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Original Article

Comparison of Low vs. High Dose Pulsed Methylprednisolone on Proteinuria in Lupus Nephritis

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ABSTRACT

Background: Lupus Nephritis (LN) is a serious complication of systemic lupus erythematosus, with proteinuria being a predominant clinical challenge. The use of glucocorticoids, particularly Methylprednisolone, is established in the management of LN. However, the precise dosing that ensures optimal outcomes is still under investigation.

Objective: This study aimed to ascertain the efficacy and safety profile of low versus high dose pulsed Methylprednisolone in ameliorating proteinuria in Lupus Nephritis patients.

Methods: A comparative cohort study was conducted involving LN diagnosed patients aged between 18 and 60 years, excluding those with other comorbid renal conditions or prior high-dose steroid treatments. Participants were segregated into two groups receiving either low or high dose pulsed Methylprednisolone. Proteinuria levels, serum creatinine, blood sugar levels, and blood pressure were monitored at specified intervals. Data were analysed using the SPSS 25.0 software, employing t-tests for continuous variables.

Results: The high dose group exhibited a pronounced reduction in proteinuria (from 3346.95±547.12 mg/24hr at baseline to 267.84±43.83 mg/24hr at 3 months) and serum creatinine (from 2.05±0.79 mg/dl at baseline to 1.12±0.43 mg/dl at 3 months). However, a notable increase in blood sugar levels was observed (from 115.65±7.89 mg/dl at baseline to 136.95±9.38 mg/dl at 3 months). No significant variation in blood pressure was recorded in either cohort.

Conclusion: High dose Methylprednisolone offers superior proteinuria reduction, but the concurrent rise in blood sugar emphasizes the need for a judicious, individualized therapeutic approach. The findings advocate for a harmonized strategy, balancing renal benefits against potential adverse outcomes.

Keywords: Lupus Nephritis, Methylprednisolone, proteinuria, glucocorticoid therapy, serum creatinine, blood sugar elevation.

INTRODUCTION

Lupus nephritis (LN) stands as a significant cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE), predominantly due to visceral complications (1). Existing literature highlights that approximately 35-40% of those diagnosed with SLE eventually develop LN (2). Interestingly, a larger proportion may exhibit histopathological signs of LN, even in the absence of overt clinical symptoms. Demographic analyses have identified young individuals, males, and those of Asian, African, and Hispanic descent as particularly susceptible to LN (3). Certain studies have further emphasized the heightened severity of the disease in paediatric populations and in those of Asian and African ancestry (4-6). Two key biomarkers, proteinuria, and serum albumin, serve as reliable indicators of renal outcomes in LN. Specifically, proteinuria levels ≤500mg per day and serum albumin levels of 3.7g/dl are associated with favourable renal outcomes at 1-year and 4-year follow-ups, respectively (7).

Despite advances in our understanding of LN, its precise aetiology remains elusive (8). A consensus suggests that a genetic predisposition is instrumental in the onset of both SLE and LN. The therapeutic mainstay for LN has traditionally been immunosuppression using glucocorticoids (GC) (9). Contemporary guidelines advocate for an induction phase lasting 3-6 months, succeeded by a maintenance phase of variable duration (10). The ultimate therapeutic aim is to attain early, sustained remission while concurrently mitigating the long-term adverse effects of medications. Prior to the widespread adoption of GC in LN management, the 5-year prognosis was grim, with a dismal rate of around 17% (11). Consequently, GCs have been lauded as "miracle drugs" for their profound inhibitory effects on pro-inflammatory cytokines, including TNFα, IL 1, 6, and 8 (12). Their use has been linked to reduced SLE-related cardiovascular events and a decreased mortality rate. The European Alliance of Association for Rheumatology (EULAR) and the American College of Rheumatology (ACR) have both endorsed GC as a frontline treatment for SLE and LN, despite associated side effects with prolonged usage (13).

Emerging research has illuminated a promising association between oral GC and decreased LN damage (14). Studies indicate that pulsed methylprednisolone therapy (three pulses between 0.25–0.50 g) may permit reduced initial oral GC doses and more rapid tapering, achieving response rates ranging from 47-80% at the 6-month mark (15). While high doses of prednisone have been implicated in increased toxicity, lower doses and pulse therapies are believed to be safer and exhibit reduced toxicity (16). Notably, there exists a dichotomy in the literature: while some studies advocate for the comparable efficacy of low-dosed pulsed methylprednisolone to its high-dosed counterpart, others report contradictory findings (17).

