



# Prospective evaluation of oral corticosteroid as a predictor of postoperative olfactory recovery after functional endoscopic surgery for nasal polyposis

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Received: 2 February 2019 / Accepted: 26 June 2019 / Published online: 3 July 2019  
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## Abstract

**Purpose** Anticipating the possibility of olfactory recovery after functional endoscopic surgery (FES) in nasal polyposis (NP) is difficult. The main objective of this study was to assess the predictive factors of recovering the sense of smell after radical bilateral ethmoidectomy. Secondary objectives were to identify other predictors of olfactory recovery.

**Methods** Open prospective study was conducted at the Nantes University Hospital including all patients with NP operated on in the Ear, Nose, and Throat Department between January 2011 and September 2017. These patients underwent functional endoscopic surgery (radical ethmoidectomy) after medical treatment failure. Olfaction was quantified prospectively and systematically during the preoperative consultation using a visual analog scale. Multivariate analysis evaluated the presence of predictive factors of postoperative olfactory recovery.

**Results** One hundred nineteen patients were included in the study. Overall, olfaction was partially improved after surgery. For patients who presented greater than 50% recovery of olfaction after systemic corticosteroid therapy before surgery, we observed a predictive better rate of olfactory recovery after surgery ( $p < 0.001$ ). Age over 65 years, a history of sinonasal surgery, associated asthma, and bacterial colonization were not associated with less postoperative olfactory recovery.

**Conclusion** This study identified an objective factor that may influence olfactory recovery after FES using a therapeutic trial for olfactory recovery after oral corticosteroid treatment taken before surgery.

**Keywords** Nasal polyposis · Smell · Predictive factors · Oral corticosteroid therapy postoperative · Quality of life

## Introduction

Nasal polyposis (NP) is a frequent disorder in the general population, whose prevalence reaches 2% [1]. The main symptom is nasal obstruction, one of the first reasons for consultation. NP is frequently accompanied by alteration of olfactory function. The frequency of these problems is not consistently evaluated in the literature [2–4] and, depending on the study, varies from 41 to 84% in patients presenting an indication for surgery.

Treatment of NP and the resulting olfactory problems is mainly based on controlling the chronic inflammation of the respiratory and olfactory mucous membranes with local and systemic corticosteroids. In addition to systemic twice-daily nasal corticosteroid treatment, a short course of oral prednisone therapy, dosed at 1 mg/kg/day, is part of the latest recommendations for medical treatment of NP [5]. Surgery is always optional and reserved for forms of the disease that are resistant to medical treatment.

It has been demonstrated that surgical treatment, after failure of well-managed medical treatment, improves breathing impairment and reduces nasal obstruction [6]. However, predicting olfactory recovery is much more haphazard. Yet in clinical practice, many patients ask their surgeons the probability of recovering their sense of smell after surgery. The lack of statistical data on these questions makes responding to patients difficult, particularly since a variety of surgical techniques are used. Predicting olfactory function

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recovery after surgery is, therefore, a major issue for both patient and surgeon.

Different studies have demonstrated the possibility of olfactory function recovery after functional endoscopic surgery [3, 7, 8]. Improving the sense of smell after surgery could depend on the duration of the olfactory disorder and the patient's surgical history of NP [9].

The possibility of recovering the sense of smell after a short course of oral corticosteroids has not been assessed to date.

The objective of this study was to assess whether or not the presence of olfactory function recovery after oral corticosteroid treatment was a predictor of olfactory recovery after functional endoscopic surgery (i.e., bilateral radical ethmoidectomy). The secondary objective was to identify other predictors of olfactory recovery.

## Materials and methods

### Population study

This was a monocentric prospective open study conducted at the Nantes University Hospital that included all patients with NP undergoing surgery between January 2011 and September 2017. All patients underwent bilateral radical ethmoidectomy after functional failure of well-managed medical treatment (the opening of the maxillary sinus and the sphenoid sinus was only used as surgical landmarks). Patients requiring frontal sinus surgery were excluded. All underwent a short course of oral prednisolone benefit evaluation on smell (1 mg/kg/day 3 months before surgery, during 5 days). Corticosteroid nasal spray was prescribed to patients postoperatively. The protocol was reviewed and approved by the local independent ethics committee, and the study was conducted in accordance with French legislative and regulatory measures, and the European Good Clinical Practice Directive 2005/28/EC.

