



THE EFFICACY OF USE OF PHYSIOLOGICAL DOSES OF METHYLPREDNISOLONE ON GRANULOMATOUS MASTITIS TREATMENT

General Surgery

Edip Erdal Yılmaz General Surgery Clinic, Diyarbakir Gazi Yaşargil Education and Research Hospital, Diyarbakir/Turkey. - Corresponding Author

Metehan Gümüş Department of General Surgery, Dicle University Medical School, Diyarbakir/Turkey.

Hatice Gümüş Department of Radiology, Dicle University Medical School, Diyarbakir/Turkey.

ABSTRACT

Background: Granulomatous mastitis (GM) treatment many treatment protocols. Methylprednisolone at physiological dose, which results is 2/3 of the dose in the morning and 1/3 of the dose in the evening, has not been sufficiently investigated in studies on GM treatment in literature. The aim of this study is to investigate the efficacy of the physiological dose.

Methods: The patients were divided into two groups: normal dose (ND) and physiological dose (PD). Retreatment with methylprednisolone or different treatments was determined for patients with recurrence according to their response in the previous treatment process.

Results: There was no statistically significant difference found between the two groups.

Conclusion: The total dose was reduced by halving the evening dose in accordance with the biorhythm, in which the same results were obtained. We believe that it would be statistically significant with a larger number of patients.

KEYWORDS:

Granulomatous Mastitis, Methylprednisolone, Drug Dosage Calculations

Introduction

Granulomatous mastitis (GM) is one of the rare inflammatory diseases of the breast. It was identified for the first time by Kessler E, Wolloch Y in 1972⁽¹⁾. Even though it is common in young breastfeeding mothers, it can be observed in all age groups ranging from the 2nd to 9th decade. The first presentation complaint is frequently breast swelling. Biopsy is important in the diagnosis since it can be confused with breast cancer^(2,3). Various surgical methods ranging from abscess drainage to total mastectomy can be performed. Furthermore, many drugs such as methylprednisolone, methotrexate (MTX), and azathioprine (AZT) are used in medical treatment^(4,5).

Methylprednisolone has taken its place in GM treatment either by itself or in combination with other treatments. It was proposed for the first time at a dose of 60mg/day by DeHertogh in 1980⁽⁶⁾. Many treatment protocols ranging from 5mg/day to 60mg/day have been administered in studies conducted until today, furthermore the dose of 0.5mg/kg/day has been widely accepted in equal doses in the morning and evening in many studies⁽¹⁻⁶⁾. Reviewing literature, 2/3 of the total dose has been administered in the morning and 1/3 of the total dose has been administered in the evening in treatment of adrenal insufficiency^(7,8). Moreover, it was reported in the 2009 England Rheumatology guideline and in many studies that the use of low-dose steroids does not suppress HPA (hypothalamic-pituitary-adrenal) axis. The use of low-dose steroid was recommended in the treatment protocols of rheumatology patients^(9,10). This issue has not been sufficiently investigated in GM treatment. The aim of this study is to compare the use of equally divided doses of methylprednisolone, which is widely accepted in MG treatment, and the use of the same dose in the morning with half of the evening dose in terms of efficacy in treatment, recurrence rates, and side effects of methylprednisolone on patients.

Material and Methods

This prospective study was conducted with the approval of Dicle University Clinical Research Ethics Committee. Thirty three patients, who presented to Dicle University Medical Faculty Hospital General Surgery Breast Clinic between February 2013 and October 2014 and who were diagnosed with GM as a result of pathology after a biopsy due to any breast related complaint, were included in this study. The patients undergoing surgery as an initial treatment, patients with hypertension or diabetes, or pregnant patients were excluded from this study. The first group of patients were administered a total of 32mg methylprednisolone, 16mg in the morning, and 16mg in the evening (normal dose = ND). The second group was administered a total of 24mg methylprednisolone, 16mg in the morning, and 8mg in the evening (physiological dose = PD). Patients were controlled by time intervals of three weeks. Drug doses were either reduced or continued without changing according to the results in controls. The patients

were expected to respond to the treatment up to a maximum of three months. The groups were examined in terms of treatment response, relapse, complications, and patient satisfaction. In patients with recurrence; those with rapid improvement with methylprednisolone during the previous treatment process were re-treated, those with no rapid improvement with the drug during the previous treatment process were planned to receive a different drug (MTX) protocol or surgery if the patient's condition was suitable. Methylprednisolone therapy was used for a total of 6 months at most. The patients with no recurrence within the last year were considered to have a complete response to treatment and were excluded from follow-up by being suggested to present again in case of any complaint. In the first year controls patients were asked if they experienced any difficulties due to the drug during medication period, they were recorded and compared between the two groups. The complaints of patients were hair growth, weight gain, glucose intolerance, Cushing-like muscle joint pains, and stomach complaints. The patients were followed up for a period between 12 months to 22 months.