Considering this discrepancy and the paucity of comprehensive comparative research, the authors embarked on this study. Their objective was to juxtapose the efficacy and safety profiles of low vs. high dose IV methylprednisolone in LN patients, aspiring to establish evidence-based local protocols and guidelines for their target population. The central objective of this research was to comprehensively evaluate the therapeutic effects of low dose and high dose IV Methylprednisolone on proteinuria in patients diagnosed with Lupus Nephritis. Considering this overarching aim, the study was rooted in two distinct hypotheses:

MATERIAL AND METHODS

The study found its locus at the Department of Rheumatology and Immunology, housed within the esteemed Shaikh Zayed Hospital in Lahore. With an emphasis on rigorous scientific rigor, the research was orchestrated around a randomized active-controlled design. This methodological choice not only bolstered the integrity of the findings but also diminished potential biases, paving the way for more credible and actionable insights.

To ensure robustness in the results, an optimal sample size of 86 participants (split into two groups of 43) was meticulously calculated. This figure emanated from rigorous statistical paradigms anchored on a 95% confidence level and 90% power analysis. Such precision was underpinned by anticipated response rates from both intervention groups: 80% for the low dose and 47% for the high dose recipients (18).

The study leveraged a non-probability purposive sampling strategy, further complemented by a randomized lottery method for unbiased dose allocation. Integral to the study's scaffolding were key operational definitions: Low Dose IV Methylprednisolone: A cumulative dosage of 1.5g. High Dose IV Methylprednisolone: A cumulative dosage totalling 3g. Lupus Nephritis: Patients conclusively diagnosed via biopsy as per the rigorous standards set by the ACR 2019 criteria.

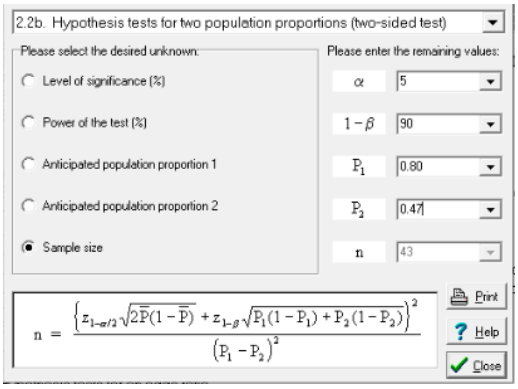

Figure 1 Sample Size Estimation Parameters

The demographic spectrum for the study included SLE-diagnosed individuals confirmed to have lupus nephritis through biopsy. Age parameters were set between 18 to 50 years, extending an inclusive embrace to all genders. However, the study meticulously excluded pregnant participants, those already grappling with end-stage renal disease, and individuals diagnosed with either hypertension or diabetes. An added exclusion criterion was the presence of poor prognostic indicators pertinent to lupus nephritis (19, 20). Upon securing the requisite ethical clearances and ensuring participants' informed consent, a systematic data collection regimen was set in motion. Participants were diligently monitored using a standardized proforma. Indicators, including proteinuria and serum creatinine levels, were consistently gauged at multiple junctures: the baseline, immediate aftermath of treatment (days 3 and 6), and the longer horizons of 1 and 3 months. This granular data capture facilitated a nuanced understanding of methylprednisolone's temporal impact on both proteinuria and the broader disease remission landscape.

All data fragments were then collated and subjected to rigorous statistical analysis using the SPSS 25.0 software. Depending on the data's inherent distribution, a suite of statistical tests was deployed. The empirical threshold for significance was judiciously set at a p-value ≤ 0.05, ensuring that the findings were both statistically robust and clinically relevant.

RESULTS

The study delineated a distinct distribution in terms of gender across both dosage regimens of Methylprednisolone. Within the 43 participants administered the low dose, males were predominant, constituting 58.1% (25 individuals), while females accounted for 41.9% (18 individuals). Conversely, in the high dose group, out of the 43 recipients, there was a more balanced gender distribution with males making up 51.2% (22 individuals) and females 48.8% (21 individuals).

