there is no tenderness at fracture site.[13] American Society of Anesthesiology (ASA) Score used to determine physical status before surgery.[14] Abbreviated mental test score was used to exclude patient with any cognitive impairment (e.g. Dementia).[15]

Surgical technique

All of our patients were operated under spinal anesthesia. Fracture table was used and patients were positioned supine. The standard lateral approach was applied to reach the proximal femur. Guidewire placement was directed below the center of the femoral head in the A-P view and in the center or slightly posterior on lateral view. After Triple reaming was done, appropriate size lag screw was inserted. We used 4-hole side plate, only 2nd and 4th hole of side plate used to hold the plate with femur by 2 cortical screws. When necessary, contouring the proximal end of the TSP done to fit the mass of the greater trochanter. Positioning done of the TSP over the DHS plate in such a way that it is securely seated and that the screw holes line up. Then TSP fixed using 2 cortical screws in remaining 2 holes, with washer if needed. Then compression screw was inserted. Whole process done under fluoroscopic guidance. Skin closure was done in layers.[1,16]

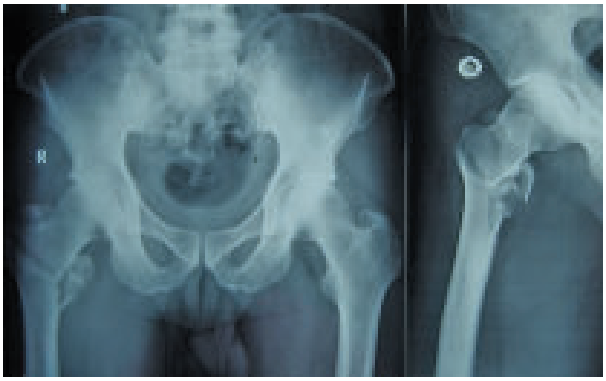

Figure 1: *Pre-operative x-ray of a 60 years old male.*

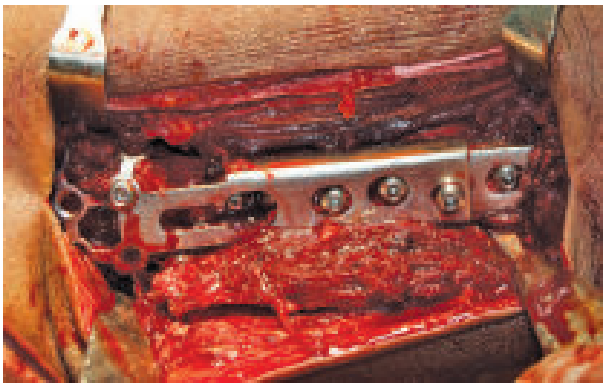

Figure 2: *DHS-TSP applied.*

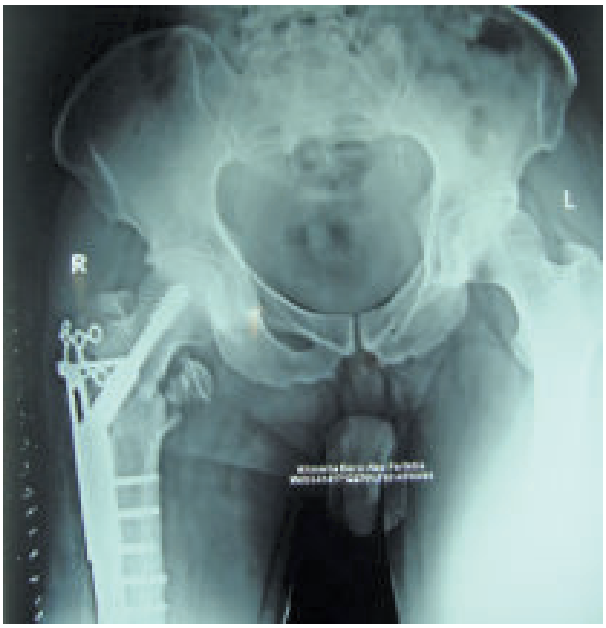

Figure 3: *Post Operative X-ray.*

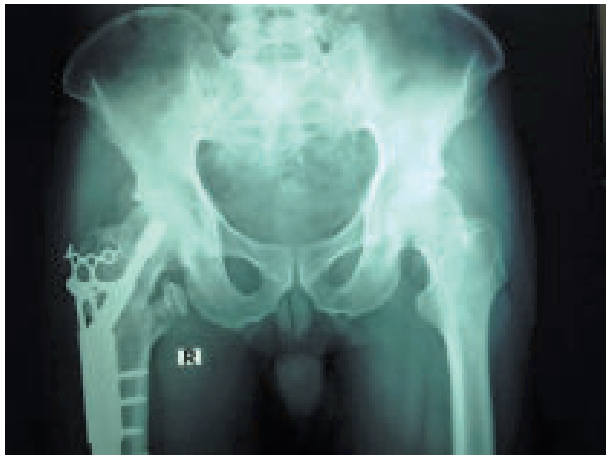

Figure 4: *Follow-up at 12th weeks.*

On 1st POD, patient advised for to sit on bed, breathing exercise and static quadriceps exercise. Drain off done after 24 to 48 hours. Then knee bending exercise begun. Stitch off done on 14th postoperative day. Non weight bearing walking by crutch advised. After 12 weeks – If radiological union occurred, then full weight bearing permitted. Follow up done at week 4th, 12th and 24th week. The cases evaluated both clinically and radiologically.

Parker mobility score used to assess pre-fracture and last follow up mobility level.[15] Salvati & Wilson Hip Score used to assess Hip function[17] Data were collected by interview, observation and clinical examination and investigations. Data were processed and analysed using IBM SPSS (version 20).

Results:

A total of 22 patients, who fulfilled the inclusion & exclusion criteria were enrolled in this study. Two patients were lost during follow-up. So, data analysis was done on 20 patients. Age of patients range from 30 to 85 with mean 62.05 and SD 12.589. Highest numbers of patients are in equal to or above 60 years age group. Of them 13 (65%) were male and 7 (35%) were female. Among them 6(30%) was house wife, businessman 5(25%), service 4(20.0%), farmer 2(10%) and labor 3(15%).

Among cause of injury, Low velocity injury (e.g., fall on ground) is the leading cause with 11 cases (55%), followed by high velocity injury (e.g., RTA) with 9 cases (45%). Interestingly among 7 female patients, 6(86%) had history of fall and only 1(14%) had history of RTA. Among fracture type, AO 31-A2.2 is the leading type with 9 cases (45%), followed by 31-A2.3 with 8 cases (40.0%) and lastly 31-A3.3 with 3 cases (15%). Fractures of the left side (11, 55%) were more common than the right (9, 45%).

ASA Score (Bhattacharya & Wray, 2004; American Society of Anesthesiologists, 2015) distribution shows 8 patients (40%) had ASA score stage I, 9 patients (45%) had stage II and 3 patients (15%) had stage III. Of these 3 patients 2 had uncontrolled DM and 1 had uncontrolled hypertension. All these 3 comorbid conditions were controlled before going for operation. Almost all the patients had good Abbreviated mental test score with mean 9.55 with SD 0.76. None of the patients had any cognitive impairment.

Time interval between injury and operation was from 5 days to 15 days, mean 9.10 with SD 3.31. Eleven cases (55%) within 7 to 13 days of initial injury, where 7 cases (35%) less than 7 days and only 2 cases (10%) after 14 days of injury. Operation duration were from 80 minutes to 130 minutes, mean 101.75 and SD 14.63. Hospital stays were from 8 days to 21 days, mean 13.30 with SD 3.57.

None of the 20 cases had any immediate post-operative complications. One patient had superficial wound infection, which was healed by conservative management. There was

Table-I

Range of motion at different follow-up.

Movement	2nd follow-up	3rd follow-up	p – value
Flexion	104.25 ± 15.92	127.75 ± 13.23	< 0.0005
Internal rotation	30.50 ± 7.28	38.50 ± 6.51	
External rotation	27.75 ± 7.16	36.25 ± 7.41	
Abduction	26.50 ± 5.16	35.75 ± 6.54	
Adduction	21.50 ± 5.64	27.25 ± 5.96	
Knee Flexion	111.75 ± 16.082	130.25 ± 14.01	

*Paired T-test was employed to analyze the data.

