

P-PACK, ENLARGED YET CONTRACTED TAPERING DOSE OF PREDNISONE CONCLUDES TREATMENT TARGETS FOR PRIMARY SAFETY AND EFFICACY ENDPOINTS.

- Efficacy was tolerable across all studied populations with rapid decline in symptoms after first dose.
- Effectiveness was achieved, at the end of treatment, across all the therapeutic indications that were intervened.
- Safety data during and post treatment revealed no toxicity or hospitalization for acute or chronic undesirable pharmacodynamic properties.

Abstract

It is common practice in ambulatory medicine and outpatient specialties for doctors and care practitioners to prescribe a course of glucocorticoids as a crucial armamentarium for symptomatic disease relief, if there is appropriate use. Yet, there are limited and efficacious options for pre-pack corticosteroid protocols that are effective. Our goal was to test the safety, effectiveness and efficacy of two tapering prednisone therapies for common disease complaints.

Doses were administered only based on rudimentary data of therapy from specialty disease conditions, and a final balancing for a cardinal pack. To comply with standard of care, patients received referrals to respective specialties as needed.

Methods: The study cohort consisted of a group receiving 60mg- day- one loading dose of prednisone with tapering versus the another group receiving 80mg loading dose on day one with a tapering. Each participant started at a different time when they reported sick and were followed during the treatments. The end points for the two cohorts on the agents were: dose size response, complaints of adverse effects and adherence to the course.

Results:

Of a total of 109 patients, 30 received the 60mg initiated tapering dose and 79 received the 80mg loading dose course. The average age for the participants was forty-eight for which majority was male gender. Of the 30 patients receiving the 60mg loading dose with tapering, the mean of the response is 0.57, with variance of 0.05 and SD 0.22 CI [0.4101, 0.7327] over the course of the seven days. On the 80mg loading dose arm, the mean is 0.82 variance of 0.05, SD 0.23 CI [0.6561, 0.9925] . The response percentiles at 25, 50, 75 were 0.43, 0.5, and 0.7 for the 60mg loading dose taper, and 0.73, 0.95, and 0.96 for the 80mg arm. The two – tailed P value equals 0.0549. At day five, the 80mg loading dose of prednisone was 43% more effective than the 60mg tapering across all the conditions treated without any adverse events or hospitalizations.

Conclusion:

In this study, we have compared tapering doses of prednisone. Across common conditions treated, we have shown more effectiveness with prescribing four of 20mg on day one to be taken at the same time with morning dosing preferred, three on day number two, and two daily on days three , four and five and then two daily to complete over seven days for a total count of fifteen.

Introduction

The upward spending in hospital admissions and cost in the United States, a \$ 14101 per admission in 2019¹ and overall, 3.5 trillion costs between 2012 and 2019,² stirs a challenge for effective solutions that will stem this tide. One such solution is rigorous use of efficient treatments in outpatient services such as primary care doctors' offices and urgent care units.

Common diseases such as ear, nose and throat infections, asthma, chronic obstructive pulmonary disease, cellulitis, inflammatory cardiac conditions, as a few examples, can rapidly deteriorate into hospital admissions without swift action; hence ambulatory centers need to match one of the advantages deployed by Hospitals and that is, use of more pharmacodynamically effective intravenous therapies.

The inflammatory cascade is ultimately a restorative reactive process that commences with epithelial disruption from tissue injury resulting in a structured formation of dynamic mechanisms and a smorgasbord of immune-mediating chemoglobulins. The chemical mediators for tissue protection elicit leukocytes and cytokines production thereby propagating the inflammatory chain cycle. Post injury, this formation is inevitable: platelet aggregation, macrophages, nitric oxide, prostaglandins, macrophages, TNF- α , IFN- γ , IL-6, IL-8, IL-1, B – cell activation, IL- 10, classes of cytokine receptors and their cytokines, fibroblast production, transitioning into a chronic phase with formation of IL2 all the way through to IL-15.^{3,4} Chronic cytokine involved inflammatory processes are horrendously perilous by progressively shortening telomere spans, thereby portending shorter lifespans.