### Exclusion criteria

- Incomplete uni- or bilateral polypectomy surgery,
- patients < 18 years,
- chronic rhinosinusitis with no polyposis,
- inverted papilloma or any associated tumoral disease.
- traumatic anosmia or any other neurological impairment influencing olfactory function (parkinsonian or Alzheimer's patients),
- polyposis that is symptomatic of a non-primary disease (i.e., cystic fibrosis, primary ciliary dyskinesia, purulent oedematous sinusitis, etc.),

- patients treated systemically with corticosteroids for a long period for another disease (autoimmune diseases, steroid-dependent asthma, etc.),
- refusal to participate.

### Endpoints

Predictive factors for olfactory recovery at 1, 3, 6 months, 1 year and every year after surgery (i.e., bilateral radical ethmoidectomy) were evaluated:

- correlation between the sense of smell 1 year after surgery, and the benefit a short course of oral corticosteroids given in preoperative (main objective),
- age > 65 years, sex, and tobacco consumption,
- duration of olfactory impairment > 5 years,
- history of endonasal surgery,
- associated asthma, aspirin-exacerbated respiratory disease (Widal syndrome),
- bacterial colonization and type of bacteria when intra-operative samples were existing.

Polyps were graded from 1 to 4 according to the Hadley's clinical scoring system of nasal polyposis.

### Preoperative and postoperative assessment of olfaction

Olfaction was quantified during the preoperative consultation as a percentage according to a visual analogic scale (VAS) from 0% (absence of olfaction) to 100% (olfaction considered normal), assessed subjectively by the patients. The duration of the olfactory impairment was described. The missing data were completed with the patient by telephone. All patients enrolled in this study underwent the test of oral prednisolone benefit on smell prior to surgery.

Preoperative: olfactory recovery after a course of oral corticosteroid treatment and 1 mg/kg/day of prednisone equivalent for 7 days (percentage according to a VAS and its duration).

Postoperative: olfactory recovery after surgery, and correlation with preoperative recovery after a course of oral corticosteroid treatment, were investigated. The reference value selected was olfactory recovery  $\geq 50\%$ .

An analysis of variance delineated three groups: absence of recovery; olfactory recovery < 50%, and olfactory recovery  $\geq 50\%$ . All patients receive the same postoperative care using nasal saline irrigations followed by corticosteroid intranasal spray. None received courses of oral steroids.

## Statistical analyses

Olfaction at 1 year in relation to olfaction recovery after oral corticosteroid treatment groups was compared using the ANOVA test or analysis of variance. The odds ratio was calculated for the predictors of greater than 50% postoperative olfactory recovery.

## Results

### Demographic and clinical characteristics of the population

The demographic and clinical characteristics are described in Table 1. The mean age was  $54.8 \pm 11.7$  years. Within the total population, asthma was associated with NP in 60% of the cases and aspirin-exacerbated respiratory disease in 25% of the cases. Fifty-two percent of the patients had already undergone a previous intervention (polypectomy or ethmoidectomy). The patients who had undergone surgery had an advanced grade of NP: 5% had grade 2, 58%

presented grade 3, and 36% grade 4. Preoperatively, 87% of the patients described anosmia and 13% hyposmia. The mean duration of impairment of the sense of smell was  $6 \pm 3.9$  years.

### Evaluation of olfaction after oral corticosteroid treatment

Within the total population before surgery, an average of 75% of the patients described olfactory recovery after a course of oral corticosteroids. This recovery was estimated at a mean of 38.8%. The mean duration of recovery was 14 days.

In the anosmic group, an average of 73% of the patients recovered olfaction after a course of oral corticosteroids. The mean percentage of recovery estimated was 36.4%, with a mean duration of 13.7 days.

In the group of hyposmic patients, 87% recovered olfaction with a mean 54% recovery. The mean duration was 17 days (Table 2).

