EFFECTS OF TIMING OF PREDNISOLONE ON THE DURATION OF EARLY MORNING STIFFNESS, PAIN AND DISEASE ACTIVITY SCORE (DAS-28) IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Objective: To determine the effects of timing of prednisolone on duration of early morning stiffness, pain score, number of swollen and tender joints, erythrocyte sedimentation rate (ESR) and disease activity score 28 (DAS-28) in joints in patients with rheumatoid arthritis.

Study Design: It was quasi experimental study.

Place and Duration of Study: This study was conducted in the department of rheumatology Fauji Foundation Hospital Rawalpindi over a period of 3 months, from Dec 2015 to Feb 2016.

Material and Methods: Total sample size of 85 was calculated by using non probability consecutive sampling technique. Patients with established rheumatoid arthritis diagnosed on the basis of ACR 1987 criteria were included in the study. All these patients had a disease duration of minimum 6 months and were on disease modifying anti rheumatic drugs and were taking ≤7.5mg of prednisolone and these patients were treated with the same dose of prednisolone given in morning at 8:00 A.M. for the first 15 days followed by treatment with same single daily dose of prednisolone given at the night 10:00 P.M. for next 15 days. This study compared duration of early morning stiffness, pain scores, number of swollen and tender joints, DAS-28 and ESR on day 15th and day 30th.

Results: A total of 85 patients of established rheumatoid arthritis were included in the study. All patients were female with a mean duration of disease of 7.87 ± 6.41 years. The mean age of patients was 49.39 ± 10.24 years. Mean of pain score, duration of morning stiffness, DAS-28, number of tender and swollen joint count, and ESR was decreased in patients who took prednisolone at 10:00 pm and had significant statistical difference (p-value<0.001).

Conclusions: Administration of low dose of prednisolone at night has good effects on duration of early morning stiffness, pain scores, number of swollen and tender joints, ESR and DAS-28.

Keywords: Arthropathy, Joint diseases, Prednisolone, Rheumatoid arthritis.

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INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease. It is characterized by pain, swelling and stiffness of predominantly small joints of hands. These symptoms are more marked in the early morning and follow a circadian rhythm[1]. This circadian rhythm is explained by diurnal variations in cytokine release and the metabolism and secretion of endogenous cortisol. Plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF) alpha and other cytokines peak during middle of night and early morning hours, resulting in marked early morning symptoms in patients with RA[2].

Work disability remains a considerable problem in patients with RA. Morning stiffness, a feature of RA results in impaired functional ability and early retirement from work[3]. In patients without RA an increase in inflammatory cytokine levels, trigger a release of hypothalamic corticotrophin releasing hormone, followed by pituitary production of adrenocorticotrophic hormone, and glucocorticoid secretions by adrenal cortex. This results in inhibition of production of inflammatory cytokines. However in patients with active RA, the cortisol response is impaired which leads to relative glucocorticoid insufficiency and unopposed cytokine mediated

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inflammation in early hours of morning[4]. So a relative glucocorticoid insufficiency, and unopposed cytokine mediated inflammation late at night and early morning hours of the day leads to early morning symptoms of RA. These observations support the role of appropriately timed exogenous glucocorticoid therapy to replenish the deficient cortisol and provide a balance between the pathological circadian mismatch between cytokine and glucocorticoid production[5]. This in turn will help to control the early morning symptoms of RA i.e it will help to reduce the duration of early morning stiffness, pain and disease activity scores.

While treating RA there are certain targets to be achieved like disease remission or low disease activity for better outcomes and this is known as a treat to target approach. This treat to target approach has been recommended by the American college of rheumatology (ACR) and European League against rheumatism[6]. To follow this approach the disease activity should be monitored frequently. There are various disease assessment tools like patient activity scale (PAS), patient activity scale-II (PAS-II), Routine Assessment of Patient Index Data with 3 measures (RAPID-3), Clinical Disease Activity Index (CDAI), and Disease Activity Score with 28-joint counts (DAS28) and the Simplified Disease Activity Index (SDAI)[7]. These disease assessment tools helps in following treat to target approach in RA to effectively control disease activity.

Disease modifying anti rheumatic drugs (DMARDs) are the hallmark of treatment of RA. Synthetic DMARD like methotrexate (MTX) is the first line drug which is often used in combination with prednisolone as part of tight control strategy in early RA[8]. Evidence from the CAMERA-II trial (a 2-year, prospective, randomized, placebo-controlled, double-blind, multicenter trial) showed that the combination of methotrexate and prednisone was more effective in reducing disease activity, physical disability, and attaining sustained remission[9]. It has also demonstrated that use of low dose prednisolone in combination with MTX reduced erosive joint damage two years after the initial diagnosis[9].

In another study low dose prednisolone along with MTX resulted in clinical and ultrasonographic remission rates in early RA[10]. Prednisolone has been used as part of remission induction therapy in early RA and undifferentiated arthritis in IMPROVED study which revealed high percentage of remission rates. In this study high dose prednisolone was used with tapering over a period of 7 weeks[11].

