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EDITORIAL

Recent Development in the Journal

Prof G. M. Malik

MD, FACG(USA)

Editor-In-Chief – JK Practitioner

Ex HOD Medicine & GAST Department, SMHS, GMC Srinagar

President /CWC Member IMA & IDPD- J&K State Branches

Member- J&K Medical Council

Corresponding Author: Prof G. M. Malik (drgmalik70@gmail.com)

Keywords: JK Practitioner, Journal, Scholarly publication, Academic publishing

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Dear Researchers,

It is an honour for me to consolidate and finalize the first issue of the year 2025. We are pleased to summarize the scholarly publications of the issue in a more reader-friendly format with detailed online presence. The Journal is now being hosted with richer metadata and global academic publishing expectations.

This issue publishes some original research studies such as diagnostic accuracy of ultrasonography (USG) in the evaluation of the knee joint injuries compared to MRI and arthroscopy, CyBorD vs. VRD as Induction Therapy in Multiple Myeloma, clinical and biochemical effectiveness of Ursodeoxycholic acid and S-adenosylmethionine in intrahepatic cholestasis of pregnancy, quantitative estimation of piperacillin and tazobactam in generic and branded pharmaceutical formulations by RP-HPLC, cytological analysis of body fluids, and biomechanical correction by lateral wedge outsole in osteoarthritis knee joint.

Further, this issue brings an interesting case study presenting a silent muscle story focusing on clinical insights from Amyopathic Dermatomyositis

We are excited to encourage the researchers to read and join our journey for further improving *Quality of Life*.

Happy Researching!

Editor,
Prof G. M. Malik,
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ORIGINAL ARTICLE

Diagnostic Accuracy of Ultrasonography in the Evaluation of Knee Joint Injuries Compared to Magnetic Resonance Imaging and Arthroscopy

Imran Nazir Salroo[1], Muzammil Rasool[2], Mohd Farooq Mir[1], Zahoor Ahmad Raina[1]

[1]*Department of Radiodiagnosis & Imaging, SKIMS medical college, Srinagar, Jamu & Kashmir, India.*
[2]*Department of Obstetrics & Gynecology, SKIMS medical college, Srinagar, Jamu & Kashmir, India.*
Corresponding Author: Zahoor Ahmad Raina (zahoorraina2226@gmail.com)

ABSTRACT

Introduction: Knee joint injuries are common especially in sports persons. Injuries to soft tissues, such as ligaments, cartilage and tendons are commonly encountered. Ultrasound has become very popular modality in recent years for evaluation of knee joint injuries because of easy availability, non-invasiveness, and possibility of dynamic imaging assessment.

Aim: To evaluate the role of ultrasound in evaluation of knee joint injuries compared to MRI.

Materials and Methods: The prospective study included 60 patients with knee joint injuries. Ultrasound was done on both injured as well as normal knee, including dynamic assessment. It was followed by MRI of injured knee in all patients. MRI was used as Gold standard for comparison.

Results: Knee injuries are commonly seen in young age with maximum number of patients in the age group of 21-40 years. Most common cause of knee injuries is sports related trauma fallowed by road traffic accidents. It has been observed that Knee injuries show a definite male preponderance with male to female ratio of approximately, 5:1. Right knee was involved more frequently than left knee. Most frequent finding in knee injuries in our study was joint effusion. Medial meniscal tear was most common injury seen in this study.

Conclusion: Based on our results, it can be concluded that USG is an effective imaging modality that has positive effect on the management of many patients presenting with knee injuries. Knee USG has high accuracy in diagnosing menisco-ligamentous injuries. A wide availability, lower cost and fair reliability make it a modality of first choice for evaluation of knee injuries. MRI can be reserved for patients with suspicious USG results.

Keywords: Knee injuries, cartilage, ligaments, Ultrasound.

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INTRODUCTION

The knee joint is a compound type of synovial joint that consists of hyaline cartilage articulations between femur, tibia and patella. Due to limited bony support, stability of knee joint is highly dependent on its ligamentous structures and therefore injuries of ligaments and menisci are extremely common. Knee injuries are especially common in sports persons.[1–8] Clinical examination by even by the most experienced staff using the strictest of clinical methods is not always enough to diagnose knee injuries. Arthroscopy has been considered as the gold standard for the diagnosis of knee injuries.[9–15] But it is invasive, expensive and requires day surgery admission. MRI is now the non-invasive gold standard for the diagnosis of knee injuries, but MRI has long examination times and is expensive. Also, MRI is not always available on demand and does not allow dynamic testing.[16–18] High resolution ultrasonography (HRUS) is becoming a leading imaging modality in the evaluation of the Musculo-skeletal system as it is readily available and economical. USG evaluates the fibrillary anatomy of muscles, tendons and ligaments. Other advantages of USG are ability to compress, dynamically assess structures and compare easily with the contralateral side. There have been studies done in the past that evaluated accuracy of either USG or MRI in detection of knee injuries and only few studies have compared the two methods.[19–27]

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MATERIALS AND METHODS

The study was conducted in the Department of Radiodiagnosis and Imaging, Sher-i-Kashmir Institute of Medical Sciences, Srinagar in collaboration with the Department of Orthopaedics over a period of two years commencing from July 2018 and ending on July 2020.

Inclusion criteria

Clinically suspected patients having knee ligamentous or meniscal injuries.

Exclusion criteria

- Patients with contraindications to MRI.
- Patients with known or diagnosed fracture/dislocation involving the knee on plain radiography.
- Patients having undergone knee surgeries for any reason.

Method

From July 2018 to July 2020, 60 patients (50 males, 10 females) clinically suspected of having knee ligamentous or meniscal injuries were sent to our department from the department of orthopaedics. All the patients were informed about the study and their informed consent was taken. All the patients underwent ultrasonography of the injured knee as well as normal knee using high frequency linear probe (7-15 Hz) and MRI of the injured knee on the same day. All the sonographic exams and MRI were performed by consultant radiologists who were blinded to the results of other test. The decision to do arthroscopy was done according to the MRI findings and clinical findings by the orthopaedic surgeons. Arthroscopy was done in 23 patients.

Ultrasound Imaging Technique

Sonographic exams were performed with 7-15Hz linear probe in supine and prone positions through the anterior, lateral and lateral approaches using static and dynamic techniques. In supine position, the knee was flexed 20-30 degree to examine anterior, medial, and lateral aspects of knee and prone position for posterior aspect of knee.

MRI Technique and Protocol

MRI was carried out using 1.5 T MR system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) using fallowing protocol.

Statistical Analysis

Collected data is presented in form of tables and diagrams. Continuous variables are expressed as Mean/ SD and categorical variables are summarized as frequencies and percentages. Frequency distribution tables, bar and pie charts are used for data presentation.

Sensitivity, specificity and diagnostic accuracy of USG is calculated keeping MRI as standard for comparison by using fallowing formulas:-

$$\text{Sensitivity: } \frac{\text{True positive results}}{\text{True positive + False negative results}} \times 100\%$$

$$\text{Specificity: } \frac{\text{True negative results}}{\text{True negative + False positive results}} \times 100\%$$

$$\text{Accuracy: } \frac{\text{TP + TN}}{\text{No. Of examinations.}}$$

RESULTS

We evaluated sixty patients with knee injuries in our department. Collected data is presented as follows:

Table 2: Gender distribution.

Gender	Frequency	Percentage (%)
Male	50	83.3
Female	10	16.7
Total	**60**	**100**

**Approx. 5/6th of patients was of male gender*

Table 1: MRI protocol.

Sequences	TR	TE	THK	FOV	RFOV (%)	NSA
T1W TSE SAG	450–500	15–25	3.0/ 0.7	210	80	2
TIW TSE COR	450–500	15–25	3.0/ 0.7	210	100	2
PD SPAIR COR	1500–3000	12–18	3.0/ 0.7	210	100	3
PD SPAIR TRA	1500–3000	12–18	3.0/ 0.7	210	100	3
PD SPAIR SAG	1500–3000	12–18	3.0/ 0.7	210	100	3
T2W SAG	3500	102	3.0/ 0.7	210	100	2

Table 3: Age distribution.

Age (years)	Frequency	Percentage (%)
≤+20	07	11.7
21 - 30	15	25
31 - 40	16	26.7
41 - 50	11	18.3
51+	11	18.3
Total	**60**	**100**

**Mean age = 35.78 years.*

** Half of the patients were in the age group of 21–40 years.*

Table 4: Right vs. Left knee involvement.

KNEE INVOLVED	Frequency	Percentage (%)
Right	38	63.3
Left	22	16.7
Total	**60**	**100**

Table 5: Mode of trauma.

Mode of trauma	Frequency	Percentage (%)
RTA	15	25
Fall on ground.	15	25
Sports injury.	16	26.6
Fall from height.	10	16.6
Blunt trauma.	01	1.6
Physical assault.	02	3.33
Fall from stairs.	01	1.6
Total.	**60**	**100**

Table 6: Frequency of types of knee injuries as seen on USG.

Structure involved	Frequency
aCL	11
PCL	15
MM	23
LM	11
MCL	15
LCL	07
EFFUSION	33

Most frequent finding was joint effusion fallowed by medial meniscal injury.

Arthroscopy was done in only 23 patients with high grade meniscal tears and cruciate ligament ruptures requiring intervention.

We used MRI as standard for comparison of USG findings to calculate sensitivity, specificity and diagnostic accuracy for the following reasons:

1. MRI was done in all the 60 patients in our study, while as arthroscopy was done in only 23 patents.
2. There was absolute agreement (Kappa value >0.9) for all findings between MRI and Arthroscopy in these 23 patients.
3. As it is mentioned in literature, some intra-substance meniscal tears can be missed on arthroscopy.

DISCUSSION

Ultrasonographic diagnosis of orthopaedic conditions has gathered pace in recent years. It has become popular because it is quick, easily available and fairly reliable. USG diagnosis of knee injuries has been tried in various studies with variable results.[28–30] The current study was carried out at SKIMS Soura Srinagar, a tertiary care institute of the valley in the department of radiodiagnosis and imaging. A total of 60 patients were included in the study. All the 60 patients underwent USG and MRI of the knee and 23 patients underwent Arthroscopy. As there was absolute agreement between MRI and Arthroscopic findings in these 23 patients and also it is mentioned in literature that some intra-substance meniscal tears can be missed on arthroscopy, MRI was used as a standard for comparison of USG findings to calculate its sensitivity, specificity and diagnostic accuracy.

In our study, the mean age of patients was 35.7 years (range 16–59 years), the percentage of males was 83.3% and the percentage of females was 16.7%. The findings were similar to study carried out by Nasir *et al.*[31], where mean age was 35.3 years and percentage of males and females was 78% and 22 %, respectively. The high male to female ratio may be because of the fact that males are more involved in outdoor activities, sports and industrial works and are thus more prone to injuries. Knee joint effusion was the most frequent finding seen in 29 out of 60 patients. Ultrasound was consistent with MRI in 60 out of 60 patients (29 true positives and 31 true negatives) resulting in accuracy of 100%. The results were consistent with the study conducted by Singh B *et al.*,[32] which showed 100% accuracy of ultrasound in detecting knee joint effusion.

Regarding statistical results for ACL tears, Ultrasound was consistent with MRI in 55 (91.67%) out of 60 patients as it yielded 09 true positive, 46 true negative, 02 false positive and 03 false negative results. Sensitivity, specificity

Table 7: Sensitivity, Specificity and Accuracy of USG as compared to MRI.

	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)	Lower-upper 95% CIs	Chi- square test	p-value
ACL	75	95.83	91.67	75.60–92.05	16.36	0.002
PCL	77.7	84.31	83.33	73.09–90.20	10.73	0.010
MCL	78.94	100.0	93.35	85.00–97.54	43.15	0.001
LCL	70.0	100.0	95.0	81.23–95.84	26.03	0.001
MM	83.33	91.67	88.3	79.11–94.60	34.2	0.000
LM	55.55	88.23	88.33	70.71–88.30	4.49	0.080
EFFUSION	100	100	100	98.39–100	56.97	0.000

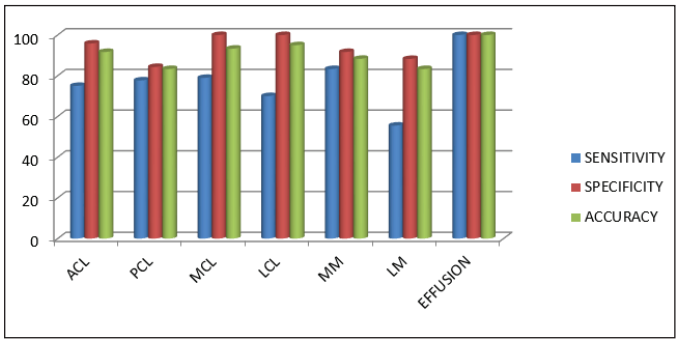

Figure 1: BAR diagram showing sensitivity, specificity and accuracy of USG.

and accuracy of ultrasound in detecting ACL injury was 75%, 95.8% and 91.67 %, respectively. Our results were concordant with the study done by Fried W *et al.,*[24] who has documented sensitivity and specificity of 70% and 98%, respectively. Our results were slightly lower than the study conducted by Ptasznik R *et al.,*[26] who has documented sensitivity and specificity of 91% and 100%, respectively. Our results were also complemented by the study done by Abdel El Monem *et al.,*[29] which showed USG sensitivity of 81% and specificity of 84% for detection of ACL tears.

For PCL tears, ultrasound was consistent with MRI in 50 (83.3%) out of 60 patients as it yielded 07 true positives, 43 true negatives, 08 false positives and 02 false negatives. Sensitivity, specificity and accuracy of USG was found to be 77.7%, 84.3% and 83.3%, respectively. The study conducted by Singh B *et al.*[32] reported sensitivity, specificity and accuracy of 75 %, 93.4% and 92%, respectively.

The statistical results of medial meniscal tears in our study are: 20 true positives, 03 false positives, 33 true negatives and 04 false negatives. Sensitivity, specificity and accuracy of 83.3%, 91.67% and 88.3% was seen, respectively. For lateral meniscal tears, our study resulted in 05 true positives, 45 true negatives, 06 false positives and 04 false negatives with sensitivity, specificity and accuracy of 55.5%, 88.23%, and 88.33%, respectively. The results were concordant with the study conducted by Singh B *et al.*[32] which had sensitivity, specificity and accuracy of 83.8%, 89.4% and 86% for medial meniscal tears and 40%, 91% and 78.3% for lateral meniscal tears, respectively. However, we were not able to identify types of meniscal tears on ultrasound. On MRI evaluation, types of tears were easily found. Out of 25 meniscal tears, 17 (68%) were horizontal type, 05 (20%) were bucket handle type and 03 (12%) were flap type tears. The morphology of tear was also seen easily on arthroscopy.

Table 8: Diagnostic accuracy of ultrasound in present study in comparison with other studies in detecting knee injuries.

Studies	ACL	PCL	MCL	LCL	MM	LM	Effusion
Abdel El Monem et al.	83	90	_	_	73	86	_
Singh B et al.	90	92	96	96	96	94	100
Singh A et al.	73.3	83.3	96.5	95	95	86.6	_
Present study.	91.6	83.3	93.3	95	95	88.3	100

Figure 2: Medial meniscal tear. **(A)** USG image depicts hypoechoic cleft within medial meniscus. **(B)** PD/SPAIR saggital image depicts hyperintense signal in PHMM. **(C)** Horizontal MMT seen on arthroscopy.

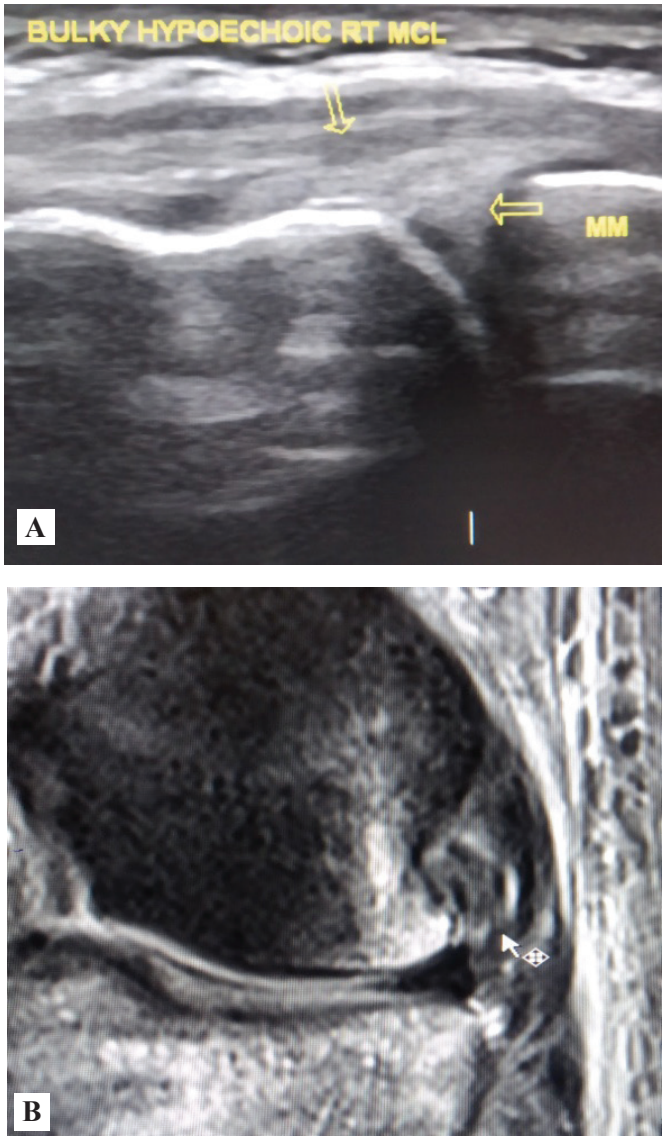

Figure 3: Medial collateral ligament sprain. **(A)** USG image depicts bulky hypoechoic MCL. **(B)** MRI depicts high signal intensity of MCL on PD/SPAIR coronal image.