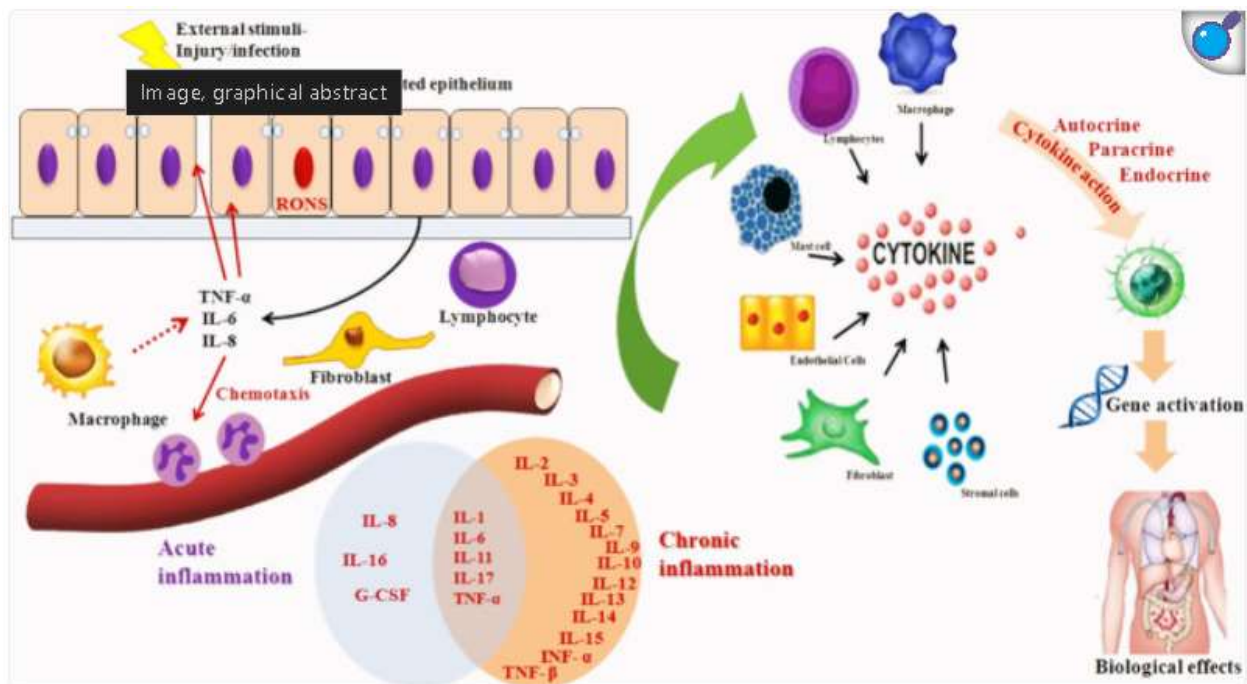


Fig 1: Depiction of a ripple of events involving multiple immune mediators and pathways after tissue injury. KB Megha et al.⁵

Albeit the function of the immune responses is only natural to curbing tissue – damaging events before a terminal nadir, their parallel consequences leave patients with fevers, unbearable symptoms of diaphoresis, severe fatigue, relentless cough, peri-organ effusions with possible hemodynamic collapse, insomnia, gastrointestinal symptoms and cerebral events. The adrenal gland plays a counter homeostatic role in producing glucocorticoids to reduce these painful intermediary metabolic processes. The glucocorticoid production is a six-pathway stream with anti-inflammatory response through the immune-adrenal axis. Further, each enzyme, receptor and dot on this known inflammation constellation has been met with drug development. Old, but one such medication class that is shifting the paradigm in patient care is glucocorticoids.

Prednisone is intermediate – acting and advantageous in reducing myopathy associated with other long-acting glucocorticoids. Prednisone is much less expensive. The dosing conversion of 120mg of methylprednisolone equals 150mg of Prednisone. Prednisone moderates inflammation by controlling protein synthesis, suppression migration of polymorphonuclear leukocytes (PMNs), fibroblast, and restricting lysosomes. The bioavailability is 92 percent with peak plasma time of two hours for immediate release and 6 hours for delayed release. It is extensively metabolized in the liver with half – life of 2.6 – 3 hrs.

PATIENTS AND METHODS

At the time of patient treatment, informed written consent was obtained. Standards of patient autonomy and safety were adhered to.

