

Treatment of smell loss with systemic methylprednisolone*

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Summary

Background and aim: Olfactory dysfunction is a common complaint in a large number of people. As the aetiologies of olfactory dysfunction vary greatly so do the treatment approaches. The aim of this retrospective study was to evaluate treatment with systemic corticosteroids, particularly focusing on its effectiveness on the different olfactory dysfunction aetiologies. Although a prospective randomized control trial is preferred for such an investigation, using the current approach, we were able to test a very large patient population.

Material and methods: A total of 425 patients with olfactory dysfunction were treated with systemic corticosteroids for 14 days. Olfactory performance was measured using the 'Sniffin' Sticks' battery before and after the treatment.

Results: The treatment with systemic corticosteroids significantly increased the performance on the TDI score and on each of the three subtests; threshold, discrimination and identification. In 26.6% of the patients improvement of more than six points of the TDI score was observed. The treatment proved to be more effective in patients with sinusasal olfactory dysfunction, where this percentage increased to 36.7, compared to other aetiologies. In addition, the increase in olfactory function was negatively correlated with the TDI score before the treatment.

Conclusion: This study confirms the effectiveness of systemic corticosteroids on olfactory dysfunction in a large patient population. Specifically, the results show that treatment is: (a) more effective in patients with sinusasal than in patients with idiopathic olfactory dysfunction, (b) most effective in patients with sinusasal disease with nasal polyps, and (c), at best, effective in half of the patients. The current study may provide help in counselling patients.

Key words: sinusasal disease, inflammation, smell, nose, methylprednisolone

Introduction

Many people are affected by olfactory dysfunction. It is estimated that in Germany every year approximately 50,000 patients with olfactory dysfunction seek specialist help ⁽¹⁾. It is presumed that the actual number of people with olfactory dysfunction is even higher because patients are often unaware of their condition. For example, according to Nordin et al., up to 77% of elderly people with smell loss do not report olfactory problems ⁽²⁾.

Olfactory dysfunction is caused by a variety of aetiologies. The most common reasons for olfactory loss found in smell and taste

clinics are: sinusasal, post infectious, idiopathic, post traumatic, iatrogenic, toxic, and congenital ⁽¹⁾. In addition, it is known that many other reasons such as neurodegenerative diseases or age can cause olfactory dysfunction ^(3,4). A study by Damm et al. showed that sinusasal olfactory dysfunction with 72% is by far the most frequent aetiology being followed by post infectious (11%) and idiopathic (6%) causes. These numbers vary in relation to the source of the survey, for example in some specialised smell and taste clinics the number of post infectious olfactory dysfunction reaches 91% of all patients ⁽¹⁾.

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Although the number of patients suffering of olfactory dysfunction is large, there is still no universally accepted treatment protocol available. As a result, there are many different treatment suggestions for olfactory dysfunction. These can be summarised in three major groups: surgical, pharmacological, and others. The surgical approach addresses mainly sinusal olfactory dysfunctions. The outcome of this treatment is rather modest. Studies have shown, that after surgery the sense of smell improved only in 25% of the pre surgical hyposmic and 5% of the pre surgical anosmic patients^(5,6). A recent review on this topic by Rudmik and Smith reported olfactory improvement after endoscopic sinus surgery in 0 – 75% of the patients⁽⁷⁾. In this study, predictive factors for the outcome of endoscopic sinus surgery on the olfactory function, such as eosinophilia or preoperative anosmia, were also identified⁽⁷⁾.

Other approaches to treat olfactory dysfunction include olfactory training. Again, with this method approximately 25% of the patients show an improvement of olfactory function⁽⁸⁾. The most commonly used treatment modality in olfactory dysfunction is pharmacological. From the wide range of substances that are in use, only a few have been found to be effective. For example, the effectiveness of vitamins and of antiviral agents is controversial^(1,9,10).

Corticosteroids are the most frequently used drugs in the treatment of olfactory loss⁽¹¹⁾. There are two ways of corticosteroid application; topically in the nasal cavity and systemic. With the former it is hoped to prevent the systemic side effects of corticosteroids. An improvement of the sense of smell has been found for both topical⁽¹²⁻¹⁴⁾ and systemic application^(1,15,16) of corticosteroids.