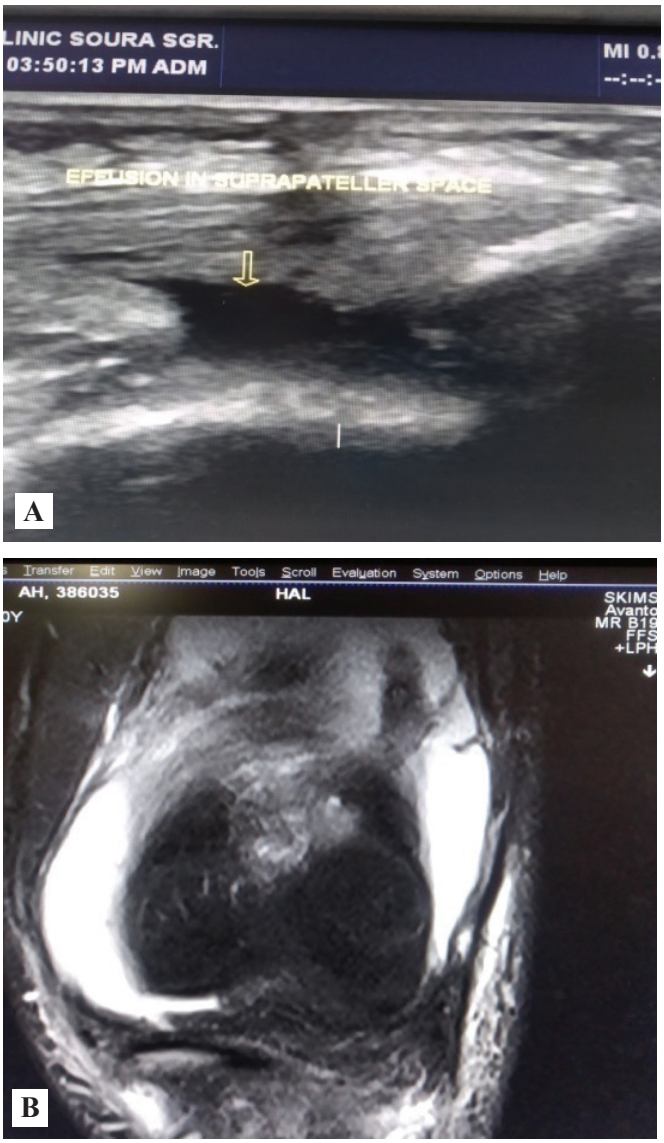

Figure 4: (A) USG image shows mild to moderate fluid accumulation in suprapatellar joint space. **(B)** PD/SPAIR coronal image shows moderate knee joint effusion.

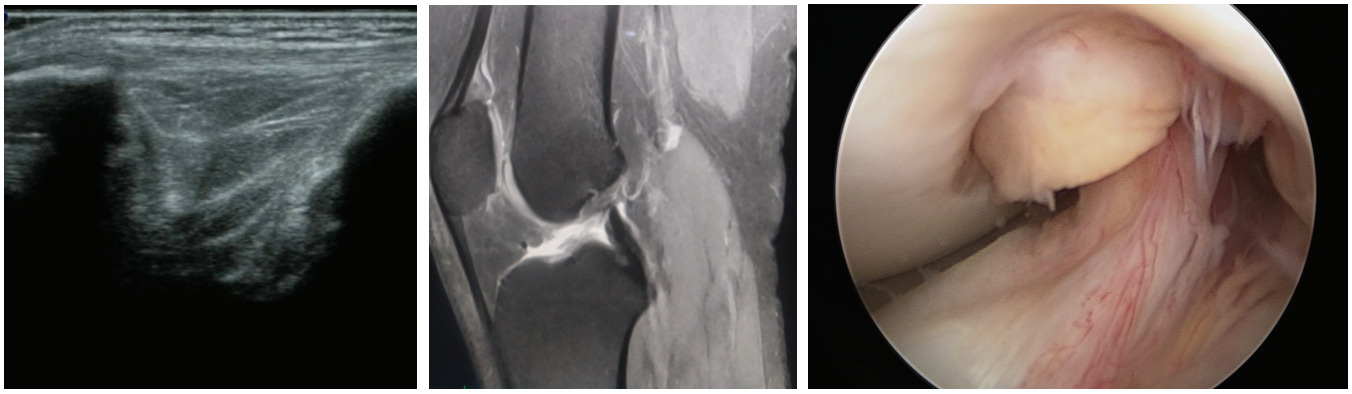

Figure 5: ACL tear. (A) On USG. (B) PD/SPAIR image showing near total tear of ACL. (C) Partial ACL tear on Arthroscopy.

In our study, the sensitivity, specificity and accuracy of ultrasound for detection of MCL injury was 78.9%, 100%, and 93.3% and for LCL injury was 70%, 100%, and 95%, respectively. The results were nearly similar to the study conducted by Singh A *et al.*[33] that revealed sensitivity, specificity and accuracy of 84.6%, 100%, and 96.6% for MCL injury and 84.6%, 97.8%, and 95% for LCL injury, respectively. So, for collateral ligament injuries, ultrasound is a specific, and accurate investigation.

CONCLUSION

Knee injuries are commonly seen in young age with maximum number of patients in the age group of 21–40 years. Most common cause of knee injuries is sports related trauma fallowed by road traffic accidents. It has been observed that Knee injuries show a definite male preponderance with male to female ratio of approximately, 5:1. Right knee was involved more frequently than left knee. Most frequent finding in knee injuries in our study was joint effusion. Medial meniscal tear was most common injury seen in this study.

Based on our results, it can be concluded that USG is an effective imaging modality that has positive effect on the management of many patients presenting with knee injuries. Knee USG has high accuracy in diagnosing menisco-ligamentous injuries. A wide availability, lower cost and fair reliability make it a modality of first choice for evaluation of knee injuries. MRI can be reserved for patients with suspicious USG results.

Ethical standards: There were no ethical issues

Informed Consent: Consent was taken from all the participants.

Acknowledgement: We express our sincere gratitude to all the participants

Data Availability Statement: yes

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ORIGINAL ARTICLE

CyBorD vs. VRD as Induction Therapy in Multiple Myeloma: A Retrospective Study on Kashmiri Patients

Reashma Roshan[1], Aakash Chozkade[2], Imran Nazir[1], Santosh Rathod[3], Sumyra Qadri[4], Javid Rasool[1]

[1]*Department of Clinical Hematology, Sher-i-kashmir Institute of medical Sciences, Srinagar, J&K, India*

[2]*Department of Clinical Hematology, Believer's church medical College, Srinagar, J&K, India*

[3]*Department of Clinical Hematology, All India Institute of medical sciences (AIIMS), Nagpur, Maharashtra, India*

[4]*Department of Pathology, Sher-i-kashmir Institute of medical Sciences, Srinagar, J&K, India*

Corresponding Author: Reashma Roshan (reshma.wani12@gmail.com)

ABSTRACT

Background: Multiple Myeloma (MM) is a clonal plasma cell malignancy that commonly presents with anemia, bone pain, renal dysfunction, and hypercalcemia. While combination regimens like VRD (bortezomib, lenalidomide, dexamethasone) are globally preferred as first-line induction therapy for transplant-eligible patients, real-world data comparing VRD with CyBorD (cyclophosphamide, bortezomib, dexamethasone) remain limited in specific ethnic and resource-constrained settings, including the Kashmiri population.

Objective: To compare the clinical profile, treatment response, and survival outcomes of CyBorD versus VRD as induction regimens in newly diagnosed multiple myeloma patients from Kashmir.

Methods: This retrospective observational study included 101 MM patients treated between January 2015 and June 2022 at a tertiary care center in Kashmir. Patients received either CyBorD (n = 81) or VRD (n = 20). Baseline characteristics, biochemical parameters, response rates, and survival outcomes were analyzed. Kaplan-Meier analysis was used for progression-free survival (PFS) and overall survival (OS).

Results: The median age was 60-years in both groups, with a male predominance. A higher proportion of CyBorD patients presented with ISS Stage III disease (65.4% vs. 40%) and renal dysfunction, reflected by elevated creatinine levels. Lenalidomide, a key component of VRD, was either contraindicated in renal impairment or not freely available during the early study period, influencing treatment selection. The overall response rate (ORR) was comparable between the two regimens (64.3% for CyBorD vs. 68.7% for VRD). The three-year PFS was 67.2% for CyBorD and 60% for VRD. Despite the unequal group sizes, CyBorD showed efficacy even in patients with poor-risk features such as renal impairment.

Conclusion: CyBorD is an effective, accessible, and well-tolerated alternative to VRD in the real-world management of multiple myeloma, especially in patients with renal dysfunction or in settings with limited access to lenalidomide. This study provides valuable regional data and supports the use of CyBorD in resource-constrained environment while highlighting the need for prospective studies with balanced group sizes.

Keywords: MM, VRD, Outcomes, CyBorD, Myeloma.

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INTRODUCTION

Multiple Myeloma (MM) is a hematologic malignancy marked by the uncontrolled proliferation of plasma cells within the bone marrow, leading to various clinical complications such as bone pain, anemia, renal dysfunction, and increased susceptibility to infections. The therapeutic landscape for MM has evolved significantly over recent decades, with induction therapy playing a pivotal role in achieving disease control and preparing patients for subsequent treatment like autologous stem cell transplantation (ASCT). Among the induction regimens, two combinations have garnered considerable attention, CyBorD (cyclophosphamide, bortezomib, and dexamethasone) and VRD (bortezomib, lenalidomide, and dexamethasone).

The VRD regimen has been extensively studied in phase III clinical trials, such as the SWOG S0777, which demonstrated that VRD significantly improves progression-free survival (PFS) and overall survival (OS)

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Conflict of Interest: None

Source of Funding: None

compared to lenalidomide and dexamethasone alone.[1] Based on these findings, VRD is considered the preferred induction regimen for transplant-eligible MM patients in many international guidelines.[2]

In contrast, the CyBorD regimen, which replaces lenalidomide with cyclophosphamide, has been associated with high response rates and is considered effective, as an alternative, particularly in patients with contraindications to lenalidomide, such as renal impairment, or in regions where access to lenalidomide is limited.[3] The safety profile of both regimens are crucial consideration in treatment selection. VRD has been associated with manageable toxicities, with the most common adverse events being hematologic in nature, such as neutropenia and thrombocytopenia, as well as peripheral neuropathy. The tolerability of VRD makes it a viable option for a broad patient population.[4]

CyBorD is generally well-tolerated, with a safety profile that includes manageable adverse events. The regimen's tolerability has been demonstrated in various studies, making it a viable option, especially in resource-constrained settings.[5]

Despite the global preference for VRD, there is limited data comparing CyBorD and VRD in real-world settings, particularly in specific ethnic groups such as the Kashmiri population. The Kashmir region has a unique demographic and genetic profile, which may influence disease presentation and treatment response. Moreover, access to medications remains a critical factor in treatment decisions, with lenalidomide, an essential component of the VRD regimen, often being less accessible due to cost or availability constraints. Additionally, lenalidomide is not suitable for patients with significant renal impairment, which is a common presentation in this population. In such scenarios, the CyBorD regimens serve as a practical and effective alternative, offering both affordability and suitability for patients with renal dysfunction by using cyclophosphamide, which is more widely available and better tolerated in renal compromise.[6]

This study aims to generate real-world evidence comparing CyBorD and VRD in a tertiary care setting in Kashmir. Given the limited literature on MM treatment outcomes in this population, the findings will help guide clinicians in selecting the most appropriate induction therapy based on efficacy, safety, and feasibility. Understanding the comparative benefits and challenges of these regimens in the Kashmiri population will contribute to more personalized and resource-conscious treatment approaches for multiple myeloma.

METHODOLOGY

This retrospective observational study was conducted at the Department of Clinical Hematology and Bone Marrow Transplant Unit, Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar. The study included all patients diagnosed with multiple myeloma based on standard diagnostic criteria and registered at the Regional Cancer Centre (RCC) between January 2015 and June 2022. Patients with smoldering myeloma, monoclonal gammopathy of undetermined significance (MGUS), incomplete investigations, or those who did not receive treatment after diagnosis were excluded.

Data were extracted from RCC medical records, covering the period from patient registration to the follow-up, defined as the date of death, last available medical record, or the end of the study observation period, whichever occurred first. Collected variables included socio-demographic characteristics (age, sex, ethnicity), clinical presentation, laboratory parameters, and comorbidities. Treatment-related data encompassed induction chemotherapy regimens (CyBorD or VRD), treatment duration, and response assessment.

The primary outcomes were overall survival (OS) and progression-free survival (PFS). Time-to-event analyses were performed using Kaplan-Meier survival curves, with OS measured from the date of diagnosis to disease progression or death from any cause. The study was approved by the Institutional Ethics Committee (IEC) of SKIMS, Srinagar (IEC Approval no: SIMS-131/IEC-SKIMS/2022-57). Informed consents were obtained from all the patients before enrollment.

The objective of the study is to assess the efficacy of CyBorD vs. VRD as induction therapies in newly diagnosed multiple myeloma patients, with a focus on response rates and progression-free survival.

Statistical Analysis

Statistical analysis was conducted using SPSS software version 23. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using descriptive statistics such as mean and standard deviation. Kaplan Meier survival analysis was performed to estimate OS and PFS, with log-rank tests used for comparisons between treatment groups. A *p-value* of < 0.05 was considered statistically significant. Median survival times were reported with two-sided 95% confidence intervals.

RESULTS

A total of 101 patients were included in the study, with 81 (80.2%) receiving the CyBorD regimen and 20 (19.8%) receiving the VRD regimen. The median age at presentation was 60 years in both groups, with a slightly wider range in the CyBorD group (34–77 years) compared to the VRD group (45–75 years). The male-to-female ratio was similar between the two regimens, at approximately 2.25:1 for CyBorD and 2.3:1 for VRD.

Presenting Complaints and Performance Status

Generalized weakness was the most common presenting complaint in both groups, observed in 46.9% of CyBorD-treated patients and 45% of VRD-treated patients. Boney pain was more frequently reported in the VRD group (50%) compared to the CyBorD group (27.2%). Azotemia was noted exclusively in the CyBorD group (16.1%), whereas fever was a rare finding in both groups (1.2% in CyBorD, absent in VRD). ECOG performance status at presentation was comparable, with the majority of patients in both groups scoring 1 (51.9% in CyBorD vs. 50% in VRD). However, a slightly higher proportion of VRD-treated patients had an ECOG 0 (10% vs. 1.2% in CyBorD). ECOG 2 was observed in 38.3% of CyBorD patients and 40% of VRD patients, while ECOG 3 was present in 8.6% of CyBorD patients but absent in the VRD group.

Hematological and Biochemical Parameters

The median hemoglobin level was 8.3 g/dL in both groups, but anemia (Hb < 10 g/dL) was more prevalent in CyBorD-treated patients (81.5%) compared to VRD-treated patients (55%). The median total leukocyte count was identical in both groups (5200/ cumm), but a wider range was observed in CyBorD (1400–21500) compared to VRD (2100–10900). Platelet counts were also similar, with a median of 140,000/cumm in both groups. Hypercalcemia was more frequent in CyBorD-treated patients (23.4%) compared to those receiving VRD (10%). Lytic bone lesions were more common in the VRD group (60% vs. 42% in CyBorD). Similarly, elevated lactate dehydrogenase (LDH) levels were more frequently observed in CyBorD-treated patients (29.6%) compared to VRD-treated patients (10%). The median β-2 microglobulin level was significantly higher in CyBorD-treated patients (10,534 mg/dL) than in those receiving VRD (4,705 mg/dL). Conversely, serum albumin levels ≥ 3.5 mg/dL were more frequently observed in the VRD group (55%) compared to CyBorD (40.7%). An albumin-to-globulin (A/G) ratio ≥ 1 was noted in 30% of VRD patients and 24.7% of CyBorD patients.

Staging and Myeloma-Defining Events

Myeloma-defining events (MDE) were more common in CyBorD-treated patients (65.4%) compared to VRD-treated patients (45%). According to the International Staging System (ISS), a higher proportion of CyBorD-treated patients were classified as Stage III (65.4%) compared to VRD (40%). Conversely, ISS Stage I was more frequent in VRD-treated patients (25%) than in CyBorD (6.2%). The Revised ISS (R-ISS) classification showed that the majority of patients in both groups were in Stage II (74.1% in CyBorD vs. 75% in VRD). However, Stage III disease was more frequent in CyBorD-treated patients (22.2%) compared to VRD (10%), while Stage I was more prevalent in the VRD group (15% vs. 3.7% in CyBorD).

Treatment Outcomes

The treatment details and outcomes of patients receiving first-line therapy with CyBorD and VRD regimens were analyzed. Supportive therapies, including radiation therapy, zoledronate administration, antiviral prophylaxis, and aspirin usage, varied between the two groups. Radiation therapy was utilized in 21% of patients receiving CyBorD, whereas six patients in the VRD group received this intervention. Zoledronate was initiated at diagnosis in 58% of CyBorD-treated patients compared to 100% in the VRD group. Antiviral prophylaxis was more commonly administered in the CyBorD group (66.7%) than in VRD (100%). Aspirin usage was reported in 22.2% of patients receiving CyBorD, whereas all VRD patients were prescribed aspirin.

Response to Treatment

The overall response rate (ORR), defined as the sum of complete remission (CR) and partial remission (PR) was comparable between the two treatment arms, with 64.3% in CyBorD and 68.7% in VRD. The proportion of patients achieving CR was slightly higher in the CyBorD group (35.7%) compared to VRD (31.2%). However, partial remission was more frequently observed in the VRD-treated group (37.5%) than in the CyBorD group (28.6%). A very good partial response (VGPR) was achieved in 26.8% of CyBorD-treated patients and 31.2% of VRD-treated patients. Stable disease (SD) was observed in 3.6% of CyBorD

patients, while none of the VRD-treated patients had SD. Progressive disease (PD) was recorded in 5.3% of CyBorD patients, whereas no VRD-treated patients exhibited disease progression following upfront therapy.

Survival Outcomes and Follow-up

At the last follow-up, 47 patients (46.5%) were alive, with 33 patients in the CyBorD group and 14 from the VRD group. A total of 23 deaths were recorded in the study cohort, with a higher mortality rate observed in the CyBorD group (n = 20; Progressive disease = 3, Others = 17) compared to the VRD group (n = 3; Progressive disease = 1, Others = 2). Additionally, 31 patients were lost to follow-up, with a significant proportion from the CyBorD group (n = 28), whereas only 3 patients from the VRD group were lost to follow-up.

The three-year OS was comparable between the two regimens, with CyBorD achieving an OS of 82.4% and VRD slightly higher at 83.1%. This suggests that both regimens effectively prolong survival, with a marginal advantage observed in the VRD group. Median OS has not been reached for either group. However, when assessing progression-free survival (PFS), a notable difference was observed. The 3-years PFS for CyBorD-treated patients was 67.2%, which was higher than that observed in the VRD group (60%).