**Table 1** Patient demographic and clinical characteristics

	Anosmia (n = 104)	Hyposmia (n = 15)	Total (n = 119)	p value
Age (years)	$55.1 \pm 10.5$	$48.7 \pm 11.6$	$54.3 \pm 11.7$	0.09
Sex				
Female	35% (n = 36)	40% (n = 6)	35% (n = 42)	0.76
Male	65% (n = 68)	60% (n = 9)	65% (n = 77)	
Clinical characteristics				
Asthma	59% (n = 61)	60% (n = 9)	60% (n = 70)	0.84
Widal syndrome	25% (n = 26)	28% (n = 4)	25% (n = 30)	
Allergy	25% (n = 27)	35% (n = 5)	27% (n = 32)	1.0
Smoking	10% (n = 11)	10% (n = 2)	10% (n = 13)	0.63
History of surgery	54% (n = 56)	40% (n = 6)	52% (n = 62)	0.0016
Polypectomy	25% (n = 26)	20% (n = 3)	24% (n = 29)	
Ethmoidectomy	29% (n = 31)	20% (n = 3)	28% (n = 34)	
NP stage				
1	0%	0%	0%	
2	5% (n = 6)	0%	5% (n = 6)	
3	60% (n = 61)	60% (n = 9)	60% (n = 70)	
4	35% (n = 37)	40% (n = 6)	35% (n = 43)	
Duration of impairment (year)	$5.6 \pm 2.8$	$6 \pm 4$	$6 \pm 3.9$	

**Table 2** Olfactory recovery after oral corticosteroid therapy

	Anosmia n = 104	Hyposmia n = 15	Total n = 119	P value
Olfactory recovery after corticosteroid course:				
Yes, n (%)	76 (73%)	13 (87%)	89 (75%)	0.51
% Recovery	$36.4 \pm 26.1\%$	$54 \pm 28.3\%$	$38.8 \pm 26.9\%$	0.009
Mean duration in days	$13.7 \pm 10.1$	$17.3 \pm 10.9$	$14.2 \pm 10$	0.49
No, n (%)	28 (27%)	2 (13%)	30 (25%)	0.51

## Postoperative olfactory recovery as a function of the recovery rate after preoperative oral corticosteroid therapy

The ANOVA statistical test or analysis of variance allowed us to determine three groups in relation to olfactory recovery after a course of oral corticosteroid therapy:

- First group: no recovery.
- Second group: recovery < 50%.
- Third group: recovery  $\geq$  50%.

In the anosmic group, among the 86 patients describing improvement in their sense of smell following oral corticosteroid therapy, 44% presented recovery  $\geq$  50% and 29% recovery < 50%. In the hyposmic group, olfaction was improved in 13 patients: 60% presented recovery  $\geq$  50% and 27% recovery < 50%. The results are summarized in Table 3.

Within the group of patients with recovery  $\geq$  50%, the mean percentage of olfactory recovery at 1 year was  $53.1 \pm 25.2\%$  ( $p < 0.001$ ). Within the group with recovery < 50%, the mean percentage of olfactory recovery at 1 year was  $29.2 \pm 21.6\%$  ( $p < 0.001$ ). Finally, within the group presenting no olfactory recovery after a course of oral corticosteroids, the mean percentage of olfactory recovery at 1 year was  $21.1 \pm 20.25\%$  ( $p < 0.001$ ) (Fig. 1). This trend was confirmed during the study's follow-up.

Better postoperative olfactory recovery was observed in patients with olfactory recovery  $\geq$  50% after corticosteroid therapy. At 6 months postoperation, the mean recovery was 60%; it was 55% at 72 months. This recovery was, therefore, relatively stable over time. Moreover, this recovery remained greater compared to the other two groups ( $p < 0.001$ ).

In the group with recovery less than 50%, the sense of smell improved postoperatively. At 6 months postoperation, the mean recovery was 35% and then a progressive reduction was observed, with a mean 5% at 72 months. Beginning at the 36th postoperative month, we observed a recovery rate similar to the third group with no recovery.