Study Design, Setting and Patient Population

This study was conducted between June 2020 and September 2024. This is an outpatient -based study of patients presenting with complaints and finally diagnosed to receive treatment for various conditions involving a systemic corticosteroid. Patients older than 16 years of age were included in the study. Demographic characteristics recorded were age, gender, and race. Diagnosis for inclusion was confirmed with patients’ presenting complaints, physical examination and diagnostic tests that were applicable. Exclusion included osteoporosis, cataract, and pregnant patients.

In this effectiveness study population, the prospective cohort consisted of a group receiving 60mg on day one loading dose of prednisone with tapering versus another treatment group receiving 80mg loading dose on day one with the tapering. Each participant started at a different time when they reported sick and were followed during the treatments. Patients were initially randomized in a 1:1 ratio to receive either one of the treatment tapering courses. Physician’ s enthusiasm for using the 60mg loading dose declined during the study.

DAY	1	2	3	4	5	6	7
60mg Loading Dose	60mg	40mg	20mg	20mg	20mg	20mg	20mg
80mg Loading Dose	80mg	60mg	40mg	40mg	40mg	20mg	20mg

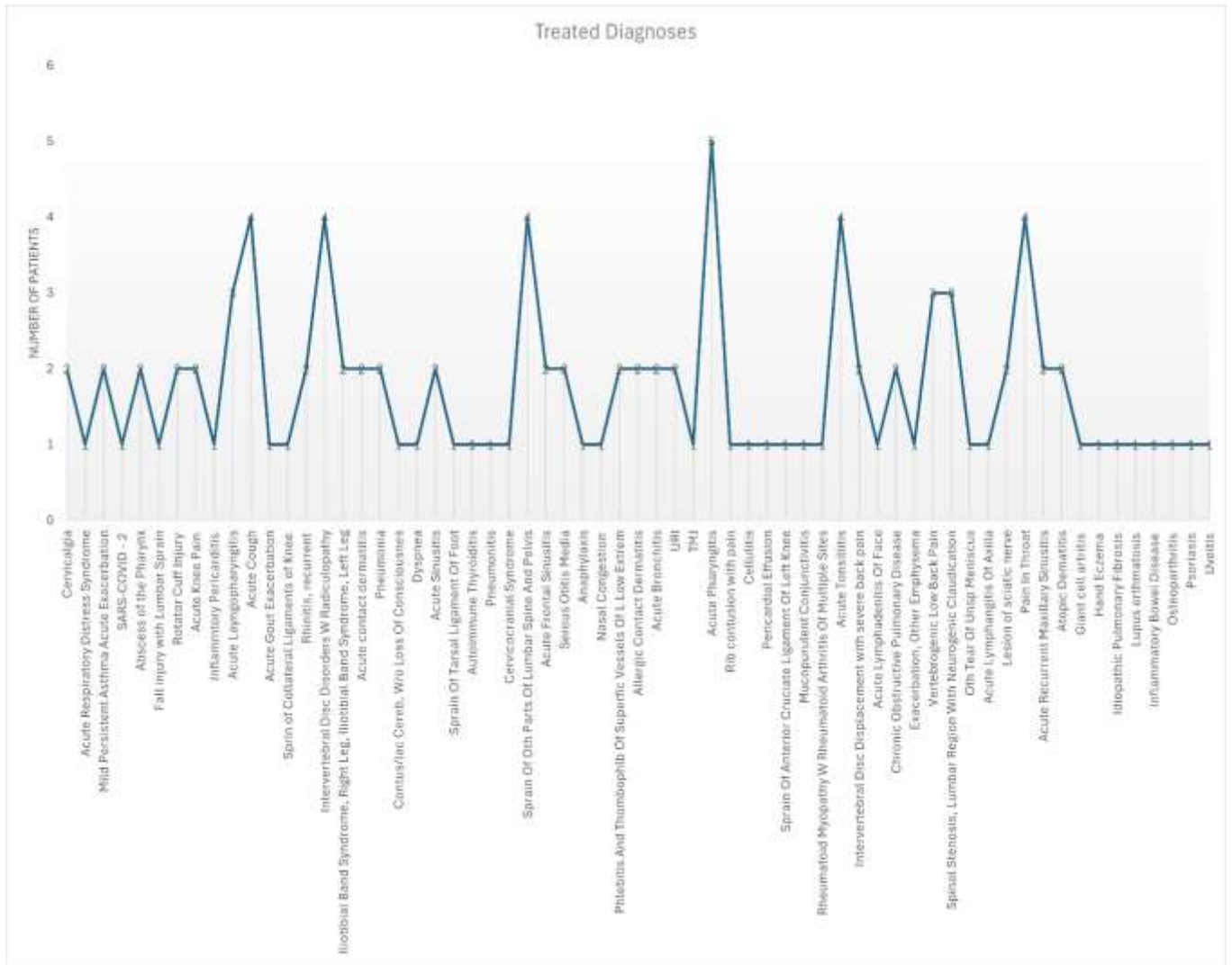


FIG 2: Conditions that were treated in the group and their frequencies.

Data Collection

To measure effectiveness, The ECOG performance status questionnaire was used to collect data post treatment initiation on each arm of the study. Through telephonic questionnaire, patients were inquired about their symptoms and progress after initiating intake of the medication taper. The medications had been prescribed by a physician and dispensed by licensed pharmacists in the community. A few patients also obtained the medications directly through our in-house pharmacy.

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
 Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.:
 Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol
 5:649-655, 1982.

FIG 3: Eastern Cooperative Oncology Group (ECOG) questionnaire was adopted to estimate the recovery of patients after treatment.

Outcomes

Patients were followed for symptomatic improvement, hospitalization and for adverse effects. The end points for the two cohorts on the agents were: dose size response, complaints of adverse effects and adherence to the course.

Statistical Analysis and Model Description

Descriptive statistics are provided and tabulated with Microsoft Excel. Our study did not divulge any personal health information.

RESULTS

The study population comprised of a total of 109 patients with 30 receiving the 60mg initiated tapering dose and 79 receiving the 80mg loading dose course. The average age for the participants was forty-eight for which majority was male gender.

Of the 30 patients receiving the 60mg loading dose with tapering, the mean of the response is 0.57, with variance of 0.05 and SD 0.22 CI [0.4101, 0.7327] over the course of the seven days. On the 80mg loading dose arm, the mean is 0.82 variance of 0.05, SD 0.23 CI [0.6561, 0.9925]

Effectiveness

The 80mg arm showed effectiveness of 0.98 for 78.6 treatments and for the same duration of treatment, the clinical effectiveness was 0.55 for 16.5 treatments.

Number Needed to Treat NNT,

On average for the 5th day, 2.4 patients would have to receive the 80mg loading taper for one additional patient to have the study outcome. At day three, most patients reported return-to-work ready.

The response percentiles at 25, 50, 75 were 0.43, 0.5, and 0.7 for the 60mg loading dose taper, and 0.73, 0.95, and 0.96 for the 80mg arm. The two – tailed p value equals 0.0549. The mean of 80mg with tapering minus that of the 60mg with tapering equals 0.2529. 95% confidence interval of this difference is -0.0062 to 0.5119, using t value of 2.1268 standard of error difference 0.119