DISCUSSION

Multiple myeloma is a hematological malignancy characterized by the clonal proliferation of plasma cells, resulting in a range of clinical manifestations. While extensive data exist on MM in Western populations, studies focusing on specific ethnic groups, such as the Kashmiri population, remain limited. This discussion aims to compare the clinical characteristics, treatment regimens, and outcomes of MM patients in the Kashmiri cohort with existing data from both Western and Indian studies, with a particular focus on the efficacy of CyBorD versus VRD as frontline therapies.

In our study, the median age at diagnosis was 60-years for both the CyBorD and VRD groups, with a male-to-female ratio of approximately 2.25:1 and 2.3:1, respectively. This aligns with findings from other Indian studies, which report a median age of 55-years and a male predominance (69%). Similarly, a South Indian study observed a mean age of 64 with a male-to-female ratio of 1.3:1. In contrast, Western studies typically report a higher median age at diagnosis, around 66 years, with a male-to-female ratio of approximately 1.5:1. These differences suggest that MM present at a younger age in the Indian population, including the Kashmiri cohort.[7,8]

Generalized weakness was the most common presenting complaint in both treatment groups, observed in 46.9% of CyBorD-treated patients and 45% of VRD-treated patients. Bone pain was more frequently reported in the VRD group (50%) compared to the CyBorD group (27.2%). These findings are consistent with other Indian studies, where bone pain and fatigue were predominant symptoms. In Western populations, bone pain is also a common presenting symptom, reported in approximately 68% of patients. The similarity in clinical presentations across different populations underscores the universal nature of MM symptoms.[8,9] Anemia was more prevalent in the CyBorD group (81.5%) compared to the VRD group (55%). This is higher than the 50% prevalence reported in some Indian studies. Hypercalcemia was observed in 23.4%of CyBorD-treated patients and 10% of VRD-treated patients, which is higher than the 18.8% reported in the South Indian cohort. Lytic bone lesions were more common in the VRD group (60%) compared to the CyBorD group (42%), aligning with the 84% prevalence reported in other Indian studies. Elevated β-2 microglobulin levels, another marker of tumor burden, were also markedly elevated in the CyBorD group (median 10,534 mg/dL) than in the VRD group (4,705 mg/dL), yet the response and survival outcomes remained comparable to VRD.[8]

A higher proportion of CyBorD-treated patients were classified as ISS Stage III (65.4%) compared to the VRD group (40%). This is consistent with other Indian studies, where a majority of patients presented with advanced-stage disease.[7] In contrast, Western studies often report a more even distribution across ISS stages.[3] The predominance of advanced-stage presentation in the Indian population may be attributed to delayed diagnosis and limited access to healthcare facilities. The higher ISS Stage III prevalence in CyBorD-treated patients (65.4% vs. 40%) further supports the argument that CyBorD can be effective in advanced disease.

In our study, 80.2% of patients received the CyBorD regimen, while 19.8% received the VRD regimen. The overall response rate (ORR) was comparable between the two groups: 64.3% in the CyBorD group and 68.7% in the VRD group. These response rates are consistent with those reported in other studies, where CyBorD demonstrated an ORR of 84%, with 63% achieving VGPR or better.

Table 1: Baseline characteristics of the study patients.

Characteristics	CyBorD	VRD	Total
Total Patients	81	20	101
Median Age in years, range	60 (34–77)	60 (45–75)	60 (34–77)
Gender, n (%)			
Male	56 (69.1%)	14 (70%)	70 (69.3%)
Female	25 (30.9%)	6 (30%)	31 (30.7%)
M : F	2.24:1	2.3:1	2.25:1
Presenting complaints, n (%)			
Azotemia	13 (16.1)	-	13 (12.9%)
Bony Pains	22 (27.2)	10 (50%)	32 (31.7%)
Fever	1 (1.2)	-	1 (0.9%)
Generalized Weakness	38 (46.9)	9 (45%)	47 (46.5%)
ECOG, n (%)			
0	1 (1.2%)	2 (10%)	3 (3%)
1	42 (51.9%)	10 (50%)	52 (51.5%)
2	31 (38.3%)	8 (40%)	39 (38.6%)
3	7 (8.6%)	-	7 (6.9%)
Hemoglobin (gm/dL), median (range)	8.3 (4.2–15)	8.3 (5.5–14.4)	8.3 (4.2–15)
Anemia (< 10 gm/dL) at presentation, n (%)	66 (81.5%)	11 (55%)	77 (76.2%)
Total Leukocyte Count /cumm, median (range)	5200 (1400–21500)	5200 (2100–10900)	5200 (1400–21500)
Platelet Count x 10^6 /cumm	140000 (13000–386000)	140000 (52000–305000)	140000 (13000–386000)
Hypercalcemia, n (%)	19 (23.4%)	2 (10%)	21 (20.8%)
Lytic lesions, n (%)	34 (42%)	12 (60%)	36 (35.6%)
Elevated LDH, n (%)	24 (29.6%)	2 (10%)	26 (25.7%)
β-2-microglobulin (mg/dL), median (range)	10534 (1909–40804)	4705 (2269–17682)	7975 (1909–40804)
Sr. Albumin (≥ 3.5 mg/dL), n (%)	33 (40.7%)	11 (55%)	44 (43.6%)
A/G (≥ 1) Ratio, n (%)	20 (24.7%)	6 (30%)	26 (25.7%)
Plasma cell (%), median (range)	55 (6–90)	40.5 (2–90)	53.5 (2–90)
M-Spike (%), median (range)	2.8 (0–9.7)	3.7 (0.4–6.9)	3 (0–9.7)
Immunofixation electrophoresis (IFE), n			
IgA/Kappa	6	3	9
IgA/Lambda	12	1	13
IgG/Kappa	22	9	30
IgG/Lambda	16	5	21
IgM/Kappa	1	-	1
Kappa	5	2	7
Lambda	14	-	14
Nil	1	-	6
Myeloma defining event (MDE), n (%)	53 (65.4%)	9 (45%)	62 (61.4%)
ISS Stage, n (%)			
1	5 (6.2%)	5 (25%)	10 (9.9%)
2	23 (28.4%)	7 (35%)	30 (29.7%)
3	53 (65.4%)	8 (40%)	61 (60.4%)
R-ISS Stage, n (%)			
1	3 (3.7%)	3 (15%)	6 (5.9%)
2	60 (74.1%)	15 (75%)	75 (74.3%)
3	18 (22.2%)	2 (10%)	20 (19.8%)

Table 2: Treatment details and outcomes of the study patients on first-line treatment.

Treatment details	CyBorD (n = 81), n (%)	VRD, n (%)	Total, n (%)
Radiation Therapy	17 (21%)	6	23
Zoledronate on diagnosis	47 (58%)	20	67
Antiviral prophylaxis	54 (66.7%)	20	74
Aspirin usage	18 (22.2%)	18	36
Treatment response post-upfront treatment	(assessed = 56)	**(assessed = 16)**	**(assessed = 72)**
– Overall Response Rate (CR+PR)	36 (64.3%)	11 (68.7%)	47 (65.3%)
– Complete Remission (CR)	20 (35.7%)	5 (31.2%)	25 (34.7%)
– Partial Remission (PR)	16 (28.6%)	6 (37.5%)	22 (30.5%)
– Very Good Partial Response (VGPR)	15 (26.8%)	5 (31.2%)	20 (27.8%)
– Stable Disease (SD)	2 (3.6%)	-	2 (2.8%)
– Progressive Disease (PD)	3 (5.3%)		3 (4.2%)
At Last follow-up			
Alive	33	14	47
Death	20	3	23
Lost to follow-up	28	3	31
3-years Overall Survival (OS)	82.4%	83.1%	73.1%
3-years Progression Free Survival (PFS)	67.2%	60%	66.7%

Similarly, VRD has been associated with high response rates in various studies. Our findings suggest that both regimens are effective in the Kashmiri population.[10] The three-year OS was comparable between the two groups, with CyBorD achieving an OS of 82.4% and VRD slightly higher at 83.1%. Median OS has not been reached for either group due to limited follow-up duration, but early survival trends are promising. This aligns with findings from other studies, where the median OS for the CyBorD-treated patients were 103.8 months, and for VRD-treated patients, it was 101.7 months. The PFS at 3-years was higher in the CyBorD group (67.2%) compared to the VRD group (60%). These survival outcomes are comparable to those reported in Western populations, suggesting that both regimens are effective in prolonging survival among MM patients.[3,5,10,11]

In this study, the majority of patients (80.2%) received the CyBorD regimen, while 19.8% received VRD. This skewed distribution reflects the real-world challenges faced during the early phase of the study (2015 – 2018), when lenalidomide was costly and not freely available. As a result, clinicians preferred CyBorD, which was more accessible and affordable.

Moreover, renal dysfunction at presentation, specifically elevated serum creatinine, was observed exclusively in the CyBorD group (16.1%). This is noteworthy, as lenalidomide is contraindicated in patients with significant renal impairment. Thus, CyBorD remained the only feasible option for such patients. Interestingly, despite this unfavorable prognostic factor, patients in the CyBorD group demonstrated survival outcomes comparable to those in the VRD group. This suggests that CyBorD is highly effective even in patients with poor baseline renal function. Another key limitation that needs acknowledgment is the unequal number of patients in each group (81 vs. 20). This disparity affects the robustness of direct percentage-based comparisons and statistical significance. Nevertheless, the trends observed still provide meaningful clinical insights.

This study is the first to compare CyBorD and VRD as frontline regimens in multiple myeloma patients specifically from the Kashmiri population, addressing a significant gap in regional data. Despite limitations such as its retrospective design, small sample size, and unequal group distribution, the findings suggest that while VRD remains the internationally preferred induction therapy, CyBorD is a practical and effective alternative, particularly in resource-constrained settings or in patients with renal impairment.

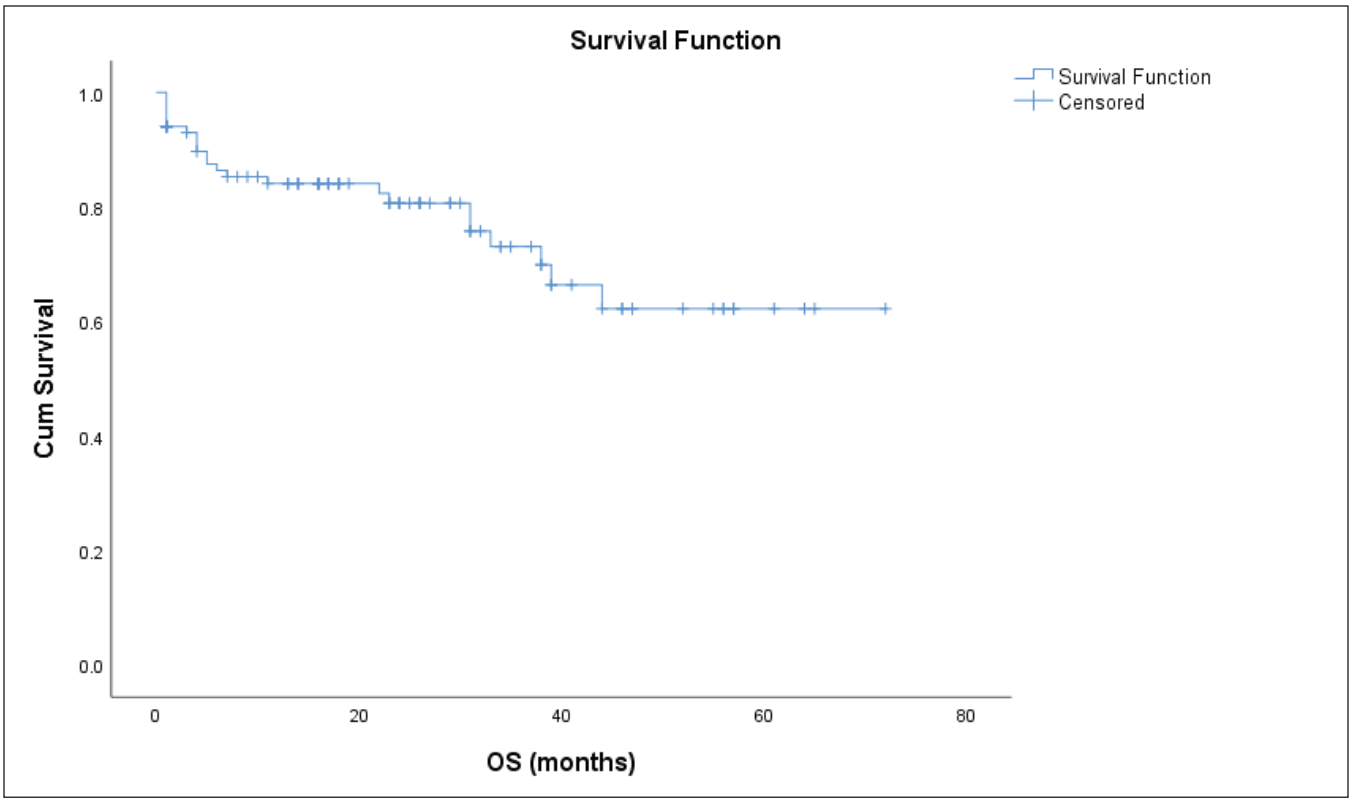

Figure 1: Kaplan-Meier curve depicting the Overall Survival (OS) of the study cohort.

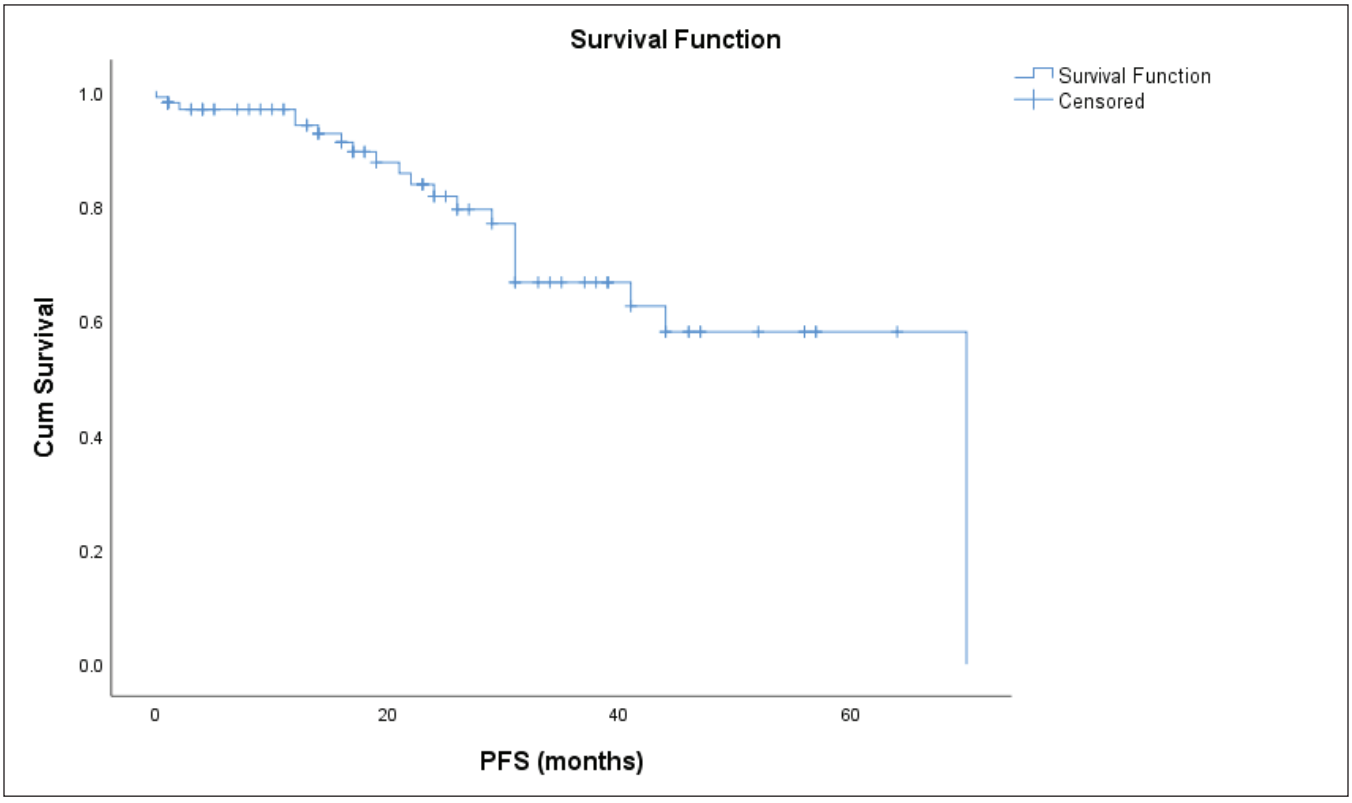

Figure 2: Kaplan-Meier curve depicting the Progression-Free Survival (PFS) of the study cohort.

CONCLUSION

In conclusion, this study provides real-world evidence comparing CyBorD and VRD as upfront therapy for multiple myeloma in the Kashmiri population. Both regimens showed comparable outcomes in terms of response and survival, with VRD showing slightly better tolerability and supportive care adherence, while CyBorD was used more frequently in patients with advanced disease and renal impairment. These findings highlight CyBorD as an effective and accessible alternative to VRD, especially in resource-limited settings or when lenalidomide use is restricted. The study underscores the importance of generating region-specific data to guide personalized treatment decisions and improve outcomes in diverse patient populations.

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ORIGINAL ARTICLE

Clinical and Biochemical Effectiveness of Ursodeoxycholic acid and S-adenosylmethionine in Intrahepatic Cholestasis of Pregnancy: An Observational Study in Kashmiri population

Naser Shaheen[1], Sameena Farhat Hakak[1], Athar Shabir[1], Shagufta Rather[2], Nisar Ahmad Shah[3], Shagufta Parveen[1]

[1]*Department of Pharmacology, Government Medical College, Srinagar, Jamu & Kashmir, India*
[2]*Department of Obsterics and Gynaecology, Government Medical College, Srinagar, J&K, India*
[3]*Department of Medicine, Government Medical College, Srinagar, J&K, India*

Corresponding Author: Athar Shabir (atharshabir786@gmail.com)

ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) occurs in the last trimester of pregnancy1 and is characterized by pruritus and raised biochemical markers. Currently, used drugs for treating ICP include ursodeoxycholic acid (UDCA) and S-adenosyle methionine (SAMe). In our study we are comparing both the drugs in pregnancy induced cholestasis in terms of clinical effectiveness, biochemical changes, as no such study has been done so far in our setup.