Results

There were total of thirty three patients included in the study, seventeen patients were in the ND group and sixteen patients were in the PD group. The mean age of patients was 38±6.5 in the ND group and 37±6.4 in the PD group. The mass size of patients was 3.98±2.10 cm in the ND group and 4.04±2.06 in the PD group. The collections emerging in lesions of patients at either first presentation or during treatment were aspirated or drained in nine patients (52%) in the ND group and in seven patients (43%) in the PD group. The follow-up durations of both groups were similar to each other. There was no response to treatment in two patients from each group. The two patients failing to respond to the treatment in the ND group underwent surgical treatment, while one of the patients in the PD group underwent surgical treatment and the second patient underwent MTX treatment. There was a recurrence in four of the patients in the ND group. One of the aforementioned patients was administered steroid repeat, two of them were administered MTX, and one patient received surgical treatment. Recurrence was observed in five of the patients in the PD group. Two of the aforementioned patients were administered steroid repeat, two of them were administered MTX, and one patient received surgical treatment. There was no statistically significant difference between the two groups in terms of failure to respond to the treatment and recurrence ($p > 0.005$). Eight (47%) patients in the ND group and six (37%) patients in the PD group were complaining of side effects due to treatment. However, the complaint rate was less in the PD group and the difference was not statistically significant (Table 1).

Discussion

There was no difference between the PD and ND groups in this study in

terms of recurrence, resistance to treatment, and positive response to treatment. In addition, patients' complaints due to use of drug were less in the PD group.

GM is observed at any age. It has been reported in literature as occurring from eleven to eighty one years of age^(11,12). It has been observed mostly in breastfeeding mothers and in women whose age is in the 3rd or 4th decades⁽¹¹⁾. The median age was thirty two, the youngest age was twenty four, and the oldest age was fifty in our study. Although autoimmune diseases, immune response, local trauma, hyperprolactinemia, alpha-1 antitrypsin, OKS, pregnancy, lactation, and DM have been attributed to be the cause; the etiology of GM has not yet been made clear⁽¹³⁾. Similar to the condition in etiology, there have been many protocols proposed for GM treatment such as surgery, medical treatment, and exclusively follow-up^(14,15,16). The doses and durations of steroid treatment have been observed quite variously in the review of literature. The treatment was administered as 60mg/day in a patient by DeHertogh and a cure was obtained after four months⁽⁶⁾. It was administered at different doses and in different durations in following studies. Kuba S et al. used doses of 5mg/day in two patients and 10mg/day in a patient for two to five months resulting in a cure⁽¹⁷⁾. Corticosteroid treatment has been suggested at various doses ranging from 5mg/day to 60mg/day. The dose of 0.5mg/kg/day has been commonly accepted in most of the studies, and the dose has been used equally in morning and evening^(18,19). The doses of 32mg and 24mg were used in this study and no difference was observed between the two groups in treatment.