In this study, we examined the effects of systemic corticosteroids on the sense of smell in a population of 425 patients. The study focuses on the comparison of the effectiveness of the treatment in the various aetiologies of olfactory dysfunction and in particular the sinusal and idiopathic aetiologies. It is hoped that this retrospective study will contribute to better understanding and applying of this treatment modality.

Materials and methods

The retrospective study was approved by the institutional review boards of the University of Dresden Medical School, Germany (EK number 251112006), and the The Ipswich Hospital, UK, respectively. The study was designed to examine effects of the treatment of olfactory dysfunction with systemic corticosteroids.

Patients

A total of 425 patients with subjective olfactory dysfunction (213 females and 212 males) with an age range from 14 to 85 years (mean \pm standard deviation (SD) = 56.6 \pm 12.1 years) from

the Smell and Taste Clinic in Dresden and The Ipswich Department of ORL were included in this study. The data was collected between 07/2000 and 12/2010.

Inclusion criteria

To evaluate the effectiveness of systemic corticosteroid treatment on the olfactory function, patients with olfactory loss due to sinusal, idiopathic, post-traumatic, post-infectious, and post-surgical aetiologies were included in the study. Because patients were unequally distributed among the different aetiologies, it was only possible to compare treatment between three aetiology groups: sinusal, idiopathic and post-infectious. In addition, all patients included in this study suffered from subjective olfactory dysfunction.

Procedure

Every patient had at least two visits to the clinic; before and after systemic treatment with corticosteroids. A detailed medical history was obtained at the patients' first visit with a focus on olfactory dysfunction followed by a clinical examination of the upper respiratory tract including an endoscopy of the nose. Hence, the aetiology of the olfactory dysfunction was determined for each patient. The aetiologies were classified in three groups: sinusal (n = 221), idiopathic (n = 157) and other causes (n = 47), e.g., post traumatic, post infectious etc. (Figure 1). If no reason for the olfactory dysfunction could be found, the patient was included in the idiopathic group. Thus, this group is very heterogeneous and might include a variety of undetected causes of olfactory dysfunction. The mean duration of the symptoms was 67 \pm 76 months at the time of the first visit. The majority - 253 patients - had olfactory dysfunction for more than 24 months; 172 patients had the symptoms for less than two years. On each visit, the patients' olfactory function was assessed. The second visit was scheduled at the last day of treatment.

Olfactory testing

The 'Sniffin' Sticks' were used to evaluate olfactory function. This olfactory test battery consists of three tests: (a) phenyl ethyl alcohol odour thresholds (T), (b) odour discrimination (D), and (c) odour identification (I). The maximum score for each test was 16 points resulting to a maximum sum of 48 points (TDI score) for the three tests. The 'Sniffin' Sticks' test allows for a classification of olfactory function as normosmia, hyposmia, or functional anosmia^(17,18).

Treatment

Patients received systemic treatment with methylprednisolone for 14 days. The starting daily dose was 40 mg p.o. and the dosage was reduced by 5 mg every other day. Above corticosteroid and its dosing regimen has been part of our management protocol of patients with suspected olfactory dysfunction due to inflammatory causes for more than 20 years with no major

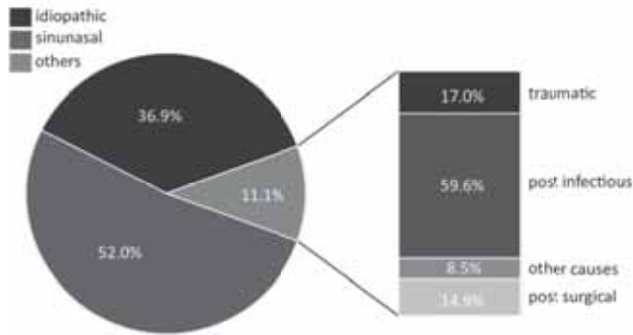


Figure 1. Aetiology of the patients' olfactory dysfunction. The diagram shows the aetiology of the olfactory function for the 425 patients treated in this study. 52.0% of all patients had sinusal olfactory dysfunction. For 36.9% the aetiology was idiopathic and 11.1% had other aetiologies. The reasons of the olfactory dysfunction of the 11.1% are shown in the right part of the diagram.