Materials And Methods: Patients were divided into two groups A and B. Group A was given 300 mg of (UDC) twice daily. Group B was given 400 mg (SAM) twice daily. Both the groups were first evaluated for clinical and biochemical changes at day one and record was kept. Patients in both the groups were given the drugs as described above. After two weeks both the groups were monitored for clinical improvements and after four weeks both groups were investigated for clinical and biochemical improvements. The efficacy of two drugs was established.

Results: In our study we discover that both the drugs used in the study were effective in terms of both clinical and biochemical improvement in ICP. The bilurubin, ALT, AST and ALP levels in SAM group before treatment were 1.70 ± 0.17 mg/dL, 39.31 ± 8.45 IU/L, 54.1 ± 9.09 IU/L and 175.96 ± 22.12 IU/L, respectively. After treatment, the respective values were 1.54 ± 0.66, 36.67 ± 7.67, 56.17 ± 7.45, and 169.67 ± 19.98. The bilurubin, ALT, AST and ALP levels in UDC group before treatment were 1.80 ± 0.07, 49.25 ± 4.92, 54.35 ± 5.13, and 166.5 ± 18.23, respectively. After treatment the values were 0.84 ± 0.06, 36.25 ± 7.67, 35.67 ± 5.64, and 95.55 ± 23.12, respectively. Pruritus improved in both the groups, but more in UDCA group.

Conclusion: UDCA is a better drug for improving biochemical and clinical parameters as compared to SAM.

Keywords: Adenosylemethionine, Intrahepatic cholestasis of pregnancy (ICP), Ursodeoxycholic acid.

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a condition whose cause is poorly understood and may occur in the last trimester of pregnancy.[1] ICP is characterized by mild to severe pruritus and disturbed liver function.[2,3] ICP may be triggered by the cholestatic effects of pregnancy hormones and their metabolites in genetically predisposed women.[4] Multiple factors have been implicated in the pathogenesis of ICP, including environmental influences, nutritional deficiencies, hormonal changes and genetic variations.[5,6]

ICP may seriously affect the fetus, and is associated with complications such as premature delivery, meconium-stained amniotic fluid, fetal distress, sudden intrauterine fetal death, stillbirth and even neonatal death. Thus, women with ICP should be considered high-risk and the fetus should be carefully monitored during the third trimester.[7,8] ICP is characterized by its occurrence in the last trimester, higher incidence in twin pregnancies, resolves promptly after delivery and recurrence in 45–70% of the patients.[9] The higher incidence in third trimester and in multiple pregnancies and the induction of cholestasis by oral contraceptive pills containing estrogen

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in high dose or progesterone treatment indicate a major role of sex hormones.[10] Furthermore, specific alterations in progesterone and bile acid metabolism have been defined. It has been suggested that there is a combination of increased synthesis and impaired biliary excretion of sulfated progesterone metabolites.[11]

Incidence of intrahepatic cholestasis of pregnancy varies in different countries, like in USA the incidence of intrahepatic cholestasis of pregnancy is 70/10000,[2] in Canada 10/10000,[3] and in India 1.24%.[12] The clinical features of intrahepatic cholestasis of pregnancy are itching all over the body, abnormal liver function tests, sleep deprivation and sometimes jaundice,[13] but most of the authorities accept even only elevation of liver enzymes during pregnancy as intra hepatic cholestasis of pregnancy after other causes of elevation of these enzymes have been ruled out.[14]

Bile acids are the most sensitive indicator of ICP and ICP-specific changes, though their role as pruritogens is unclear. Serum bile acid levels only weakly reflect the degree of itch.[14] Transaminases (alanine aminotransferase/aspartate aminotransferase [AST/ALT]) are elevated in about 80% of cases in ICP.[3] In normal pregnancy serum concentrations of bile acids remain unaltered, but in intrahepatic cholestasis of pregnancy, there is 10–100 times increase of serum bile acid concentrations.[15] Though the clinical importance of intra hepatic cholestasis of pregnancy lies in the potential fetal risk that include small for gestational age, premature delivery, still birth and neonatal death,[16] but the symptoms experienced by the mother, as well as the psychological burden on the mother also needed to be taken into consideration. In view of its effect on foetus, regular tests of feto-placental function in late pregnancy are advised.[17] Currently, the major goal of ICP treatment is to improve symptoms in mother, decrease bile acid level, restore liver function and decrease the rate of neonatal asphyxia and even perinatal death. Primarily the aim of the treatment should be to relieve her symptoms without causing any harm to her foetus. A major goal of pharmacologic therapy in ICP is to provide relief from pruritus. An optimal therapeutic strategy against ICP has not yet been identified. The drugs that have so far been used in the treatment of ICP include ursodeoxycholicacid, S-adenosyl methionine, dexamethasone and some chinese herbs.[18,19] Previous studies have shown that both S-adenosylmethionine and Ursodeoxycholic acid are beneficial in intrahepatic cholestasis of pregnancy.[20,21]

Clinical trials and observational studies conducted over the last 20-years have indicated that ursodeoxycholic acid (UDCA) and S-adenosylmethionine (SAMe) can improve pruritus and serum biochemical abnormalities, further improving perinatal outcomes.[20-23] UDCA is a hydrophilic bile acid that detoxifies hydrophobic bile acids, preventing injury to the bile ducts. SAMe is the principal glutathione precursor and methyl group donor involved in the synthesis of phosphatidylcholine. SAMe not only influences the composition and fluidity of hepatocyte plasma membranes, but it also increases the methylation and biliary excretion of hormone metabolites.[24]

Currently, used drugs for treating ICP include Ursodeoxycholic acid (UDCA) and S-adenosine methionine (SAMe),[22,23] and they need to be compared in terms of their effectiveness, cost benefits and foetal outcome. Since 1992, UDCA has become the standard medication for ICP.[25] Although having remarkable efficacy in treating ICP by these drugs, further substantiation is required due to inherent different scenarios in these previous studies and due to lack of any such study having been done in our setup. In addition to this, the different efficacies of these two therapies may be attributed to their different pharmacological effects. Further studies should examine how both of these drugs influence ICP, as well as the differences in the mechanisms by which these therapies improve symptoms in ICP patients.

MATERIALS AND METHODS

The study was conducted by the department of pharmacology in collaboration with the department of gastroenterology and the department of obstetrics and gynaecology, Government Medical College Srinagar, over a period of 2-years on 38 patients after seeking a proper clearance from institutional ethical committee. Patients with the diagnosis of ICP who were attending the Gastroenterology department (either directly or referred by the department of obstetrics and gynaecology) were prescribed the drugs under study and were observed and followed up 2 weekly for clinical, and monthly for biochemical improvement, as well as for monitoring adverse drug reactions, if any, for the drugs under study.

Patients after proper examination and all relevant investigations had been divided into two groups, A and B. Group A was given 300 mg of Ursodeoxycholic

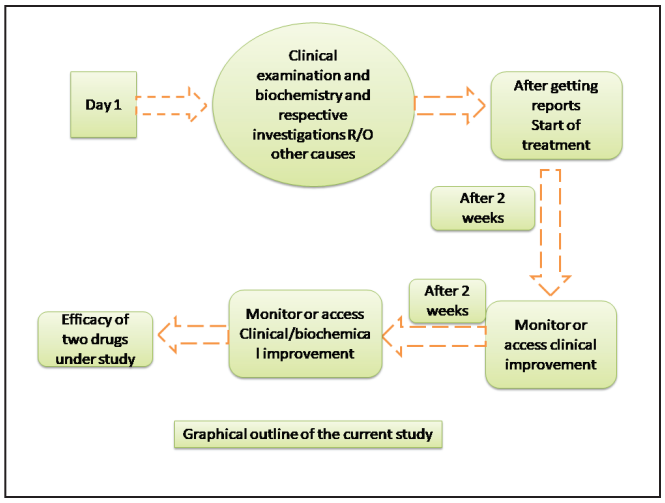

Figure 1: The graphical outline of whole study.

acid (UDC) twice daily. Group B was given 400 mg of S-Adenosyl menthionine (SAM) twice daily. The graphical outline of whole study is shown in Figure 1.

Statistical Analysis

Continuous variables were expressed as Mean ± S.E; while as categorical variables were expressed as count/percentage. Comparison for continuous variables was estimated by Mann-Whitney U-test and categorical data was compared by Chi-square test. Time dependent events in groups were compared by two-sided log-rank test (Hazard Ratio and 95% CI). *p-value* of less than 0.05 was considered Statistically significant and statistics was performed with IBM SPSS Statistics, version 20 and statographics.[18]

RESULTS

From 2017 to 2019, a total of 39 pregnant women met the inclusion criteria and chose to participate in the study, and they were randomized to Groups U and Groups S on a (n = 19) 1: (n =19) 1 ratio.

Table 1: Mean ± S.E of Biochemical parameters in clinical cases with ICP after randomization in two groups.

Parameter	Group U (N = 19)	Group S (N = 19)	p-Value
Bilirubin (mg/dL)	1.8 ± 0.20	1.73 ± 0.17	0.987
ALT (IU/L)	49.25 ± 4.92	39.31 ± 2.89	0.571
AST (IU/L)	54.35 ± 5.13	54.1 ± 4.13	0.897
ALP (IU/L)	166.5 ± 18.23	175.96 ± 14.13	0.345

Table 2: Comparison of Biochemical levels before and after treatment in ursodeoxycholic acid treatment group.

Parameters	Groups		p-value
	Before treatment	After treatment	
Bilirubin (mg/dL)	1.80 ± 0.07	0.84 ± 0.06	<0.001
ALT (IU/L)	49.25 ± 4.92	36.25 ± 7.67	<0.01
AST (IU/L)	54.35 ± 5.13	35.67 ± 5.64	0.06
ALP (IU/L)	166.5 ± 18.23	95.55 ± 23.12	<0.001

Table 3: Comparison of Biochemical levels before and after treatment in S-adenosylmethionine treatment group.

Parameters	Groups		p-value
	Before treatment	After treatment	
Bilirubin (mg/dL)	1.70 ± 0.17	1.54 ± 0.66	0.09
ALT (IU/L)	39.31 ± 8.45	35.67 ± 7.67	0.78
AST (IU/L)	54.1 ± 9.09	56.17 ± 7.45	0.79
ALP (IU/L)	175.96 ± 21.12	169.67 ± 19.98	0.67

Tables 2 and 3, show the mean changes in liver function tests and bilirubin before and after treatment with the different treatment protocols, in each group and between the two groups.

DISCUSSION

Liver diseases unique for pregnancy are not uncommon and may have a serious impact on fetal and/or neonatal outcomes.[26] One of the major areas of progress over the last decade in the hepatology field is the recognition and understanding of the pathogenesis of ICP.[27] Intrahepatic cholestasis of pregnancy is the most common liver disease during pregnancy with reported incidence rates between 0.2 and 12% in different countries.[12] ICP is characterized by otherwise unexplained pruritus in late second and third trimester of pregnancy, elevated bile acids and/or elevated transaminases and spontaneous relief of symptoms and complete normalization of biochemical aberrations within a few weeks after delivery.[2]

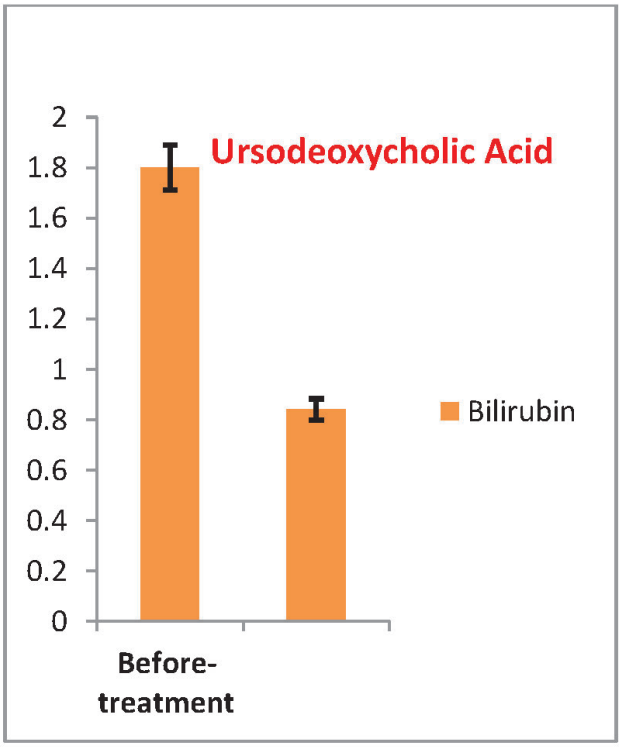

Figure 2 A: comparison of bilirubin levels before and after treatment in ursodeoxycholic acid treatment group.

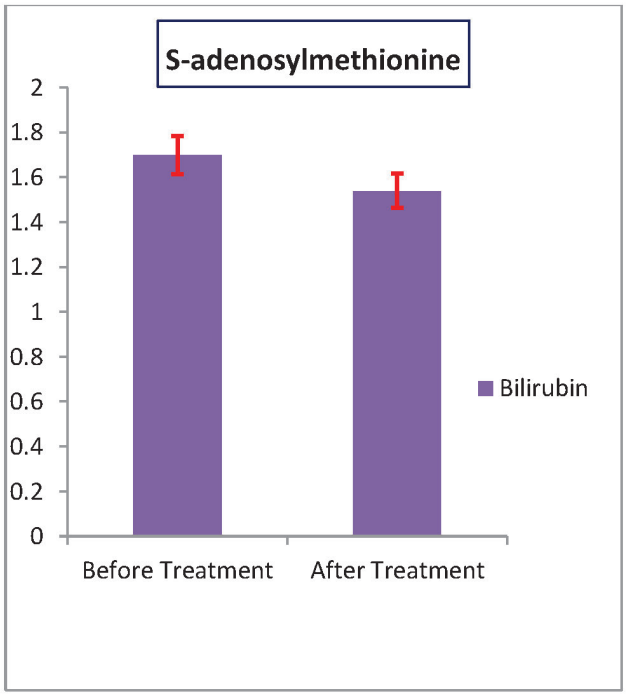

Figure 2B: Comparison of bilirubin levels before and after treatment in S-adenosylmethionine group.

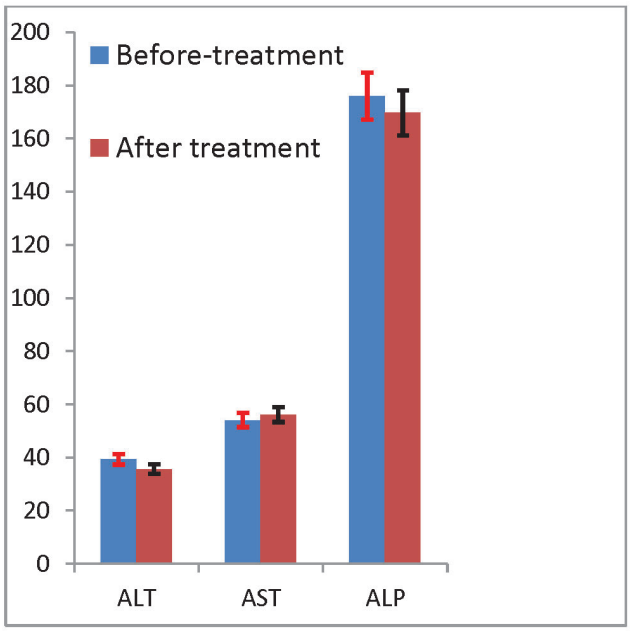

Figure 3A: Comparison of Liver specific biomarkers before and after treatment in S-adenosylmethionine group.

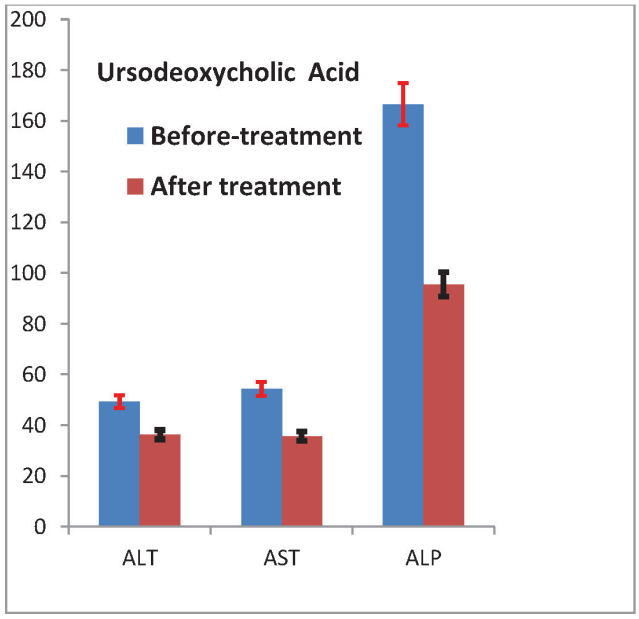

Figure 3B: Comparison of Liver specific biomarkers before and after in ursodeoxycholic acid treatment group.

Transaminases (alanine aminotransferase/aspartate aminotransferase [AST/ALT]) are elevated in about 80% of cases.[28] There are reports of ICP with debut of pruritus already in the first trimester, but majority (about 80%) of the patients present with itching in gestational weeks 30–32.[17] A major goal of pharmacologic therapy of ICP is to provide relief from pruritus. The gold standard for ICP treatment is drugs capable of reducing itching

and normalizing liver function tests and improving the outcome of pregnancy with minimal side effects on the mothers and the fetuses.[2,3]

The guidelines of the European Association for the Study of Liver (EASL) recommend ursodeoxycholic acid (10–20 mg/kg per day) as the first-line treatment for ICP as it also improves liver function tests in many cases.[29] S-adenosylmethionine (SAMe) aiming to enhance methylation and biliary excretion of hormone metabolites has also been reported to ameliorate symptoms of ICP.[30]

The present study was conducted in the Department of Pharmacology, Government Medical College, Srinagar in collaboration with the Department of Gastroenterology, Obstetrics and Gynecology, GMC Srinagar after getting approved by Institutional Ethics Committee, from January 2018 to June 2020, to compare the efficacy of S-adenosyl-L-methionine and ursodeoxycholic acid in the treatment of ICP. In our prospective unicentric study carried out on a sample size of 38 pregnant women with deterioration of liver function tests, we were able to prove that ursodeoxycholic acid administered to ICP patients was therapeutically efficient and not associated with serious side effects for pregnant women, fetuses, or neonates. Our data are consistent with all previous clinical studies published thus far,[28-31] but compared to the others, our study strongly supports the therapeutic potency as well as safety of this drug in ICP patients. In fact, the first case report on pregnant woman with ICP, treated with ursodeoxycholic acid was published as early as 1999.[32] Palma *et al.* reported that the administration of ursodeoxycholic acid to patients with ICP significantly improved pruritus, serum levels of bile acids, and ALT activities without adverse effects for mother or fetus,[33] with further studies following subsequently. Furthermore, the Cochrane review on treatment of ICP,[34] concluded that ursodeoxycholic acid treatment significantly improves pruritus, with the potential to decrease fetal distress and asphyxia. Together with the results from our large prospective clinical observation, all the available data strongly suggests the therapeutic efficacy as well as safety of ursodeoxycholic acid in ICP patients, which calls for a revision of the current obstetrics guidelines, changes of the current information, which should lead to wider use of ursodeoxycholic acid in pregnant patients.