Table 1 Comparative Gender Distribution

Methylprednisolone Dosage		Frequency	Percent
Low Dose	Male	25	58.1
	Female	18	41.9
	Total	43	100.0
High Dose	Male	22	51.2
	Female	21	48.8
	Total	43	100.0

Delving into the comparative analysis of demographic and physiological attributes between the dosage groups, subtle differences emerged, although none were statistically significant. The average age for participants in the low dose regimen stood at 41.81 ± 3.59 years, marginally younger than the high dose

group which averaged at 42.33 ± 3.54 years. A similar trend, albeit with smaller differences, was observed in the weight and height categories. The low dose group averaged a weight of 71.16 ± 9.19 kg and a height of 164.21 ± 8.33 cm. In comparison, those in the high dose group recorded an average weight of 71.91 ± 8.78 kg and a height of 164.37 ± 7.92 cm. Lastly, when evaluating the Body Mass Index (BMI), participants from the low dose bracket exhibited an average BMI of 26.3 ± 1.86, while their high dose counterparts had a slightly elevated mean BMI at 26.54 ± 1.88. However, it's imperative to note that these variations across all parameters were not statistically significant, rendering the two groups comparable in these respects.

Table 2 Comparative Demographics for Quantitative Demographics

Variables	Methylprednisolone Dosage		MS	t	P Value
	Low Dose	High Dose			
	M±SD	M±SD			
Age	41.81±3.59	42.33±3.54	-0.51	-0.67	0.508
Weight	71.16±9.19	71.91±8.78	-0.74	-0.38	0.702
Height	164.21±8.33	164.37±7.92	-0.16	-0.09	0.926
Body Mass Index	26.3±1.86	26.54±1.88	-0.23	-0.58	0.562
M±SD: Mean ± Standard Deviation, MS: Mean Square, t: T-Statistic, P Value: P-Value					

Table 3 Comparative Analysis of Outcome Variable between low vs high dosage groups

Variables	Methylprednisolone Dosage		MS	t	P Value
	Low Dose	High Dose			
	M±SD	M±SD			
Proteinuria (mg/24hr) at Baseline	3250.51±652.6	3346.95±547.12	-96.44	-0.74	0.460
Proteinuria (mg/24hr) Immediately post-treatment	2600.42±521.98	2342.91±382.94	257.51	2.61	0.011
Proteinuria (mg/24hr) at 1 Month	1625.53±326.29	1004.12±164.16	621.42	11.16	0.000
Proteinuria (mg/24hr) at 3 Months	357.6±71.77	267.84±43.83	89.77	7.00	0.000
Serum Creatinine (mg/dl) at Baseline	1.89±0.55	2.05±0.79	-0.16	-1.11	0.270
Serum Creatinine (mg/dl) Immediately post-treatment	1.7±0.5	1.64±0.63	0.06	0.48	0.636
Serum Creatinine (mg/dl) at 1 Month	1.53±0.45	1.32±0.5	0.22	2.11	0.038
Serum Creatinine (mg/dl) at 3 Months	1.38±0.4	1.12±0.43	0.26	2.91	0.005
M±SD: Mean ± Standard Deviation, MS: Mean Square, t: T-Statistic, P Value: P-Value					

Proteinuria Levels: At baseline, the proteinuria level for the low dose group averaged 3250.51 ± 652.6 mg/24hr, a tad lower than the high dose group, which recorded 3346.95 ± 547.12 mg/24hr. However, there was a noticeable difference immediately post-treatment. The low dose group reported an average of 2600.42 ± 521.98 mg/24hr, while the high dose group showed a reduction to 2342.91 ± 382.94 mg/24hr, which was statistically significant. This trend persisted at the 1-month mark, where the low dose group reported 1625.53 ± 326.29 mg/24hr and the high dose group exhibited a steeper reduction to 1004.12 ± 164.16 mg/24hr. By the 3-month assessment, the proteinuria levels reduced substantially

for both groups, with the low dose group recording 357.6 ± 71.77 mg/24hr and the high dose group settling at 267.84 ± 43.83 mg/24hr. The difference was statistically significant across these time points. Serum Creatinine: Baseline serum creatinine values for the low dose participants averaged at 1.89 ± 0.55 mg/dl, slightly below the high dose group's average of 2.05 ± 0.79 mg/dl. Following treatment, the readings at 1 month for the low dose group showed an average of 1.53 ± 0.45 mg/dl, compared to the high dose group's 1.32 ± 0.5 mg/dl. By the third month, the levels continued to show a declining trend with the low dose group averaging 1.38 ± 0.4 mg/dl and the high dose group at 1.12 ± 0.43 mg/dl. These differences at 1- and 3-months post-treatment were statistically significant.

