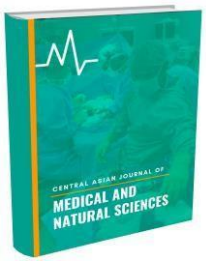

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Article

Intrapolyp Steroid Injection Versus Systemic Steroid Therapy for Nasal Polyposis Associated with Chronic Rhinosinusitis

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Abstract: Intrapolyp Steroid injection (IPSI) involves injection of corticosteroids inside the sinonasal polyposis for treating conditions of chronic rhinosinusitis with nasal polyps (CRSwNP). IPSI varies from the systemic steroid (SCs) administration in providing steroids locally into the nasal polyps without resulting in side effects associated with the use of SCs. This study compares the effectiveness and the clinical outcomes of IPSI versus SCs administration in patients with CRSwNP. The study recruited 100 patients diagnosed with CRSwNP. Patients with CRSwNP were randomly assigned into two treatment groups. Group 1 received intrapolyp steroid injection (IPSI) of budesonide at a final concentration of 250 µg/ml/sinus for every fortnight and for a total of three times. Group 2 was treated with oral prednisolone 1 mg/kg/day for three days, then tapering the dose by 5 mg/day for 2 weeks. Patients were then followed up for three months to assess the impact of the treatment on polyp size, olfactory function, serum cortisol levels, and quality of life. Both IPSI and SCs treatment plans demonstrated efficacy in improving clinical outcomes in patients with CRSwNP. SCs resulted in a greater reduction in nasal polyp size (8.67 ± 2.6 vs. 10.15 ± 3.01, $p < 0.001$), greater improvement in olfactory function (27.32 ± 10.68 vs. 23.32 ± 10.05, $p < 0.001$), and a more significant reduction in SNOT-22 scores (36.32 ± 9.13 vs. 45.7 ± 12.66, $p < 0.001$) compared to IPSI. However, serum cortisol levels were found significantly higher in the SCs group (15.57 ± 5.35 vs. 13.22 ± 5.78, $p = 0.001$). Regression analysis revealed a significant impact of SCs on reducing polyp size ($\beta = -0.26$, $p = 0.01$) and improving the quality of life ($\beta = -0.39$, $p < 0.001$). SCs were more effective in treating signs and symptoms associated with CRSwNP compared to IPSI. However, systemic cortisol was significantly higher. Treatment selection should consider both efficacy and potential adverse effects.

Keywords: CRSwNP, Intrapolyp Steroid Injection, Systemic Steroids, Nasal Polyposis, Lund-Mackay Score

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1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disease of the nasal and paranasal sinus mucosa, marked by the existence of benign tissue hypergrowths from the internal lining of the nasal cavity causing the development of nasal polyps[1]. The disease was reported to impact patients' quality of life through the associated symptoms of nasal blockage, hyposmia or anosmia, face pressure, and rhinorrhea[2]. Although there are several etiological factors that have been proposed to play a central role in the induction and progression of the disease, CRSwNP is still considered very complex and not yet completely understood[3]. The is due to the complexity of the inflammatory mediators involved in the process, immune dysregulation,

extensive tissue remodeling, biofilm formation, and various genetic and environmental factors that could contribute to disease severity and recurrence[4-6].

The type-2 immune response associated with CRSwNP characterized by excessive production of interleukins (IL-4, IL-5, IL-13), infiltration of the nasal sinus with eosinophils, and increase concentration of IgE in the affected sinus[4]. Additional features include disruption of the epithelial barrier, through altering the expression of tight junctions, and reducing ciliated cells in the nose, allowing more allergens and pathogens to penetrate the mucosal lining and worsening the inflammatory condition[7]. Pathophysiology also involves extensive tissue remodeling and polypogenesis. Although studies associate nasal polyp formation with epithelial to mesenchymal tissue transition, the trigger for polypogenesis is still to be determined[8]. The affected region with nasal polyp formation characterized by edema, glandular hyperplasia, fibrine deposition, and extracellular matrix deposition[9].

Conventional treatment methods include the use of local intranasal corticosteroids (INCS), systemic corticosteroids (SCs), and saline irrigation. Surgical interventions are usually followed for severe cases presented with persistent infections and refractory cases of CRSwNP [1,10]. The usage of INCS is commonly recognized as the primary treatment approach for CRSwNP that provides effective anti-inflammatory actions without resulting in number of side effects associated with systemic SCs [11]. This approach has significantly led to improve signs of polypogenesis, nasal obstruction, and hyposmia [12]. However, number of limitations have been reported in cases with extensive formation of polyp or severe inflammatory reactions [13]. SCs are also used in treatment of CRSwNP, mainly for those with symptom aggravation or those who show limited improvements on INCS [14]. However, side effects following prolonged treatment with high doses of systemic corticosteroids is well-documented, specifically in a number of conditions, such as diabetes, osteoporosis, and adrenal suppression [15]. Whether following the use of INCS or SCs, the subject remains a matter of active research and clinical debate among specialist. These approaches are evidently influenced by significant concerns such as efficacy, safety, and patient adherence to treatment approach [16].