UDCA and SAMe have been applied in the treatment of ICP for decades.[5,7] Previous reports have shown that both drugs are effective and safe, but available data are limited hitherto. We, therefore, performed a single-centered, randomized controlled, open clinical trial to compare the efficacy of UDCA, and SAMe, monotherapy. So, we compared ursodeoxycholic acid treatment with S-adenosylmethionine treatment in clinical series of 18 patients in each group. There are some clinical trials in the published literature however, the sizes of these studies are small, and the results are inconsistent. Thus, to our knowledge, we have completed the largest randomized clinical trial comparing the efficacy of UDCA and SAMe in the treatment of ICP to date. In our study, both UDCA and SAMe were equally effective at alleviating pruritus. We also found that the treatment by UDCA, in monotherapy is more effective than SAMe monotherapy in the improvement/normalization of bilirubin level. Our results based on statistical analysis shows ursodeoxycholic acid treatment was significantly more effective than S-adenosylmethionine (SAMe) in amelioration of biochemical anomalies observed in intrahepatic cholestasis of pregnancy. Furthermore, in the present study in the group treated by SAMe, no appreciable improvement was observed in the biochemical parameters, except in few isolated cases. In majority of cases, the values remained unaffected or increased. The group treated by the ursodeoxycholic acid recorded a marked improvement of the values; hence the comparative data indicate that treatment by ursodeoxycholic acid, in the form of monotherapy improves significantly the values of the biochemical manifestations of ICP whereas SAMe monotherapy has no significant effect on ICP biochemical symptoms. These findings are in accordance with recently published researcher results which reported similar effects in open series and case reports, and until 2019, a total of 11 randomized controlled trials have been published that compared ursodeoxycholic acid to other drugs, placebo or no treatment. The first meta-analysis reviewed nine randomized controlled trials,[32] which compared the effects of ursodeoxycholic acid to other drugs, placebo, or no treatment. Altogether, 454 patients were analyzed: 207 received only ursodeoxycholic acid, 70 only placebo, 42 cholestyramine, 36 dexamethasone (1 week, followed by placebo for 2 weeks), 65 SAMe, and 34 no treatment. Ursodeoxycholic acid compared with all controls was associated with reduced or resolved pruritus, decrease or normalization of ALT, and reduced serum levels of total bile acids. Results similar to ours have been reported by other randomised trials comparing

ursodeoxycholic acid and S-adenosyl-L-methionine.[35] Previous studies compared the effects of therapy only in women who completed at least 10 days of therapy; however, in our study treatment was conducted for 30 days. Although, S-adenosyl-L-methionine appeared to be less effective than ursodeoxycholic acid at improving laboratory parameters, there is contrasting evidence in the literature regarding its efficacy in comparison with placebo. A clinical trial of 18 women randomised to receive either S-adenosyl-L-methionine or placebo did not find a significant difference between the two groups in any of the laboratory measurements considered.[36] It is possible that these contrasting findings may reflect different dosages and routes of administration, as well as differences among populations in their response to the therapy. Similar findings have been reported in another small trial of ursodeoxycholic acid and S-adenosyl-L-methionine.[9] Our study was not large enough to assess whether either therapy had an effect on the risk of fetal mortality associated with gestational cholestasis. However, several lines of indirect evidence suggest that lowering serum bile acids may reduce foetal mortality.

CONCLUSION

We have completed the randomised clinical trial to compare the efficacy of S-adenosyl-L-methionine and ursodeoxycholic acid in the treatment of ICP. We have found that ursodeoxycholic acid is more effective than S-adenosyl-L-methionine at improving the maternal laboratory findings associated with ICP. In the prospective trial of SAMe vs. UDCA in ICP the most impressive results are (i) a positive effect of UDCA in reversing pruritus and in reducing total bile salts and liver specific biomarkers compared with SAMe; (ii) UDCA was found to be superior in restoring liver function tests to normal; (iii) UDCA monotherapy market value is 600 rupees for two week treatment, whereas SAMe monotherapy market value is approximately 2000 rupees. Thus, UDCA costs not more than SAMe, and oral medication is more convenient than intravenous route. In conclusion, with a view to the potential use of UDCA as an effective treatment for ICP, we believe that these results deserve to be confirmed in other case controlled randomized clinical trials.

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ORIGINAL ARTICLE

A Quantitative Estimation of Piperacillin and Tazobactam in Generic and Branded Pharmaceutical Formulations by Reverse Phase High Performance Liquid Chromatography

Athar Shabir, Sameena Farhat Hakak, Naser Shaheen, M Y Rather

Department of Pharmacology, Govt. Medical College, Srinagar, Jamu & Kashmir, India

Corresponding Author: Naser Shaheen (mirnasir2000@yahoo.com)

ABSTRACT

Background: In India, the incidence of sub-standard drugs has risen from 0.04% to 2.3% in 2012 as per Drug Controller General of India (DCGI). There are 66 substandard drugs found in Jammu and Kashmir (India), as per Drugs and food control organization, Jammu and Kashmir 2013. Looking at the rising incidences of sub-standard drugs in the local market of our state, we have chosen piperacillin and tazobactam, used extensively in tertiary care hospital, to verify quality and quantity by employing High Performance Liquid Chromatography (HPLC) based analytical technique.

Methods: Chromatographic separation of the two drugs was achieved using analytical column C18 250/4.6 mm, 5µm particle size, 20µL sample loop size. The mobile phase consisted of a mixture of acetonitrile, methanol and 1% orthophosphoric acid (50:30:20). The drugs were analyzed using UV detector (Diode array detector, DAD) at wavelength 226 nm. The flow rate was maintained at 0.5 ml/min. Column temperature was at 25ºC by in built column thermostat. The injection volume was 20 µL, with a run time of 8 minutes.

Results and conclusion: Amongst the six formulations (Tazar, Tazomac, Zosyn, Durataz, Jan Aushadhi and Jammu and Kashmir Medical Supplies Corporation Limited, i.e, JKMSCL), all the formulations contained piperacillin within the standards specified by the Indian Pharmacopoeia (94-115%), except JKMSCL, which had slightly higher concentration. Further, tazobactam was present in all the formulations. However, the standards for comparison of tazobactam have not been specified within the Indian Pharmacopoeia.

Keywords: Branded, Generic, Piperacillin, Tazobactam, HPLC.

JK-Practitioner 2025; 30(1).

INTRODUCTION

The term 'generic' word in India denotes the medicines which are marketed under a generic name. Another term called 'Branded generics' is used to connote medicines which are now off patent and sold under a brand name by companies, representing almost all the drugs in the Indian Pharmaceutical Market.[1] Piperacillin is a broad spectrum β-lactam antibiotic of the ureidopenicillin class of drugs.[2] Tazobactam is a pharmaceutical drug that inhibits the action of β-lactamases, especially those belonging to the sulfhydryl reagent variable (SHV-1) group. It is commonly used as its sodium salt-tazobactam sodium. Tazobactam contains a beta-lactam ring and irreversibly binds to beta-lactamase at or near its active site. This protects other beta-lactam antibiotics from beta-lactamase catalysis. Piperacillin- tazobactam is recommended as a part of a three drug regimen for the treatment of hospital-acquired pneumonias suspected as being due to infection by multi-drug-resistant pathogens.[3] In India, the incidence of sub-standard drugs has risen from 0.04% to 2.3% in 2012 as per Drug Controller General of India (DCGI). Various state drug controllers, between 2003 and 2008, concluded that 6 to 7.5 % of drug samples failed quality standard tests annually.[4] Additionally, there are 66 substandard drugs found in Jammu and Kashmir (India), as per Drugs and food control organization, Jammu and Kashmir 2013.[5] Looking at the rising incidences of sub-standard drugs in the local market of Jammu and Kashmir,

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Conflict of Interest: None

Source of Funding: None

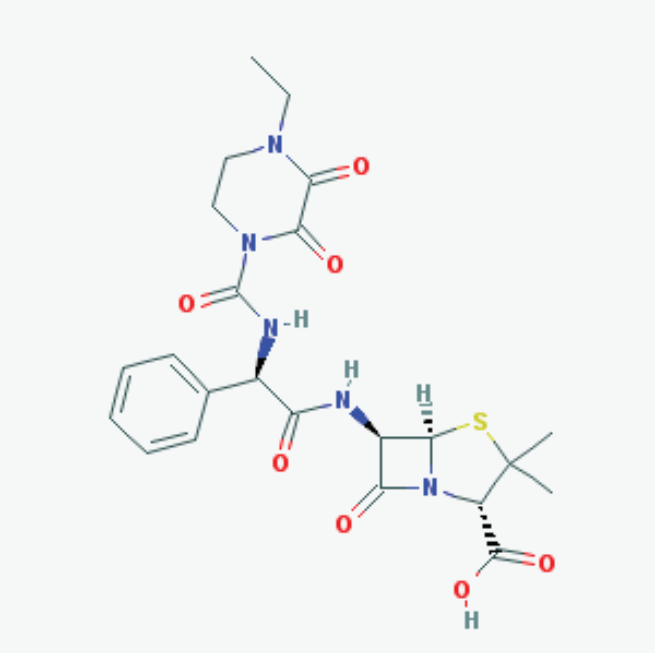

Figure 1: Chemical structure of piperacillin.

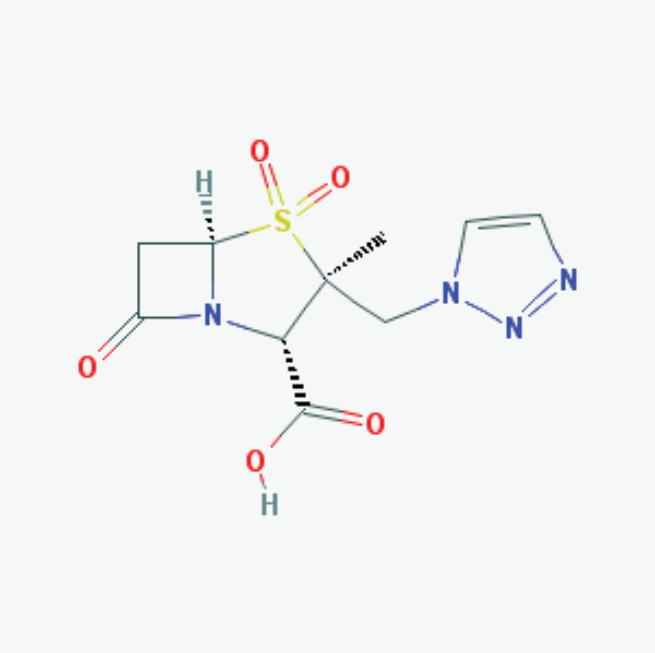

Figure 2: Chemical structure of tazobactam.

we have chosen piperacillin and tazobactam (four branded-generics namely TAZAR, TAZOMAC, DURATAZ, ZOSYN, and two generic formulations procured from Jan Aushadhi and Jammu and Kashmir Medical Supplies Corporation Limited-JKMSCL), which are used extensively in tertiary care hospital, to verify quality and quantity by employing HPLC based analytical technique.

MATERIALS AND METHODS

Chemicals and reagents

The reference sample of piperacillin/tazobactam and other HPLC grade chemicals like acetonitrile, methanol and orthophosphoric acid were procured from Sigma-Aldrich and Merck Specialties Private Limited, Mumbai, India, respectively.

Instruments

For the analysis of the pharmaceutical formulations, we used HPLC 1260 infinity model from Agilent Technologies USA, and the column was analytical column C18 250/4.6 mm, 5µm particle size, 20 µL sample loop size. Electronic balance-Mettler Toledo, was used for weighing the samples. The software which is routinely utilized in our laboratory for HPLC data processing is EZChrom S1.

Chromatographic conditions

Various combinations of eluent like methanol, acetonitrile and 1% orthophosphoric were tested by making slight modifications in reported methods to improve resolution and analysis time of the samples under study.[6] The drugs were analyzed using UV detector (Diode array detector-DAD) at wavelength 226 nm. The flow rate was maintained at 0.5 ml/min. Column temperature was at 25ºC by in built column thermostat. The injection volume was 20 µL, with a run time of 8 minutes.

Preparation of standard solution and plotting of calibration curves

Pure standards of piperacillin and tazobactam were used as external standards in the analysis. Different concentrations of the both standards (piperacillin and tazobactam) were used to plot a suitable 6-point calibration curve (25 µg/ml to150 µg/ml).

20 mg each of piperacillin and tazobactam were weighed separately using a digital weighing electronic balance. Twenty (20) mg of piperacillin was dissolved in a 20 ml capacity volumetric flask using acetonitrile and the final volume was made to 20 ml. Similarly, 20 mg of tazobactam was dissolved in 20 ml of volumetric flask using 1:1 acetonitrile and methanol and final volume was made to 20 ml. For the dilution of stock solution, 100 ml of solvent system was prepared in a ratio of 50:30:20 of Acetonitrile, methanol and 1% orthophosphoric acid respectively. Dilution of 25, 50, 75, 100, 125 and 150 µg/ml were made for piperacillin and

tazobactam separately. Each of the dilutions was injected in triplicates. Chromatographs were obtained for each of the dilutions. 6-Point calibration curves were finally plotted for piperacillin and tazobactam.

Preparation and assay of sample solution

Different branded and generic formulations of piperacillin and tazobactam (each vial of 4.5 g - contains 4 g of piperacillin and 0.5 g of tazobactam) were reconstituted as per manufacturer's instructions. 0.22-micron (μ) syringe filters were used to filter the reconstituted vial. Then stock solution for piperacillin and tazobactam were prepared in triplicates separately containing 1000 μg/ml of piperacillin and tazobactam. From the stock solutions, dilutions of 50 μg/ml and 100μg/ml were prepared in duplicates for piperacillin and tazobactam. Firstly, dilutions of piperacillin were injected followed by tazobactam to prevent any carry over. The peak area values of piperacillin and tazobactam were fit in linear equation *(y = mx + C)* and the concentration was calculated, where ***y*** is peak area, *x* is unknown concentration, ***c*** in intercept and *m* is slope of the curve.

Statistical Analysis

Data was entered in a Microsoft Excel spreadsheet. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as percentages. Data analysis was done using SPSS version 23.

RESULTS & DISCUSSION

The study was conducted in the Department of Pharmacology, Government Medical College, Srinagar, after getting approval from the Institutional Ethics Committee. In this study, concentrations of antibiotics-piperacillin and tazobactam were estimated. The studies conducted by Pai *et al.* (2006);[7] Rao *et al.* (2010);[8] Singh *et al.* (2017);[9] Navle *et al.* (2017),[10] also estimated concentrations of antibiotics piperacillin and tazobactam.

In our study, we have used RP-HPLC method to estimate the concentrations of piperacillin and tazobactam. The same method was also used for estimating concentrations of piperacillin and tazobactam in studies conducted by Pai *et al.* (2006);[7] Rao *et al.* (2010);[8] Singh *et al.* (2017);[9] Navle *et al.* (2017).[10] A study conducted by Sangeetha *et al.* (2017)[11] used UV spectrophotometric method to estimate concentrations of piperacillin and tazobactam.

In this study, six formulations were tested to estimate concentrations of piperacillin and tazobactam. The studies conducted by Pai *et al.* (2006);[7] Rao *et al.* (2010);[8] Singh *et al.* (2017);[9] Navle *et al.* (2017)[10] tested only a single formulation for quantitative estimation of

Table 1: Illustrates that all the formulations contain piperacillin within the standards specified by the Indian pharmacopoeia.

Expect ed concentration (PPCN)		N	Average percent recovery	Std. Deviation	Minimum	Maximum	%RSD
50	Durataz	6	104.4	3.57	99.2	109.5	3.4
	Jan Aushadhi	6	104.1	6.82	97.6	114.0	6.5
	JKMSCL	6	115.6	18.13	93.4	141.8	15.7
	Tazar	6	108.2	6.86	95.8	115.9	6.3
	Tazomac	6	112.7	6.02	106.9	122.4	5.3
	Zosyn	6	110.1	14.60	91.5	126.8	13.3
	Total	36	109.2	10.76	91.5	141.8	9.9
100	Durataz	6	104.5	4.30	100.5	110.4	4.1
	Jan Aushadhi	6	104.0	3.73	100.1	109.6	3.6
	JKMSCL	6	120.9	8.13	117.9	139.9	6.2
	Tazar	6	110.2	6.73	97.8	116.0	6.1
	Tazomac	6	114.2	9.60	107.8	133.4	8.1
	Zosyn	6	108.7	14.55	90.9	125.9	13.4
	Total	36	112.8	12.43	90.9	139.9	11.0

PPCN = Piperacillin, RSD = Relative Standard Deviation

Table 2: Tazobactam is present in all the formulations.

