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# STUDY OF OUTCOME OF THE PATIENTS WITH HODGKINS LYMPHOMA IN TERTIARY CARE HOSPITAL

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## Abstract

*Objective: To assess treatment responses and patient outcomes of mortality with different therapeutic regimens in pediatric patients of Classic Hodgkin lymphoma (cHL) Study Design: Quasi-experimental study Place and Duration of Study: Pediatrics department of Combined Military Hospital (CMH), Rawalpindi from January 2023-June 2024 Methodology: 90 patients in each of the two groups received chemotherapy depending upon the standard treatment of 2-6 cycles of either the ABVD or the OEPA regimen with or without radiotherapy based on the stage and severity of the disease according to the Euro-Net Hodgkin Lymphoma treatment guidelines. Primary variables measured were frequency of disease relapse between both groups, disease refractory to therapy between both groups, treatment linked mortality and event free survival between both groups. Results: Treatment outcomes measured between both groups showed disease relapse within one year post-therapy was seen in 15 (16.7%) versus 19 (21.1%) patients between both groups with mortality within one year and during treatment was reported in 05 (5.6%) versus 07 (7.8%) patients. Event free survival was reported in 70 (77.8%) versus 64 (71.1%) patients between both groups (p=0.585). Conclusion: We conclude that both the ABVD and OEPA regimens offer excellent disease remission, a very favorable one year event free survival with the ABVD group offering a slightly better adverse effects profile*

## INTRODUCTION

Hodgkin lymphoma ranks among the most prevalent cancers affecting children and adolescents. It is estimated to account for over 40% of all lymphoma cases identified within the pediatric population.[1] The advent of sophisticated diagnostic methodologies has improved significant challenges on healthcare systems regarding the management and monitoring of this condition than in the past decades. When diagnosed and treated promptly, the overall outlook for patients is favorable, given the current standard treatment protocols.[2] Patients are categorized into different treatment groups based on the stage of disease at

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diagnosis, which determines the intensity of the required interventions, including chemotherapy and/or radiotherapy.[3] With advancement in the diagnostic approaches in present medical centers, the diagnosis of Hodgkin lymphoma in the pediatric age groups have increased significantly.[4] While the disease spectrum maybe similar in pediatric and adult age groups, physiological issues with age and associated co-morbidities warrant tailored treatments.[5]

Pakistan does not have a dedicated Hodgkin lymphoma registry for the pediatric age group, and statistics in our demographics have been scarce with respect to regimens being used for treatment and their initial and long-term patient outcomes.[6] While studies done are limited, reports document excellent response to therapy with remission in more than 92% patients of Classical Hodgkin Lymphoma (cHL) if diagnosed early and compliance to therapy is ensured.[7] Multiple treatment regimens have been proposed and are being used in oncological setups throughout the country with no clear studies documenting efficacy of one treatment over the other. One very pertinent decision regarding treatment goals is the selection of the best treatment regimen offering the best remission rates but with minimal long term drug associated adverse effects.[8] The most common and preferred treatment regimens in pediatric patients include ABVD (Doxorubicin, bleomycin, vinblastine, and dacarbazine) and OEPA (Vincristine, etoposide, prednisone and doxorubicin) being used as first line standard treatment regimens in United States and United Kingdom respectively.[9]

Our study aims to assess efficacy of the above mentioned regimens being used in conjunction with radiotherapy if needed according to treatment guidelines and observe patient outcomes and survival rates at one year post therapy. This would help us identify the best possible combination providing the best favorable outcome for cHL in the pediatric age group.

## METHODOLOGY

This quasi-experimental study was carried out at the Department of Pediatrics, Combined Military Hospital (CMH), Rawalpindi from January 2023 – June 2024 after approval form the ethical review board vide letter no. The sample size was calculated keeping the confidence interval at 95%, power of test at 80% with anticipated proportion of patients with disease relapse at one year being 11% versus 26% between the two treatments regimens.[10] Minimum sample size using the WHO calculator came out to be 102 patients. Considering lost to follow-up and long nature of the study; 180 patients were included in the final study protocol divided into two group using simple random sampling using lottery method