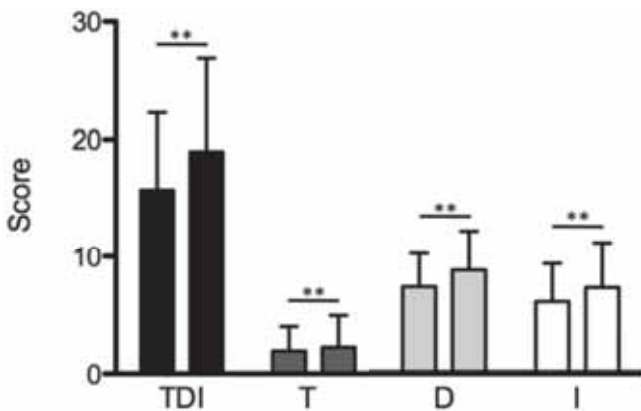


Figure 2. Effects of methylprednisolone on the TDI score. The Figure shows the TDI scores before and after treatment with methylprednisolone. The left bars show the change in TDI score. Subtest T (threshold), D (discrimination) and I (identification) are represented by the bars to the right. The treatment caused a significant change in the TDI score as well as in the subtests (** = $p < 0.001$); interestingly, all subtests responded similarly to treatment.

problems reported so far. Our choice of corticosteroid, its total dose and dosing regimen were based on our positive experiences with this treatment modality. Moreover, to our knowledge, there are no comparative studies on the effectiveness of the different corticosteroid doses in restoring olfactory function. Detailed information about the treatment and the possible side effects of methylprednisolone was given to the patients before onset of treatment.

Statistical analysis

The data was analysed using SPSS 19 (SPSS Inc., Chicago, IL, USA). Paired t-test and correlations using Pearson statistics

were used to examine the influence of the treatment with methylprednisolone on the TDI scores. The α level was set to 0.05.

Results

A total of 425 patients were included in this study. The majority of these patients were functionally anosmic (55.1%; $n = 234$) or hyposmic (40.9%; $n = 174$); only 4% ($n = 17$) were normosmic. Although these 17 patients were normosmic according to the TDI score, they complained about subjective olfactory dysfunction. None of the patients reported major side effects caused by the treatment. The average TDI score for all patients before treatment was 15.7 points (SD = 6.55). After treatment with methylprednisolone the TDI score improved significantly by on average 3.25 points (SD = 6.46) to 18.95 points (SD = 7.94) ($t = 10.4$, $p < 0.001$) (Figure 2).

All three sub-scores of the 'Sniffin' Sticks' battery showed a significant increase after treatment. Scores in the threshold test increased from 1.93 (SD = 2.03) to 2.27 (SD = 2.63) ($t = 5.94$, $p < 0.001$). In the odour discrimination test the increase ranged from 7.52 (SD = 2.83) to 8.95 points (SD = 3.23) ($t = 9.00$, $p < 0.001$). The scores in the odour identification test increased from 6.24 (SD = 3.27) to 7.43 (SD = 3.76) ($t = 7.22$, $p < 0.001$) (Figure 2).

Previous studies have reported the importance of a six or more point increase of the TDI score for the subjective improvement of the olfactory function⁽¹⁹⁾. As shown in Figure 3a, in our study 26.6% ($n = 113$) of patients showed a TDI score increase of six points or more. In contrast, only 3.5% ($n = 15$) of patients showed a deterioration of the TDI score by six or more points after treatment. In 69.9% ($n = 297$), the treatment resulted in an increase of the TDI score of no more than six points.