Table-II

Salvati & Wilson Hip function evaluation result. (Salvati & Wilson, 1973)

Result	Number of patients	Percentage		Mean ± SD
Excellent	8	40	Satisfactory	32.47 ± 6.42
Good	9	45	85%	
Fair	3	15	Unsatisfactory	
Poor	0	0	15%	

no lateralization of greater trochanter, lag screw cut-out, implant failure, non-union and significant limb shortening (≥1cm) at final follow-up. One patient showed positive Trendelenburg sign who needed reoperation after radiological union, due to persistent pain caused by impingement of proximal part of TSP. After reoperation patient regained abductor muscle function. One patient of 31-A2.3 fracture type and another one of 31-A3.3 fracture type had more than 10° varus deformity. Two patients with ASA stage III died unrelated to operation, after radiological union. All patients had a minimum of 6 months follow-up (range 6 months to 11 months), mean 7.45 with SD 2.40.

The different movement of hip like flexion, rotation, abduction and adduction were evaluated at 12 and 24 weeks which are shown in table I.

All fracture united within 17 weeks, with range of 12 to 18 weeks, mean 13.65 and SD 1.76. Highest union observed between 12 to 14 weeks. Fifteen (75%) patients had identical Parker mobility score in pre-fracture & at last follow-up. Five (25%) had decreased mobility score, of them 3 patients had only 1 point, one had 2 point and another one had 3 points difference in pre-fracture & last follow-up. There were average 5.25 mm sliding of lag screw with SD 3.18. Range from 1 mm to 10 mm.

Table II shows Salvati & Wilson Hip function evaluation result. No cases had poor result. Mean score 32.47 with SD 6.42. Satisfactory result was 85% and unsatisfactory 15%.

Discussion:

In the present study, selected unstable intertrochanteric fracture of AO type 31-A2.2, A2.3 and A3.3 was tested with a modular TSP in addition to DHS. The mean age of 62.05 years in our study, was significantly lower in other studies, such as Madsen et al. (1998) 78.9 years in DHS/TSP group, Cho et al. (2011) 76 years, Babst et al. (1998) 79.7 years.[9,11,13] This lower mean age can be due to that in developing countries, the average age is lower than developed countries.[18]

In this study, the highest incidence was in older age group with 60% cases, because in this group sedentary work more predominate and is more affected by osteoporosis and tendency to fall.[19] They showed low velocity injury the leading cause, which agrees with other studies.[5,9] High velocity injuries like road traffic accident were the cause of injury in rest of the cases in this series, as younger age group are relatively mobile and thus more susceptible to RTA.[20]

In our study male was the predominantly effected with ratio of 13:7. This differ with finding of Cho et al. (2011) with male female ratio of 8:22, Madsen et al. (1998) 13:72 and Gupta et al. (2010) 17:20.[5,11,13] This can be justified with study by Parker et. al. (2003) which stated in developed countries hip fracture is more common in female, but in developing country greater proportion of male are affected.[18]

In current study we found AO 31-A2.3 fracture type more common, left ITF more fractured, ASA stage II predominant. These findings are in consistence with other studies.[1,9,11] All the fractures in Babst el al. (1998) study fixed within 1 to 2 days of injury. In current study range of time interval between injury and operation was from 5 days to 14 days (mean 7.10). This was due to lack of proper logistic support in 3rd world country like Bangladesh.

The average operation time observed in study by Babst el al. (1998) was 119 minutes (range 50 to 240 minutes).[9] Sliding hip screw systems such as the DHS have become the standard type of implant for the fixation of stable ITF during the past decade. Thus, most surgeons are familiar with this technique. The superposition of the TSP is technically simple once the DHS is applied. For surgeons familiar with the DHS, the learning curve seems minimal, that is brings better outcome since it reduces operative time and operative complications.[1,5] Surgeons in current study were familiar with the DHS, the additional surgical time for adding modular TSP over DHS was only needed. That's why this study mean operation time was 101.75 minutes which is lower than former study.

Hip fracture is associated with considerable mortality during the first year after fracture, studies suggested a range of 8.4% to 36%.[21] Russell (2015) mentioned that Bentler et al. reported on Medicare data from the United States during 1993 to 2005 and stated that mortality rate of intertrochanteric fracture at 6 months is 19%. In present study, there was 2 death (10%), which is within that range and lower than other studies.[9,11] Mean mobility score in study of Cho et al. (2011) in pre-fracture state was 7.2 (SD 4.6) and at last follow-up 6.2 (SD 3.5) with difference of 1 point. In the present study, that difference was less than half point. These figures show better result, probably due to that relatively younger age group of study population.

Most studies have reported some incidence of complications in their series. Madsen et al. (1998) reported low infection rate of 2.4% in their DHS/TSP group compared with Gamma group with 10% and Compression Hip Screw group with 8.5%. And Babst et al. (1998) found that 2 cases (5%) in their study had infections. In current study, there was only one case (5%) of superficial wound infection, which did not seem to prolong the patient's hospital stay or the rate of fracture healing. The cause of low infection can be due to general increased awareness of the infection problem in these patients, increase of general hygiene and a somewhat more aggressive approach to the diagnosis and treatment infections.

There were no cases of non-union in current study. Same result also found in Cho et al. (2011). Madsen et al. (1998) found in their comparative study varus mal-union of more than 10° in 2.4% cases of DHS/TSP group, but 12% cases in Gamma Nail group and 14% cases in Compression Hip Screw(CHS) group. In present study we found 10% patients had varus mal-union of greater than 10°. This is more than DHS-TSP group of previous study, but below Gamma Nail & CHS group. The mal-alignment was probably caused by loss of fracture reduction during operation and should have been avoided by adequate reduction. Radiological union was observed in all cases at an average of 13.56 weeks in study by Gupta et al. (2010). Our study shows very similar result (mean 13.65).

In a recent study it has been found that more patients had reoperations because of fracture around the implant and local pain from the implant in the IM nail group than Siding Hip Screw group (7.1% vs. 4.5%).[22] In another study 5 patients (6%) out of 85 of DHS/TSP group needed reoperation.[11] In the current study only 1 patient (5%) had a reoperation after radiological union due to persistent pain in the hip region caused by impingement of the proximal part of the TSP, which within the range of former studies. After re-operation the patient gained pre-fracture mobility status completely.

Babst et al. (1998) stated that Müller-Färber et al. found an association between the extent of screw sliding and postoperative mobility, which stated a screw sliding below 6.7 millimeters did not affect the level of mobility. The mean sliding in our study has an average of 5.25 mm, which is significantly lower than other studies in unstable ITF treated with DHS.[7,9] No significant limb length discrepancy was observed in present study. which compares favorably to the reports by Gupta et al. (2010). This outcome can only be possible if stability of these fractures is achieved by buttressing the lateral wall. Our findings reinforce the results of Babst et al. (1998), who also reported significant reduction in excessive collapse and subsequently reduced limb length discrepancy by using a TSP in combination with DHS. Madsen et al. (1998) compared the results in 170 patients in whom an unstable intertrochanteric hip fracture had been treated with a Gamma nail, a compression hip screw, and DHS-TSP. They found both DHS-TSP and Gamma nail group prevented lateral displacement of greater trochanter. This proves effectiveness of DHS-TSP equal to intramedullary devices in case of prevention of lateralization of the greater trochanter.

McGrory et al. (1995) stated excessive collapse at the fracture side will alter lever arm and cause abductor muscle weakness, which results positive Trendelenburg sign.[23] Prevention of limb shortening could be an important contribution for improving functional outcome. Also, intramedullary device has iatrogenic abductor injury, which may affect the functional outcome of hip.[6] In the present study, results of assessment for hip abductor function at final follow-up were significantly better, and this is supportive of the view that the DHS in combination with TSP is likely to ensure a better abductor function.