In the group with no olfactory recovery after oral corticosteroid therapy, a low rate of postoperative olfactory recovery was observed. At 12 months postoperation, the mean recovery rate was 24%, it stabilized until the 60th month at 18% and then decreased. The results are presented in Fig. 1.

## Predictive factors

Logistical regression with the calculation of the odds ratio for the predictors of postoperative olfactory recovery  $\geq$  50% within the overall population allowed us to study three factors: age > 65 years, duration of olfactory impairment > 5 years, and the presence of asthma associated with NP. The results are summarized in Table 4. No difference was significant.

We studied olfactory recovery in patients with or without a history of surgery, asthmatic or nonasthmatic, and with or without bacterial colonization. Within the overall population, 60% of the patients had asthma associated with NP. At 1 year after surgery, we observed improvement in olfaction in both groups ( $p < 0.001$ ) (Fig. 2).

Within the overall population, 52% of the patients had undergone a previous surgery. After the last surgery, olfactory improvement was observed in patients both with and without a history of surgery. This difference was significant ( $p < 0.001$ ) (Fig. 2).

Postoperatively, within the overall population, the sense of smell was greater at 1 year in patients with a negative intraoperative bacterial sample, estimated at a mean 50% by the patients, versus 40% olfaction estimated in the group of patients with bacterial colonization ( $p < 0.001$ ) (Fig. 2).

## Discussion

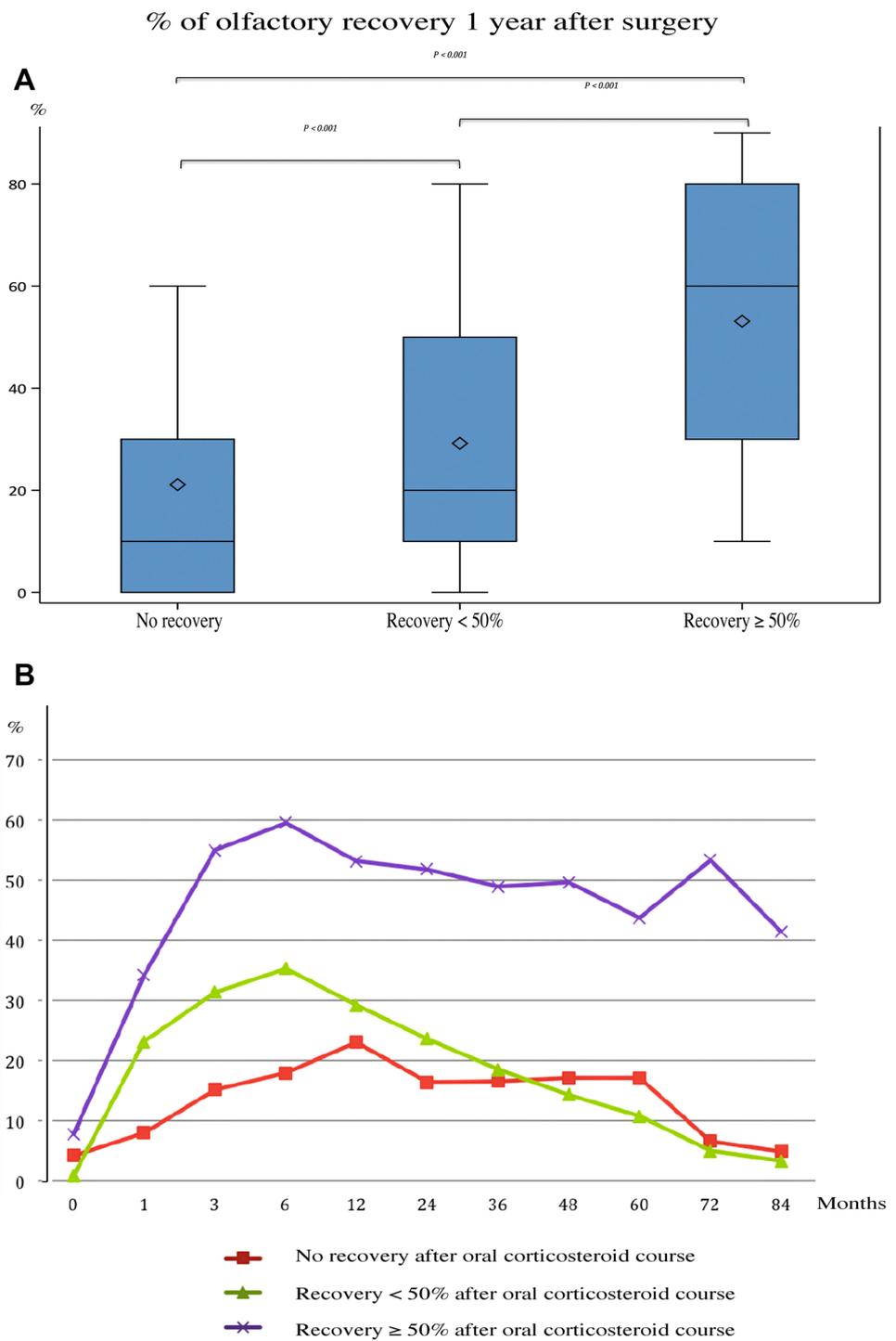
Assessment of olfaction in NP is critical. However, exploration of olfaction using psychophysical methods requires a long examination, which is difficult and relatively unreachable for the clinician.

