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Original Article

Factors Associated with the Development of Adrenal Insufficiency in Patients with Juvenile Idiopathic Arthritis Who Received Systemic Corticosteroids

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ABSTRACT

Aim: In juvenile idiopathic arthritis (JIA), systemic corticosteroids are reserved for cases with serious organ involvement, those with macrophage activation syndrome, and in the presence of high disease activity in oligoarticular and polyarticular JIA. However, systemic steroids may lead to serious side effects linked to adrenal insufficiency (AI). This study aimed to investigate factors related to AI in children with JIA who received systemic steroids.

Materials and Methods: Twenty-five children with AI (serum cortisol <18 µg/dL 30 minutes after adrenocorticotropic hormon stimulation) and 25 children without AI were included in this study. The subjects' characteristics, type of JIA, arthritis location, laboratory measurements, and number of joints involved were recorded. The type of glucocorticoid administered, the treatment protocol, and the cumulative steroid dose were recorded. The primary endpoint was the difference in clinical characteristics, laboratory measurements and systemic corticosteroid dose in those children with or without AI.

Results: The median cumulative steroid dose was significantly higher in those patients with AI compared to those without [2,500 (1,370-4,400) mg vs. 963 (650-2,500) mg, p=0.010]. Patients with oligoarticular JIA had a 6.7-fold lower risk of AI compared to those with other JIA types [odds ratio (OR): 0.149, 95% confidence interval (CI): 0.035-0.643, p=0.011]. Those patients with higher cumulative steroid doses (>1,000 mg) had a 7.5-fold higher risk of AI than those with lower doses (OR: 7,500, 95% CI: 1,634-34,416, p=0.010).

Conclusion: Our findings show that non-oligoarticular JIA and high cumulative steroid doses are predictive for AI development in this patient subset; thus, systemic corticosteroids should be reserved for more aggressive JIA types and the cumulative dose should be limited to 1,000 mg.

Keywords: Juvenile idiopathic arthritis, systemic corticosteroids, adrenal insufficiency

Introduction

Juvenile idiopathic arthritis (JIA) is described as persistent arthritis of unknown etiology present for at least 6 weeks. In JIA, there is often multi-organ involvement in addition to arthritis, including the eyes, skin, and internal organs (1,2). Although its etiology is unclear, several factors

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such as genetic predisposition, infections, and trauma may contribute to JIA development. Abnormal activation of T-cells, B-cells, natural killer cells, dendritic cells, macrophages, neutrophils, and the resultant increase in pro-inflammatory mediators are considered to cause JIA and are also implicated in joint involvement and systemic complications (3,4).

Treatment options include non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate or sulfasalazine as a disease-modifying anti-rheumatic drug, systemic or intra-articular corticosteroids, and biologic agents (5-8). Corticosteroids reduce the activation and proliferation of immune cells via cellular and transcriptional alterations, resulting in reduced production of pro-inflammatory cytokines including interleukin (IL) 1 and IL6 (9,10). In JIA, systemic corticosteroids are reserved for systemic JIA with serious organ involvement (such as myocarditis and pericarditis), in the presence of associated macrophage activation syndrome, and when disease activity is high in oligoarticular and polyarticular JIA. However, systemic corticosteroids may lead to serious complications including infections, myopathy, neuropsychiatric symptoms, osteoporosis, obesity, insulin resistance, gastric intolerance, cataract, glaucoma, and/or adrenal insufficiency (AI). Particularly, AI has been associated with fatigue, growth failure, obesity, hypertension, hyperglycemia, osteoporosis and muscle weakness. Given the likelihood of such serious complications, identifying the factors associated with AI development in patients with JIA receiving systemic corticosteroids is important.

As such, this study aimed to investigate those factors independently associated with AI in children receiving systemic corticosteroids for JIA.