In reviewing literature, 2/3 of total dose has been administered in the morning and 1/3 of total dose has been administered in the evening in the treatment of adrenal insufficiency^(7,8). Steroid administrations used in granulomatous mastitis treatment can be performed by taking advantage of the practices of rheumatologists in many ways. Rheumatologists have reported the effect of dose and duration of steroid use on side effects. In addition, they have demonstrated that low evening dose is effective in the suppression of the HPA axis^(9,10). In the literature, there have been similarities between the doses at which treatment efficacy has been shown in granulomatous mastitis and doses used in the treatment of rheumatic diseases^(9,10). This study was planned as a preliminary study to investigate the effects of halving the evening dose of the generally accepted dose. Since similar results were obtained with the routine use in treatment efficacy, further study that would reduce the evening dose more was initiated. There was no statistically significant difference between the PD group, in which methylprednisolone was used in accordance with biorhythm, and the ND group in terms of resistance to treatment, recurrence, and positive response to treatment. Although there was no difference in treatment and no statistical significance, there was a decrease in patient's complaints due to steroid. Either the combination or sequential therapy is necessary in most of the patients in GM treatment. Surgery has been argued by many authors in GM treatment^(20,21). The development of complications such as skin ulceration especially on the excision region, abscess formation, and recurrence with secondary infection have made wide excision necessary^(11,16,22). This approach results in mastectomy in some patients, or at least deformity of the breast. The introduction of steroid therapy has reduced the rate of surgery. The side effects of steroid therapy have directed surgeons to use a lower dose of the drug. Moreover, it has been reported in some series that patients improved only by observation⁽²³⁾. These results have indicated that the most important factor in GM treatments is the management of the process. It should be kept in mind that treatments can be performed also at lower doses and the reduction of evening dose does not affect the treatment in GM patients, for which there are many treatment alternatives. The duration of treatment is also another important issue. We did not administer more than three months steroid treatment at a time in our patients and used other treatment alternatives in patients failing to respond. In this way, all patients improved without any permanent complications.

Although surgery rates have decreased due to successful treatments as a result of medical treatment and follow-up, small or large interventions are necessary during GM treatment in most of the patients. Out of thirty three patients treated with methylprednisolone, surgical resection in three (0.9%) patients and aspiration or drainage in sixteen (48%) patients due to collections developing at the presentation or during treatment were needed in this study, independent of the drug dose. The use of antibiotic therapy to combat the cause is very useful in patients with abscess formation^(21,11). Since our observation was not centered on reproduction in this study, we considered aspiration or drainage sufficient in patients with collection.

Furthermore, we administered empirical antibiotic therapy in cases in which we suspected superinfection. All inflammatory masses were removed in patients failing to respond to the treatment considering negative surgical margins. Since surgery was performed after steroid treatment occurred for shrunk lesions, there was no need for mastectomy and no significant deformity in any of the patients. These patients improved and there was no recurrence. The recurrence rate has been reported to be less than 5% in series with negative surgical margins⁽¹¹⁾. In accordance with literature, we administered steroid therapy for six weeks in addition to surgical treatment. We did not insist on the use of steroid in any of the patients failing to respond to treatment for three months independent of the dose. Five patients (two in the ND group, three in the PD group) received surgical indication and five patients (two in the PD group, three in the ND group) were administered MTX treatment independent of the dose of methylprednisolone⁽⁵⁾.

The limitations of this study are limited to the number of patients and that this is a preliminary study for a study that's purpose is on dose not suppressing the HPA axis.

Conclusion

- There is a need for combination therapy in most of the patients in GM treatment. Furthermore, aspiration or drainage is performed for collections in most of them.
- Corticosteroid therapy should not be insisted upon, and the decision for alternative treatments should not be delayed.
- We suggest halving the evening dose of methylprednisolone in accordance with physiology in GM treatment instead of the commonly accepted dose, since the same treatment success and lower patient dissatisfaction can be achieved with a smaller dose in the physiological dose in those receiving corticosteroid therapy. Although the complaints for side effects of methylprednisolone were decreased, it was not statistically significant due to the limited number of patients.
- Further studies that are similar to the current study are necessary to follow up on this study and to investigate the treatment efficacy with the doses that are reported not to suppress the HPA axis.

Table 1: The characteristics of the ND and PD patients

	Normal dose = ND Group	Physiological dose= PD Group	
Number of Patients(n)	17	16	
Age	38±6.5	37±6.4	
Mass size at presentation (cm)	3.98±2.10	4.04±2.06	
Steroid dose	Morning: 16 mg Evening: 16 mg	Morning: 16 mg Evening: 8 mg	
Fail to respond to treatment	2 (surgery was planned for both patients)	2 (MTX in one patient and surgery in second patient were planned)	
After failing to respond to treatment	Number of patients undergoing surgery	2	1
	Number of patients undergoing another drug protocol	0	1
Recurrence		4	5
Process performed after recurrence	Steroid dose repeat	1	2
	MTX	2	2
	Surgery	1	1
Scoring to determine the patient's complaints against side effects due to drugs during treatment process	8	6	

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