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Is Corticosteroid Safe Enough for the Treatment of Sudden Hearing Loss and Bell's Palsy in Diabetic and Hypertensive Patients?

Diyabetik ve Hipertansif Hastalarda Ani İşitme Kaybı ve Bell's Palsi Tedavisinde Kortikosteroid Yeterince Güvenli midir?

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ABSTRACT Objective: To investigate the side effects of systemic corticosteroid (CS) treatment in the idiopathic sudden sensorineural hearing loss (ISSHL) and Bell's palsy patients. **Material and Methods:** The patients were retrospectively evaluated for the major side effects of systemic CS. The patients with systemic diseases (hypertension and diabetes mellitus) were further investigated with respect to alterations on antidiabetic or antihypertensive drug regimens. The categorization was performed according to the dosage alterations of antidiabetic or antihypertensive drugs and the patients were divided into 3 groups: Group 1 (stable group), Group 2 (acute dysregulated group) and Group 3 (chronic dysregulated group). **Results:** Among the 276 patients, there was only one major complication which was a femur avascular necrosis during a mean follow up 4,5 months. In the diabetic group, the acute and chronic drug alteration was statistically significantly higher with respect to hypertensive group ($p<0.001$). HbA1c≥8% (64 mmol/mol) caused a significant increase in Group 3 ratio ($p<0.05$). **Conclusion:** The risk of major side effect of the systemic CS was extremely low (<1%). Corticosteroids in patients with hypertension did not alter the antihypertensive doses however, diabetic patients needed drug alteration. HbA1c level<8% (64 mmol/mol) can be used as a safety criterion for starting systemic CS therapy in the diabetic patients with ISSHL and Bell's palsy.

Keywords: Sudden hearing loss; Bell's palsy; corticosteroids; side effects of drugs; glycosylated hemoglobin A1c

ÖZET Amaç: Ani idiopatik sensörinöral işitme kaybı ve Bell's palsi hastalarında kortikosteroid tedavisinin yan etkilerini araştırmak. **Gereç ve Yöntemler:** Hastalar sistemik steroid tedavisinin major yan etkileri açısından retrospektif olarak değerlendirilmiştir. Sistemik hastalığı (diabetes mellitus ve hipertansiyon) olan hastalar antidiyabetik veya antihipertansif ilaç rejimlerindeki değişimlere göre ayrıca araştırılmıştır. Kategorizasyon antidiyabetik ve antihipertansif ilaçlardaki doz değişikliklerine göre yapılmış ve hastalar 3 grup altında toplanmıştır: Grup 1 (stabil grup), Grup 2 (akut disregüle olan grup) ve Grup 3 (kronik disregüle olan grup). **Bulgular:** 276 hasta arasında ortalama 4,5 aylık takip süresinde 1 tane majör komplikasyon görülmüştür: femurun avasküler nekrozu. Diyabetik grupta hipertansif gruba göre, akut ve kronik ilaç değişikliği istatistiksel olarak anlamlı yüksek olarak bulunmuştur ($p<0,001$). HbA1c >%8 (64 mmol/mol) olması, Grup 3 oranında anlamlı bir artışa neden olmuştur ($p<0,05$). **Sonuç:** Sistemik kortikosteroide bağlı majör yan etki görülme riski oldukça düşük bulunmuştur (<%1). Hipertansiyonu olan hastalarda kortikosteroid kullanımı antihipertansif dozlarını değiştirmese de, diyabetik hastalar ilaç değişimine ihtiyaç duymuşlardır. HbA1c <%8 (64 mmol/mol), ani idiopatik sensörinöral işitme kaybı ve Bell's palsi olan diyabetik hastalarda kortikosteroid başlamak için bir güvenlik kriteri olarak kullanılabilir.

Anahtar Kelimeler: Ani işitme kaybı; Bell's palsi; kortikosteroidler; ilaç yan etkisi; glikolize hemoglobin A1c

Corticosteroid (CS) is still the recommended treatment for otologic emergencies currently.[1,2] Potent anti-inflammatory action, immune system depression, and blood flow increment are the mechanisms of action of the CS in the inner ear.[3] Nevertheless, the etiopathogenesis of Bell's palsy (BP) and

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idiopathic sudden sensorineural hearing loss (ISSHL) which are the most common otologic emergencies are clearly unknown, both can result in troublesome sequelae such as permanent hearing loss and facial cosmetic deformities.