**Inclusion criteria** included all pediatric patients between ages 6-12 years of age diagnosed as Classical Hodgkin Lymphoma (cHL) with non-metastatic disease (Stages I-III) on the basis of clinical suspicion, CECT (contrast enhanced computed tomography) scan and confirmed by histopathology

**Exclusion criteria** included children with advanced Stage IV metastatic disease, children presenting with disease relapse after remission, patients having already received chemotherapy and presenting for follow-up, patients having missed treatment cycles, patients lost to follow-up, patients not tolerating chemotherapy having stopped treatment mid-cycles and non-consent of parents or next of kin to be included in the study

The study method included all patients as per the inclusion criteria furnished. The parents of the children were thoroughly informed and counseled regarding the study procedure and possible outcomes and complications. Due to the long nature of follow-up, all parents were counseled to follow-up at the specified intervals at the end of each cycle. Patients were divided into two groups of 90 patients each, Group-A (n=90) to receive ABVD chemotherapy regimen while Group-B (n=90) to receive OEPA chemotherapy regimen. Before the start of therapy, disease diagnosis and corresponding stage was confirmed using CECT scan and tissue diagnosis confirmed through histopathology. Baselines investigations including blood complete picture, liver function tests, renal function tests, C-reactive protein, coagulation profile, Hepatitis B, C and Epstein Barr virus serology was done in all patients. Blood complete picture, renal and liver function tests were repeated after each course for chemotherapy. Severe anemia, chemotherapy induced liver and renal toxicity was treated accordingly and severe organ dysfunction was deemed as reason to discontinue treatment in all patients. Disease remission was defined as tumor size reduction of more than 95% from initial presentation after at least 2 cycles of

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chemotherapy on based on PET (positron emission tomography) results according to Euro-Net guidelines for remission. Patients with inadequate remission were additionally given radiotherapy at 20-30 Gy. Patients with refractory disease even after combined chemotherapy and radiotherapy were added to other treatment groups and non-remission was considered endpoint of treatment in these patients. Patients in complete remission were followed up for a period of one year and disease relapse was documented. Relapse was defined as presence of disease in previously diagnosed sites or new sites after confirmation of complete remission on PET scans done previously.

Patients in both groups received chemotherapy depending upon the standard treatment of 2-6 cycles based on the stage and severity of the disease according to the Euro-Net Hodgkin Lymphoma treatment guidelines.[11] Adverse effects during treatment including severe anemia, bleeding tendencies, major organ dysfunction, severe weight loss were documented for each treatment regimen. Minor treatment related adverse effects including nausea, vomiting, constipation, headache, and night sweats were also documented. Primary variables measured were frequency of disease relapse between both groups, disease refractory to therapy between both groups, treatment linked mortality and event free survival between both groups. Absence of disease relapse and patient survival at one year was termed as disease free survival for all patients.

Demographic data were statistically described in terms of mean and SD, frequencies, and percentages when appropriate. Independent samples t-test was used to compare statistically significant means. Frequency variables were used using the Chi-square test. A p value of $\leq 0.05$ was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0.