Intrapolyp steroid injection (IPSI) has emerged as an effective treatment for conditions with sinonasal polyposis [17]. This approach exhibited comparable results to INCS and SCs in reducing CRS symptoms and polyp size [17-20]. This method involve using higher concentrations of steroids injected into the polyps with potential reduction of systemic side effects [17]. Research has shown considerable enhancements in the polyps score, symptom score, and Lund-Mackay score following the IPSI [17-20]. Studies also showed that IPSI exhibit superiority over nasal sprays and nasal irrigations in number of documented cases [20,21], with treatment efficiency that can exceed a duration of three months [18]. However, IPSI were reported with significant limitation in conditions with considerable size polyposis that presented resistant to complete eradication following this approach [18], and local side effects associated with nasal dryness and crusting [22]. Further research is required to comprehensively determine the long-term safety and effectiveness of IPSI compared to SCs treatment approach. Therefore, this study aims to investigate effectiveness and the clinical outcomes of IPSI versus SCs administration in patients with CRSwNP.

2. Materials and Methods

The study recruited a total of 100 patients who were diagnosed with CRSwNP at the outpatient clinic of the Department of Otorhinolaryngology (ENT) / Al-Zahraa Teaching Hospital, Kut City, Iraq, between December 2023 and January 2024. The study population was divided randomly into two groups in a 1:1 ratio to follow different treatment approaches: Group 1 consisted of 50 patients treated with IPSI, and Group 2 consisted of 50 patients treated with CRs. The study was approved by the Ethics Committee in the

College of Medicine, University of Wasit, Iraq. Patients were informed about the objectives of the study and those who agreed to participate were provided with a written informed consent. Patients' diagnosis, selection, and treatment were in accordance with the principles outlined in the Declaration of Helsinki.

The inclusion criteria included patients with symptoms of CRSwNP that lasted for at least 12 weeks. Exclusion criteria included patients with unilateral nasal polyps, pregnancy or breastfeeding, tobacco smokers, history of atopy, asthmatic patients, patients with a history of aspirin-exacerbated respiratory disease, and history of sinus surgery. Patients with other medical conditions, such as diabetes, osteoporosis, adrenal suppression, and cardiovascular diseases were also excluded. The study also excluded CRSwNP patients who previously received steroid treatment during the last three months.

All patients underwent a general examination and a comprehensive ENT assessment of the CRSwNP. The procedures involved evaluation of the nasal polyp size, olfactory function, and quality of life score. The serum cortisol levels were also assessed before treatment.

The IPSI procedure (group 1) was performed according to Elzayat et al. (2023). In brief, patients were positioned in a semi-reclined position, and a nasal rigid endoscope was utilized to guide a sterile syringe (28-gauge) for the intrapolyp budesonide injection at a final concentration of 250 μg/ml/sinus. The injection volume was distributed equally on all the affected regions with polyps' growth, and the injection procedure was performed by the same specialist to prevent variability in technique and ensure consistency in steroid delivery. Those patients received IPSI every fortnight and for a total of three times. Patients of group 2, however, received oral prednisolone 1 mg/kg/day for three days, then tapering the dose by 5 mg/day for 2 weeks. All patients were directed to refrain from using any other medications for the duration of the current study. All patients were followed up for three months, and the patient's outcomes, including nasal polyp size, nasal congestion score, olfactory function, serum cortisol level, and quality of life were assessed at the end of three months from the start of the procedure.

Nasal polyp size was assessed following the use of the Lund-Mackay scoring system which is based on utilizing computed tomography (CT) scans of the paranasal sinuses. Each nasal sinus was scored according to the degree of opacification: 0 (completely clear), 1 (partial opacification), and 2 (complete opacification). The osteomeatal complex was also scored as either 0 (not obstructed) or 2 (obstructed). Lund-Mackay scoring system ranged from 0 to 24 where higher scores represent higher disease impact. All patients were also examined with CT scans before and after treatment to evaluate treatment efficacy in reducing polyp size and sinus obstruction.

The Sniffin' Sticks test was utilized to assess olfactory function. The test assessed odor threshold, odor discrimination, and odor identification. Patients were provided with special pens immersed in odorants and were asked to detect, distinguish, and identify different smells. The test result ranges from 1 to 48 and higher scores indicate good olfactory function. This test was performed before the start of treatment and at the end of the three-month follow-up period.