Statistically we found improvement of range of motion from 2nd follow-up to 3rd follow-up. We used Salvati & Wilson hip functional scores to compare our result with other studies, as significant them used this scoring system. The earliest study of TSP-DHS was by Babst et al. (1998), they applied TSPs in 46 unstable ITFs. They found Salvati & Wilson hip functional scores of 51% excellent, 36% good, 13% cases fair and none of the cases had poor result, with total satisfactory result was 87%. Where Gupta et al. found 74% satisfactory result. The clinical result in a comparative study found satisfactory in 69% in Gamma group and 91% in TSP-DHS group, which indicate better result in TSP group than Gamma group.[11] In out study we found satisfactory 85% result which is close to Babst et al (1998) study. This study therefore does indicate that addition of a TSP over DHS is likely to improve the outcome of surgery in these selected unstable intertrochanteric fracture types. In unstable intertrochanteric fractures owing to posterior, medial and lateral comminution, the collapse at the fracture site that occurs with sliding hip screw fixation alone. TSP seems to act as a buttress plate against the greater trochanter and prevent significantly the incidence of lateralization of the greater trochanter. Also, TSP allows the sliding screw to slide freely, thereby allowing the controlled fracture impaction following weight bearing, which is importance for healing of these difficult fractures, while retaining the basic philosophy of the sliding screw plate systems. These factors resulted in better hip abductor function and final Salvati-Wilson functional score with restoration of mobility.

This study has several limitations. First, it had small sample size. Second, the follow-up duration was relatively short. Thus, the result may have been pre-mature. Lastly, the operations were not performed by a single surgeon. The operative skills of the surgeons may have varied and this could have affected the treatment outcome. However, all the procedures were performed in expert hands. Study with larger sample size, long follow-up and operations performed with single surgeon may overcome the limitations.

Conclusion:

The current study indicates the combination of TSP and DHS is a useful solution to stabilize difficult unstable AO type 31-A2.2, 2.3 and 3.3 intertrochanteric fractures. It creates a biomechanically stable construction allowing lateral buttressing which prevents lateralization of greater trochanter and thus restricts medialization of femoral shaft. This modular addition to the DHS offers a sound solution to the internal fixation of selected unstable trochanteric fractures.

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Vol.-7, No.-2, July 2022 green life journal

ORIGINAL ARTICLE

Prescribing Patterns of Dipeptidyl Peptidase-4 (DPP-4) Inhibitors in Type-2 Diabetes Mellitus: A Cross-sectional Observational Study

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Abstract

Introduction: *Globally, an estimated 540 million diabetic people are considered to be at greater risk of death and disability. In Bangladesh, currently 13.2 million individuals are diagnosed with diabetes mellitus (DM) which is projected to be 22.3 million by 2045. Hence, various therapeutic approaches have evolved to combat such disease burden, and dipeptidyl peptidase-4 inhibitors (DPP4i) group is one of them. DPP4i are incretin-based therapy which also possess weight neutral effect and no tendency to develop hypoglycaemia, and therefore, recommended to be used with other anti-diabetic agents.*

Methods: *This observational cross-sectional study was conducted at the Medicine as well as Endocrinology and Metabolism outpatient departments in Dhaka Medical College Hospital from April 2016 to September 2016 involving 230 participants. Prescriptions advised with DPP4i for type-2 DM were taken by convenient purposive sampling to assess the frequency and trends of prescribing this drug.*

Results: *Majority of the participants were male (56.1%), belonged to ≥51 years of age (66.6%) and 77% respondents were from urban areas. The most commonly used DPP4i was linagliptin (45.2%) followed by vildagliptin (29.1%) and then, sitagliptin (25.7%). DPP4i were mostly found as 2nd line drug (55.65%) followed by 3rd line agent (40%), as monotherapy (3.04%) and then, as 4th line option (1.3%) in this study. Mean±SD body mass index (BMI) and HbA1c(%) of the patients were (25.35 ± 2.27) kg/m² and (9.05 ± 1.37), respectively. However, significant association of prescribing patterns of DPP4i with BMI and HbA1c of the participants were not found (P>0.05).*

Conclusion: *DPP-4 inhibitors are considered as a well-preferred orally given adjunct therapy in the management of type-2 DM.*

Keywords: *Dipeptidyl peptidase-4 inhibitors (DPP4i), Prescription patterns of anti-diabetic drugs, Type-2 DM management*

Journal of Green Life Med. Col. 2022; 7(2): 61- 67

Introduction:

Diabetes is one of the largest global health emergencies of the 21st century. Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both.[1] The International Diabetes Federation (IDF) has estimated[2] age-adjusted comparative prevalence of diabetes (20–79 years) in Bangladesh is ≥10%. According to the American Diabetes Association (ADA), management of Type-2 DM involves a combination of life-style modifications and pharmacological approaches.[3] Various agents are available as monotherapy or combination therapy for the management of type-2 diabetes mellitus. Some of these agents come with adverse effects such as weight gain, hypoglycaemia, and gastrointestinal distress.[1] Balancing treatment-induced hypoglycaemia and weight gain, along with ensuring sustained adherence to therapy, presents common challenges in diabetes management.[4-8] Maintaining

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Received: 21.03.2024 **Accepted:** 06.07.2024

reasonable glycaemic control is crucial, as even 1% reduction in HbA1c can potentially decrease the risk of diabetes complications.[9] Given these challenges, there is a demand for alternative therapies that can address the limitations associated with conventional anti-hyperglycaemic medications. Dipeptidyl Peptidase-4 Inhibitors (DPP4i) are effective oral anti-diabetic agents which belongs to incretin-based therapy. They lower blood glucose levels by increasing levels of glucagon-like peptide (GLP-1) and gastric inhibitory polypeptide (GIP), which inhibit glucagon release and stimulate insulin secretion.[10] Guidelines from the ADA, American Association of Clinical Endocrinologists (AACE), and National Institute for Health and Clinical Excellence (NICE) suggested adding a DPP4i as a second-line treatment to metformin, especially in cases where there is a significant risk of hypoglycaemia or when a sulfonylurea is contraindicated or not tolerated.[11] DPP4i possess weight-neutral effect and no risk of hypoglycaemia, but they are relatively more expensive than other oral anti-diabetic agents.[1] Studying prescribing patterns is crucial for monitoring and evaluating prescribers' practices and recommending necessary modifications to achieve rational and cost-effective medical care. Reviewing prescribing habits provides valuable feedback to prescribers and ensures quality medical care. This study aims to observe the prescription patterns of drugs used in treating type-2 diabetes mellitus patients, as DPP4i are typically advised as adjunct therapy rather than monotherapy.[12] The findings of this study are expected to offer relevant feedback to allied physicians and pharmaceuticals. It may reduce polypharmacy and improve therapy adherence while maintaining reasonable control of diabetes. In that case, it will warrant attention from health management administration, policymakers, and drug and therapeutic committees to establish national guidelines as well as ensure better availability of these drugs. During this study, there were five drugs in the DPP4i group mentioned as sitagliptin, vildagliptin, linagliptin, saxagliptin, and alogliptin. Therefore, the study shows which available DPP4i was commonly preferred by the physicians when these were used to be considered as newer agents. Moreover, as this study explores the trends of DPP-4 inhibitor prescription patterns along with the other anti-diabetic medications at one point of time in a tertiary care hospital of Bangladesh, the findings might be compared for analysis of further changing patterns of prescribing drugs with even newer available modalities of treatment for type-2 DM as well. In addition, utilization as well as frequency patterns of DPP4i prescription in different groups of body mass index and HbA1c of the participants, duration of DM, and several socio-demographic characteristics of the type-2 diabetic patients were also observed in this study. Thus, in upcoming days, it can also help to find out the changing prescription patterns in this regard.

Methods:

This observational cross-sectional study was conducted at outpatient department of Medicine and department of Endocrinology and Metabolism in Dhaka Medical College Hospital (DMCH) from April 2016 to September 2016. The study was aimed to describe the trends and assess the frequency of prescribing DPP4 inhibitors (DPP4i) in the management of type-2 diabetes mellitus (DM). The sampling technique employed was purposive convenient sampling. The sample size was determined based on a survey conducted in Malaysia[12] (as no relevant study was available in Bangladesh) having an estimated prevalence of 86% prescriptions with DPP4i, resulting in a total of 230 samples collected during this limited period. Inclusion criteria encompassed both male and female patients who were advised DPP4i in their prescriptions for type-2 DM, aged over 18 years, and in apparently good general health. Exclusion criteria involved severely ill patient, established cardiovascular or renal diseases, having impaired liver or pancreatic function, and diagnosed case of diabetes other than type-2 DM. Ethical clearance was obtained from the Dhaka Medical College's ethical review committee, and informed written consent was secured from all participants. Data collection involved face-to-face interviews using a semi-structured questionnaire covering socio-demographic characteristics as well as other relevant information regarding type-2 DM and snapshot of prescriptions were taken accordingly. Upon data collection, these were meticulously checked to ensure accuracy and consistency, and then coded for analysis. Data processing and statistical analysis were conducted using Microsoft Excel and SPSS version 16, respectively. Categorical data were represented as proportions (percentages), while numerical data were presented as means (standard deviations) and ranges. Chi-square test was used to find out any association of the prescription pattern of DPP4i with the socio-demographic parameters, duration of DM, BMI and HbA1c of the participants. Graphs and charts were generated to illustrate the findings visually. The results were summarized and presented in tables and charts.