The TDI score before treatment was negatively correlated with the increase of the TDI score after treatment ($r = 0.25$, $p = 0.01$), indicating that improvement was higher in subjects with a low pre-treatment TDI score. In other words, patients with functional anosmia ($t = 9.90$, $p < 0.001$) and hyposmia ($t = 4.39$, $p < 0.001$) improved to a higher degree than normosmic patients where, in fact, no significant effect of treatment was seen ($t = 0.26$, $p = 0.80$). Neither gender, age nor the length of the olfactory dysfunction were found to have any influence on the outcome of the systemic treatment with methylprednisolone.

We found that the aetiology of the olfactory dysfunction had an impact on the outcome of the treatment. As described above, we divided the patients according to their history into three aetiological groups: sinusal ($n = 221$), idiopathic ($n = 157$), and other causes ($n = 47$). As the causes of olfactory loss in the third group were very heterogeneous, the focus of this analysis was on the post infectious group ($n = 27$), which had been extracted from the 'other causes' group. In all three groups treatment increased

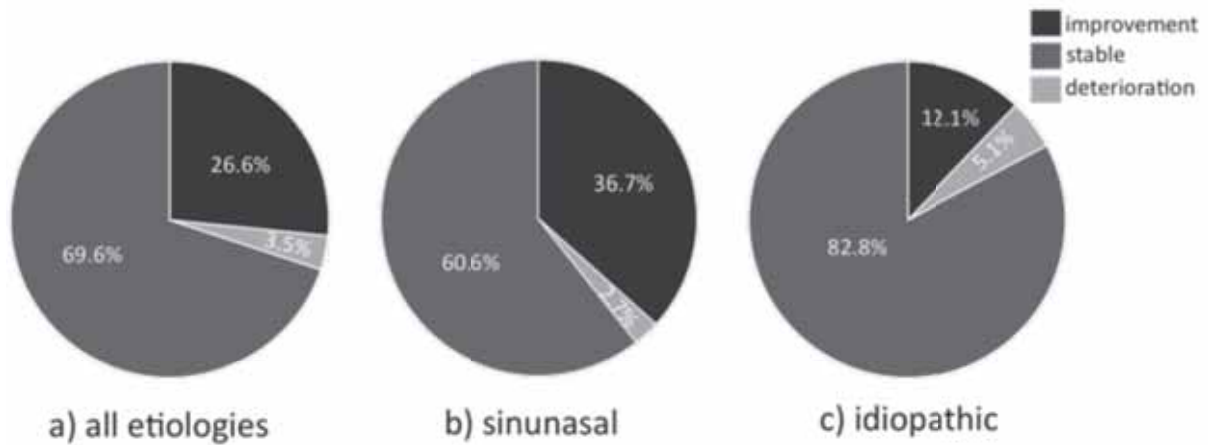


Figure 3. Effectiveness of the treatment considering the aetiology of the olfactory dysfunction. The figure shows the effectiveness of the treatment with methylprednisolone. An improvement is considered as an increase of the TDI score of six or more points. Deterioration means a decrease of the DTI score of 6 points or more and stable stands for a change less than six points. a) all patients, b) patients with sinunasal olfactory dysfunction, c) patients with idiopathic olfactory dysfunction. For 36.7% of the patients with sinunasal olfactory dysfunction the TDI score improved six points of more. Only 12.1% of patients with idiopathic olfactory dysfunction showed this improvement.

the TDI scores significantly. The differences in results between these aetiologies will be pointed out in the discussion below.

For the patients in the idiopathic group, the TDI score increased with an average of 1.0 point (SD = 4.78) from 14.71 (SD = 5.47) to 15.71 (SD = 5.99) ($t = 2.62$, $p = 0.01$). No significant increase of the olfactory threshold was observed ($t = 0.13$, $p = 0.90$). Only 12.1% of this group showed an improvement – an increase of six or more points on the TDI score (Figure 3c). The TDI score remained stable in 82.8% of patients. In 5.1%, the score deteriorated by six or more points. As pointed out in the ‘all patients group’, gender, age or the length of the olfactory dysfunction had no influence on the results of the treatment.