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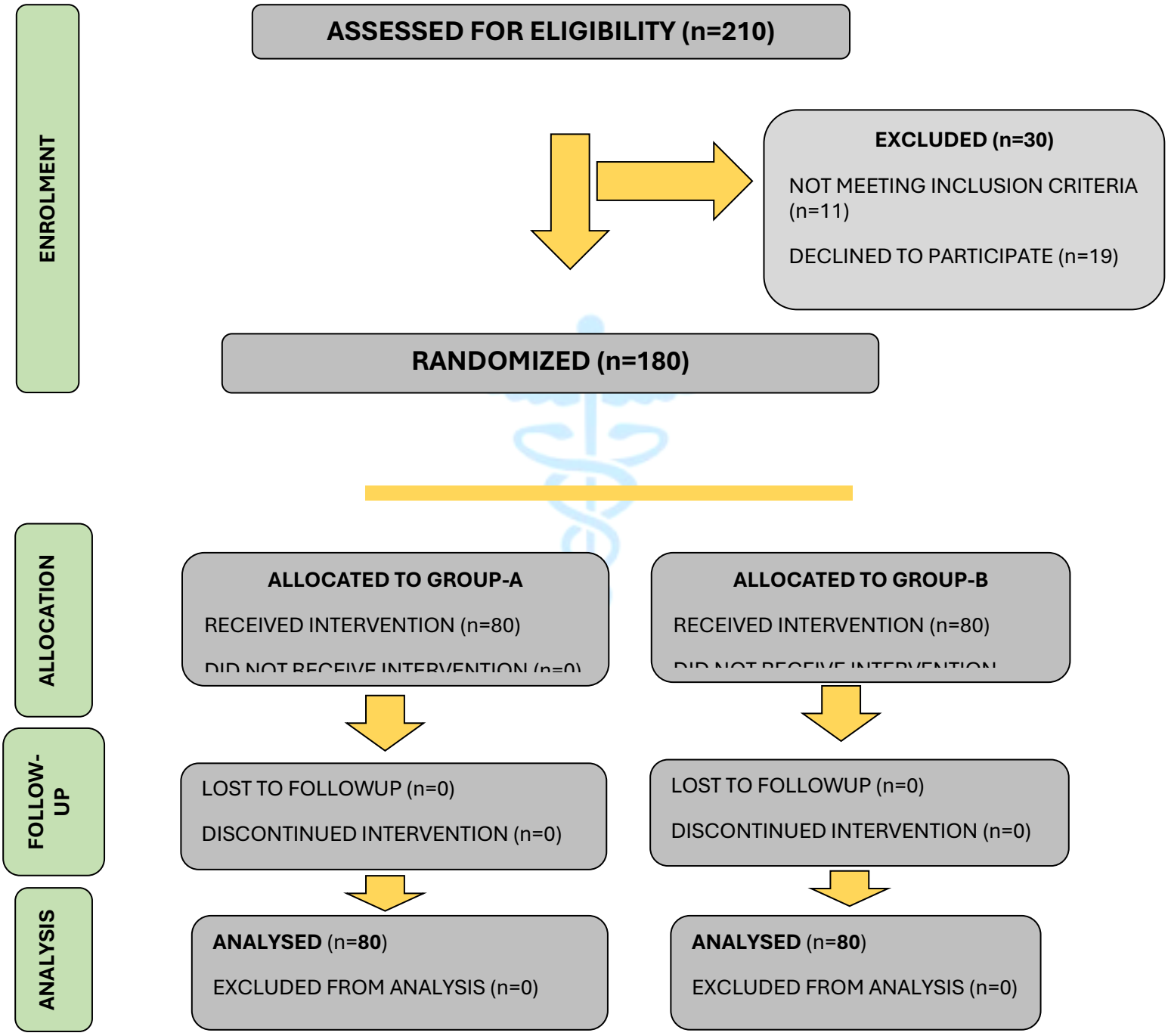
## FIGURE-I: PHASES OF THE STUDY



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## RESULTS

A total of 210 patients were assessed for inclusion in the study and 180 patients who met the inclusion criteria were added into the study protocol divided into Group-A (n=90) and Group-B (n=90). Mean age of patients in Group-A was 9.04±1.68 years versus 9.26±1.70 years in Group-B (p=0.379). Mean weight was 20.97±2.54 kg versus 21.45±1.92 kg between both groups (p=0.157). Gender distribution revealed 68 (75.6%) males and 22 (24.4%) females in Group-A versus 71 (78.9%) males and 19 (21.1%) females in Group-B. Disease stage assessment at the time of diagnosis showed 14 (15.6%) patients with Stage-I, 66 (73.3%) patients with Stage-II and 10 (11.1%) patients with Stage-III disease in Group-A versus 19 (21.1%) patients with Stage-I, 59 (65.6%) patients with Stage-II and 12 (13.3%) patients with Stage-III disease in Group-B. Involvement of spleen was seen in 05 (5.6%) patients in Group-A versus 03 (3.3%) patients in Group-B (Table-I).

Courses of treatment regimens given to disease remission between both groups showed chemotherapy including 2-4 courses was given in 12 (13.3%) versus 11 (12.2%) patients, chemotherapy including 2-4 courses with adjunct radiotherapy was given in 25 (27.8%) versus 27 (30.0%) patients, chemotherapy including 6 or more courses was given in 32 (35.6%) versus 29 (32.2%) patients, chemotherapy including 6 or more courses with adjunct radiotherapy was given in 18 (20.0%) versus 17 (18.9%) patients between both groups while 03 (3.3%) patients in Group-A and 06 (6.7%) patients in Group-B were refractory to therapy (Table-II).