Materials and Methods

This retrospective study was conducted at the Department of Pediatrics of İstanbul Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey. Data regarding children with JIA diagnosed according to the criteria established by the International League of Associations for Rheumatology (ILAR) who were <18 years of age and were treated with glucocorticoids between 2007 and 2013 were retrieved from their patient charts and the institutional digital database (11). From these children, those who received low dose (1 mcg) adrenocorticotropic hormon (ACTH) tests for the assessment of the pituitary-adrenal axis were included in the final analyses. Children with underlying chronic disorders, particularly those with conditions predisposing to infectious diseases (primary or secondary immune insufficiency, chronic kidney disease, nephritic syndrome, and immunosuppressive drug use) and those with endocrine disorders which may interfere with the optimal functioning of the pituitary-adrenal axis (diabetes mellitus, diabetes insipidus, hypo- or hyperthyroidism, precocious puberty, congenital adrenal hyperplasia, or pituitary insufficiency) were excluded. This study was approved by the İstanbul Medeniyet University Göztepe Training and Research Hospital, Clinical Research Ethics Committee (no: 2013/0011, date: 25.06.2013). Informed consent was received from the legal guardians of the children. This study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients' demographic characteristics, clinical characteristics, type of JIA, arthritis localization, laboratory measurements, including complete blood count, C-reactive protein (CRP) level and rheumatoid factor (RF) levels, erythrocyte sedimentation rate (ESR), and number of joints with arthritis were recorded. The type of glucocorticoid, the treatment protocol, and the cumulative steroid dose were obtained from the patient files, in addition to the results of the low-dose (1 mcg) ACTH tests. The definition for AI was as follows: Having a serum cortisol level of <18 µg/dL 30 minutes after stimulation with ACTH.

The primary endpoint of this study was the difference in clinical characteristics, laboratory measurements and systemic corticosteroid dose in those children with AI and those without AI.

Statistical Analysis

The analyses were performed on the SPSS software, version 25.0 (SPSS Inc., Chicago, IL, USA). To check the normality of the distribution of continuous variables, the Shapiro-Wilk test was used. Continuous data obtained by descriptive analyses are given as mean ± standard deviation or median (1^{st} quartile - 3^{rd} quartile) according to the findings of normality analysis, and as frequency (absolute count and proportions) for categorical variables. Continuous variables which demonstrated normal distribution underwent testing with the independent samples t-test; whereas, those with non-normal distribution were analyzed with the Mann-Whitney U test. Categorical variable distributions were compared with chi-squared or Fisher's Exact tests. The significant risk factors independently associated with AI development were identified via multiple logistic regression analysis (forward conditional). P-values of <0.05 were accepted as being statistically significant.

Results

A total of 50 children [median age 12.35 (8.5-16.8) years] with JIA were analyzed. The comparison of those children with and without AI with regard to their clinical characteristics is given in Table I. The two groups were similar in terms of their ages, gender, body mass index and body surface area, Tanner stage, arthritis localization, joint scores, presence of morning stiffness, and the levels of leukocytes, CRP, and ESR at diagnosis.

Comparison of the laboratory tests is presented in Table II. Leukocyte count was significantly higher in those children with AI than in those without [9 (7.4-10.3)×10^3 vs. 7 (6-8)×10^3, p=0.008]. However, ESR was lower in those children with AI than in those without [13 (12-20) mm/hr vs. 21 (15-29) mm/hr, p=0.009]. Both baseline and stimulated cortisol levels were significantly lower in those children with AI than in those without AI (p<0.001). Finally, ACTH levels were also significantly lower in those children with AI than in those without [10.1 (5-29) vs. 17.9 (13.9-20.7), p=0.033].

The frequency of children receiving corticosteroids was higher among those with AI compared to those without AI [21 (84%) vs. 13 (52%), p=0.034]. However, the median cumulative steroid dose was significantly higher in those patients with AI compared to those without [2,500 (1,370-4,400) mg vs. 963 (650-2,500) mg, p=0.010]. The patients with AI were also grouped according to their daily dose. AI was detected in 60.9% (n=14) of those patients who used corticosteroids <10 mg/day, and 63.6% (n=7) of those patients who used corticosteroids >10 mg/day (p=0.052).

The duration of steroid use was similar between the two groups. The patients were categorized into two subgroups according to their duration of steroid use as those using for less than one month (short time) and those for more than one month (long time). The adrenal response was suppressed in 24% (n=2) of those patients using corticosteroids for less than one month and in 76% (n=23) for those patients using corticosteroids for longer than one month (p=0.009).