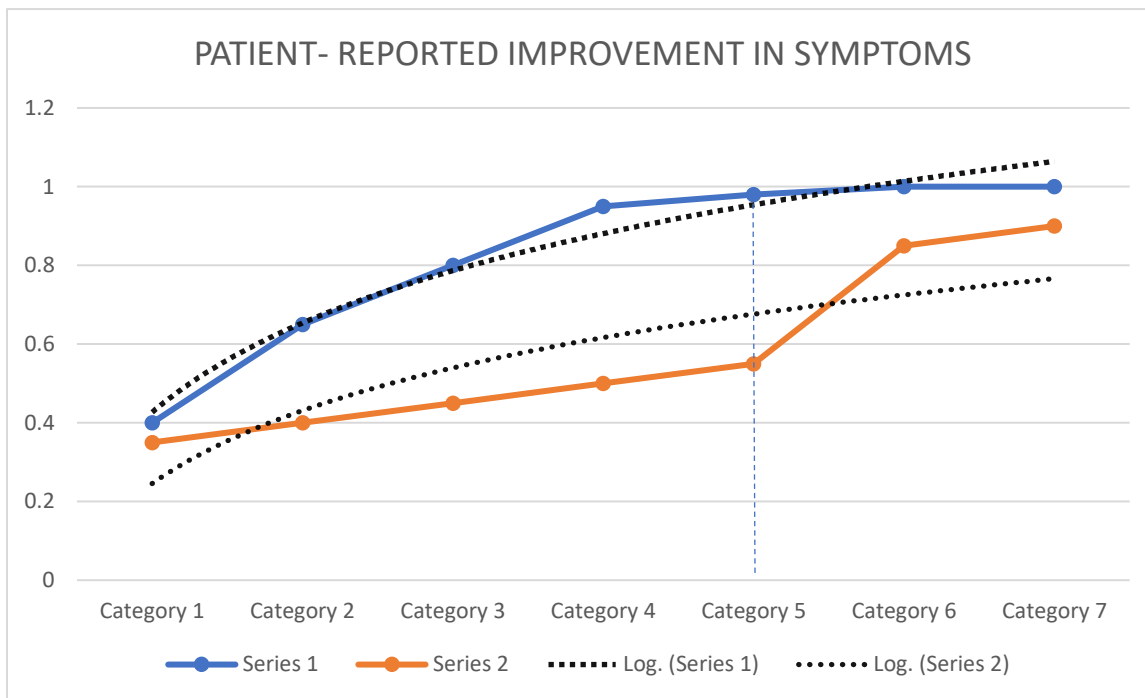


Chart 1: On the horizontal axis, number of days for a total of seven days in categories. Y – axis representing proportion of treatment responses for each group. 60mg loading dose is represented by the orange curve in series whereas the blue curve is trending the 80mg – specified loading dose course.

Adherence was addressed by patient self – report of complaints or inquired by the research team. The team adopted a format of the MARS questionnaire to obtain data on compliance.

MARS questionnaire

	Question	Answer
1	Do you ever forget to take your medication?	Yes / No
2	Are you careless at times about taking your medication?	Yes / No
3	When you feel better, do you sometimes stop taking your medication?	Yes / No
4	Sometimes if you feel worse when you take the medication, do you stop taking it?	Yes / No
5	I take my medication only when I am sick	Yes / No
6	It is unnatural for my mind and body to be controlled by medication	Yes / No
7	My thoughts are clearer on medication	Yes / No
8	By staying on medication, I can prevent getting sick.	Yes / No
9	I feel weird, like a 'zombie' on medication	Yes / No
10	Medication makes me feel tired and sluggish	Yes / No

FIG 4: The 5-item Medication Adherence Report Scale (MARS) questionnaire which has been validated in other studies was used for assessing compliance.