In the group of post-infectious olfactory dysfunction, the TDI scores improved by on average 4.47 points (SD = 7.09) i.e. from 14.39 (SD = 6.61) to 18.86 (SD = 8.41) ($t = 3.28$, $p = 0.003$). All three sub-scores of the TDI showed a significant increase. Since the number of patients in this group was relatively small ($n = 27$) it was not possible to determine the influence of gender, age or length of olfactory dysfunction on the outcome. 29.6% of the patients in this group showed an increase of six or more points in the TDI score. The score stayed stable for 70.4% and no deterioration of the TDI score was found in any of the patients in this group. Further studies are needed to address this group of patients separately in order to optimize treatment.

Patients with sinunasal olfactory dysfunction showed an average increase of the TDI score of 4.79 points (SD = 6.92) i.e. from 16.65 (SD = 7.07) to 21.45 (SD = 8.10) ($t = 10.29$, $p < 0.001$). Scores in the three subtests, threshold ($t = 6.15$, $p < 0.001$),

discrimination ($t = 9.40$, $p < 0.001$) and identification ($t = 6.62$, $p < 0.001$) all increased significantly. In line with the other aetiology groups, no influence of gender, age or the length of olfactory dysfunction was observed in this group. Individual improvement was found in 36.7% of this group all with an increase of their TDI score by six or more points (Figure 3b). In 60.6%, the TDI score remained stable and in 2.7% the score deteriorated by six or more points. Before treatment, 49.3% of the patients with sinunasal olfactory dysfunction were anosmic. After treatment, 50.5% of them were found to be hyposmic and 6.4% improved to normal olfactory function. Patients who were hyposmic before the treatment in this group had a higher rate of regaining normal olfactory function (21.0%).

Sinunasal olfactory dysfunction can be divided further into at least two subgroups, patients with and patients without nasal polyps. Patients with nasal polyps ($n = 68$) showed a large increase in the TDI score of on average 9.06 points (SD = 9.20) i.e. from 16.36 (SD = 9.22) to 25.43 points (SD = 10.15) ($t = 4.47$, $p < 0.001$). It is interesting that no significant increase of the olfactory threshold was observed ($t = 1.56$, $p = 0.13$). Scores in the discrimination ($t = 5.85$, $p < 0.001$) and the identification test ($t = 3.31$, $p = 0.003$) both increased significantly with treatment. 50.0% of this group showed an increase of the TDI score of six or more points. For 5.0% the TDI score deteriorated by six or more points and the rest (45.0%) showed stable TDI scores. In addition to the large increase of TDI score, 18.2% of the pre-treatment anosmic patients and 57.1% of the pre-treatment hyposmic patients were considered normosmic after treatment. Unfortunately, in this retrospective study no data were available that

would have allowed for a more refined definition of subgroups of patients with polyps.

Although the treatment increased significantly, the TDI score in all aetiology groups, it was more effective in patients with sinonasal olfactory dysfunction. The average TDI increase in patients with sinonasal olfactory dysfunction (4.79 (SD = 5.45)) was significantly higher when compared to all other patients (1.57 (SD = 6.92)) ($t = 5.35$, $p < 0.001$). Not only was the average increase in this group higher, but also more patients with sinonasal olfactory dysfunction showed an increase of six or more points on the TDI score (36.7% compared to 15.7%; $\chi^2 = 23.9$, $p < 0.001$). In addition, more patients with sinonasal olfactory dysfunction regained a normal sense of smell (13.4%) compared to patients suffering from other aetiologies of olfactory dysfunction (3.5%) ($\chi^2 = 13.6$, $p < 0.001$).

Discussion

With this retrospective study, we substantiated the effectiveness of systemic corticosteroids in the treatment of olfactory dysfunction in a very large group of patients ($n = 425$). We found, that the TDI score increased significantly after treatment. In addition, all individual sub-scores of the TDI increased significantly. However, on an individual level improvement was only found in an approximately one third of the patients when looking at the different aetiologies. This number was greatly increased when nasal polyps were taken as a factor. In this group 50% showed an improvement of six or more point in the TDI score.