Expected concentration (TZB)		N	Average percent recovery	Std. Deviation	Minimum	Maximum	%RSD
50	Jan Aushadhi	6	67.2	2.91	64.3	71.1	4.3
	JKMSCL	6	84.4	9.05	76.0	95.4	10.7
	Durataz	6	77.0	3.06	73.3	80.8	4.0
	Tazomac	6	97.4	15.24	73.9	117.9	15.6
	Zosyn	6	85.8	4.56	81.5	91.3	5.3
	Tazar	6	82.3	3.95	77.6	87.0	4.8
	Total	36	82.3	11.76	64.3	117.9	14.3
100	Jan Aushadhi	6	62.7	2.54	60.0	65.4	4.1
	JKMSCL	6	76.2	8.15	67.8	84.6	10.7
	Durataz	6	70.3	3.27	66.1	74.0	4.6
	Tazomac	6	83.9	17.74	69.2	113.5	21.1
	Zosyn	6	79.6	4.25	75.1	84.4	5.3
	Tazar	6	76.1	4.99	70.9	81.4	6.6
	Total	36	74.8	10.52	60.0	113.5	14.1

TZB = Tazobactam, RSD = Relative Standard Deviation.

piperacillin and tazobactam. This is the first study of its kind where multiple formulations were tested to estimate piperacillin and tazobactam quantitatively.

Table 1 illustrates that all the formulations contain piperacillin within the standards specified by the Indian pharmacopoeia (94-115%), except JKMSCL which has slightly higher concentration. The studies conducted by Rao AL *et al.* (2011)[8]; Pai PNS *et al.* (2006)[7]; Singh H *et al.* (2017)[9] also contained the concentrations of piperacillin within the standards specified by the Indian pharmacopoeia (94-115%).

From Table 2, it is clear that tazobactam is present in all the formulations. However, the Indian pharmacopoeia standards for tazobactam has not been specified.

CONCLUSION

It can be concluded that all the formulations contain piperacillin within the limits specified by the Indian pharmacopoeia, except JKMSCL which contains slightly higher concentration, which may be due to dilution or instrumental errors. Further, tazobactam is present in all the formulations. However, the Indian pharmacopoeia standard for tazobactam has not been specified.

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ORIGINAL ARTICLE

Cytological Analysis of Body Fluids in A Tertiary Care Hospital of Jammu Region: A One-year Retrospective Observational Study

Syed Aanif, Deepti Gupta

Department of Pathology, Government Medical College and Hospital, Jammu, Jamu & Kashmir, India

Corresponding Author: Syed Aanif (aanifali17@gmail.com)

ABSTRACT

Introduction: Exfoliative cytology of body fluids involves the analysis of cells present in fluids such as cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid and synovial fluid. The cytological interpretation of individual cells exfoliated into these fluids provides an insight into the diagnosis, prognosis and therapeutic aspects of various pathological conditions. It also helps in staging of malignancies.

Objective: To evaluate the significance of fluid cytology for various pathological conditions, including malignancies.

Materials and Methods: This observational retrospective study was carried out for a period of one year from 31st May 2023 to 1st June 2024. A total of 392 cases of peritoneal, pleural, cerebrospinal, synovial, and pericardial fluids received during the study period in the cytology section, Department of Pathology, Government Medical College and Hospital, Jammu, J&K, India were included in this study. Gross and clinical findings were noted from the requisition forms. The fluids were centrifuged at 2000 rpm for 5-minutes and the sediment was used to prepare smears that were stained by May-Grunwald-Giemsa (MGG) stain and Papanicolaou (Pap) stain.

Results: A total of 392 cases of serous effusions were studied. The most common fluid was peritoneal fluid, 230 (58.67%) cases, followed by pleural fluid, 145 (36.99%) cases, CSF, 15 (3.83%) and least common were pericardial fluid and synovial fluid, 1 (0.26%) case each. The age ranged from 4-years to 98-years. Most cases, 85 (21.68%) belonged to 51-60 years age group. Female preponderance was observed with M:F ratio of 1:1.23. 43 (10.97%) of the total effusions were malignant, out of which 23 were malignant peritoneal effusions. 23 (5.87%) cases were suspicious of malignancy, which 13 (56.52%) cases were peritoneal fluids. Carcinoma ovary was the most common primary site causing malignant peritoneal effusion.

Conclusions: Exfoliative cytology is a valuable tool in evaluation of body cavity fluids. It is relatively painless, simple, cost effective, rapid technique that yields quick and reliable results. Some cases may present major interpretative challenges to the pathologist like presence of reactive mesothelial cells which at times poses difficulty in diagnosis, being close mimicker of malignancy. It is especially helpful in evaluation and staging of malignancy.

Keywords: Body fluids, Exfoliative cytology, Malignant effusions.

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INTRODUCTION

Exfoliative cytology, the microscopic examination of shed or desquamated cells from body surfaces, offers a diagnostic tool of significant value in medical science. The study of cells within the fluids of serous cavities is known as effusion cytology.[1] This technique, pivotal in the detection and monitoring of various pathological conditions, involves the analysis of cells present in body fluids such as cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid and synovial fluid. By examining these cells, pathologists can identify malignancies, infections, inflammatory conditions, and other abnormalities.[2,3] The diagnostic yield, sensitivity and specificity of effusion fluid is higher than that of needle biopsy, as the cells present in the sediment are representative of a much larger surface area and the sample size is greater.[1,4,5]

There are three major body cavities, namely peritoneal, pleural and pericardial.[6] The fluid cavities are lined by single layer of epithelium. Normally these cavities contain minimal fluid that is required for lubrication and protecting the underlying viscera. The dynamics of fluid accumulation is governed by Starling's law, which stated that fluid is accumulated when there is a decrease in the plasma colloidal

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pressure and increase in the hydrostatic pressure. An effusion results in imbalance between fluid formation and removal.[4] The body fluids, being in constant contact with different tissues and organs, serve as a reservoir of shed cells that mirror the health status of these tissues.[1-3] Morphological analysis of these cells helps in understanding the disease process and in reaching a final diagnosis.[7] For instance, the presence of specific inflammatory cells can signal infection or autoimmune conditions, guiding appropriate therapeutic interventions.[1,3] The malignant cells exfoliated into body fluids can be an early indicator of neoplastic processes, thus providing crucial, timely information for cancer diagnosis and treatment planning. In 1882, Quincke published a detailed description of cancer cells in pleural and peritoneal fluids, which was the first authenticated description of cancer cells in body fluids.[6,8]

The cytological interpretation of individual cells, exfoliated into these fluids, is important since they provide an insight into the diagnosis, prognosis and therapeutic aspects of various pathological conditions.[4,9] Some conditions in effusions may often have overlapping features and mimic one another cytomorphologically. The accurate identification of cells due to these overlapping features, such as malignant and reactive mesothelial cells, can pose a diagnostic challenge.[10–12] Most important is the recognition of a malignant pathology, but many other conditions such as inflammatory diseases, parasitic, fungal, viral and bacterial infections can also be identified.[4,13]

This study aims to delve into the application of exfoliative cytology in the analysis of body fluids, highlighting its diagnostic relevance for various pathological conditions and malignancies in a tertiary care hospital. Also, to know the trends of different effusions and categorize effusions according to age, gender, predominant cell type and diagnosis.

MATERIALS AND METHODS

The present study was carried out in the Department of Pathology, Government Medical College, Jammu, from 31st May 2023 to 1st June 2024. All effusion samples of pleural, peritoneal, pericardial, synovial, and CSF irrespective of age and sex received in the cytology section of the Department during that period were studied. Other fluids were excluded. All the faded slides and those with inadequate material were excluded from the study. Ethical permission was duly taken from the institute's ethical committee. The study included 392 cases. All the relevant clinical information regarding age, sex, and accompanying clinical symptoms were documented. Radiological and biochemical data was also obtained from the requisition forms. The gross findings were noted, cell count was done in improved Neubauer's chamber, then centrifuged at 2000 rpm for 5 minutes. For hemorrhagic fluids, glacial acetic acid was used as a hemolysing agent and then processed routinely. Cytospin was also used for some samples. Smears were made from the sediment. Both wet-fixed and air-dried smears were prepared. The air-dried slide was stained with May Grunwald Giemsa stain. The other slide was immediately fixed in 95% alcohol and stained with Papanicolaou stain. The stained smears were studied on light microscopy and evaluated for cellularity, predominant cell type, size, nuclear and cytoplasmic features, chromatin, degree of inflammation, reactive changes and other background features. All the data was analyzed and summarized.

RESULTS

A total of 392 cases of serous effusions were examined cytologically, which included pleural, peritoneal, pericardial, synovial and CSF. The age ranged from 4-years to 98-years. The most common fluid was peritoneal fluid, 230 (58.67%) cases, followed by pleural fluid, 145 (36.99%) cases, CSF, 15 (3.83%), and least common were pericardial fluid and synovial fluid, 1 (0.26%) case of each.

The present study showed a female preponderance with a male to female ratio of 1:1.23. Peritoneal fluid was the most common fluid received. Most Peritoneal fluids were received from the patients who were aged between 51 to 60 years, followed closely by 41 to 50 years age group. Most Pleural fluids were received from patients of age group 61 to 70 years. CSF was received mostly from 61 to 70 years age group. One sample of pericardial fluid was received from a 60-year-old female. One sample of Synovial fluid was received from a 29-year-old male patient.

According to this study, 83.16% of the total cases were benign/non-malignant lesions. Most benign lesions were of peritoneal fluid cases (59.51%). Out of 43 malignant cases, 23 (53.48%) were peritoneal and 20 (46.51%) pleural. 23 cases were diagnosed as suspicious of malignancy, of which 13 (56.52%) were peritoneal and 10 (43.48%) were pleural.

Table 1: Age and gender wise distribution of cases.

Age Group	CSF n (%)		Pericardial n (%)		Peritoneal n (%)		Pleural n (%)		Synovial n (%)		Total n (%)		Grand Total n (%)
Sex	M	F	M	F	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	
0–10	0	2	0	0	0	1	0	1	0	0	0	4	4 (1.03%)
11–20	0	0	0	0	2	1	5	0	0	0	7	1	8 (2.04%)
21–30	0	1	0	0	2	22	8	2	1	0	11	25	36 (9.18%)
31–40	1	0	0	0	8	26	8	5	0	0	17	31	48 (12.24%)
41–50	0	1	0	0	15	36	11	10	0	0	26	47	73 (18.62%)
51–60	0	0	0	1	25	32	18	9	0	0	43	42	85 (21.68%)
61–70	2	4	0	0	11	25	23	12	0	0	36	41	77 (19.64%)
71–80	2	1	0	0	7	9	11	10	0	0	20	20	40 (10.20%)
81–90	1	0	0	0	1	3	9	1	0	0	11	4	15 (3.83%)
91–100	0	0	0	0	3	1	2	0	0	0	5	1	6 (1.54%)
Total	6 40%	9 60%	0	1 100%	74 32.17%	156 67.83%	95 65.52%	50 34.48%	1 100%	0	176 44.90%	216 55.10%	392 (100%)
Grand Total	15 (3.84%)		1 (0.25%)		230 (58.67%)		145 (36.99%)		1 (0.25%)		392 (100.00%)		

**n = number*

Table 2: Distribution of effusions on the basis of cytological examination.

Fluid	Malignant n (%)	Non-Malignant			Suspicious Of Malignancy n (%)	Total n (%)
		Lymphocyte Rich n (%)	Mixed Inflammatory Infiltrate n (%)	Neutrophil Rich n (%)		
CSF	0	7 (46.67%)	5 (33.33%)	3 (20%)	0	15 (3.83%)
Pericardial	0	1 (100%)	0	0	0	1 (0.26%)
Peritoneal	23 (10%)	74 (32.17%)	92 (40%)	28 (12.18%)	13 (5.65%)	230 (58.67%)
Pleural	20 (13.80%)	57 (39.31%)	40 (27.58%)	18 (12.41%)	10 (6.90%)	145 (36.99%)
Synovial	0	0	1 (100%)	0	0	1 (0.26%)
Total	43 (10.97%)	139 (35.46%)	138 (35.20%)	49 (12.50%)	23 (5.87%)	392 (100%)

**n = number*

Table 3: Distribution of peritoneal fluid according to the diagnosis and the associated malignancies.

Primary site n (%)	Malignant n (%)	Non Malignant n (%)	Suspicious Of Malignancy n (%)	Total n (%)
Acute Lymphocytic Leukemia	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.69%)
Anal Canal	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.69%)
Bladder	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.69%)
Breast	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.69%)
Cervix	1 (4.35%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Colon	1 (4.35%)	4 (17.38%)	0 (0.00%)	5 (8.47%)
Gall Bladder	2 (8.70%)	2 (8.70%)	0 (0.00%)	4 (6.78%)
Gastroesophageal Junction	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.69%)
Kidney	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.69%)
Lung	1 (4.35%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Ovary	9 (39.13%)	3 (13.04%)	3 (23.08%)	15 (25.42%)
Pancreas	0 (0.00%)	3 (13.04%)	0 (0.00%)	3 (5.08%)
Rectum	1 (4.35%)	1 (4.35%)	0 (0.00%)	2 (3.39%)
Stomach	1 (4.35%)	3 (13.04%)	0 (0.00%)	4 (6.78%)
Unknown Primary	7 (30.42%)	0 (0.00%)	10 (76.92%)	17 (28.81%)
Uterus	0 (0.00%)	1 (4.35%)	0 (0.00%)	1 (1.69%)
Total	23 (38.99%)	23 (38.99%)	13 (22.02%)	59 (100%)

**n = number*

Table 4: Distribution of pleural fluid according to the diagnosis and the associated malignancies.

Primary site n (%)	Malignant n (%)	Non Malignant n (%)	Suspicious Of Malignancy n (%)	Total n (%)
Breast	3 (15.79%)	1 (16.67%)	1 (10.00%)	5 (14.29%)
CML	1 (5.26%)	0 (0.00%)	0 (0.00%)	1 (2.86%)
Colon	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (2.86%)
Lung	9 (47.37%)	1 (16.67%)	1 (10.00%)	11 (31.43%)
Multiple Myeloma	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (2.86%)
NHL	1 (5.26%)	0 (0.00%)	0 (0.00%)	1 (2.86%)
Ovary	2 (10.53%)	0 (0.00%)	0 (0.00%)	2 (5.71%)
Pyriform Fossa	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (2.86%)
Tongue	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (2.86%)
Unknown Primary	3 (15.79%)	0 (0.00%)	8 (80.00%)	11 (31.43%)
Total	19 (54.29%)	6 (17.14%)	10 (28.57%)	35 (100%)

**n = number*

Out of 194 cases of non-malignant peritoneal effusion, mixed inflammatory infiltrate was most common (47.42%) followed by lymphocyte-rich exudates (38.14%). Out of 115 cases of non-malignant pleural effusion, maximum number of cases were lymphocyte-rich (49.56%) followed by mixed inflammatory infiltrate (34.78%). Out of 15 CSF cases, all were non-malignant with most (46.67%) lymphocyte rich effusions. The single case of pericardial effusion received was lymphocyte rich and the only case of synovial fluid showed mixed inflammatory infiltrate.

Out of 230 peritoneal effusions, 59 were associated with a known case of malignancy. Out of these cases, 23 (38.99%) were diagnosed as malignant effusion with carcinoma ovary being the most common primary site; 23 (38.99%) were diagnosed as non-malignant with colon as the most common primary site of malignancy and 13 (22.02%) diagnosed as suspicious of malignancy with 76.92% from an unknown primary site.

Out of 145 cases of plural effusion, 35 were known cases of primary malignancy amongst which 19 (54.29%) were diagnosed as malignant effusions. Most common primary site of malignancy for malignant pleural effusion cases was lung. 6 (17.14%) cases of pleural effusion were diagnosed as non-malignant and 10 (28.57%) were diagnosed as suspicious of malignancy.

DISCUSSION

Main body fluids like pleural, peritoneal, pericardial, cerebrospinal fluid (CSF) and synovial fluid are normally present within respective body cavities in minimal quantities with their constituents in specific proportions. These fluids during a disease process undergo qualitative and quantitative changes.[4,5,9,14] The cytological examination of effusion fluids in body cavities is a simple procedure and yields vital information of the cell population involving the cavities thereby suggesting the etiology.[2,10] The advantages of this method are that it is a relatively simple, rapid, inexpensive and less invasive tool having a high accuracy with low incidence of false positive diagnosis.[4,15] It helps in diagnosing of both non neoplastic and neoplastic conditions.[1-6]

Most important is the recognition of a malignant pathology. Since, mesothelial and synovial tumors are rare, this method is useful to detect metastatic malignant cells in the body cavities. The method is more of prognostic value rather than for the early detection or prevention of further tumor growth. It also helps in staging of the malignancy.[1,4,16] The development of a malignant pleural effusion is a common complication and indication of advanced stages of cancers like lung, breast and stomach cancer, while development of malignant peritoneal effusion is due to ovary, colon, liver and pancreatic carcinoma. Thus, the examination of body fluids for the presence of malignant cells has been accepted as a routine laboratory procedure for detection of metastasis of unknown primary origin.[11]

In the present study, a total of 392 cases of serous effusions were studied. The age ranged from 4-years to 98-years. The age range in most of the other studies was

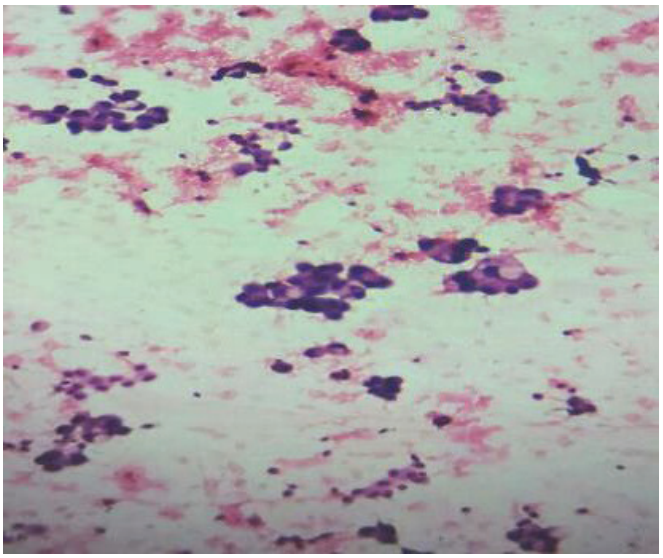

Figure 1: Metastatic ovarian papillary serous cystadenocarcinoma. Malignant cells in cohesive clusters and papillae in peritoneal fluid. (H&E, 100X)

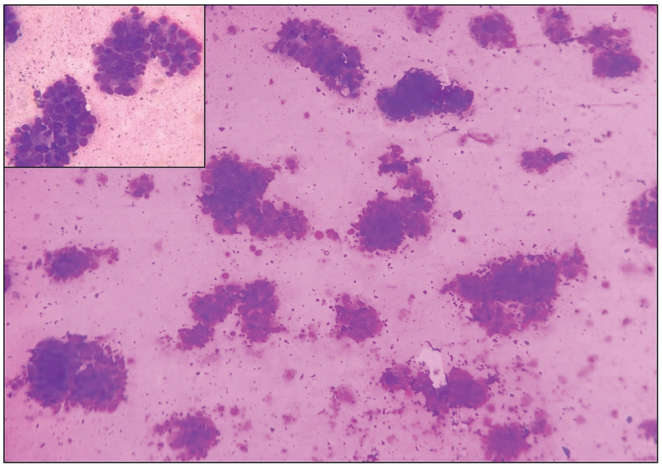

Figure 2: Papillary adenocarcinoma in pleural fluid: Photomicrograph showing clusters with focal acinar arrangement (MGG, 100X). Inset: (MGG, 400X).

from first to ninth decade which is in concordance with our study.[4,6,8–10,12,14,17–21] Female preponderance was observed with M:F ratio of 1:1.23 in our study, which is similar to the studies carried out by Ayyagari S *et al.*[10], Gupta R *et al.*[8] and Tiwari A *et al.*[6]

The most common fluid was peritoneal fluid (58.67%), followed by pleural fluid (36.99%), CSF (3.83%), and least common were pericardial fluid and synovial fluid each 0.26%. The findings of the present study correlated with the findings of Chakrabarti PR *et al.*[5], Shulbha VS *et al.*[14], Bhagat R *et al.*[20], Bhade SD *et al.*[21], Gupta R *et al.*[8] and Tiwari A *et al.*[6] Other authors found pleural fluid as the commonest fluid.[4,9,10,12,17,18]

In 230 cases of peritoneal fluid, most common age group involved was 51-60 years with a female preponderance with M:F ratio of 1:2.1. These findings were in concordance with Ayyagari S *et al.*[10], Chakrabarti PR *et al.*[5] and Tiwari A *et al.,*[6] who also observed female preponderance. However, age group affected was different.[5,10] 194 (84.35%) cases of peritoneal effusions were non-malignant showing mainly mixed inflammatory infiltrate. In our study, 23 (10%) cases of peritoneal effusion were malignant in nature with ovarian malignancy (39.13%) being the most common primary site shedding malignant cells into the peritoneal cavity. Most studies showed findings similar to our study.[5,6,10,12,14] Rest of the malignant peritoneal effusions were from malignancies of unknown primary site (30.42%), malignancies of gall bladder (8.70%), stomach (4.35%), cervix (4.35%), colon (4.35%), rectum (4.35%) and lung (4.35%).