Treatment outcomes measured between both groups showed disease relapse within one year post-therapy was seen in 15 (16.7%) versus 19 (21.1%) patients between both groups with mortality within one year and during treatment was reported in 05 (5.6%) versus 07 (7.8%) patients. Event free survival was reported in 70 (77.8%) versus 64 (71.1%) patients between both groups (p=0.585) (Table-III).

Frequency of major adverse effects showed severe anemia in 06 (6.7%) versus 09 (10.0%) patients, bleeding disorder or coagulopathy in 07 (7.8%) versus 09 (10.0%) patients, major organ dysfunction including heart, liver, kidneys reported in 05 (5.6%) versus 04 (4.4%) patients and severe weight loss reported in 02 (2.2%) versus 06 (6.7%) patients (p=0.486). Frequency of minor adverse effects showed nausea/vomiting in 22 (24.4%) versus 24 (26.7%) patients, constipation or diarrhea in 05 (5.6%) versus 06 (6.7%) patients, headache in 04 (4.4%) versus 06 (6.7%) patients while night sweats were reported by 04 (4.4%) versus 05 (5.6%) patients between Group-A and Group-B (p=0.904) (Table-IV).

**TABLE-I: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS (n=180)**

| VARIABLE | GROUP-A (n=90) | GROUP-B (n=90) | p VALUE |
|---|---|---|---|
| MEAN AGE (YEARS) | 9.04±1.68 | 9.26±1.70 | 0.379 |
| MEAN WEIGHT (KGS) | 20.97±2.54 | 21.45±1.92 | 0.157 |
| GENDER DISTRIBUTION | | | |
| • MALE | 68 (75.6%) | 71 (78.9%) | - |
| • FEMALE | 22 (24.4%) | 19 (21.1%) | - |
| HODGKIN LYMPHOMA STAGE | | | |
| • STAGE-I | 14 (15.6%) | 19 (21.1%) | - |
| • STAGE-II | 66 (73.3%) | 59 (65.6%) | - |
| • STAGE-III | 10 (11.1%) | 12 (13.3%) | - |
| SPLEEN INVOLVEMENT | | | |
| • YES | 05 (5.6%) | 03 (3.3%) | - |

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TABLE-II: DETAILS OF TREATMENT REGIMENS GIVEN IN BOTH GROUPS TO ACHIEVE REMISSION (n=180)

| VARIABLE | GROUP-A (n=90) | GROUP-B (n=90) |
|---|---|---|
| CHEMOTHERAPY (2-4 COURSES) | 12 (13.3%) | 11 (12.2%) |
| CHEMOTHERAPY (2-4 COURSES) + RADIOTHERAPY | 25 (27.8%) | 27 (30.0%) |
| CHEMOTHERAPY (6+ COURSES) | 32 (35.6%) | 29 (32.2%) |
| CHEMOTHERAPY (6+ COURSES) + RADIOTHERAPY | 18 (20.0%) | 17 (18.9%) |
| REFRACTORY TO TREATMENT | 03 (3.3%) | 06 (6.7%) |

TABLE-III: TREATMENT OUTCOMES BETWEEN BOTH GROUPS AFTER COMPLETION OF THERAPY (n=180)

| VARIABLE | GROUP-A (n=90) | GROUP-B (n=90) | p VALUE |
|---|---|---|---|
| DISEASE RELAPSE WITHIN ONE YEAR AFTER THERAPY | 15 (16.7%) | 19 (21.1%) | 0.585 |
| MORTALITY WITHIN ONE YEAR POST-THERAPY OR DURING THERAPY | 05 (5.6%) | 07 (7.8%) | |
| EVENT FREE SURVIVAL AFTER ONE YEAR | 70 (77.8%) | 64 (71.1%) | |