Although CS has a broad spectrum of indications in various diseases such as rheumatologic, allergic, chronic inflammatory and connective tissue diseases, it has several side effects which result in significant morbidities.[4,5] The risk of adverse effects after chronic usage was well established, but its potential damage in short-term has not been clarified yet.[6-9]

There are very few studies investigating the adverse effects of CS in otologic diseases. Alexander et al. found that hyperglycemia was the most common side effect and there was no other serious side effect of long-term CS in the autoimmune inner ear disease.[10] In literature, there is no data about the adverse effects of short-term use of CS for the treatment of ISSHL and BP.

The first aim of this study was to investigate the major side effects related to the CS usage during the hospitalization and follow-up period in the ISSHL and BP patients. The second aim was to exhibit the effect of CS on the antihypertensive and antidiabetic drug alterations in the ISSHL and BP patients with hypertension and diabetes mellitus.

MATERIAL AND METHODS

This clinical study with ISSHL and BP patients was conducted in a tertiary referral center after the approval of the local ethics committee (56/27-12.11.2018). The recordings of these patients who were treated between January 2016 and June 2018 were evaluated retrospectively. Informed consent was obtained from all individual participants.

Inclusion criteria:

1. Patients who completed the steroid treatment protocol and the follow up period regularly with the diagnosis of ISSHL and BP.

2. Patients who have the recordings of the hospitalization interval and follow up period.

3. Type II diabetic and essential hypertensive patients whose antidiabetic and antihypertensive drug alterations were arranged by endocrinology and cardiology department during hospitalization and follow up period.

The patients were evaluated according to diseases related with major side effects of CS which were composed of adrenal diseases (Addison disease, Cushing syndrome), gastrointestinal diseases (gastritis, peptic ulcer, hemorrhage), cardiovascular diseases (myocardial infarction, coronary heart disease, congestive heart failure), systemic infections, musculoskeletal diseases (myopathy, osteoporosis, avascular necrosis), psychiatric diseases (depression, psychosis, delirium), ophthalmological diseases (cataract, glaucoma) and dermatologic diseases. This evaluation was performed as detailed questioning of the patients whether any sign and symptoms of a newly diagnosed steroid side effect related diseases occured or not. The follow-up period was defined as the time between 3 and 6 months after the beginning of the steroid therapy.

The further analysis was performed according to the disease-based comparison. The BP and ISSHL patients with the systemic disease were divided into subgroups as diabetic group and hypertensive group.

Furthermore, the doses and modalities of the antihypertensive and antidiabetic drugs of the patients at the beginning, during the hospitalization and at the end of the follow-up period were evaluated. After hospitalization all the diabetic and hypertensive patients were consulted to endocrinology and cardiology departments, respectively. The patients were categorized into 3 groups according to the dosage alterations of these drugs. Group 1 was the stable group in which there was no change in doses during hospitalization and follow-up. Group 2 was the acute dysregulated group in which there was a temporary increment in dosage or exchange or addition of any other drug during hospitalization but return to initial dosage at the end of follow up period. Group 3 is the chronic dysregulated group in which antihypertensive or antidiabetic drug treatment modalities were permanently changed at the end of the follow-up period.

These drug alterations were analyzed in diabetic and hypertensive groups of ISSHL and BP patients separately.

Additionally, the hemoglobin A1c (HbA1c) scores before starting to steroid treatment were analyzed in diabetic groups of ISSHL and BP. The correlation of the HbA1c levels with drug alteration groups was investigated.

SYSTEMIC STEROID PROTOCOL

All patients with ISSHL and BP patients with systemic diseases such as hypertension and diabetes mellitus were hospitalized. All ISSHL and the BP patients were treated with systemic steroids. Intravenous methylprednisolone was used as steroid with single bolus dosage of 250 mg for the first day, 150 mg for the second day and 100 mg for the third day. After the third day, 1 mg/kg/d oral form was started and tapered 16 mg in every 3 days. In addition to steroids, all ISSHL patients were treated with 5 mg/kg intravenous dextran for 5 days plus 3x1600 mg oral piracetam till the end of therapy. After the initial systemic CS treatment, the ISSHL patients without complete recovery were directed to salvage therapy with firstly intratympanic steroid treatment of 5 doses of 2 mg intratympanic dexamethasone (0.5 ml from 4 mg/ml ampul form) once in every 2 days and secondly hyperbaric oxygen protocol of 120 minutes of 2.5-atmosphere for 20 consecutive days. Moreover, oral acyclovir 5x200 mg daily for 7 days was added to ISSHL protocol if there was an upper respiratory tract infection history within a week before the onset of hearing loss. All patients were discharged at the 3rd or 5th day if there were no complication of steroid treatment such as acute elevation of blood pressure or glucose.