Pleural fluid was found to be the second most common effusion fluid having 145 cases (36.99%). It was similar to the observation by various authors.[4-6,8,14,20,21] Most common involved age group was 61–70 with male preponderance and M:F of 1.9:1.115 (79.30%) cases of pleural effusion were non-malignant showing lymphocyte rich exudates on microscopy. 20 (13.89%) cases were of malignant pleural effusion with lung as the most common primary site of malignancy. Sudha A *et al.,*[10] Chakrabarti PR *et al.* [5], Gupta S *et al.,*[22] and Tiwari A *et al.,*[6] also established similar findings. After lung other common primary sites were breast and ovary. We also found a case of Chronic Myeloid Leukemia and a case of Non-Hodgkin Lymphoma infiltrating into the pleural fluid.

CSF remained the third most common fluid in most of the studies including our study.[4-9,17,20,21–23] 15 cases of CSF were studied with most being in 61–70 age group. Female preponderance was noted with M:F ratio of 1:1.5. All 15 cases were non-malignant, most commonly showing lymphocyte rich cellularity followed by mixed inflammatory infiltrate. It is important to identify infectious causes of exudative CSF effusion for early diagnosis, prevention of spread of disease and complications. Study done by Shulbha VS *et al.,*[14] found Cryptococcus in CSF and Bhade SD *et al.,*[21] found tuberculosis as the cause of exudative effusion. However, we did not find any infective causes in our study. AFB was done and was negative in all cases. One case of Synovial fluid was received from a 29-year-old male, diagnosed as non-malignant showed mixed inflammatory infiltrate. One Pericardial fluid sample of a 60-year-old female was non-malignant showed lymphocyte predominance.

CONCLUSION

We conclude in our study that exfoliative cytology is a valuable tool in evaluation of serous cavity fluids. It is relatively painless, simple, cost effective, rapid technique that yields quick and reliable results. Some cases may present major interpretative challenges to the pathologist like presence of reactive mesothelial cells which at times poses difficulty in diagnosis, being close mimicker of malignancy. In our study, peritoneal fluid was the most common type of fluid received for analysis. Most of the fluid samples belonged to females. The frequency of malignancy in peritoneal fluids studied was 10% with ovarian carcinoma being the common primary malignant lesion to deposit malignant cells into the peritoneal fluid. In pleural fluid, 13.89% cases were malignant with adenocarcinoma of lung being the most common malignant lesion. No malignancy was diagnosed in CSF, pericardial and synovial fluid samples. Thus, fluid cytology is an important diagnostic tool and can be used as first line diagnostic procedure which reduces the need for more invasive investigations. Fluid cytology is useful complementary investigation for categorizing benign as well as malignant conditions. It is especially helpful in evaluating and staging malignancies thereby guiding the clinician in further management. This result in the upstaging or down staging of tumor and thereby affects treatment plan and prognosis for the patient.

Ethical approval: The study was approved by the Institutional Ethics Committee

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ORIGINAL ARTICLE

Biomechanical Correction by Lateral Wedge Outsole in Osteoarthritis Knee Joint

Ruquiya Ali[1], U Singh[1], Sonu Singh[1], Ali Mohammad Buhroo[2]

[1]*Department of Physical Medicine & Rehabilitation, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India*

[2]*Department of Physical Medicine & Rehabilitation, GMC Baramulla, Srinagar, Kashmir, India*

Corresponding Author: Ali Mohammad Buhroo (dr.ambuhroo@gmail.com)

ABSTRACT

Background: Osteoarthritis (OA) Knee is one of the leading causes of pain and functional disability among painful joint conditions in adults. The overall prevalence of OA in India has been estimated to be around 28.7% which has been calculated based on data from five Indian states. Worldwide the prevalence of OA is estimated to be around 9.6% in men and 18% in women aged over 60 years. Nearly, 45% of women over the age of 65-years have symptoms while radiological evidence is found in 70% of them. OA of knee joint is diagnosed using American College of Rheumatology Criteria (ACR).

Lateral wedges reduce the peak knee adduction moment and are advocated for knee osteoarthritis. However, some patients demonstrate adverse biomechanical effects with treatment. Clinical management is hampered by lack of knowledge about their mechanism of effect. We evaluated effects of lateral wedges on frontal plane biomechanics, in order to elucidate mechanisms of effect.

Materials and Methods: This prospective observational study was conducted on 80 patients between 40-65 years of age, 56 were females and 24 males. With grade II & grade III osteoarthritis according to Kallgren-Lawrence grading scale, who reported to OPD of PMR Department of MGMCH, Jaipur from April 2022 to September 2024.

- Diagnosis of knee osteoarthritis was established clinically based on ACR criteria.
- Pain was recorded on Visual Analogue Scale (VAS) and quality of life by SF-36.
- History, clinical examination and X-rays were taken in all patients.
- Biomechanical correction was given by using ¼ inches lateral wedge outsole in the footwear.
- Follow up was conducted on monthly bases from 1 ½ months and on 6 months for evaluation of results. Patients improved symptomatically with pain and in quality of life.

Results: The mean age of the patients included was 52-years. All our patients presented with chronic pain in the knees and stiffness. The mean duration of symptoms at the time of presentation was 8-years. All of our patients had bilateral involvement of the knees showing medial joint space narrowing in radiographs. 56/80 patients were females, mostly housewives, and 24/80 were males with a history of prolonged standing at workplace. The mean weight of the patients was 60 ± 10 kg. The majority of our patients (50/80) were overweight having a BMI between 25 and 30 kg/m^2, (18/80) were obese, and (12/80) had a BMI < 25kg/m^2.

Conclusion: Use of lateral wedge outsoles signifies the redistribution of pressure and change in the ground reaction forces after shoe modification. Hence, lateral wedging provides symptomatic benefits in the mild and moderate OA knee.

Keywords: Osteoarthritis, Knee pain, Lateral wedge, KL grading, Visual Analog Scale, SF-36.

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INTRODUCTION

With increasing life expectancy, age-related diseases such as osteoarthritis (OA) have become a significant public health concern. Knee OA, in particular, is a leading cause of chronic pain and functional disability among older adults. The overall prevalence of knee OA in India is estimated at 28.7%, based on data from five states,[1,2] while globally, it affects approximately 9.6% of men, and 18% of women over the age of 60.

The knee is the most commonly affected joint, followed by the hip and other weight-bearing joints.[3] OA is typically classified as either primary (idiopathic) or secondary (resulting from trauma, deformities, or other conditions).

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Risk factors include advancing age, joint misalignment, repetitive stress, obesity, and prior injury. [4] The condition progresses through cartilage degradation, subchondral bone remodelling, osteophyte formation, and synovial inflammation, resulting in joint pain, stiffness, instability, and reduced mobility.[5]

From a biomechanical perspective, OA arises when mechanical stresses exceed the cartilage's ability to resist them, often due to poor joint alignment or weakened cartilage. The viscoelastic nature of cartilage, its ability to absorb shock, and its role in load distribution are central to joint function. Malalignment—such as varus (bow-legged) deformities—can exacerbate medial compartment loading, accelerating OA progression.[6]

Management of knee OA focuses on alleviating pain, improving joint function, and slowing disease progression. A stepped-care approach is commonly recommended, beginning with non-pharmacological strategies such as education, exercise therapy, weight management, and biomechanical interventions. Pharmacological options include acetaminophen, NSAIDs, and supplements like glucosamine. Orthotic devices, such as lateral wedge insoles, can redistribute joint loads and have shown potential in reducing pain and improving function.[7]

Despite their clinical promise, biomechanical interventions remain underexplored in the Indian context. This study aims to assess the efficacy of lateral wedge footwear as an affordable, non-invasive treatment for knee OA. It also seeks to promote preventive strategies and lifestyle modifications, particularly for patients who have limited access to advanced medical treatments.

Epidemiology

Osteoarthritis is the second most common rheumatologic problem and it is most frequent joint disease. Worldwide, the prevalence of OA is estimated to be around 9.6% in men, and 18% in women aged over 60-years of age, and 4 out of every 5 will have limitations in movement and 1/4 out of these will have issues performing their major daily activities.[6] It is estimated that over 14 million people are having symptomatic OA and 7 million among this group are having advanced OA.[2] Nearly, 45% of women over the age of 65-years have symptoms while radiological evidence is found in 70% of those over 65-years. OA was estimated to be the 10th leading cause of nonfatal burden. Two randomized controlled trials demonstrated that the use of lateral wedging in shoes can decrease patient consumption of oral analgesics in medial KOA at 6 months and 2-years.[1] One study included patients in the age group 50 ± 10 years, and a slight female predominance was observed with 50 out of 70 patients being females.

AIMS: Aim of this study is to analysis the beneficial effect of biomechanical correction in the management of KOA.

OBJECTIVES

- To compare the X-ray findings pre and post biomechanical correction.
- To assess pain severity changes in VAS and quality of life by SF-36.
- To delay the progression of the KOA.

MATERIALS AND METHODS

This prospective pre-post observational study was conducted at the Department of Physical Medicine and Rehabilitation, Mahatma Gandhi Medical College and Hospital, Jaipur, over 18 months. We included 80 patients aged 40–65 years with knee osteoarthritis (KOA), diagnosed according to the ACR criteria and classified as grade II or III on the Kellgren-Lawrence (K-L) scale. Patients able and willing to provide informed consent were included, while those with secondary knee OA due to trauma, systemic illnesses, or prior surgeries were excluded.

Patients underwent baseline assessments, including X-rays, Visual Analog Scale (VAS) pain scores, and Short Form-36 (SF-36) for quality of life. All participants were given ¼ inch lateral wedge outsoles, modified into their existing footwear to minimize discomfort and costs. In addition, a home exercise program focusing on quadriceps, abdominal, and gluteal strengthening, along with calf, hamstring, and hip adductor stretches, was prescribed twice daily for the duration of the study.

Statistical Analysis

Data will be entered in Microsoft Office Excel worksheet. Appropriate statistical tests will be used to find significant association. *p-value* < 0.05 will be considered statistically significant.

RESULTS

This was an observational cross-sectional study conducted in the out-patient department of Physical Medicine and Rehabilitation of Mahatma Gandhi Hospital, Jaipur, for duration of 18 months. A total number of patients were screened for study, 80 patients satisfying the inclusion

criteria were enrolled into the study after written informed consent and rest were excluded from the study. Following observations were made in the study.

Demographic Data

Age Distribution

In our study age of the patients ranged from 45–65 years. Out of the 80 enrolled patients most of them fall in the age group of 45–50 years. The mean age of the patients was 52-years as shown in table 1.

Gender distribution

In our study, 80 subjects (70 %) were females and (30 %) were males as shown in table 2 and figure 2.

Table 1: Age Distribution.

Age group	No. of subjects
45–50	30
51–55	17
55–60	14
60–65	18

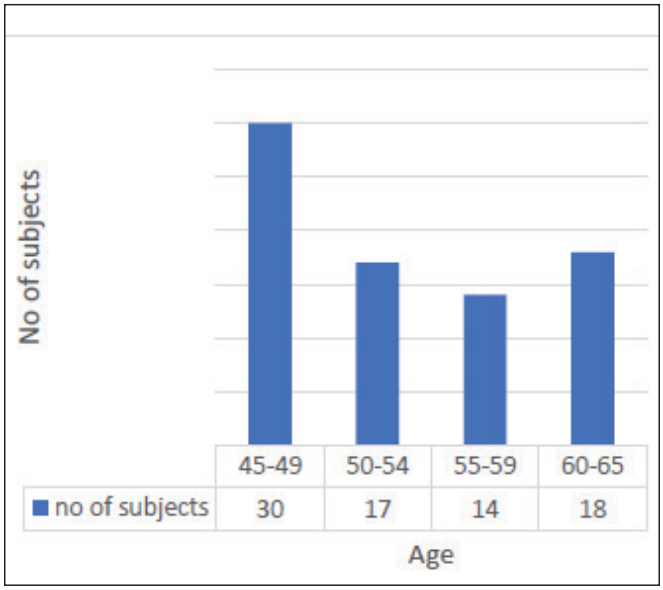

Figure 1: Age Distribution.

Table 2: Gender distribution.

Gender	Frequency	Percent (%)
Female	56	70%
Male	24	30%
Total	80	100%

Distribution of Level of Education

In our study of the subjects 44 (55%) were illiterate and 23 (28.75%) are educated up to primary class as shown in table 3 and figure 3.

Duration of Disease

Among the 80 patients, 22 patients were having disease duration between 2-5 years, 34 patients with disease duration between 5-10 years, and 11 patients with disease duration between 10-15 years, and 13 patients were having disease duration between 15-20 years. The mean duration of illness found in our study is 8-years, as shown in table 4.1, 4.2 and figure 4.

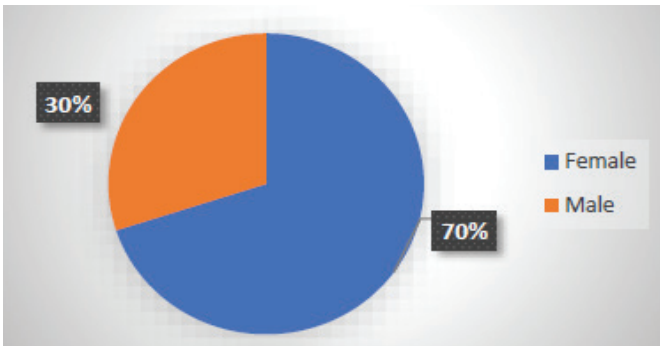

Figure 2: Gender distribution.

Table 3: Level of education.

Level of education	Frequency	Percent (%)
Illiterate	44	55%
Inter	9	11.25%
Middle	4	5%
Primary	23	28.75%
Total	80	100%

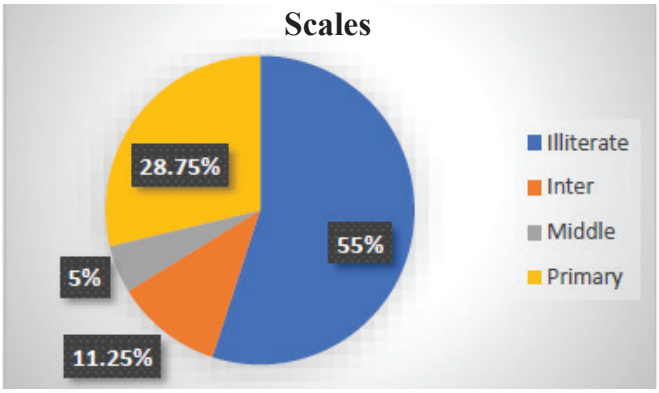

Figure 3: Level of education.

Body Mass Index (kg/m^2) of study Patients

In our study, subjects around 5 (6.25%) were having BMI > 30, 40 (50%) were having BMI between 25–30 and 36 (45%) were having BMI below 25, majority being females. Shown in table 5 and figure 5.

Table 4.1: Showing mean duration of disease.

	Minimum	Maximum	Mean	Std. Deviation
Duration	2	18	8.0375	4.484

Table 4.2: Total duration of disease.

Duration in yrs	2–5 years	5–10 years	10–15 years	15–20 years
No of patients	22	34	11	13

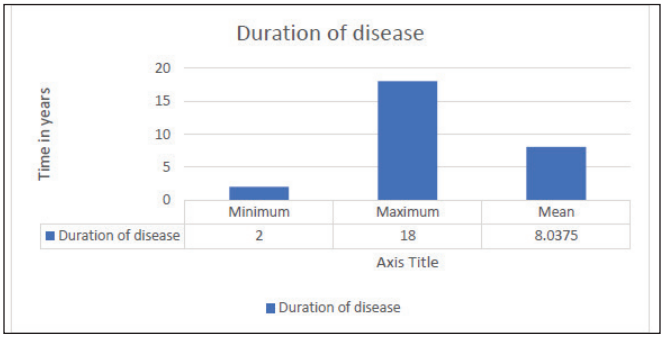

Figure 4: Duration of disease.

Table 5: BMI of Patients.