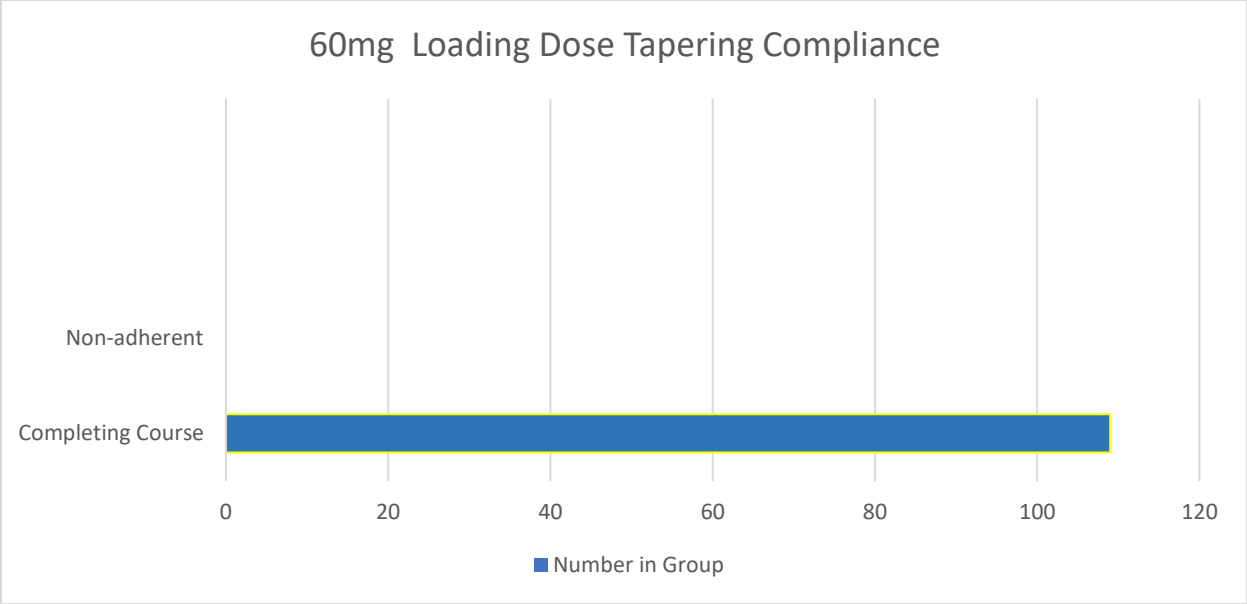


CHART 2: A hundred percent compliance to the 60mg loading tapering

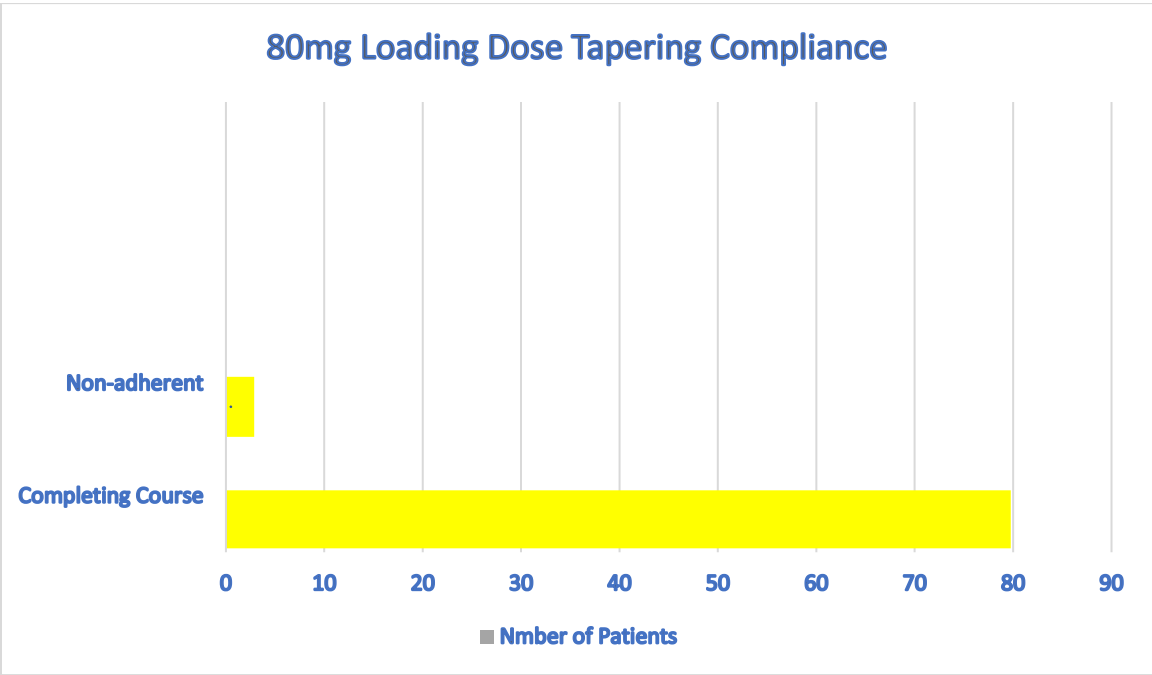


CHART 3: One patient reported mental status changes and discontinued the treatment.