Table 4 Comparative Analysis of Outcome Variable between low vs high dosage groups

Variables	Methylprednisolone Dosage		MS	t	P Value
	Low Dose	High Dose			
	M±SD	M±SD			
Blood Sugar (mg/dl) at Baseline	116.7±8.04	115.65±7.89	1.05	0.61	0.544
Blood Sugar (mg/dl) Immediately post-treatment	145.93±10.04	161.88±11.11	-15.95	-6.99	0.000
Blood Sugar (mg/dl) at 1 Month	128.4±8.85	133.09±8.98	-4.70	-2.44	0.017
Blood Sugar (mg/dl) at 3 Months	122.44±8.39	136.95±9.38	-14.51	-7.56	0.000
Blood Pressure (Sys) (mmHg) at Baseline	125.65±7.12	124.84±7.07	0.81	0.53	0.596
Blood Pressure (Sys) (mmHg) Immediately post-treatment	128.21±7.56	127.4±7.51	0.81	0.50	0.618
Blood Pressure (Sys) (mmHg) at 1 Month	121.79±6.92	121.05±6.78	0.74	0.50	0.616
Blood Pressure (Sys) (mmHg) at 3 Months	124.65±7.12	123.84±7.07	0.81	0.53	0.596
Blood Pressure (Dia) (mmHg) at Baseline	82.07±5.7	81.56±5.92	0.51	0.41	0.684
Blood Pressure (Dia) (mmHg) Immediately post-treatment	84.51±6.13	84.05±6.36	0.47	0.35	0.731
Blood Pressure (Dia) (mmHg) at 1 Month	85.33±6.01	84.74±6.16	0.58	0.44	0.659
Blood Pressure (Dia) (mmHg) at 3 Months	79.63±5.28	79.07±5.48	0.56	0.48	0.632
M±SD: Mean ± Standard Deviation, MS: Mean Square, t: T-Statistic, P Value: P-Value					

Initial baseline measurements displayed similar levels for both groups with 116.7 ± 8.04 mg/dl for the low dose group and 115.65 ± 7.89 mg/dl for the high dose group. However, a sharp increase was observed immediately post-treatment, particularly in the high dose group, which peaked at 161.88 ± 11.11 mg/dl, in contrast to the low dose group's 145.93 ± 10.04 mg/dl. At subsequent evaluations, the high dose group consistently registered elevated blood sugar levels, culminating in a significant difference by the third month.

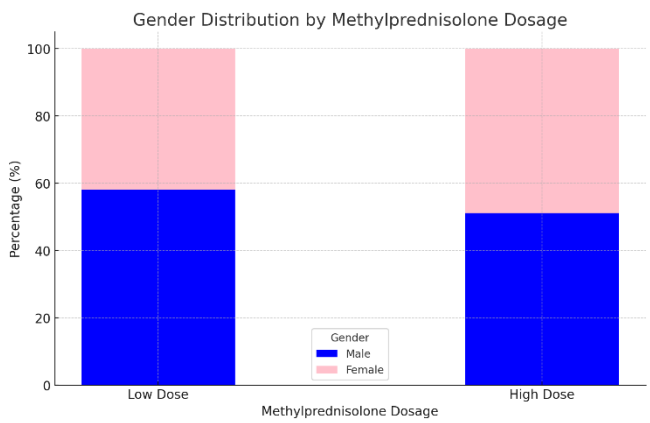

Figure 2 Gender Distribution by Methylprednisolone Dosage

Systolic blood pressure readings remained closely matched between the two groups

across all intervals, ranging from baseline values of 125.65 ± 7.12 mmHg for the low dose and 124.84 ± 7.07 mmHg for the high dose to the 3-month values of 124.65 ± 7.12 mmHg and 123.84 ± 7.07 mmHg, respectively. Diastolic readings followed a similar pattern, with values remaining closely knit, and no significant difference emerged between the two groups at any given point.