But the higher doses of prednisolone have been associated with serious adverse effects and infections. High dose glucocorticoids use has shown association with serious infections especially in elderly populations[12].

However evidence suggests that low dose of prednisolone is well tolerated and minimizes the risk of undesirable side effects associated with higher doses[13]. Their effect is brought about by their anti-inflammatory and immuno suppressive properties but Hypothalamic Pituitary adrenal axis (HPA axis) support is a crucial rule of low dose glucocorticoids in stable RA[14]. When a potentially harmful drug such as a prednisolone is prescribed, a balance between adverse effects and therapeutic benefits is attempted, and it is necessary to administer the minimal possible dose for the shortest duration to avoid side effects[15].

As the concept of chronotherapy is emerging (in which delivery of treatment is coordinated with circadian rhythm), timely administered prednisolone will have a more significant effects on early morning symptoms. If we match the administration of prednisolone to circadian rhythm, it has more beneficial effect on suppression of cytokine release and also give support to HPA[16]. This will lead to utilization of lesser dosage of prednisolone and better symptom control.

Various studies have been conducted on administration of prednisolone at night including the famous CAPRA-1 and CAPRA-2 trials, and the studies conducted by Arvidson and Owlia

Mohammad Bagher[17-20]. These studies have shown beneficial effects of using prednisolone on early morning symptoms of RA. No such studies have been conducted locally. In this study effort was made to see the effects of prednisolone on early morning symptoms of RA by giving it at 10:00 PM. In order to reduce the chance of HPA suppression, it was planned to use low dose of prednisolone.

MATERIAL AND METHODS

It was a quasi experimental study conducted in the department of rheumatology Fauji Foundation Hospital Rawalpindi over a period of 3 months with total sample size of 85 by using non probability consecutive sampling technique. With the help of WHO sample size calculator, following are the calculations; Confidence level=95%, Anticipated population proportion= 22.7%[4], Absolute precision required=10%, Sample size=85 patients.

Diagnosed cases of RA according to ACR 1987 Criteria[21] with disease duration of at least 6 months were included. Patients needing change of therapy either addition of DMARDs or increasing the dose of prednisolone or those requiring intramuscular or intravenous steroids were excluded from the study. Those patients who were given intramuscular depomedrol injection within 3 months, those who were in remission and those having no complaints of early morning stiffness were exclude.

Patients with established RA and already taking ≤ 7.5mg of prednisolone and DMARDs for atleast 6 months were included in the study, from Dec 2015 to Feb 2016. All patients were enrolled from rheumatology department Fauji Foundation Hospital Rawalpindi after obtaining informed consents and approval of the local ethics committee. At the start of the study, all of the patients had been on treatment with a daily dose of prednisolone (7.5mg/day) and one or more disease modifying anti rheumatic drugs (DMARDs). Patients were advised to take the same dose of prednisolone in the morning at 8: AM for the first 15 days, and, for the next 15 days, the patients received the same dose of prednisolone at 10 PM. No change in the dose of prednisolone was done and no change in the dose and number of DMARDs was scheduled during the study. Patients took their drug at 10 PM to prevent interference with their sleep. A questionnaire including age, gender, timing of prednisolone, duration of morning stiffness, pain score, DAS-28, number of swollen and tender joints and ESR was used. Duration of morning stiffness was the difference between the time of complete resolution of morning stiffness and the time of waking and it was calculated in terms of minutes. Pain score was assessed by using visual analogue scale 0 to 10 where 0 means no pain and 10 means maximum pain. These questionnaire were filled on day 15th and day 30th and comparison was done. Data were entered and analyzed in SPSS version 20.0. Mean and standard deviation were calculated for

Table: Comparison of means of variables.

Variables	After morning dose of prednisolone mean (mean ± SD)	After night dose of prednisolone (mean ± SD)	*p*-value
Pain score	4.94 ± 2.0	3.64 ± 2.00	<0.001
Morning stiffness duration in minutes	36.99 ± 25.52	24.97 ± 19.33	<0.001
DAS 28	4.57 ± 0.8	3.99 ± 0.81	<0.001
Number of tender joints	5.42 ± 4.7	4.18 ± 4.14	<0.001
Number of swollen joints	2.11 ± 1.80	1.35 ± 1.51	<0.001
ESR	30.08 ± 8.18	26.48 ± 8.24	<0.001

quantitative variables like pain score, duration of morning stiffness, DAS-28, tender joint count, swollen joint count & ESR. Frequency and percentages were calculated for qualitative variables like gender of patient. Paired sample t-test was used to compare pre-post pain score, stiffness, DAS-28, tender joint count, swollen joint count & ESR. A *p*-value<0.05 was taken as level of significance.

RESULTS

Total number of patients included in study were 85. All patients were female with a mean duration of disease of 7.87 ± 6.41 years. The mean age of patients was 49.39 ± 10.24 years. Mean of pain score, duration of morning stiffness, DAS-28, number of tender and swollen joint count and ESR has decreased when patients took prednisolone at 10:00 pm and had significant statistical difference (*p*-value<0.001) (table).