Further to any previous studies, we applied high threshold criteria to the effectiveness of the treatment. Only an increase of the TDI score by six or more points was considered as an improvement of olfactory function⁽¹⁹⁾. This criterion was fulfilled in 26.6% of our patients.

In our further analysis, we focused on sinonasal and idiopathic olfactory dysfunction, due to the inhomogeneous distribution of aetiologies in the patient population. We were able to show that the treatment with methylprednisolone is more effective in patients with sinonasal olfactory dysfunction than in patients with idiopathic olfactory dysfunction. We observed a significantly higher increase of the TDI score in the sinonasal group compared to the idiopathic group with a higher proportion of individual patients from the sinonasal group exhibiting improvement. More specifically, improvement was found in 36.7% of patients with sinonasal disease compared to 12.1% of patients with idiopathic olfactory loss. Therefore, treatment with systemic corticosteroids should not be considered the first option in the management of patients with idiopathic olfactory dysfunction. We also observed that the patients with a low pre-treatment TDI score showed a greater increase in olfactory function. Even though idiopathic olfactory dysfunction was diagnosed

very carefully, it might be that patients with undetected sinonasal or other causes of olfactory dysfunction were included in this group. These patients are expected to respond better to treatment with systemic corticosteroids compared to patients with real idiopathic olfactory dysfunction.

Corticosteroids are widely used as anti-inflammatory medication. Their exact mechanism of action in patients with olfactory dysfunction is not yet known. There is some evidence that glucocorticoid receptors and the adenosine triphosphatase may play a role⁽²⁰⁻²²⁾. Furthermore, one proteomics study indicated that the administration of glucocorticoids triggers the apoptosis pathway in nasal polyps⁽²³⁾. Patients with nasal polyps benefit a great deal from treatment with corticosteroids in terms of airflow, although, not all of these patients benefit in terms of olfactory function. Why some patients with idiopathic olfactory loss responded to corticosteroid treatment is still subject to speculation. It is likely that a small portion of this group exhibits inflammation, which is not seen macroscopically.

Comparison between surgical treatment and pharmacological treatment is difficult. The numbers for improvement of olfactory function with surgical treatment vary greatly between studies. Bonfils et al., reported improvement of olfactory function in 13 - 91% with a mean of 31% of the patients responding⁽²⁴⁾. Part of this deviation between studies is due to the fact that in most, evaluation of the sense of smell was based only on questioning the patients without performing smell tests. Results of these studies are difficult to interpret as most people typically confuse changes in respiratory function with changes in olfactory function⁽²⁵⁾. When measuring olfactory function, Delank et al., found an improvement in 25% of their patients, which is in line with the mean of 31% in Bonfils' review⁽⁵⁾. Finally, an excellent study by Blomqvist et al., shows no benefit of a surgical treatment over treatment with corticosteroids⁽²⁶⁾. These divergent data suggest a careful application of the surgical treatment. Thus, it appears that overall, surgical and conservative treatment produce similar rates of olfactory improvement.

The treatment protocol used in this study starting methylprednisolone at 40 mg and reducing the dosage by 5 mg every other day has shown to be effective in the treatment of olfactory dysfunction, especially in cases with a sinonasal aetiology. However, more research is required to optimize the treatment protocol on the aetiology of the olfactory dysfunction.

With the retrospective design of this study, we were able to show the effectiveness of corticosteroids in the treatment of olfactory dysfunction in a very large patient population. A prospective randomized control trial should be considered for further investigations to examine the benefit of this treatment.

Conclusion

This study confirms the effectiveness of systemic corticosteroids on olfactory dysfunction in a large patient population. Specifically, the results show that treatment is (a) more effective in patients with sinunasal than in patients with idiopathic olfactory dysfunction, (b) most effective in patients with sinunasal disease with nasal polyposis, and (c), at best, effective in half of the patients. We hope that the results of the current study will provide help in counselling patients.

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Authorship contribution

Data collection and patient treatment: MC, TH. Data analysis: VAS, CH, TH. Writing the manuscript: VAS, CM, NG, CH, TH.

Conflict of interest

None of the authors declares a conflict of interest.

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