The impact of the disease on the quality of life was assessed following the sino-nasal outcome test-22 (SNOT-22) questionnaire. The test examines the impact on nasal, sleep, and emotional functions for before and after three months of treatment. Patients were instructed to answer selected 22 questions which were evaluated on a Likert scale ranging from 0 (no problem) to 5 (severe problem).

Serum cortisol levels before and after treatment were assess to examine the impact of the treatment on systemic steroid levels. Blood samples were collected from all patients in the morning, and cortisol levels were analyzed at the laboratory unit of the hospital using chemiluminescence immunoassay. Comparisons were made between the intrapolyp

steroid injection and systemic steroid therapy groups to evaluate the relative systemic impact of each approach.

Statistical analysis was performed on SPSS version 26 (IBM, USA). Scale variables such as age and BMI were expressed as mean ± standard deviation (S.D.) and tested for significant differences between treatment groups with the use of an independent sample t-test. Sex as a categorical variable was expressed as a count (%) and was tested for differences between groups with chi-square (Fisher's exact test). Multiple comparisons of outcome variables, the serum cortisol levels, nasal polyp size, olfactory function, and quality of life score, between groups with before and after treatment plans were analyzed with the use of repeated measure ANOVA (the Bonferroni test). A p-value of less than 0.05 was considered statistically significant. Linear regression analyses were used to examine the impact of the treatment plans on the outcomes. Beta coefficients (Beta) was calculated to measure the level of improvement after three months of treatment.

3. Results

The patients' characteristics, including age, BMI, and sex distribution, showed no significant differences between the two groups ($p > 0.05$), Table 1. Serum cortisol levels were measured before and after treatment to assess systemic steroid absorption. Before treatment, the mean serum cortisol levels were 12.66 ± 1.45 μg/dL in the IPSI group and 12.13 ± 1.41 μg/dL in the SCs group. At three months post-treatment, cortisol levels were found significantly higher in SCs group 15.57 ± 5.35 μg/dL compared to 13.22 ± 5.78 μg/dL in the IPSI, ($p = 0.001$). Regression analysis confirmed that SCs significantly influenced serum cortisol levels after treatment ($\beta = 0.21$, $p = 0.037$), Table 2.

Nasal polyp size was assessed using the Lund-Mackay scoring system. Before treatment, both groups had comparable polyp scores, with mean values of 16.88 ± 3.75 in the IPSI group and 16.64 ± 4.08 in the SCs group. After three months, the polyp score presented a significant reduction in the SCs group (8.67 ± 2.6) compared to the IPSI group (10.15 ± 3.01) ($p < 0.001$), and the negative beta value in regression analysis ($\beta = -0.26$, $p = 0.01$) confirmed that SCs had a higher effect on polyp size.

Olfactory function showed significant improvement in both groups. The mean scores of the baseline were 15.67 ± 5.79 in the IPSI group and 14.79 ± 5.28 in the SCs group. After three months the scores showed improvement to 23.32 ± 10.05 in the IPSI group and 27.32 ± 10.68 in the SCs group. This result demonstrated an enhancement in olfactory function ($p < 0.001$). However, the regression analysis presented no statistical significance ($p = 0.056$) between groups. This would suggest that both treatments approaches were equally beneficial to our patients.

Baseline analysis of quality of life showed the mean SNOT-22 score was 64.11 ± 32.21 in the IPSI group and 69.27 ± 27.88 in the SCs group. Statistical analysis revealed a significant reduction in the scores to reach 45.7 ± 12.66 in the IPSI group and 36.32 ± 9.13 in the SCs group ($p < 0.001$) after three months of treatment. The findings indicate a greater improvement in the SCs group. Regression analysis further confirmed that SCs had a significant impact on quality of life improvement compared to IPSI, being $\beta = -0.39$, $p < 0.001$) Table 2.

Table 1. Baseline characteristics and treatment outcomes in patients receiving intrapolyp steroid injection (IPSI) or systemic corticosteroids (SCs).

Patients' characteristics		Treatment groups				P value
		Group 1 (IPSI)		Group 2 (SCs)		
		Mean ± S.D.	Count (%)	Mean ± S.D.	Count (%)	
Age (years)		39.3 ± 11.8		42.79 ± 11.9		0.144
BMI (kg/m²)		24.23 ± 2.97		25.09 ± 3.29		0.171
Sex	Male		35 (52.24%)		32 (47.76%)	0.532
	Female		15 (45.45%)		18 (54.55%)	
Serum cortisol level (μg/dL)	Before treatment	12.66 ± 1.45		12.13 ± 1.41		0.001*
	3 months post-treatment	13.22 ± 5.78		15.57 ± 5.35		
Nasal polyp size (Lund Mackay Scores)	Before treatment	16.88 ± 3.75		16.64 ± 4.08		<0.001*
	3 months post-treatment	10.15 ± 3.01		8.67 ± 2.6		
Olfactory function (Sniffin' Sticks test)	Before treatment	15.67 ± 5.79		14.79 ± 5.28		<0.001*
	3 months post-treatment	23.32 ± 10.05		27.32 ± 10.68		
Quality of life score (SNOT-22 questionnaire)	Before treatment	64.11 ± 32.21		69.27 ± 27.88		<0.001*
	3 months post-treatment	45.7 ± 12.66		36.32 ± 9.13		

*Significant difference.