The relationship between steroid discontinuation time and AI was investigated in those patients who were not using corticosteroids at the time of their AI test. In 50% (n=2) of the patients with AI, steroid treatment had been discontinued less than one month previously [minimum (min): 14 days, maximum (max): 30 days], and in 50% (n=2) of them, more than one month previously (min: 31 days, max: 90 days). This result points out that in those patients whose steroid treatment was discontinued, AI may continue for more than one month after the treatment.

The amount and duration of corticosteroids used by our patients were divided into four groups as follows; 10 mg (low-dose) and above 10 mg (high-dose) for less than one month (short time) and more than one month (long time). According to these groups, among those patients using low-dose (<10 mg) corticosteroids, AI was not detected in any patient with a duration of less than one month of use; and AI was present in 46% (n=23) of those patients using both low and high doses for longer than one month. AI insufficiency was found in 40% (n=2) of patients using high doses (>10 mg) for a short time (<1 month), and in 83.3% (n=5) of patients using high doses (>10 mg) for a long time (>1 month) (p=0.01).

We performed multiple logistic regression analysis (forward conditional method) in order to determine any risk factors independently associated with AI (Table III). We found that the type of JIA and the cumulative steroid dose were significant risk factors. Patients with oligoarticular JIA had a 6.711-fold lower risk of AI than other types of JIA [odds ratio (OR): 0.149, 95% confidence interval (CI): 0.035-0.643, p=0.011] (Figure 1). Those patients with higher cumulative steroid dose (>1,000 mg) had a 7.5-fold higher risk of AI compared to those who had received lower dosages (OR: 7.5, 95% CI: 1,634-34,416, p=0.010) (Figure 2). Other variables included in the model, age (p=0.699), gender (p=0.286), family history (p=0.082), age at JIA onset (p=0.332), steroid use at stimulation testing (p=0.060) and the duration of steroid use (p=0.983) were found to be non-significant.

Discussion

This study aimed to investigate risk factors associated with AI in patients with JIA who had received systemic corticosteroids. Our findings show that those children developing AI during treatment with corticosteroids had received significantly higher cumulative corticosteroid doses compared to those children without AI. Moreover, having non-oligoarticular type JIA and cumulative corticosteroid doses were predictive for the development of AI during treatment with corticosteroids in children with JIA. Children with higher cumulative steroid doses (>1,000 mg) had a 7.5-fold higher risk of AI than those children with lower cumulative steroid doses (<1,000 mg).

JIA is the most common pediatric rheumatic disease in the world (12,13). The seven subtypes of JIA classified by the ILAR are oligoarticular, RF-positive polyarticular, RF-negative polyarticular, enthesitis-related arthritis, systemic onset, psoriatic arthritis, and undifferentiated arthritis (11). The prevalence of JIA is estimated to vary

Table I. Summary of patient- and JIA-related characteristics with regard to adrenal insufficiency