Results:

The majority were male (56.1%) while the rest were female (43.9%). Participants were distributed across different age groups, with the highest proportion being in the (51-60) year age range (45.7%), followed by ≥61 year (20.9%). Most participants were Muslim (79.6%), followed by Hindu (19.1%) and Christian (1.3%). More participants were from

urban areas (77%) compared to rural areas (23%). The highest proportion had completed HSC (36.5%), followed by graduates and above (31.3%). Most participants had a monthly income greater than 20,000/- (63.5%), followed by (10,000-20,000)/- (34.3%), and less than 10,000/- (2.2%).

Table I

Socio demographic characteristics of the participants (N=230)

Characteristics	Parameters	Frequency	Percentage
Gender	Male	129	56.1 %
	Female	101	43.9 %
Age (year)	18-30	02	0.9 %
	31-40	20	8.7 %
	41-50	55	23.9 %
	51-60	105	45.7 %
	≥61	48	20.9 %
Religion	Islam	183	79.6 %
	Hindu	44	19.1 %
	Christian	03	1.3 %
Residence	Rural	53	23 %
	Urban	177	77 %
Occupation	Govt. Employee	31	13.5 %
	Non-Govt Employee	22	9.6 %
	Business	61	26.5 %
	Housewife	88	38.3 %
	Unemployed	06	2.6 %
	Others	22	9.6 %
Education	Uneducated	06	2.6 %
	Below SSC	31	13.5 %
	SSC	37	16.1 %
	HSC	84	36.5 %
	Graduate & above	72	31.3 %
Monthly income (BDT)	<10,000/-	05	2.2 %
	(10,000-20,000)/-	79	34.3 %
	>20,000/-	146	63.5 %

In this study, the observed prescription pattern of DPP4i reveals that the most commonly 104 (45.2%) used DPP4 inhibitor was linagliptin followed by vildagliptin in 67 (29.1%) and then sitagliptin in 59 (25.7%) patients. Saxagliptin was not prescribed in this study. Each drug was available in oral form.

Table II

Prescribing pattern of DPP-4 inhibitors (N=230)

DPP-4 inhibitors	Frequency	Percentage
Sitagliptin	59	25.7 %
Vildagliptin	67	29.1 %
Linagliptin	104	45.2 %

DPP4i- Dipeptidyl Peptidase 4 Inhibitors

DPP-4 inhibitor was used as 1st line drug only in 7 (3.04%) participants. Linagliptin was prescribed in those cases. Sitagliptin and vildagliptin were not prescribed as 1st line agents in this study. Among 230 prescriptions, DPP4i was most commonly (55.65%) used as 2nd line agent (128 cases), where it was found that DPP4 inhibitor was prescribed with either metformin or insulin in almost equal frequency (25.65% and 25.22% respectively). Only 11 (4.78%) prescriptions revealed advice of DPP4i with sulphonylureas. DPP4i was prescribed as 3rd line drug in 92 (40%) diabetic patients in this study. In 56 (24.35%) cases, it was considered along with metformin and insulin; in 34 (14.78%) cases, it was considered with metformin and sulphonylureas. DPP4i was advised with metformin and GLP-1 analogue (liraglutide) in 1 (0.43%) patient who had a BMI of 35kg/m². DPP4i was prescribed with sulphonylurea and insulin (insulin glargine) in 1 (0.43%) participant only. In this study, DPP4i was considered the 4th line anti-diabetic drug in 3 (1.3%) participants. In these cases, DPP4i, metformin, and alpha-glucosidase inhibitors were used with sulphonylureas or insulin (0.87% and 0.43%, respectively).

Table III

Patterns of using DPP4 Inhibitors with other anti-diabetic medications (N=230)

Choice	Combination	Number	Percentage
1st line agent	DPP4i (Linagliptin only)	07	3.04%
2nd line agent		128	55.65%
	Metformin+DPP4i	59	25.65%
	Insulin+DPP4i	58	25.22%
	SU+DPP4i	11	4.78%
3rd line agent		92	40%
	Metformin+Insulin+DPP4i	56	24.35%
	Metformin+SU+DPP4i	34	14.78%
	Metformin+GLP-1 analogue+DPP4i	01	0.43%
	SU+Insulin+DPP4i	01	0.43%
4th line agent		03	1.3%
	Metformin+SU+AGI+DPP4i	02	0.87%
	Metformin+Insulin+ AGI+DPP4i	01	0.43%

DPP4i- Dipeptidyl Peptidase 4 Inhibitors, SU- Sulphonylureas, GLP-1 analogue- Glucagon like peptide-1 analogue, AGI- alpha-glucosidase inhibitors

Comparison of DPP4i as 1st line, 2nd line, 3rd line and 4th line agents is mentioned in Table III and frequency of prescribed DPP4i (i.e. sitagliptin, vildagliptin and linagliptin) with other anti-diabetic agents are shown in figure 1(a-e).

Among 230 participants, metformin was prescribed in 153 (66.5%) cases. Insulin used in this study was seen in 116 (50.43%) prescriptions. Metformin and insulin were prescribed in 57 (24.78%) patients. Combined (premixed) insulin was prescribed in 56 (24.3%) cases. Among 52 (22.6%) prescriptions of short-acting human insulin, 20

participants also received intermediate-acting human insulin, and 10 patients had insulin glargine (long-acting analogue). In the rest, 22 cases received no other insulin but the short-acting one. Insulin aspart (rapid-acting analogue) and insulin detemir (long-acting analogue) were prescribed in 2 cases. Sulphonylureas were found in 48 (20.87%) prescriptions, of which the most commonly used drug was glimepiride in 27 (11.7%) cases. AGI were prescribed in 3 (1.3%) patients. A single prescription had liraglutide (GLP-1 analogue), which is also an incretin-based therapy like DPP-4 inhibitors. Other anti-diabetic drugs such as thiazolidinediones, meglitinides, and SGLT-2 inhibitors were not found in any prescription in this study. The observed pattern of other anti-diabetic drug utilization in this study is shown in Table IV.