In this study, olfaction was quantified as a percentage according to a VAS, from 0 to 100%, described by the patient at the preoperative consultation and then at the postoperative evaluation. Even if a strong correlation has been observed between self-rating scores and measures of olfactory function before and after surgery in NP patients, this analog scale evaluation has many limits. Thus, the gold standard remains objective measurements of olfactory function and finally VAS cannot replace measurements of olfactory function. Although subjective, VAS is an easily available tool to rate overall olfactory disorders of patients in everyday practice, but is only complementary to standardized measures

**Table 3** Rate of olfactory recovery after oral corticosteroid therapy

	Anosmia $n = 104$	Hyposmia $n = 15$	Total $n = 119$	$p$ value
Rate of olfactory recovery after oral corticosteroid therapy				
No recovery	28 (27%)	2 (13%)	30 (25%)	0.084
Recovery < 50%	30 (29%)	4 (27%)	34 (28%)	
Recovery > 50%	46 (44%)	9 (60%)	55 (46%)	

**Fig. 1** Percentage of postoperative olfactory recovery. **a** At 1 year depending on olfactory recovery after oral corticosteroid course. **b** According to time after surgery

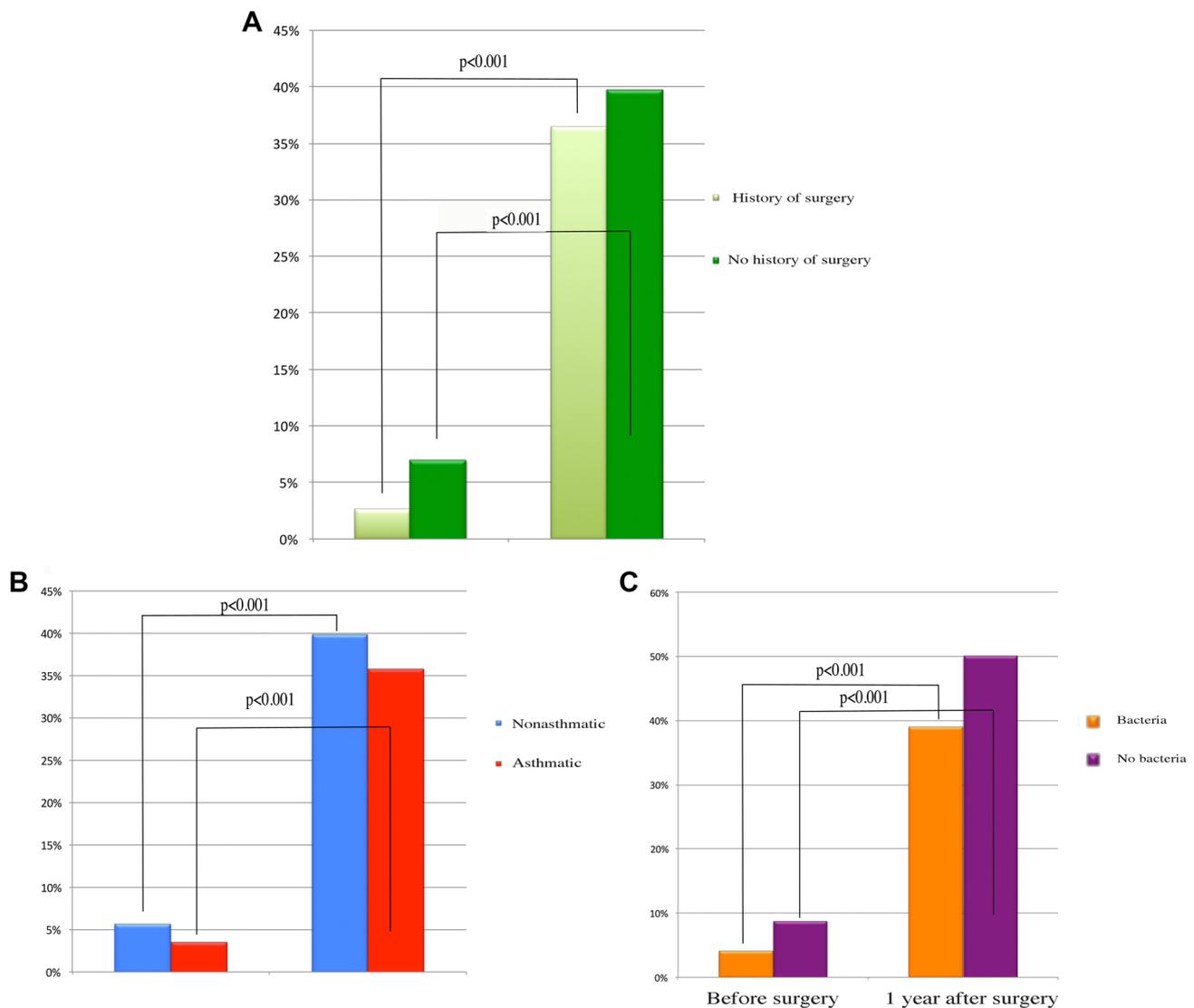


**Table 4** Odds ratio of predictors of ≥50% olfactory recovery

Variable	OR	95% CI	P value
Age > 65 years	1.14	(0.12–10.81)	0.909
Duration of olfactory impairment > 5 years	0.7	(0.12–4.07)	0.688
Asthma	1.94	(0.33–11.32)	0.461

of the olfactory function, particularly in patients with smell fluctuation that are hardly revealed when objective test is performed.