		Adrenal insufficiency		
	Total (n=50)	**No (n=25)**	**Yes (n=25)**	**p-value**
Age (years)	12.35 (8.5-16.8)	11.9 (8.5-16.5)	13.1 (9.5-16.8)	0.600
Gender				
Female	34 (68.00%)	19 (76.00%)	15 (60.00%)	0.363
Male	16 (32.00%)	6 (24.00%)	10 (40.00%)	
Height, m (SD)	-0.973±0.889	-0.896±0.75	-1,051±0.556	0.872
Weight, kg (SD)	-0.813±0.23	-0.624±0.25	-1,021±0.747	0.882
Body mass index, kg/m^2	18.62±3.55	18.90±3.59	18.33±3.56	0.575
Body surface are, m^2	1.27 (0.91-1.55)	1.36 (0.93-1.50)	1.23 (0.86-1.55)	0.992
Tanner stage				
Prepubertal	22 (44.00%)	12 (48.00%)	10 (40.00%)	0.776
Pubertal	28 (56.00%)	13 (52.00%)	15 (60.00%)	
Age at diagnosis (years)	9.56±4.45	9.02±4.52	10.10±4.41	0.397
Number of arthritis at diagnosis	2 (2-4)	2 (2-3)	2 (2-4)	0.630
Number of arthritis, last 6 months	2 (1-2)	2 (1-2)	2 (1-3)	0.584
Type of JIA				
Oligoarticular	31 (62.00%)	20 (80.00%)	11 (44.00%)	0.048
Polyarticular	9 (18.00%)	2 (8.00%)	7 (28.00%)	
Enthesitis-related	8 (16.00%)	3 (12.00%)	5 (20.00%)	
Systemic	2 (4.00%)	0 (0.00%)	2 (8.00%)	
WBC (x1000/mm^3) at diagnosis	8.9 (7-11.2)	9.7 (7.4-11.2)	8.8 (6.95-11.5)	0.676
ESR at diagnosis (mm/hr)	39 (25-57)	35 (22-65)	42 (30-52)	0.641
CRP at diagnosis (mg/dL)	1.85 (0.37-4.06)	1.90 (0.35-5.00)	1.80 (0.54-3.25)	0.961
RF positivity (units/mL)	2 (4.00%)	1 (4.00%)	1 (4.00%)	1.000
ANA positivity	9 (18.00%)	5 (20.00%)	4 (16.00%)	1.000
HLA-B27 positivity	4 (15.38%)	0 (0.00%)	4 (25.00%)	0.136
NSAID use	6 (14.29%)	3 (13.64%)	3 (15.00%)	1.000
Methotrexate use	17 (40.48%)	8 (36.36%)	9 (45.00%)	0.799
Sulfasalazine use	28 (66.67%)	13 (59.09%)	15 (75.00%)	0.444
Type of steroid				
Methylprednisolone	45 (90.00%)	24 (96.00%)	21 (84.00%)	0.349
Pulse steroid + methylprednisolone	5 (10.00%)	1 (4.00%)	4 (16.00%)	
Steroid use status				
Stopped	16 (32.00%)	12 (48.00%)	4 (16.00%)	0.034
Still using	34 (68.00%)	13 (52.00%)	21 (84.00%)	
Duration of steroid use, months	3 (2-6)	2.5 (1-6)	3 (2-6)	0.220
Cumulative steroid dose	1624 (750-3516)	963 (650-2500)	2500 (1370-4400)	0.010
Once every two days steroid use	18 (36.00%)	9 (36.00%)	9 (36.00%)	1.000
Remission	18 (42.86%)	10 (45.45%)	8 (40.00%)	0.964
Relapse	11 (61.11%)	6 (60.00%)	5 (62.50%)	1.000

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.
SD: Standard deviation, JIA: Juvenile idiopathic arthritis, WBC: White blood cells, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RF: Rheumatoid factor, ANA: Anti-nucleus antibody, HLA: Human leukocyte antigen, NSAID: Non-steroid anti-inflammatory drugs

Table II. Summary of laboratory measurements with regard to adrenal insufficiency

		Adrenal insufficiency		
	Total (n=50)	**No (n=25)**	**Yes (n=25)**	**p-value**
WBC (x1000/mm^3)	7.75 (6.6-9.6)	7 (6-8)	9 (7.4-10.3)	0.008
ESR (mm/hr)	16.5 (13-27)	21 (15-29)	13 (12-20)	0.009
CRP (mg/dL)	0.33 (0.33-0.80)	0.33 (0.30-0.51)	0.33 (0.33-0.88)	0.857
Insulin (µIU/mL)	8.51 (5.95-11.60)	8.24 (6.67-10.44)	8.78 (5.94-13.64)	0.637
Free T4 (ng/dL)	0.89 (0.78-1.03)	0.82 (0.77-0.96)	0.94 (0.86-1.17)	0.030
TSH (µIU/mL)	1.85 (1.36-3.06)	1.88 (1.38-3.56)	1.74 (1.32-2.79)	0.750
Fasting blood glucose (mg/dL)	85 (80-90)	86 (79-91)	85 (80-90)	0.826
HOMA-IR (mIU/L)	1.73 (1.19-2.51)	1.68 (1.38-2.38)	2.03 (1.13-2.86)	0.733
Triglyceride (mmol/L)	68.65±24.31	65.65±15.92	71.65±30.60	0.410
Total cholesterol (mg/dL)	161 (136-191)	159 (136-188)	180 (136-208)	0.169
LDL (mg/dL)	93.76±26.51	89.22±24.75	98.30±27.96	0.250
HDL (mg/dL)	60.52±15.84	56.74±12.88	64.30±17.83	0.107
Baseline cortisol (mcg/dL)	8.08 (1.41-11.91)	11.60 (7.45-12.72)	1.41 (0.52-10.10)	<0.001
Stimulated cortisol (mcg/dL)	17.87 (10.03-20.73)	20.73 (19.60-21.43)	10.03 (5.31-15.30)	<0.001
Baseline DHEA-S (µmol/L)	32.9 (6.6-89.4)	42.1 (6.9-158.4)	19.1 (2.8-51.0)	0.133
Stimulated DHEA-S (µmol/L)	36.25 (6-96.2)	42.9 (6.6-159.3)	20.1 (2.7-57)	0.154
ACTH (pg/mL)	14.65 (7.37-21.3)	17.9 (13.9-20.7)	10.1 (5-29)	0.033