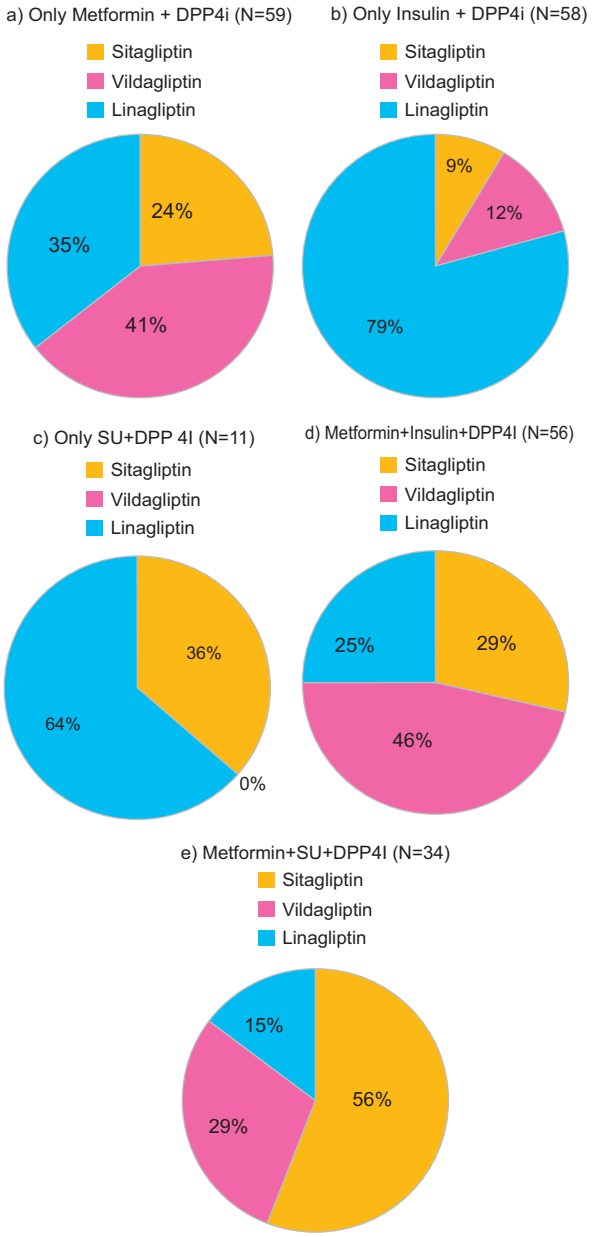

Figure 1(a-e): *Combination of different DPP4i with other anti-diabetic drugs*

Table IV

Frequency of other anti-diabetic drugs prescribed with DPP4i (N=230)

Group	Name of the Drug	Frequency	Percentage
Biguanide	Metformin	153	66.5 %
Sulphonylureas	Glibenclamide	09	3.9 %
	Glimepiride	27	11.7 %
	Gliclazide	12	5.2 %
Insulin	Short acting	52	22.6 %
	Intermediate acting	20	8.7 %
	Premix Combined	56	24.3 %
	Glargine	15	6.5 %
	Detemir	02	0.9 %
	Aspart	03	1.3 %
GLP-1 analogue	Liraglutide	01	0.4 %
AGI	Acarbose	02	0.9 %
	Miglitol	01	0.4 %

DPP4i- Dipeptidyl Peptidase 4 Inhibitors, SU- Sulphonylureas, GLP-1 analogue- Glucagon like peptide-1 analogue, AGI- alpha-glucosidase inhibitors

The average duration of diabetes among the participants in this study were (1-10) years in 146 (63.5%) patients, less than 1 year in 54 (23.5%) cases and 30 (13%) patients having type-2 DM for more than 10 years.

Table V

Duration of DM in patients using DPP4 Inhibitors

Duration	No. of patients (N=230)	Percentage
<1 year	54	23.5 %
(1-10) years	146	63.5 %
>10 years	30	13.0 %

Most of the enrolled patients 138 (60%) in this study belonged to the BMI (Body Mass Index) group (25-29.99) kg/m², 87 (37.8%) participants had (18.5-24.99) kg/m² and 5 (2.2%) cases had BMI ≥30kg/m². Among 230 diabetic patients, minimum BMI was 19 kg/m² and maximum was 35 kg/m². Their mean±SD BMI was (25.35 ± 2.27) kg/m².

Table VI

Patterns of BMI in patients using DPP-4 Inhibitors (N=230)

BMI (kg/m²)	Frequency	Percentage
18.50-24.99	87	37.8 %
25.00-29.99	138	60 %
≥30	05	2.2 %

Distribution of BMI grouping of the participants and prescription pattern of different DPP4i is shown in figure 2.

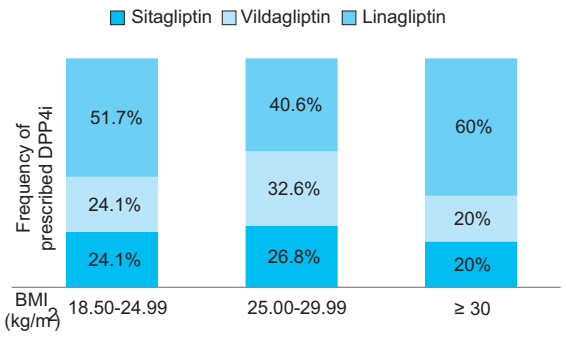

Figure 2: *Trend of prescribing DPP4i and BMI of the participants*

The minimum HbA1c among the patients was 6.8% and maximum was 16%. Their mean±SD HbA1c was (9.05 ± 1.37)%. HbA1c levels were divided into four groups of which HbA1c of the 65 (28.3%) diabetic patients were found in a range of (9-9.8)%, 60 (26.1%) cases from (8-8.9)%, 57 (24.8%) participants had >9.8% and 48 (20.9%) patients had HbA1c <8%.

Table VII

Patterns of HbA1c in patients using DPP-4 Inhibitors (N=230)

HbA1c Group	Frequency	Percentage
<8 %	48	20.9 %
(8-8.9) %	60	26.1 %
(9-9.8) %	65	28.3 %
>9.8 %	57	24.8 %

Distribution of HbA1c & prescription pattern of different DPP4i is shown in figure 3.

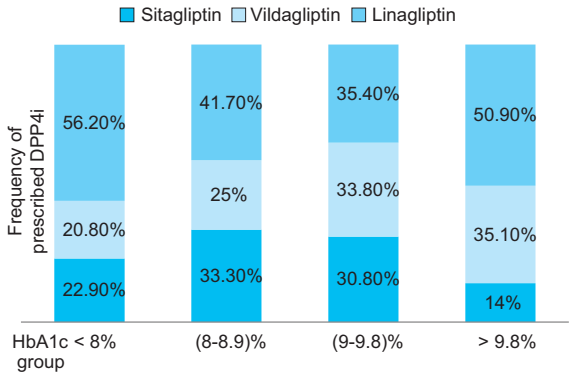

Figure 3: *Trend of utilizing DPP4i and pattern of HbA1c of the participants*

Association of prescription patterns of DPP4i with the socio-demographic parameters, duration of diabetes, BMI and HbA1c of the participants were also observed. But the study revealed no significant association (P>0.05).

Discussion:

Out of 230 participants, majority patients (45.7%) with type-2 DM were found in the age group (51-60) years followed by 23.9% in (41-50) years and 20.9% cases were above 60 years which corresponds with the finding of a study in India where higher percentage of study population belonged to the age group of (41-65) years as the risk of diabetes is significantly higher in this age group.[1] Greater prevalence in this age group may be due to change in life style, stress and lack of exercise.[13] Most of the (77%) respondents were from urban area, which corresponds to a previous study in Bangladesh.[14] It is probably because urban people have a more sedentary lifestyle or different dietary habits or are more likely to be overweight or obese.[15] The enrolled population in this study had a monthly income above 20,000 BDT in 63.5% cases and very less commonly given in the group <10,000 BDT monthly incoming subjects; probably because they were more expensive when compared to other oral anti-diabetic agents[1]. In this study, most (63.5 %) of the participants were diabetic for (1-10) years, 23.5% were diagnosed within last 1 year and 13% were diabetic for more than 10 years which is not in agreement with the result of a study in Malaysia[12] where 77.6% cases were diabetic for >10 years. But duration since the diagnosis of Type-2 DM did not influence the prescribers in prescribing DPP4i.[12] Prescription pattern of DPP4i showed no association with the socio-demographic parameters as well as duration of diabetes in this study.