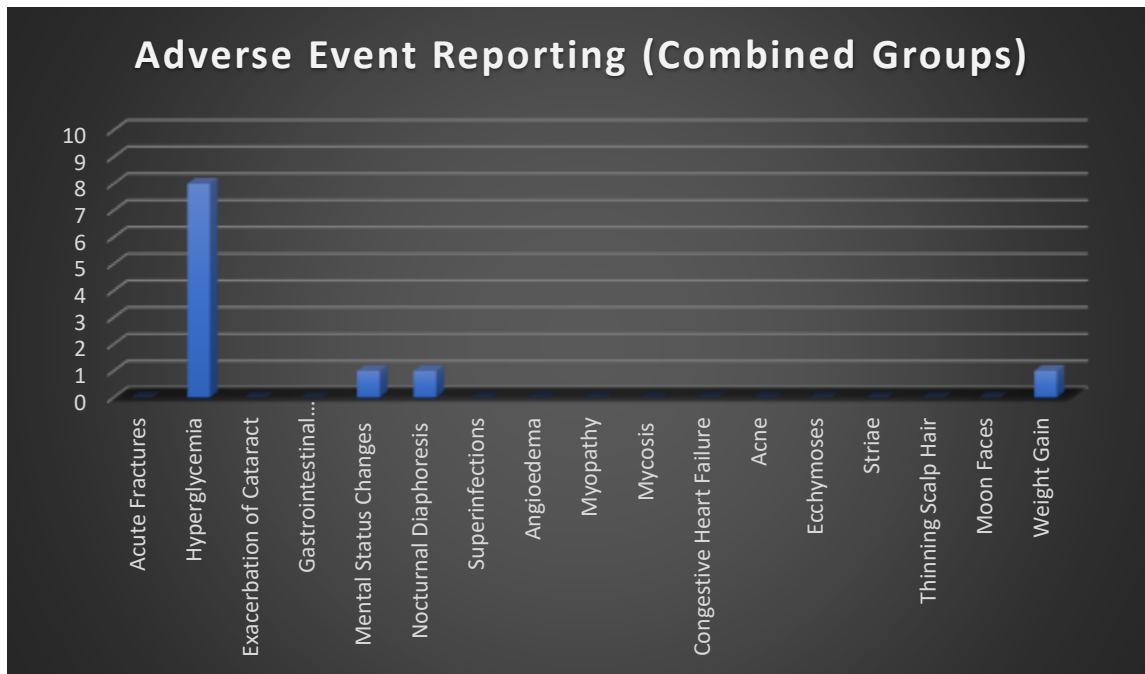


CHART 4: Reported adverse events not unique to prednisone with the most common complaint being elevations in blood glucose levels from baseline. ⁶

Discussion

With increasing patient volumes, practitioners are easily distracted by pre- pack prescriptions, some of which completely upset the rules of pharmacodynamics and pharmacokinetics guiding proper prescribing. A situation which may be contributing to the problem of increasing hospitalizations. Perhaps, keeping a more supervisory role is the right approach.

By sampling common intravenous and oral glucocorticoid treatments used at hospitals and outpatient centers, this study developed two separate tapering doses. By comparison, these two protocolled doses were deemed moderately high, yet with an appropriate temporal oral intake for seven days. A 60mg loading dose with taper and an 80 milligram with taper. The difference between the mean of the 60mg taper and that of the 80mg equals 0.2529, a 95% confidence interval from minus 0.0062 to positive 0.5119. A two tailed p -value of 0.0549, with some statistical significance; meaning a chance of type 1 error, that is rejecting a correct H_0 , is small. The standard error of difference being 0.119. On the 5th day, the larger loading dose showed superiority in effectiveness than the smaller loading taper, by a difference of 43 percent. The log curve of the higher dose continued over higher area than the lesser dose to the end of the study.

On average, if the 60mg served as a control, then only 2 patients would have to receive the 80mg dose for one patient to reach the study endpoints. The low number fortifies a more effective therapy with the 80mg load dose. It is noteworthy that there were no serious adverse events with all reported concerns already associated with glucocorticoids.

Limitations

Although specific disease conditions were treated in this study, understanding the etiology of any case is necessary in validating the addition of the prescribed 80mg taper in any specific regimen. The study did not account for confounding factors originating from other medications such as anti-infectives in the outcomes. Comprehensive assessment of glucocorticoids will require multiple institutional data with laboratory and imaging analysis for better tracking of the response to treatment.

Conclusion

Acute illness requiring glucocorticoids are met with doses for which we have shown that there is opportunity for increasing the dose with better tapering in physician offices; hence the P- PACK 80mg-20mg loading dose shown here in this study with superiority.

Citations

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