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.
WBC: White blood cells, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, TSH: Thyroid stimulating hormone, HOMA-IR: Homeostatic model assessment for insulin resistance, LDL: Low dansity lipoprotein, HDL: High dansity lipoprotein, DHEA-S: Dehydroepiandrosterone sulfate, ACTH: Adrenocorticotropic hormon

Table III. Significant risk factors of adrenal insufficiency, multiple logistic regression analysis

	β coefficient	**Standard Error**	**p-value**	**Exp (β)**	**95% CI for Exp (β)**	
Type of JIA (oligoarticular)	-1.902	0.745	0.011	0.149	0.035	0.643
Cumulative steroid dose (>1000 mg)	2.015	0.777	0.010	7.500	1.634	34.416
Constant	-0.161	0.697	0.818	0.852		
Dependent variable: Adrenal insufficiency; nagelkerke R^2=0.351; correct prediction=72.00%						
JIA: Juvenile idiopathic arthritis, CI: Confidence interval						

between 16 and 150 per 100,000 individuals. The clinical features of JIA differ greatly according to the type of disease. Greater severity of arthritis at onset, symmetrical disease, early wrist or hip involvement, the presence of RF, persistent active disease, and early radiographic changes are indicative of poor prognosis in children with JIA, and therefore, are often relevant to treatment decisions (14). There are various studies which have examined risk factors for steroid-induced AI (15), but information is lacking where specific diseases and pediatric patients are concerned (16).

Understanding the aforementioned basis of therapy is crucial for the management of JIA, as it requires a multimodal approach including pharmacological interventions, physical and occupational therapy, and psychosocial support (17,18). Additionally, the potential side effects of ever-changing therapeutic approaches necessitate the constant evaluation of factors associated with these side effects. NSAIDs and the intra-articular injection of triamcinolone hexacetonide are the first-line treatment options frequently used in those children with JIA (19,20). However, in those children whose disease is poorly controlled by these approaches, the selective use of systemic corticosteroids may be considered

despite their potentially serious side effects, such as growth failure, obesity, hypertension, hyperglycemia, osteoporosis and/or muscle weakness. Even intra-articular glucocorticoid administration has been occasionally associated with iatrogenic AI, and the systemic use of glucocorticoids frequently leads to a suppression of the hypothalamic-pituitary-adrenal axis (21-23), while adverse effects on growth and bone health have also been reported (24).

Data concerning the predictors of secondary AI in JIA patients receiving systemic corticosteroids is lacking. Our findings show that AI was more prevalent among those children who were still on systemic corticosteroids and those with a higher cumulative dose of systemic corticosteroids. Multiple logistic regression analysis revealed that being diagnosed with non-oligoarticular type JIA and having received a cumulative steroid dose of >1,000 mg were the only two factors predictive for AI. Previous studies on patients with JIA have shown that low-dose glucocorticoid treatment, even when applied for extended periods, did not increase the risk of AI (25), which supports our results. From this point of view, it is clear that the use of systemic corticosteroids should be reserved only for more aggressive types of JIA and in JIA types with non-favorable long-term prognosis. Additionally, our data indicates that local administration should be preferred to systemic administration if possible. Although this approach has the potential to be satisfactory in some patients, intra-articular corticosteroids cause partial suppression of cortisol production (26) and some studies have reported a considerable rate of transient or long-lasting AI development in JIA cases receiving intra-articular corticosteroid injections. In those studies, AI likelihood was associated with the child's age (27) and the injection dosage (27,28). Earlier studies also suggested a relationship between cushingoid appearance and the number of joints to which steroid injections had been performed (29). These findings infer support to our conclusion regarding cumulative dosage, and it is evident that more studies focusing on this topic are required, especially considering certain case reports