From this study, it was observed that the most commonly prescribed DPP-4 inhibitor (DPP4i) is linagliptin (45.2%) followed by vildagliptin (29.1%) and then sitagliptin (25.7%). Alogliptin was not available in Bangladesh and Saxagliptin was not advised in any prescription. This result is not similar with the findings of the studies conducted in India, Malaysia and Hong Kong where Sitagliptin was found to be used in the majority.[1,12] This reflects that the prescribing physicians of Bangladesh preferred linagliptin than the other DPP4i, probably due to its hepatic clearance was considered as an added advantage over the other DPP4i.[1] In this study, no respondent had any liver or pancreas related problem which overall ensured safer utilization of DPP4i. Out of 230 prescriptions, DPP4i was found as monotherapy in 7 (3.04%) cases only where Linagliptin was advised. The mean HbA1c of those patients

was 7.24%. Sitagliptin and Vildagliptin were not found to be used as monotherapy in this study which is not in agreement with other similar type of studies.[1,12] DPP-4 inhibitors are approved as adjunctive therapies to lifestyle modification and medications like metformin or sulfonylureas as a first-line treatment for significant lowering blood glucose levels.[16] In this study, DPP4i were most commonly (55.65%) used as 2nd line drug followed by (40%) as 3rd line agent for the treatment of type-2 DM. This finding goes in disfavour of another Asian study where DPP4i were mostly (58.05%) prescribed as 3rd line agent followed by 28.4% as the 2nd line drug.[1] Among 55.65% as 2nd line drug in this study, DPP4i was almost equally used with metformin and with insulin (25.65% and 25.22% respectively) followed by 4.78% in combination with sulphonylureas only. Among 40% as 3rd line agent in this study, it was observed that DPP4i were prescribed with concurrent use of metformin along with insulin in 24.35% cases and metformin along with sulphonylureas in 14.78% cases. Such pattern of having DPP4 inhibitors among the 230 patients was probably because of their higher percentage of HbA1c level (53.1% cases had HbA1c ≥9%) and also less chance of developing hypoglycaemia in lowering the blood glucose which is an advantageous effect of DPP4i.[16] Only 1.3% prescriptions in this study revealed DPP4i as 4th line agent reflects an attempt to reduce polypharmacy.

Considering the other anti-diabetic drugs prescribed with DPP-4 inhibitors among 230 participants, it was found that the most commonly (66.5%) used combination was with metformin. This finding corresponds with other studies conducted in Asian countries.[1,12] Overall, in this study, DPP4i were prescribed with insulin in 50.43% cases followed by 20.87% with sulphonylureas. But this result is not similar with the findings of other relevant studies where combination of sulphonylureas with DPP4i were more popular than that of insulin.[1,12] Prescriptions of alpha glucosidase inhibitors (AGI) and GLP-1 analogue with DPP4i in this study were found very negligible (1.3% and 0.4% respectively). SGLT-2 inhibitors were not advised in any prescription in this study.

According to the International classification of Body Mass Index (BMI) by World Health Organization (WHO)[17], most (60%) of the diabetic patients in this study were overweight (25.00-29.99 kg/m²), 37.8% had BMI 18.50-24.99 kg/m² and 2.2% cases were obese having BMI ≥30 kg/m². However, the cut-off point[17] for observed risk varies from (22-25) kg/m^2 in different Asian populations and for high risk, it varies from (26-31) kg/m^2. Mean±SD BMI in this study was calculated as (25.35 ± 2.27) kg/m² which is near to the result (26.9 kg/m²) of a study conducted in Malaysia.[12] DPP4i were utilized for majority patients because of its weight neutral effect.[1,18] No significant association of prescribing pattern of DPP4i with BMI of the diabetic patients was found in this study (P>0.05).

According to WHO, HbA1c ≥6.5% is the cut-off point for diagnosing diabetes.[19] In this study, the minimum value of HbA1c was 6.8%, maximum was 16% and the mean±SD HbA1c (%) was calculated as (9.05 ± 1.37). Majority (53%) patients had HbA1c ≥9% in this study. Linagliptin was more frequently used in this study which does not correspond with another Asian study[1] that says Sitagliptin was more effective in the Indian population with greater reduction of HbA1c. DPP4 inhibitors can reduce blood glucose as effective as other oral anti diabetics when prescribed as monotherapy when HbA1c levels are in between (6.5-7.5) % with minimal risk of hypoglycaemia.[1,20] However, significant association of prescribing patterns of DPP4i with HbA1c of the participants was not found (P>0.05). Hence, HbA1c was not a determinant in prescribing DPP4i and this finding is consistent with another Asian study.[12]

Limitations:

- The study was conducted in a single centre with minimum sample size and within short duration.
- Family history and some personal data were not taken into concern which may potentially influence the management of diabetes mellitus.
- Drug adherence could not be followed up though it was possible that compliance of DPP4i may be affected by its cost.

Conclusion:

From this study, it was observed that the most commonly prescribed DPP-4 inhibitor (DPP4i) is linagliptin followed by vildagliptin and then sitagliptin. The study also revealed that type-2 diabetes mellitus is more prevalent in males, middle aged urban people and among overweight persons. HbA1c was found greater than 9% in majority of the enrolled population. Considering the prescription patterns of DPP4i, it was found to be used mostly as an adjunct therapy to control blood glucose level. DPP4i were most commonly seen as 2nd line drug and then the 3rd line option in the management of type-2 DM. Other anti-diabetics preferably used along with DPP4i were metformin, insulin, and sulphonylureas respectively. However, appropriate patients for DPP4i therapy considering the cost, glycaemic status, and the

modest treatment effect associated with this group of drugs need to be particularly identified.

Conflict of Interest: None declared.

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REVIEW ARTICLE

Topiramate Induced Acute Angle Closure Glaucoma: A Review of Current Literature

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Abstract

Topiramate, a medication primarily used for epilepsy and migraine prophylaxis, has been linked to the rare but significant side effect of acute angle closure glaucoma (AACG). This literature review aims to synthesize current knowledge on the epidemiology, clinical presentation, pathophysiology, management, and impact on quality of life of Topiramate-induced AACG. A comprehensive literature search was conducted using PubMed and Google Scholar, focusing on case reports, clinical studies, and review articles. The search terms included 'Topiramate', 'acute angle closure glaucoma', and related keywords. Studies were selected based on relevance to the topic, with a focus on open-access and peer-reviewed literature. The review found that Topiramate-induced AACG, while rare, can affect a diverse demographic. Clinical presentation often mimics other forms of glaucoma, making diagnosis challenging. The hypothesized mechanism involves ciliochoroidal effusion leading to anterior rotation of the ciliary body. Management typically includes immediate discontinuation of Topiramate and initiation of anti-glaucoma therapy, with most cases showing reversibility of the condition. The condition significantly impacts patients' quality of life and vision, with potential psychological and social implications. Topiramate-induced AACG is a critical condition requiring heightened clinical awareness and prompt management. The condition's reversibility with timely intervention highlights the importance of early recognition and diagnosis. This review underscores the need for further research to understand the full scope of this condition and to develop standardized treatment protocols. The findings emphasize the importance of patient education and a comprehensive approach to care for individuals on Topiramate therapy.

Keywords: Topiramate, Acute Angle Closure Glaucoma, Management of Acute Angle Closure Glaucoma

Journal of Green Life Med. Col. 2023; 8(1): 68- 71

Introduction:

The intricate relationship between pharmacotherapy and ocular health is an area of growing concern, particularly in the context of drug-induced secondary glaucoma. Among the various medications implicated, Topiramate, a sulfamate-substituted monosaccharide, has garnered attention due to its association with acute angle closure glaucoma (AACG). Topiramate is primarily prescribed for epilepsy and migraine prophylaxis, but its utility extends to managing peripheral neuropathies, idiopathic intracranial hypertension, and as adjunctive therapy in alcohol dependence and nicotine cessation.[1,3] The prevalence of Topiramate use in clinical practice, coupled with its broad therapeutic spectrum, underscores the importance of understanding its potential ocular side effects.Acute angle closure glaucoma, a subset of glaucoma, is characterized by a rapid rise in intraocular pressure (IOP) due to the abrupt closure of the anterior chamber angle. This condition, if not promptly recognized and treated, can lead to irreversible vision loss. The pathophysiology of AACG typically involves a relative

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Received: 29.04.2024 **Accepted:** 06.07.2024

pupillary block, leading to the anterior displacement of the iris-lens diaphragm and subsequent angle closure.[4,5] However, the mechanisms by which Topiramate induces AACG are hypothesized to be distinct, involving ciliochoroidal effusion, which results in anterior rotation of the ciliary body and forward movement of the lens-iris diaphragm.[6,7] This mechanism, while reversible upon drug discontinuation, necessitates early detection and intervention.The significance of recognizing drug-induced secondary glaucoma, particularly with a commonly prescribed medication like Topiramate, cannot be overstated. Case reports have highlighted instances where patients, often on Topiramate for unrelated medical conditions, presented with symptoms mimicking primary AACG.[8,9] These presentations underscore the need for heightened clinical vigilance. The impact of AACG on vision and quality of life is profound. Patients with glaucoma experience diminished visual function, which in turn affects their psychological well-being and overall quality of life[1]. This impact is further exacerbated in cases of drug-induced AACG, where the sudden onset and rapid progression of symptoms can be particularly distressing. Initial observations and case reports have been pivotal in establishing the link between Topiramate and AACG. Instances of bilateral acute angle closure glaucoma following Topiramate treatment, presenting with symptoms such as severe eye pain, redness, and blurred vision, have been documented.[2,3] These reports not only highlight the clinical presentation of Topiramate-induced AACG but also emphasize the reversibility of the condition with prompt cessation of the drug and appropriate management.