STATISTICAL ANALYSIS

Statistical analyses were performed with the IBM SPSS for Windows Version 22.0. Numerical variables were summarized as mean±standard deviation or median [minimum-maximum]. Categorical variables were given as frequencies and percentages. Categorical variables were compared by chi-square test. Normality of the continuous variables was evaluated by the Kolmogorov Smirnov test. Homogeneity of variances was tested by Levene test. Differences between the groups according to continuous variables were determined by independent samples t-test or Mann Whitney U test as appropriate. Kruskal Wallis test was used to compare more than two independent groups. A p value less than 0.05 was considered as significant.

RESULTS

THE RESULTS OF DEMOGRAPHIC DATA

The medical records of 320 patients who were hospitalized with the diagnosis of ISSHL and BP were analyzed. There were 203 patients with ISSHL. Nineteen patients with ISSHL were excluded from the study due to either lack of follow-up data or irregular use of antidiabetic or antihypertensive medications. Thus, 184 patients with ISSHL were included in the study. One hundred eighteen of the ISSHL patients had no systemic disease history and 66 patients with ISSHL had systemic diseases (DM or HT). There were 88 male, 96 female patients with a mean age of 59.24+/-9.534 years.

There were 117 BP patients with a history of HT or DM. Twenty-five patients with BP did not come to follow-up. Thus, 92 BP patients with systemic disease (HT or DM) were included in the study. There were 44 male, 48 female patients with a mean age of 62,47+/-9,996.

The study was completed with 276 patients with a mean follow-up period of 4,55+/-1,291 months. We excluded 118 ISSHL patients without a systemic disease history for the disease based evaluation. Among 66 ISSHL and 92 BP patients with systemic diseases, 50 patients had history of both DM and HT. Thus, group comparisons were based on the number of the systemic diseases instead of the number of the patients.

THE RESULTS OF MAJOR COMPLICATIONS OF STEROIDS

All patients were analyzed with respect to major complications of steroids during the follow-up period. There was only one 48-year-old female ISSHL patient who had applied to orthopedics department due to right hip pain after the 4 months of the CS treatment. She had no history of diabetes mellitus, trauma,

chronic alcohol and tobacco use, autoimmune and myeloproliferative disease, radiotherapy, chemotherapy and thrombophilia. According to magnetic resonance imaging, bilateral avascular necrosis of femur was diagnosed. Medical treatment was started, right total hip replacement surgery was performed after 1 year of CS use. The ratio of the major side effect of systemic CS was 0.4%.

THE RESULTS OF DRUG ALTERATION COMPARISON BETWEEN THE DIABETIC AND HYPERTENSIVE GROUPS

The patients were classified according to diabetic and hypertensive groups and analyzed according to drug alteration ratios. The ratio of Group 3 (chronic dysregulated) was statistically significantly higher in the diabetic group with respect to the hypertensive group (p<0.001) (Table 1).

The diabetic group (n: 119) was composed of 42 ISSHL and 77 BP patients. There was no statistically significant difference between ISSHL and BP patients in the diabetic group with respect to drug alteration (p:0.116) (Table 2).

The hypertensive group (n: 89) was composed of 42 ISSHL and 47 BP patients and there was no statistically significant difference in ISSHL and BP patients in the hypertension group according to drug alteration ratios (p:0.526) (Table 3).

THE RESULTS OF HEMOGLOBIN A1c SCORES IN THE DIABETIC GROUP

There was a statistically significant increment in HbA1c levels of BP patients with respect to ISSHL patients in the diabetic group which was shown in Table 4 (p:0.015). Moreover, HbA1c scores were significantly higher in Group 3 (chronic dysregulated group) as compared to Group 1 (stable group) in both ISSHL and BP patients (p<0.001) There was a significant increase in numbers of patients in Group 3 if

TABLE 1: Comparison of drug alteration ratio between diabetic and hypertensive groups.

		Number of patients according to drug alteration		
	Total (n)	Group 1 (%)	Group 2 (%)	Group 3 (%)
Diabetic group	119	35 (29.4%)	32 (26.9%)	52 (43.7%)
Hypertensive group	89	74 (83.1%)	2 (2.2%)	13 (14.6%)
p value			<0.001	

Group 1: Stable group, Group 2: Acute dysregulated group, Group 3: Chronic dysregulated group.

TABLE 2: Drug alteration ratios in the diabetic group.