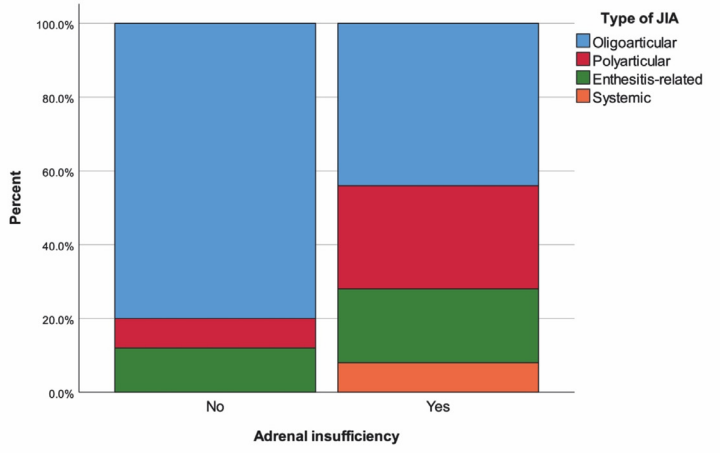

Figure 1. Type of JIA with regard to adrenal insufficiency
JIA: Juvenile idiopathic arthritis

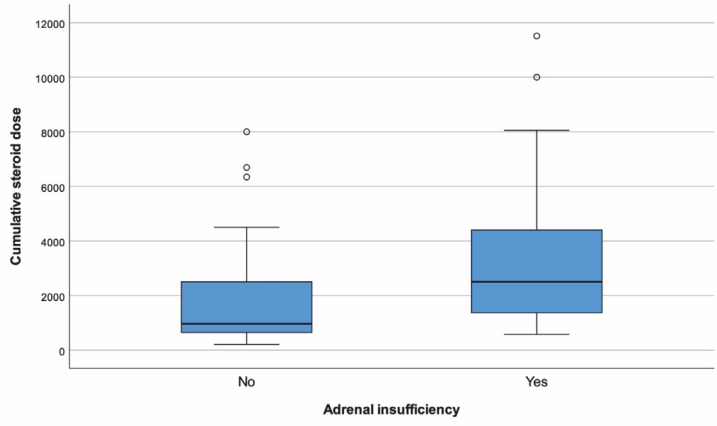

Figure 2. Cumulative steroid dose with regard to adrenal insufficiency

which have demonstrated the development of Cushing's syndrome in patients with JIA who had received intra-articular corticosteroid treatment (21,30).

Clinicians should be aware that they should seek methods allowing for the limitation of the cumulative dose of systemic corticosteroids administered, particularly below 1,000 mg. With this in mind, our findings indicate for the first time that a high cumulative dosage of corticosteroids is predictive for the development of AI in those patients who receive systemic corticosteroids for JIA management.

Study Limitations

There are some limitations to be mentioned. First, this was a retrospective data analysis. Second, our sample size was relatively small. Further prospective data with a larger sample size will be necessary to support the results of this study and to clarify the factors associated with AI in JIA patients receiving systemic corticosteroids.

Conclusion

In conclusion, AI is a serious side effect of systemic corticosteroids in children with JIA. Our findings show that presence of non-oligoarticular JIA and a high cumulative corticosteroid dose are predictive for the development of AI in this patient subset. We believe that systemic corticosteroids should be reserved only for more aggressive types of JIA and that, in patients requiring corticosteroids, the cumulative dose should be limited to 1,000 mg in order to prevent the development of AI.

Ethics

Ethics Committee Approval: This study was approved by the İstanbul Medeniyet University Göztepe Training and Research Hospital, Clinical Research Ethics Committee (no: 2013/0011, date: 25.06.2013).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Z.E., Concept: G.Z.E., M.E., M.Y., Design: G.Z.E., M.E., M.Y., Data Collection or Processing: G.Z.E., M.E., Analysis or Interpretation: G.Z.E., Literature Search: G.Z.E., Writing: G.Z.E.

Conflict of Interest: The authors declared that there were no conflicts of interest.

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