Epidemiology of Topiramate-Induced Acute Angle Closure Glaucoma

The epidemiology of Topiramate-induced AACG, while considered rare, is crucial for understanding the risk profile of this drug. The prevalence and incidence rates of this condition are not well-defined due to its rarity, but several case reports indicate its occurrence across various populations.[1,2,4] Demographically, affected individuals span a wide range of ages and include both genders, although there seems to be a slight predilection towards younger adults.[1,4] These case reports suggest that the risk of AACG is not confined to any specific demographic group, making it imperative for clinicians to maintain vigilance in all patients prescribed Topiramate.

Clinical Presentation and Diagnosis

Patients with Topiramate-induced AACG commonly present with symptoms such as ocular pain, redness, blurred vision, and headache.[1,2,4] These symptoms often mimic those of primary AACG, making diagnosis challenging. Diagnostic criteria include a sudden increase in intraocular pressure, shallowing of the anterior chamber, and myopic shift, often confirmed through ophthalmic examination and imaging.[10,11] Early and accurate diagnosis is critical, as it directly influences the management and prognosis of the condition.

Mechanisms of Topiramate-Induced Acute Angle Closure Glaucoma

The pathophysiological mechanisms underlying Topiramate-induced AACG are complex and not entirely understood. The prevailing hypothesis suggests that Topiramate may cause ciliochoroidal effusion, leading to anterior rotation of the ciliary body and forward movement of the lens-iris diaphragm.[5,6] This mechanism results in a shallow anterior chamber and angle closure, differing from the typical pupillary block mechanism seen in primary AACG.[5,6] Some studies also suggest a role for idiosyncratic reactions to the drug, indicating a multifactorial etiology.[5,6,12,13] Understanding these mechanisms is crucial for developing targeted treatment strategies and for informing patients about potential risks associated with Topiramate use.

Case Reports and Clinical Studies

The literature on Topiramate-induced acute angle closure glaucoma (AACG) is particularly enriched by detailed case reports and clinical studies, which shed light on the diverse manifestations and management of this condition. One notable case report describes a 32-year-old female who developed bilateral AACG after using Topiramate. This patient, initially prescribed Topiramate for migraine management, presented with classic symptoms of AACG, including ocular pain and blurred vision. Her condition was promptly diagnosed as AACG secondary to Topiramate, underscoring the drug's potential to induce this rare but severe side effect.[14] The rapid resolution of her symptoms following the discontinuation of Topiramate and initiation of appropriate glaucoma therapy highlights the importance of early recognition and intervention.

Another significant case involves a 40-year-old man who experienced acute ocular symptoms, such as severe eye pain and vision loss, following the use of Topiramate for alcohol dependence.[1] This case is particularly instructive as it illustrates that Topiramate-induced AACG can occur irrespective of the primary indication for the drug's use. The patient's symptoms were initially mistaken for common ocular conditions, delaying the correct diagnosis. Once Topiramate-induced AACG was identified and the medication was discontinued, there was a notable

improvement in his condition, emphasizing the reversible nature of this drug-induced complication.

These cases, along with others in the literature, demonstrate the varied clinical presentations of Topiramate-induced AACG. They range from typical symptoms like ocular pain and headache to more severe manifestations including significant vision loss.

Management and Treatment Outcomes

The management of Topiramate-induced AACG primarily involves the immediate discontinuation of the drug. This step is often followed by the initiation of anti-glaucoma therapy, which may include topical medications and systemic agents to reduce intraocular pressure.[1,2,14] Laser peripheral iridotomy, a common treatment for primary AACG, is generally not effective in Topiramate-induced cases due to the different underlying mechanism.[15,16] The reversibility of the condition upon cessation of Topiramate is a key finding in many case reports. Patients often experience a rapid resolution of symptoms and normalization of intraocular pressure following the discontinuation of the drug and appropriate medical management.[1,2,14] This reversibility highlights the importance of early detection and prompt withdrawal of Topiramate in affected patients.

Impact on Quality of Life and Vision

The impact of Topiramate-induced AACG on patients' quality of life and vision is a critical aspect of understanding this condition. Studies have shown that AACG can significantly impair vision, leading to symptoms like blurred vision and ocular pain, which profoundly affect daily activities and overall quality of life.[4] The psychological and social implications of this sudden and potentially severe vision loss are considerable, with patients often experiencing anxiety and a decreased sense of well-being.[14] The reversible nature of Topiramate-induced AACG, if diagnosed and managed promptly, does offer a positive outlook for affected patients. However, the fear of permanent vision loss and the stress associated with acute medical treatment can have lasting psychological impacts.

Discussion of Controversies and Gaps in Literature

While the literature provides valuable insights into Topiramate-induced AACG, there are still controversies and gaps that need addressing. One area of debate is the exact mechanism by which Topiramate induces AACG. While the ciliochoroidal effusion theory is widely accepted, there is ongoing research into other potential mechanisms and predisposing factors.[9] Additionally, there is a need for more extensive epidemiological data to understand the true incidence and prevalence of this condition. The rarity of Topiramate-induced AACG poses a challenge for large-scale studies, leaving a gap in comprehensive demographic profiling of affected individuals.

Discussion:

The analysis of the literature on Topiramate-induced acute angle closure glaucoma (AACG) reveals several critical insights. Epidemiologically, the condition, while rare, presents across various demographics, as evidenced by cases in both younger and older adults.[1,4] This broad demographic impact necessitates a heightened awareness among clinicians, irrespective of the patient population they typically serve. The limited epidemiological data, a point highlighted in several studies, underscores the need for further research to better understand the prevalence and risk factors associated with Topiramate-induced AACG.[1,2,4] Clinically, the diagnosis of Topiramate-induced AACG is challenging due to its presentation with common glaucoma symptoms like ocular pain and blurred vision.[1,2,4] This similarity to other ocular conditions necessitates a high index of suspicion, particularly in patients on Topiramate. The variability in symptom onset and severity, as demonstrated in various case reports[1,14], further complicates the diagnosis, making it imperative for clinicians to conduct a thorough assessment of patients presenting with these symptoms.The pathophysiological mechanisms behind Topiramate-induced AACG, predominantly centered around ciliochoroidal effusion, offer a plausible explanation for the condition's development[5,6]. However, the presence of contrasting theories and the suggestion of idiosyncratic drug reactions indicate a more complex pathophysiology than currently understood, warranting further investigation.[5,6] The management of Topiramate-induced AACG, when initiated promptly, generally leads to positive outcomes. Immediate discontinuation of Topiramate, coupled with appropriate anti-glaucoma therapy, has been shown to effectively reverse symptoms.[1,2,14] These findings highlight the importance of early recognition and treatment to prevent permanent ocular damage. However, the literature also points to a gap in standardized treatment protocols for this condition, suggesting an area for future clinical research.The psychological and social impact of Topiramate-induced AACG is profound. The acute nature of the condition and the fear of permanent vision loss can lead to significant psychological distress.[4,14] This aspect of the condition underscores the need for a comprehensive treatment approach that addresses both the physical

symptoms and the psychological well-being of the patient.In summary, the discussion of Topiramate-induced AACG in the literature presents a nuanced view of the condition. It underscores the need for increased clinical vigilance, comprehensive patient education, and further research to enhance understanding and improve patient outcomes. This analysis not only contributes to a deeper understanding of Topiramate-induced AACG but also highlights broader implications for clinical practice and patient care.

Conclusion:

The findings underscore the importance of clinical vigilance and awareness among healthcare providers, given the varied demographic impact and the often-ambiguous clinical presentation of Topiramate-induced AACG. The literature emphasizes the necessity for prompt diagnosis and management, highlighting the potential for complete reversibility of the condition with timely intervention. Additionally, this review brings to light the significant psychological and quality of life implications for patients, advocating for a holistic approach to patient care. While the review identifies gaps in current research, particularly in understanding the precise mechanisms and epidemiological data, it also sets the stage for future studies to further elucidate this condition. Ultimately, the insights gained from this review contribute to enhancing patient safety and optimizing treatment outcomes in individuals prescribed Topiramate.