BMI (Kg/m^2)	Class	No. of patients
20–25	Normal	12
25–30	Overweight	50
>30	Class I obesity	18

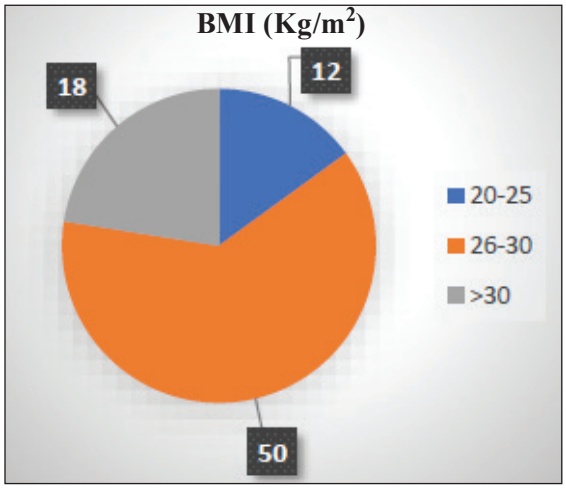

Figure 5: BMI of patients.

KL Grading Radilogically

In our study, most of the subjects around 61 (76%) were having grade II and 19 (24%) were having grade III on KL grading scale shown in table 6 and figure 6.

Disease Severity

Disease severity was assessed in terms of VAS and quality of life by Short Form (SF)-36 are shown in table 7 and figure 7 & 8.

Pain Measurement on Analog Scale

All patients reported some degree of relief in pain with the treatment. VAS after 3-months of treatment, the mean score on VAS for pain which was initially 5.5 reduced

Table 6: KL grading.

KL grading	No of patients	Percent (%)
Grade II	61	76.25
Grade III	19	23.75
Total	80	100%

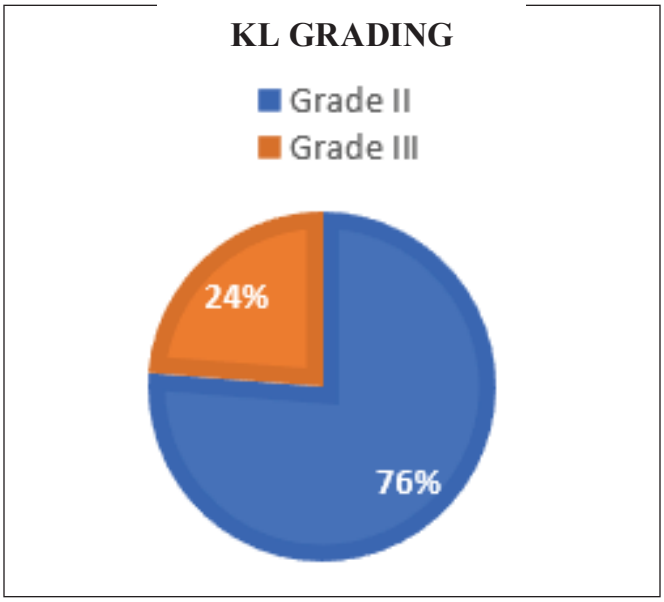

Figure 6: KL Grading.

Table 7: VAS and SF-36.

Score	Day 0 Mean	6 weeks Mean	3-months Mean	Std. Deviation
VAS	5.5	2.32	1.4	2.16
SF-36	101.3	54.17	44.28	24.65

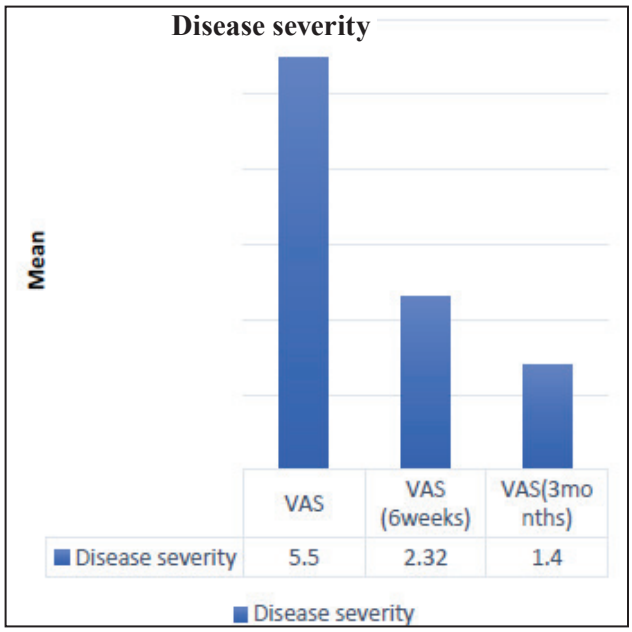

Figure 7: VAS, 6 weeks and 3-months follow up.

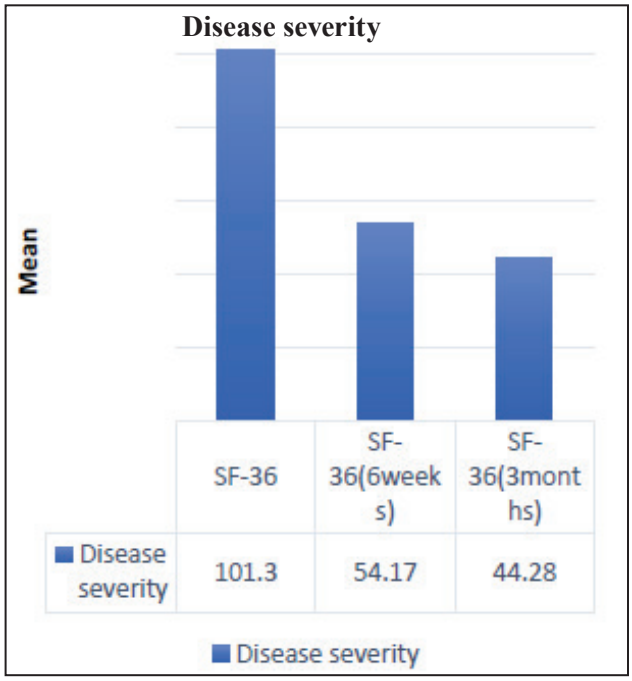

Figure 8: SF-36 ,6 weeks and 3-months of follow up.

to 1.4 which was statistically significant with *p-value* < 0.001.

DISCUSSION

Osteoarthritis (OA), also known as degenerative joint disease, is the most common musculoskeletal condition and a leading cause of disability in the elderly. It is characterized by the progressive degeneration of articular cartilage, subchondral bone sclerosis, osteophyte formation, and joint deformity. The prevalence of OA increases with age, while numerous studies have assessed the clinical effects of laterally wedged outsoles, few have objectively evaluated their impact using both pain (VAS) and quality of life (SF-36) measures.

In our study, the majority of participants (30%) were aged 45–50, with a mean age of 52 years. Women constituted 70% of the sample, aligning with findings from Somya Saxena *et al.*[8], who also reported a female predominance. However, our gender distribution contrasts with G. J. Chapman *et al.*[9], where most participants were male. A large proportion of patients (62.5%) were overweight (BMI > 25), and 22.5% were obese—consistent with obesity as a risk factor for knee OA (KOA).

Most participants (76.25%) had grade II KOA per Kellgren-Lawrence (KL) criteria, comparable to findings by Richard K. Jones *et al.*[10] and Somya Saxena *et al.*[8] Additionally, 55% of the study population was illiterate, and 28.75% had only primary education, suggesting a higher prevalence among the less educated, consistent with Venkatachalam J *et al.*[11] The average disease duration was 8-years, with 34 patients experiencing symptoms for 5–10 years.

Over half the patients presented with genu varus, which is associated with KOA progression. This malalignment increases medial knee loading and may amplify the effect of obesity. Lateral-wedged outsoles reduce this varus alignment by promoting ankle pronation, thereby offloading the medial compartment.

In our intervention, all patients received lateral-wedged footwear, as recommended by the American College of Rheumatology and OARSI. Previous randomized controlled trials have shown reduced analgesic use in KOA patients after 3-months of using wedged footwear. Although long-term effects remain unclear—especially in those with foot issues or advanced KOA—wedged outsoles are a simple, cost-effective conservative treatment option.

Our study demonstrated significant improvement in pain and quality of life. VAS scores decreased from 5.5 (moderate) to 2.32 at 6 weeks and 1.4 at 3 months. SF-36 scores improved from 101.3 to 54.17 and then to 44.28. These findings are supported by earlier research from Ahlbäck *et al.*[12] and Ivan Luis Andrade Araujo *et al.,*[13] indicating improved function and independence in KOA patients.

L. Sharma *et al.*[14] also highlighted that disease severity and deformity increase with radiological progression. We observed a shift in pressure distribution from the medial to the lateral foot in most patients' post-intervention. However, not all patients exhibited this change, and the shifts were not statistically significant—possibly due to limited transmission of the wedge effect or individual gait adaptation. These shifts may reflect changes in the center of pressure after using laterally wedged footwear.

CONCLUSION

Osteoarthritis (OA) is a prevalent chronic disease, affecting 10% of individuals over 50–60 years, leading to joint pain and disability. Poor lower limb biomechanics, often due to anatomical deformities, are key risk factors for knee OA. In our study, 30% of patients were aged 45–50, 70% were female, 55% were illiterate, 62.5% had a BMI >25, and 22.5% were obese. Most (76.25%) had grade II OA based on KL grading, with an average illness duration of 8-years.

Baseline VAS pain score was 5.5 (moderate), and SF-36 quality of life score was 101.3. Post-intervention with lateral wedge shoe modifications, VAS scores improved to 2.32 at 6 weeks and 1.4 at 3 months; SF-36 scores improved to 54.17 and 44.28, respectively. Pressure redistribution and altered ground reaction forces from lateral wedges showed statistically significant improvements in pain and quality of life. Thus, lateral wedging in footwear provides effective symptomatic relief in knee OA.

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CASE REPORT

A Silent Muscle Story: Clinical Insights from Amyopathic Dermatomyositis

Abir Aijaz[1], Judat Tasawoor[2], Manzoor Wani[1], Mariya Manzoor[3]

[1]*Department of Acute Medicine, University Hospitals Bristol and Weston, Weston Supermare, United Kingdom*
[2]*Judat Tasawoor, Medical Officer, Subdistrict Hospital Sopore, Kashmir, Jamu & Kashmir, India*
[3]*Mariya Manzoor, Acute Medicine, Lincoln County hospital, UK*
Corresponding Author: Abir Aijaz (Abir.Aijaz@uhbw.nhs.uk)

ABSTRACT

Amyopathic dermatomyositis (ADM) is a rare subset of dermatomyositis accounting for ~20% of dermatomyositis cases. The prevalence is higher in females and peaks in middle age. Diagnosis relies on hallmark skin manifestations such as heliotrope rash and Gottron's papules, supported by skin biopsy, serologic markers (anti-MDA5, anti-TIF1γ), and imaging.

Unlike classic dermatomyositis, muscle enzymes and electromyography findings are typically normal. A 15-year-old female with no significant medical history presented with a one-month history of lowgrade fever and a progressive rash, along with oral ulcers for 15-days. The rash initially began as ill-defined macular to maculopapular lesions with fine scaling, predominantly involving sun-exposed areas, including the face (sparing the eyelids), ears, chin, anterior neck, and extensor surfaces of the arms, which extended later).

There is currently no specific randomized controlled trial that primarily involves ADM only. Further, treatment is often guided by the extent of cutaneous and systemic involvement. A better understanding may improve prognostication and therapeutic strategies, reducing morbidity and malignancy-associated mortality.

Keywords: Amyopathic dermatomyositis, Malignancy-associated mortality, Rash
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INTRODUCTION

Amyopathic dermatomyositis (ADM) is a rare subset of dermatomyositis characterized by classic cutaneous findings without clinically significant muscle involvement. It accounts for approximately, 20% of dermatomyositis cases. The prevalence is higher in females and peaks in middle age. Diagnosis relies on hallmark skin manifestations such as heliotrope rash and Gottron's papules, supported by skin biopsy, serologic markers (anti-MDA5, anti-TIF1γ), and imaging. Unlike classic dermatomyositis, muscle enzymes and electromyography findings are typically normal.[1]

Management includes corticosteroids, immunosuppressants (methotrexate, mycophenolate mofetil), and biologics (rituximab, JAK inhibitors). Cancer screening is crucial due to associated malignancy risk.[1,2]

CASE

A 15-year-old female with no significant medical history presented with a one-month history of low-grade fever and a progressive rash, along with oral ulcers for 15-days. The rash initially began as ill-defined macular to maculopapular lesions with fine scaling, predominantly involving sun-exposed areas, including the face (sparing the eyelids), ears, chin, anterior neck, and extensor surfaces of the arms (Figures 1, 2 & 3). Over time, it extended to the upper back and evolved into a more erythematous appearance. The patient reported notable photosensitivity, with exacerbation of the rash following sun exposure.

Systemic review revealed no muscle weakness or arthralgia. Laboratory investigations demonstrated a positive antinuclear antibody (ANA) with a homogeneous pattern and anti-Mi-2 antibody positivity.

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Figure 1: Extended rash on upper back.

Serum creatine phosphokinase (CPK) levels were within normal range (94 U/L), and electromyography was not indicative of myositis. These findings, coupled with the absence of clinical muscle involvement, supported a diagnosis of amyopathic dermatomyositis.

Further evaluation revealed proteinuria and bicytopenia. A direct Coombs test was positive, indicating immune-mediated cytopenia. Despite the overlap of features with SLE, the combination of characteristic cutaneous findings and anti-Mi-2 positivity favored ADM. Imaging studies, including a CT scan of the thorax, abdomen, and pelvis (CT TAP), were unremarkable,

Figure 2: Rash on extensor surface on arms.

Figure 3: Rash on hands.

effectively ruling out malignancy. There was no evidence of interstitial lung disease on chest imaging.

DISCUSSION

Amyopathic dermatomyositis is an extremely rare, mostly idiopathic, multisystem connective tissue disease that is characterized by dermatologic lesions of classic dermatomyositis without myopathy or muscle weakness. Hallmark cutaneous manifestations include Gottron's sign, eyelid or periorbital heliotrope rash, and less commonly poikiloderma. There remains a substantial risk for development of interstitial lung disease or malignancy in diagnosed patients.

Amyopathic dermatomyositis (ADM), also commonly or more aptly referred to as clinically amyopathic dermatomyositis (CADM), is a distinct subtype of dermatomyositis (DM) known by the presence of pathognomonic cutaneous manifestations in the absence of clinically evident muscle weakness for a minimum duration of six months. ADM accounts for approximately 10–20% of DM cases and is increasingly recognized due to improved awareness and diagnostic techniques.[2,3] ADM falls within the idiopathic inflammatory myopathies (IIMs) spectrum. It is subclassified into 3 types usually:

1. Pure Amyopathic Dermatomyositis: Persistently present cutaneous disease without any evidence of muscle involvement, even on laboratory or imaging studies.
2. Hypo myopathic Dermatomyositis: Patients exhibit subtle or subclinical evidence of muscle inflammation (e.g., elevated muscle enzymes, abnormal MRI or electromyography) without overt weakness.

3. Evolving Dermatomyositis: Patients often present as amyopathic but subsequently develop classic myopathic features, meeting criteria for dermatomyositis with muscle involvement.[3,4]

Diagnostic Criteria

The diagnosis of ADM is primarily clinical and supported by laboratory and imaging findings. Criteria include:

1. The presence of hallmark cutaneous findings of DM (e.g., Gottron's papules, heliotrope rash, V-sign, or shawl sign).
2. Absence of clinical muscle weakness for at least six months following symptom onset.
3. Normal or mildly elevated serum muscle enzymes (creatine kinase, aldolase).
4. Normal muscle MRI, EMG, or biopsy, or findings insufficient to establish a diagnosis of inflammatory myopathy.
5. Detection of myositis-specific autoantibodies (e.g., anti-MDA5, anti-TIF1γ) may assist in classification and prognostication.

Clinical Manifestations

Characteristic cutaneous signs are central to the presentation of ADM and are often indistinguishable from classic DM. These manifestations include heliotrope rash, Gottron's papules, poikiloderma, shawl sign and photosensitive rashes. Despite the absence of muscle weakness, systemic involvement often complicates the picture with Interstitial lung disease (ILD) being a significant and potentially life-threatening complication (particularly in individuals with anti-MDA5 antibodies). Additional clinical features include arthritis, lipodystrophy, and gastrointestinal vasculopathy, especially seen and reported in paediatric populations.[5]

Management

There is currently no specific randomized controlled trial which primarily involves ADM only, and treatment is often guided by the extent of cutaneous and systemic involvement. First-line therapy dedicated for cutaneous disease includes antimalarial agents such as hydroxychloroquine which has been long used in rheumatological diseases. Topical modalities include corticosteroids and calcineurin inhibitors (e.g., tacrolimus), which are commonly used. In refractory or relatively severe cases, systemic immunosuppressive agents including antimetabolites like methotrexate, mycophenolate mofetil, and intravenous immunoglobulin (IVIG) have shown good results. In patients with ILD, particularly those with anti-MDA5 antibodies, apart from aggressive immunosuppression with corticosteroids, calcineurin inhibitors (e.g., tacrolimus or cyclosporine), rituximab has been pivotal for symptom control.[5,6]

RECENT ADVANCES

Autoantibody profiling has significantly improved the understanding and identification of ADM phenotypes. Anti-MDA5 is believed to be strongly associated with rapidly progressive ILD, while anti-TIF1γ is thought to correlate with severe cutaneous disease and confers an increased malignancy risk in adults. Radiological modalities like high-resolution chest CT and muscle specific MRI have proved valuable in assessing subtle and subclinical involvement. Therapies targeting interferon pathways and Janus kinase (JAK) inhibitors have shown promise in otherwise refractory disease.[6,7]

Prognosis

ADM usually has a favourable prognosis, particularly in those patients who do not have systemic involvement. Patients with anti-MDA5 positivity although face increased morbidity and mortality due to ILD. Nearly 20–30% of ADM cases may evolve into classic dermatomyositis lately. Vigilant monitoring is essential to detect any changes disease progression and to manage the complications promptly.[7]

CONCLUSION

Publishing on ADM is valuable due to its under-recognition, evolving diagnostic markers, and emerging therapies. Newer avenues include targeted biologics, interferon inhibition, and advanced imaging techniques. A better understanding may improve prognostication and therapeutic strategies, reducing morbidity and malignancy-associated mortality.

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