		Number of patients according to drug alteration		
	Total (n)	Group 1 (%)	Group 2 (%)	Group 3 (%)
Diabetic ISSHL patients	42	17 (40.5%)	11 (26.2%)	14 (33.3%)
Diabetic BP patients	77	18 (23.4%)	21 (27.3%)	38 (49.4%)
p value			0.116	

Group 1: Stable group, Group 2: Acute dysregulated group, Group 3: Chronic dysregulated group (ISSHL: Idiopathic sudden sensorineural hearing loss, BP: Bell's palsy).

TABLE 3: Drug alteration ratios in hypertensive group (HT).

		Number of patients according to drug alteration		
	Total (n)	Group 1 (%)	Group 2 (%)	Group 3 (%)
Hypertensive ISSHL patients	42	33 (78.6%)	1 (2.4%)	8 (19%)
Hypertensive BP patients	47	41 (87.2%)	1 (2.1%)	5 (10.6%)
p value			0.526	

Group 1: Stable group, Group 2: Acute dysregulated group, Group 3: Chronic dysregulated group (ISSHL: Idiopathic sudden sensorineural hearing loss, BP: Bell's palsy).

TABLE 4: HbA1c levels in diabetic group.

	Patient (n)	HbA1c score (%)	Group 1 HbA1c score (%)	Group 2 HbA1c score (%)	Group 3 HbA1c score (%)	p value
ISSHL	42	7.910+/-2.0092	6.6+/-0.7457	7.809+/-1.4174	9.75+/-2.2718	<0.001
BP	77	8.761+/-1.9141	6.779+/-0.8192	9.083+/-1.7399	9.354+/-1.8185	<0.001
p value		0.015				

Group 1: Stable group, Group 2: Acute dysregulated group, Group 3: Chronic dysregulated group (ISSHL: Idiopathic sudden sensorineural hearing loss, BP: Bell's palsy).

TABLE 5: Analysis of drug alteration group ratio with respect to HbA1c categorization in the diabetic group of ISSHL and BP patients.

		Diabetic group									
		ISSHL patients					BP patients				
		Patient (n)	Group 1 (n)	Group 2 (n)	Group 3 (n)	p value	Patient (n)	Group 1 (n)	Group 2 (n)	Group 3 (n)	p value
HbA1c score (%)	≥8	14	1 (7.1%)	4 (28.6%)	9 (64.3%)	0.002	44	2 (4.6%)	14 (31.8%)	28 (63.6%)	<0.001
	<8	28	16 (57.1%)	8 (28.6%)	4 (14.3%)		33	14 (42.4%)	7 (21.2%)	12 (36.4%)	

Group 1: Stable group, Group 2: Acute dysregulated group, Group 3: Chronic dysregulated group. (ISSHL: Idiopathic sudden sensorineural hearing loss, BP: Bell's palsy).

the HbA1c scores were ≥8% (64 mmol/mol) in both ISSHL and BP patients. (p:0.002, p<0.001 respectively) HbA1c score ≥8% (64 mmol/mol) caused a significant increase in Group 3 ratio in both ISSHL and BP patients with DM (Table 5).

DISCUSSION

Corticosteroid is still the most current modality in the treatment of both BP and ISSHL. Up to date, any complete therapeutic standard method has not been established due to lack of proven definitive etiopathogenetic mechanisms.[11,12] There is a chance of self- recovery of ISSHL ranging between 32% and 65% within 3 weeks.[13,14] Thus, different types of CS protocols have revealed in conflicting results about recovery rate in the literature.[1] On the other hand, BP has higher recovery rate up to 94.4% both with CS and without any treatment with respect to ISSHL.[15]

Another point to mention about is that there is still no uniform standard in dosage and duration of systemic CS. In a study by Westerlaken et al. that compared the pulse doses of 300 mg dexamethasone with 70 mg prednisolone, there was no significant superiority of recovery rate between the two doses.[16] The best dosage and duration which can result in maximal recovery rate without causing serious side effects has not been revealed yet.

The incidence of side effects of CS is related with the dose and duration.[6] Morin and Fardet investigated the side effect profile of chronic CS usage and found that several side effects were expressed by the patients after the second week of therapy.[4] Furthermore, Waljee et al. had shown the increase of the CS major side effects such as venous thromboembolism and fracture in a short-term treatment even with low doses.[9] In our study, we aimed to reveal the serious side effects of CS with our regimen in a 3 to 6 month of the follow-up period. Only one patient had a serious side effect (femur avascular necrosis). Thus, our CS protocol within 3 weeks of duration resulted in <1% major side effect ratio in a mean follow-up of 4.5 months.