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A Case of Peripheral Spondyloarthritis Presenting with Extensor Digitorum Central Slip Enthesitis Mimicking Polyarthralgia: A Mystery Solved by Musculoskeletal Ultrasound

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Abstract

Spondyloarthritis may present with a wide variety of manifestations. We describe here a 35-year-old male complaining of apparent polyarthralgia with morning stiffness who tested negative for RF, ACPA, HLA-B27 & ANA and hadnormal ESR & CRP as well as normal radiographic & MRI findings of sacroiliac joints. Ultrasonogram of hands revealed extensor digitorum central slip enthesitis which explained his symptoms. Thus musculoskeletal ultrasound proved to be an invaluable tool in the evaluation of doubtful cases.

Keywords: Spondyloarthritis, Central slip enthesitis, Musculoskeletal ultrasound

Journal of Green Life Med. Col. 2023; 8(1): 72- 74

Introduction:

The term 'spondyloarthritis' is used for a family of disorders, including ankylosing spondylitis, nonradiographic axial spondyloarthritis, psoriatic arthritis, spondyloarthritis associated with Crohn disease and ulcerative colitis, reactive arthritis, peripheral spondyloarthritis and juvenile-onset spondyloarthritis.[1] Here we report a case of peripheral spondyloarthritis presenting with extensor digitorum central slip enthesitis mimicking arthralgia of small joints of hands.

Case Report:

A 35-year-old man with sedentary occupation presented to us with pain in proximal interphalangeal (PIP) joint areas of index, middle, ring and little fingers on each side for about 2 months with morning stiffness lasting for 15-30 minutes. He did not have back pain, heel pain, eye ache, psoriatic skin lesions and an alteration of bowel habit. His mother was a chronic sufferer of pain in knee joints. There was no joint tenderness and swelling. Spine and sacroiliac joints were nontender. He was advised CBC, ESR, C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (ACPA), antinuclear antibody (ANA), HLA-B27 and MRI of sacroiliac joints which revealed no abnormality. As the initial work-up was inconclusive, musculoskeletal ultrasound (MSK USG) of hands was suggested which revealed thickened and hypoechoic extensor digitorum central slips (suggestive of enthesitis) in relation to the PIP joints (figure 1) of the involved fingers.

Considering the solely entheseal involvement, he was labeled as a case of peripheral spondyloarthritis and was put on naproxen 500 mg twice daily to which he showed a good response. He was then advised to take apremilast considering its efficacy in enthesitis as a disease modifying drug[2] with the aim to gradually withdraw naproxen.

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Received: 25.06.2023 **Accepted:** 06.07.2024

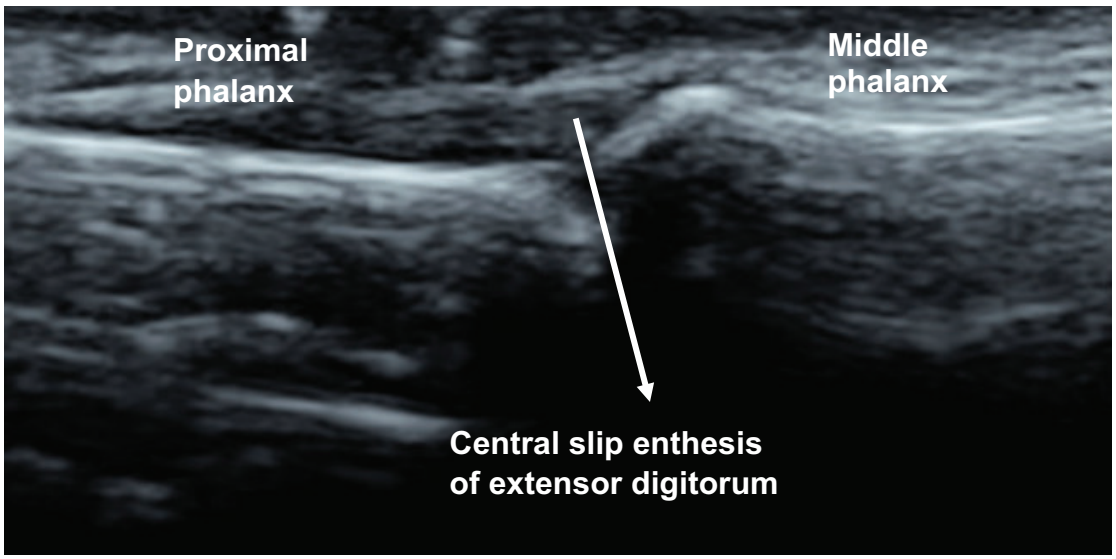

Figure 1: *Extensor digitorum centralslipenthesitis of a digit; no evidence of synovitis*

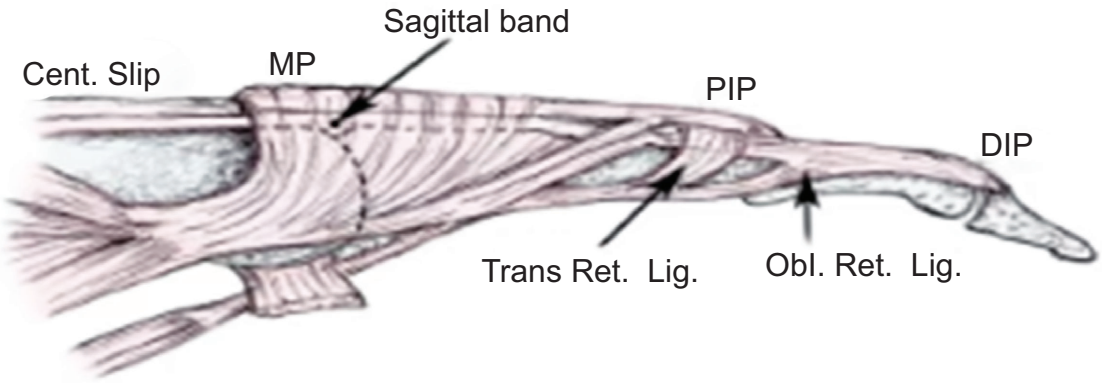

Figure 2: *Mode of insertion of the extensor digitorum*

Discussion:

Rheumatoid arthritis and spondyloarthritis are the two most common forms of inflammatory arthritis in Bangladesh. The prevalence estimates of the diseases are 1.6% and 1.2% respectively in the Bangladeshi population according to the most recent national survey.[3] When a patient presents with inflammatory joint pain with inconclusive clinical clues and initial investigation findings, it may be difficult to differentiate between seronegative rheumatoid arthritis and peripheral spondyloarthritis. Musculoskeletal ultrasound (MSK USG) may be of great value in solving the dilemma under such circumstances.

USG features that help differentiate peripheral spondyloarthritis or psoriatic arthritis affecting small joints of hands from rheumatoid arthritis are extensor digitorum central slip enthesitis, extensor digitorum enthesitis at distal phalangeal bases, extensor digitorum paratenonitis at the level of metacarpophalangeal joints, palmar plate inflammation and collateral ligament enthesitis.[4-7]

Entheses are the sites of attachment of tendon, ligament, fascia or joint capsule to bone. Entheseal inflammation or enthesitis is the distinguishing pathological feature of spondyloarthritis. Our patient was found to have extensor digitorum central slip enthesitis. The central slip of the tendon of extensor digitorum begins at the trifurcation of the tendon at proximal phalanx and inserts on the base of the middle phalanx(figure 2).[9-11]

Central slip enthesitis has not been observed in patients with rheumatoid arthritis.[7] Prakash et al. showed that

spondyloarthritis might sometimes present solely with enthesitis.[12] Based on these, we labeled the patient as a case of peripheral spondyloarthritis and treated accordingly.

Conclusion:

Point-of-care musculoskeletal ultrasound is an extension of the clinical examination of patients with rheumatic diseases. It is truly a blessing in the field of rheumatology to pinpoint the diagnosis and formulate the plan of treatment with greater confidence.

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