NP is a chronic inflammatory disease, and first-line medical treatment should be instituted. It is based on the association of daily local and occasional systemic corticosteroid treatment. Few studies have evaluated the effect of medical treatment on olfactory recovery. The results of a



**Fig. 2** Recovery of olfaction 1 year postoperation. **a** Regarding surgical history, **b** regarding asthma history, and **c** regarding to microbiological outcomes

meta-analysis demonstrated that local corticosteroids do not improve olfactory function [10].

Preoperatively, on the other hand, the benefit of oral corticosteroid courses on olfaction was demonstrated in a meta-analysis. Three studies used prednisolone (30–50 mg/day) for 14 days and one study used methylprednisone (32 mg/day) for 20 days versus placebo. All demonstrated nearly total improvement in olfaction over 10 days and then new deterioration [11, 12]. In the present study, corticosteroid therapy was prescribed at 1 mg/kg/day for 5–7 days. The mean olfactory recovery was 37% in the anosmic group versus 54% in the group of hyposmic patients.

Only four anosmic patients described total recovery of their sense of smell over a 7-day period. In our study, the mean duration of the improvement in olfaction was 15 days.

No analysis has studied whether olfactory recovery following a course of oral corticosteroids in patients treated medically was a predictor of postoperative olfactory recovery. The results of the present study show better postoperative olfactory recovery in patients who had had greater than 50% preoperative olfactory recovery after a course of oral corticosteroids. The percentage of recovery was maximum between 6 months and 1 year and then tended to decrease. It remained greater than in the other two groups.