DISCUSSION

Patients with rheumatoid arthritis (RA) have disturbances in the hypothalamic pituitary adrenal (HPA) axis and altered circadian rhythm of circulating serum cortisol, melatonin, TNF alfa and IL-6 levels. The molecular machinery responsible for the circadian time keeping is perturbed in RA[22]. It results in marked functional disability in morning.

There has been significant development in the management of RA over last 10 years. Patient of RA should be diagnosed and treated early to prevent joint damage and disability. To control the disease progression DMARDs are started early along with oral steroids. The early morning symptoms in RA are difficult to manage and in such cases if we use prednisolone at the time when proinflammatory cytokines (IL-6, TNF alfa) are released in to the circulation that is around 2:00 AM with a peak at around 6:00 AM, the administration of prednisolone at 2:00 AM will suppress this surge of proinflammatory cytokines which will help to control early morning symptoms and disease activity. This will also replenish the relative gluco corticoid insufficiency as a response to release of inflammatory cytokines as seen in cases of RA.Another beneficial aspect of administering low dose glucocorticoids at 2:00 AM is that the adrenocortical activity as part of normal circadian rhythm is maximal at 2:00 AM to 8:00 AM, and by giving prednisolone at this point of time it has minimal effect on suppression of HPA axis. Following such an approach the drug can be delivered at appropriate time and a lower dose of the drug can be used[23].

To follow this chronotherapy approach one has to wake up at 2:00 AM to take the tablet of prednisolone. This approach has been studied by Arvidson and his colleagues in which twenty six patients were randomised to receive low dose prednisolone at 2:00 AM or 7:30 AM[19]. In that study low dose of prednisolone at 2:00 AM resulting in improvement in joint pain,early morning stiffness and other parameters. However getting up at 2:00 AM can disturb the sleep of the patients.

Owlia and colleagues have used low dose prednisolone at night at 10:00 PM[20]. They have seen that disease activity, pain score and duration of early morning stiffness improved after administration of prednisolone at nightas compared to when it was administered in the morning. In this study immediate release form of prednisolone was used and it was given at bed time to avoid sleep disturbance.

Another study conducted by De Silva and his colleagues found that giving prednisolone at night is more effective in controlling early morning stiffness in RA[24].

For delivering prednisolone at around 2:00 AM a modified release formulation of prednisolone has been developed and this formulations have solved the issue of administration of prednisolone at right time. This formulation consists of a tablet with coating that dissolves after 4 hours after ingestion. The modified release prednisolone is given at 10:00 PM and it is released at 2:00 AM. The beneficial effects of modified relase prednisolone has been established in CAPRA1 and CAPRA2

trials[17,18]. In CAPRA 1 trial safety of low dose modified release prednisolone was evaluated by giving it at 10:00 PM[17]. In CAPRA 2 study results revealed a greater median reduction of duration of early morning stiffness, fatigue and disease severity[18].

Regarding effects of low dose nocturnal prednisolone on Hypothalamic Pituitary Adrenal axis (HPA), function of HPA axis was tested in subset of patients in CAPRA 1 study in which Corticotrophin releasing hormone (CRH) test was performed and cortisol levels were assessed. Over 12 month period no deterioration or adverse effect was observed on HPA axis. On the other hand the study revealed an improved HPA axis responsiveness in patients with RA who were administered prednisolone chronotherapy compared to conventional morning prednisolone treatment[25] and this specific effect is the cause of improved symptom control as compared to morning prednisolone.

As the modified release formulation is not available in Pakistan we have attempted to determine the beneficial effects of immediate release prednisolone on duration of early morning stiffness, pain score and disease activity and the results of the study were consistent with the previous studies in improving clinical response in terms of reduction in duration of morning stiffness, pain and disease activity scores, number of swollen and tender joints and ESR.

The immediate release prednisolone has a half-life of 2-3 hours with peak onset of action at 2 hours and a duration of action of around 8 hours so it is thought that by giving it at 10 pm we still can have good effects till 6:00 AM. As the proinflammatory cytokines begins to rise at 2:00 AM and peak at 6:00 AM prednisolone delivered at 10:00 PM can have an effect on rise of proinflammatory cytokines and a relative cortisol insufficiency which is seen in cases of active RA in response to proinflammatory cytokines at 2:00 AM.

Limitations related to this study were that it was conducted on relatively small number of patients and over a short period of time that was 30 days. One can determine the short term benefits however to determine the long term benefits it was needed to have an extension of study to see the sustainability of beneficial effects and to see the adverse effects of night dose of prednisolone. The study involved female patients only so effects on males cannot be determined. In this study the effects on HPA axis after night dose of prednisolone has not been observed which should also be assessed.

CONCLUSION

Night time administration of prednisolone has good results on reduction in early morning stiffness duration, pain score and disease activity in patients with established RA who are already on DMARDs.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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