Approximately half of the diabetic group of BP patients were in Group 3 according to drug alteration analysis. Although this ratio was not statistically significant, shifting the antidiabetic treatment from oral form to parenteral form and making a patient insulin-dependent may result in a decrease in life quality.[17] According to our CS protocol, a standard 80 kg patient is taking 1220 mg of methylprednisolone within 18 days. With this total dose, 49.4% of the diabetic BP patients needed to exchange their antidiabetic medication to regulate their blood glucose.

In the HT group, it was much more stable with respect to the diabetic group according to drug alteration ratio. Seventy-nine percent of ISSHL patients and 87% of the BP patients were in Group 1 and there was no need for the alteration of antihypertensive drugs due to CS. It is also evident in Table 1 which shows the drug alteration ratio differences between the diabetic and hypertensive group. The diabetic group had a significantly higher ratio of Group 3 with respect to the hypertensive group. Diabetes mellitus results in microvascular and perineural pathophysiological changes which is an important factor in ISSHL and BP patients with systemic CS therapy. Corticosteroids can result in hyperglycemia in a healthy individual. Moreover, this becomes distinctly aggravated in the diabetic patients.[6] On the other hand, there were no negative influence of CS on HT with respect to DM.

There were some patients who had both DM and HT which may disturb the results. In order to eliminate this bias, we preferred a disease-based comparison instead of patient-based analysis. Moreover, some diabetic or hypertensive patients already had uncontrolled blood glucose or pressure before the CS treatment. To eliminate this factor, we chose the initial doses of the drugs before CS treatment for the reference. The regulation of DM, HT and sustaining the blood glucose and pressure at a desired level is not always possible to achieve. Thus, antidiabetic and antihypertensive drug alterations were used instead of alterations of blood glucose and pressure.

Hemoglobin A1c is an important marker not only for the diagnosis of DM but also for the indirect demonstration of blood glucose level for the last 3 months.[19] Uncontrolled DM may result in more profound hearing loss and poorer hearing outcome in ISSHL patients.[20,21] Our study revealed significantly higher HbA1c scores in BP patients than in ISSHL patients. This result also indicates that uncontrolled DM is an important risk factor of BP.[12,22] In the diabetic patients of ISSHL and BP, Group 3 (chronic dysregulated) HbA1c scores were significantly higher with respect to Group 1. The higher level of HbA1c indicates the more dysregulated blood glucose.[23] With the addition of CS to a patient with uncontrolled DM, there will be a further rise in dysregulation which results in drug exchange.

If HbA1c level is ≥8% (64 mmol/mol), Group 3 ratio become significantly higher in both ISSHL and BP patients with DM. More than 60% of the diabetic group with ≥8% (64 mmol/mol) of HbA1c required drug alteration during the follow-up period. We thought that ≥8% (64 mmol/mol) HbA1c level may be an important marker to choose an alternative treatment instead of systemic CS in the ISSHL and BP patients.

CONCLUSION

It is hard to make a decision of starting systemic CS in the treatment of ISSHL or BP patients with systemic diseases especially with uncontrolled DM due to its possible side effects. Corticosteroid can be more harmful when compared with its recovery efficacy.

The ratio of the major side effect of 1 mg/kg/d methylprednisolone within 3 weeks of duration which is comparable with the literature, was 0,4% in a mean follow-up of 4.5 months. Thus, this study may be helpful for the future studies investigating not only the effect of healing rate with increasing the CS dosage but also the correlation between healing rate and side effect.

Systemic CS medication in ISSHL and BP patients with HT did not alter the antihypertensive doses, however, diabetic patients needed antidiabetic drug alteration. Therefore, HbA1c level ≥8% (64 mmol/mol) may be a criterion in the diabetic patients to reconsider about the pros and cons of systemic CS therapy before beginning the treatment.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct con-

nection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Kemal Keseroğlu, Sibel Alicura Tokgöz;* ***Design:*** *Kemal Keseroğlu, Bülent Öcal;* ***Control/Supervision:*** *Cem Saka, Güleser Saylam;* ***Data Collection and/or Processing:*** *Başak Yalçıner, Sibel Alicura Tokgöz;* ***Analysis and/or Interpretation:*** *Güleser Saylam, Sibel Alicura Tokgöz;* ***Literature Review:*** *Kemal Keseroğlu, Başak Yalçıner;* ***Writing the Article:*** *Kemal Keseroğlu;* ***Critical Review:*** *Cem Saka, Güleser Saylam;* ***References and Fundings:*** *Bülent Öcal;* ***Materials:*** *Kemal Keseroğlu, Sibel Alicura Tokgöz.*

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