DISCUSSION

The effectiveness and safety profile of glucocorticoid therapy, particularly methylprednisolone, in the treatment of lupus nephritis and other related conditions have been a topic of extensive research. One noteworthy observation from the provided study is the significant reduction in proteinuria levels, particularly among those administered with high doses of methylprednisolone. This finding is in tandem with previous research by Badsha and Edwards (2003), which reported a similar control trend in proteinuria among patients with lupus nephritis treated with higher doses of this drug (21).

Another parameter of renal function, serum creatinine levels, also showed promising reductions in the high dose group in the provided study. This mirrors the outcomes of Hoch and Schur's study in 1984, wherein renal function stabilization was observed following pulse therapy with methylprednisolone. However, as with many potent treatments, there are associated side effects. A surge in blood sugar levels, particularly among the high-dose recipients, aligns with the well-documented adverse effects of glucocorticoid therapy. It's essential to consider these side effects when evaluating the therapeutic efficacy and safety of methylprednisolone (22).

Interestingly, the study did not find notable differences in blood pressure between the different dosage groups. This observation is somewhat contradictory to several studies that have drawn a direct association between glucocorticoid therapy and elevated blood pressure. Furthermore, when considering the efficacy of different glucocorticoids, the study in question compared the effects of low and high doses of methylprednisolone. In a similar vein, Garin et al. (1986) made a comparison between pulsed methylprednisolone therapy and high-dose prednisone. Their findings leaned towards both treatments being effective in addressing SLE nephritis, but with methylprednisolone presenting fewer side effects (23).

In the realm of safety concerns, infections have always been at the forefront. One study highlighted that low-dose methylprednisolone had fewer serious infections as compared to its high-dose counterpart, suggesting a possible safety edge with reduced dosing (24). Lastly, in terms of achieving remission, high-dose prednisone seemed to have a better track record, as per a study by Tselios et al. in 2022, which reported better rates of complete response over a year compared to medium doses (25). This further buttresses the findings of the provided study, emphasizing the potential dosage-efficacy relationship in glucocorticoid therapy.

The provided study and existing literature largely align on the beneficial effects of high-dose Methylprednisolone in reducing proteinuria and serum creatinine levels, though at the cost of increased blood sugar levels. However, the lack of significant blood pressure differences in the provided study contrasts with some existing knowledge linking glucocorticoid therapy to elevated blood pressure. The comparative effectiveness of Methylprednisolone and Prednisone in managing Lupus Nephritis and the potential safety advantage of lower dosing in reducing serious infections are other nuanced areas of discussion, showcasing a complex interplay of factors that necessitate a tailored approach to glucocorticoid therapy in Lupus Nephritis (25).

The comparative analysis of low versus high dose pulsed Methylprednisolone on proteinuria in Lupus Nephritis patients offers valuable insights into optimizing glucocorticoid therapy. The compelling evidence of significant proteinuria and serum creatinine reduction in the high dose group underscores

the potential efficacy of elevated dosages in renal function amelioration. However, the accompanying surge in blood sugar levels demands a cautious and individualized approach, especially in patients with pre-existing glucose intolerance or diabetic conditions.

The lack of blood pressure elevation, contrasting with some existing literature, suggests that other concurrent antihypertensive therapies or intrinsic patient factors may play a role in mitigating glucocorticoid-induced hypertension. Furthermore, the comparative effectiveness of Methylprednisolone and Prednisone, as observed in existing literature, points towards a nuanced choice of glucocorticoid therapy, potentially favouring Methylprednisolone due to lesser side effects. The study also shed light on a potential safety advantage of lower dosing in reducing serious infections, aligning with existing literature. This advocates for a balanced approach, weighing the benefits of renal function improvement against the risks of adverse effects, in determining the optimal dosing regimen.

CONCLUSION

In conclusion, the findings underscore the importance of a nuanced, individualized approach in glucocorticoid therapy for Lupus Nephritis patients, considering not only the dosage efficacy in renal function improvement but also the broader impact on blood sugar levels, blood pressure, and infection susceptibility. Future studies with larger sample sizes and longer follow-up periods are imperative to furnish a more comprehensive understanding of the long-term effects and optimal dosing regimens of Methylprednisolone in managing Lupus Nephritis. The potential exploration of combinational therapies or alternative glucocorticoid agents to achieve effective renal function amelioration with minimized adverse effects could also be a significant forward stride in the clinical management of Lupus Nephritis.

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