TABLE-IV: TREATMENT RELATED ADVERSE EFFECTS BETWEEN BOTH GROUPS (n=180)

| VARIABLE | GROUP-A (n=90) | GROUP-B (n=90) | p VALUE |
|---|---|---|---|
| MAJOR ADVERSE EFFECTS | | | |
| • SEVERE ANEMIA | 06 (6.7%) | 09 (10.0%) | 0.486 |
| • COAGULOPATHY | 07 (7.8%) | 09 (10.0%) | |
| • MAJOR ORGAN DYSFUNCTION | 05 (5.6%) | 04 (4.4%) | |
| • SEVERE WEIGHT LOSS | 02 (2.2%) | 06 (6.7%) | |
| MINOR ADVERSE EFFECTS | | | |
| • NAUSEA/VOMITTING | 22 (24.4%) | 24 (26.7%) | 0.904 |
| • CONSTIPATION OR DIARRHEA | 05 (5.6%) | 06 (6.7%) | |
| • HEADACHE | 04 (4.4%) | 06 (6.7%) | |
| • NIGHT SWEATS | 04 (4.4%) | 05 (5.6%) | |

## DISCUSSION:

The study concluded important insights into patient outcomes of pediatric patients with cHL being treated with the two most common and widely accepted regimens. ABVD combination is primary the mainstay of treatment used in the United States while OEPA is primarily used in the United Kingdom.[12] While general consensus on their efficacy remains strong, we wanted to use both these regimens in our demographic setup and draw conclusions in pediatric patients with Classical Hodgkin Lymphoma (cHL).

The age range of diagnosis in our patient population was between 9-11 years of age which agrees with available literature being the most common presenting age in children after 6 years of age.[13] The other consistent finding with available studies both local and international is the pre-dominantly male gender being affected by the disease.[14] In both groups, males formed roughly more than 65% of the total treatment size corresponding to a male: female ratio of 3:1. This increases to 5:1 in children after 12 years as per latest statistics.[15] Details of disease stage revealed that Stage-II was the commonest presenting

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in the pediatric population. Since spleen involvement directly categorizes the disease as Stage-III, patients with spleen involvement formed less than 6% of the total patients in both groups but around 30% of all patients with Stage-III disease. This finding corresponds to studies done locally as well reporting spleen as the major organ involved in patients with Stage-III disease.[16]

When discussing the combination of treatment regimens used for achieving disease remission, chemotherapy with 6 or more cycles with or without radiotherapy was the most common combination which was able to achieve the best therapeutic outcome in our pediatric patients. while studies report that adding radiotherapy to standard chemotherapy regimen increases the toxicity and adverse effects profile both in adults and children, it is also an integral part of achieving complete remission especially in disease Stage-III and above.[17] While radiotherapy was used in 45% patients in both groups, the rest achieved remission without needing any radiotherapy. Refractory to treatment in both groups was reported in less than 4% in Group-A and less than 7% in Group-B which shows an excellent response to treatment in both groups with Group-A with a slightly better clinical success in response to therapy.

When assessing the primary outcomes of therapy in patients, the reported relapse within one year post-therapy was around 17% in Group-A versus 21% in Group-B. Both treatment responses were very favorable in the pediatric age group showing good response to therapy after one year post-treatment. Studies done and internationally are in line with the relapse rates seen in our study.[18] Studies also show a very low rate of mortality in the first year of less than 2% but our study shows mortality being slightly higher between 5-8% in our demographic area. This maybe attributable to modest socioeconomic factors, poor nutritional status at the time of diagnosis as well as after therapy contributing to the increased mortality. Comparing the adverse profile revealed that while the ABVD regimen was comparably better in term of both major and minor adverse effects, there was no statistical as well as clinical difference between both groups. Major organ dysfunction reported was the involvement of the spleen followed by the heart which has been reported in both local and international studies to be the major organs affected, the spleen due to tumor involvement and the heart due to treatment related toxicity.

## RECOMMEDATIONS

The study recommends the use of the ABVD and OEPA regimens in pediatric age group with cHL offering good treatment response with a very favorable one year outcome

## CONCLUSION:

We conclude that both the ABVD and OEPA regimens offer excellent disease remission, a very favorable one year event free survival with the ABVD group offering a slightly better adverse effects profile

## LIMITATIONS

The limitations are that the study is single center only. The need for long term survival and tumor remission at 5 and 10 years post-therapy needs to be studied to offer more conclusive recommendations and tailor treatment guidelines accordingly.

## CONFLICT OF INTEREST:

None.

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