However, this result needs to be interpreted cautiously. First of all, pre- and postoperative olfaction were evaluated descriptively and subjectively by the patients. Under- or overestimation is possible. The notion of duration is also subjective. To confirm this result, a more objective evaluation of olfaction would be required, using psychophysical

methods, for example, which are not dedicated to clinical practice. Here again, given the fluctuation of olfaction in NP, it can be questioned whether assessing olfaction at a single time point is representative of a patient's long-term olfactory function.

In addition, a bias may exist in patient selection. Within our population, 104 patients presented anosmia and 15 hyposmia. In the group of patients presenting  $\geq 50\%$  recovery, 84% of the patients described anosmia and 17% hyposmia. The proportion of anosmic and hyposmic patients was similar in all three groups.

In this study, all patients receive the same postoperative care using nasal saline irrigations followed by corticosteroid intranasal spray. None received courses of oral steroids.

Recent studies suggest that budesonide added to saline nasal lavage can be an effective treatment for patients with chronic rhinosinusitis. The overall results demonstrate the potential benefit of budesonide in treating chronic sinusitis when delivered as a nasal saline rinse. However, larger trials are needed to define budesonide's effect within different subgroups of patients compared to other treatment methods such as nasal steroid sprays. As we started the study in 2011, the reproducibility needed to continue with sprays postoperatively.

This is the first study examining these data, providing additional information for clinicians and patients on the chances of recovering their sense of smell after surgery.

This study examined several other factors, described in the literature as being associated with better or lesser postoperative recover of olfactory function. Age is known to be a risk factor for olfactory dysfunction [13]. An increased presence of preapoptotic genes was demonstrated, as was increased death of neuronal cells of olfactory receptors in the olfactory mucous membranes of the oldest rats [14]. Litvak et al. also demonstrated less postoperative olfactory recovery in patients older than 65 years [3]. This was due to age and not the time since NP onset. Patients with NP may present inflammation of the olfactory mucous membranes that may inhibit olfactory neurogenesis. As a consequence, whether age and NP could have a synergetic effect on the weakening of the neuroepithelium remains uncertain. The oldest patients may be more sensitive to a neuroepithelial lesion and less capable of repairing it. In the present study, no significant difference in the postoperative recovery of the sense of smell was observed in patients 65 years old and older. It may also be hypothesized that NP is slowly destroying by local infection and fibroses the nerves in olfactory cleft during evolution.

Asthma patients, 60% of the patients in this study, may also be more subject to having olfactory dysfunction. Patients suffering from NP and asthma suffered from systemic inflammatory modifications of the upper and lower airways [15]. It seems that this systemic inflammatory

process can also affect the olfactory cleft. Several studies have demonstrated that these patients may present more pronounced preoperative olfactory impairment without this being a predictor of lesser olfactory function recovery [16, 17]. The results reported herein are, therefore, in agreement with the literature.

In patients with NP, substantial *S. aureus* colonization has been described; these bacteria have been suggested to produce superantigens (enterotoxins) [18, 19]. The *S. aureus* superantigens may amplify inflammation in approximately 50% of NP cases. It is, therefore, legitimate to question the impact of bacterial infection on patients' ability to recover olfaction.

As for recovery of olfactory function within the overall population, the patients with no bacterial colonization described a better rate of olfactory recovery than did patients with bacterial colonization [20]. However, a more precise analysis of the subgroups should be carried out on a larger number of patients to validate these results.

## Conclusion

This study has identified that the response to preoperative prednisolone is shown to predict the outcome of olfactory recovery after surgery. Thus, olfactory recovery greater than 50% after a course of oral corticosteroid therapy may be a predictor of better subjective postoperative recovery.

Age 65 years or older, associated asthma, bacterial colonization, and a history of surgery may, on the other hand, are predictors of less postoperative olfactory recovery.

This study provides surgeons with additional information to respond to patients' questions as to the possibilities of improving their sense of smell.

## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

**Research involving human participants and/or animals** The protocol was reviewed and approved by the local independent ethics committee, and the study was conducted in accordance with French legislative and regulatory measures, and the European Good Clinical Practice Directive 2005/28/EC (1964 Helsinki declaration).

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

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