Table 2. Linear regression analysis of the impact of CSs therapy on the measured outcomes of serum cortisol, polyps' size, olfactory function, and quality of life after three months of treatment.

Outcome	Standardized Coefficients (Beta) ǂ	Standard error	P- value	95% CI for Beta	
				lower bound	upper bound
Serum cortisol level	0.21	1.11	0.037*	0.14	4.56
Nasal polyp size (Lund Mackay Scores -lower is better)	-0.26	0.56	0.01*	-2.6	-0.36
Olfactory function (Sniffin' Sticks test - higher is better)	0.19	2.07	0.056	-0.11	8.12
Quality of life score (SNOT-22 questionnaire - lower is better)	-0.39	2.21	<0.001*	-13.76	-4.99

*Significant difference

4. Discussions

The pathophysiology of CRSwNP is characterized by activation of type-2 pathway inflammation, mucosal barrier defect, and neurological inflammation that can lead to olfactory dysfunction [23]. Pathophysiology also includes excessive eosinophilic infiltration, elevated levels of cytokines, sinus edema, and overproduction of mucus [1]. Corticosteroids are considered the primary treatment choice due to their potent anti-

inflammatory properties and their role in managing immune dysregulation associated with the disease [10]. There are multiple routes of corticosteroid administration that can be applied to patients with CRSwNP, these include locally inside the nasal cavity, orally, and injection inside the polyp mass to treat polyposis and recurrent CRSwNP [17-20,24]. Each of these approaches has its own advantages and disadvantages in the management of CRSwNP. The current study evaluated the efficacy of IPSI compared to SCs in treating patients with CRSwNP. Our findings showed that both treatment approaches were effective in elevating signs of the nasal polyps, improving olfactory function, and enhancing quality of life. However, SCs were found with significantly improved outcomes across these parameters.

Oral corticosteroids are commonly used in treating patients with CRSwNP [25]. Studies highlighted the significant importance of short-term application of SCs on long-term use [26]. The short-term SCs were found to be very effective for managing moderate to severe signs of CRSwNP, and beneficial in cases with acute exacerbations or prior to sinus surgical intervention for the reported reduction in inflammatory responses and improving surgical outcomes [27,28]. Short-term SCs were also associated with significant improvement in tissue eosinophilia and sinus fibrosis in patients with nasal polyps [29]. In a randomized controlled trial, SCs were reported to significantly decrease symptom scores of CRSwNP, polyp scores, and CT scores, compared to findings from endoscopic sinus surgery [30]. However, most of the documented cases showed short-term improvements. This led to explore the potentials of other alternate approaches which may provide longer-term effects with fewer side effects [31]. A study found that a combination of oral and nasal spray steroid treatment can result in long-term beneficial effects without serious adverse effects on patients[32]. Long duration and higher doses of systemic corticosteroids can result in higher systemic cortisol levels which evidently can impact many metabolic, cardiovascular, and immune system processes [33]. The greater impact of the steroids administration is seen among patients who are susceptible to corticosteroid-related problems. Finding an effective strategy in treating CRSwNP is still a significant challenge in those patients.

The emerging IPSI as an alternative treatment approach to the SCs has generated significant attention in recent years. This approach involves direct administration of corticosteroids into the nasal polyps with attention on reducing CRSwNP inflammation and polyp size in patients with high susceptibility to corticosteroid-related problems [17-20]. Although the clinical efficacy of IPSI and implications in the context of CRSwNP management are still questionable, IPSI were found comparable to oral steroids in efficacy, with minimum side effects compared to SCs [20]. IPSI was also reported to provide targeted and efficient treatment intervention compared to traditional nasal spray or oral steroid regimens [34]. In a study conducted by Kiris et al. indicated that IPSI intervention for nasal polyp treatment exhibited overall outcomes comparable to short-term SCs with maintaining the normal cortisol levels [17]. Others have reported similar findings, which contradict the current study's results showing that SCs were more effective than IPSI in alleviating symptoms of CRSwNP. Additionally, serum cortisol levels in the IPSI group were lower than in patients treated with SCs, aligning with findings from other studies [18-20]. Research indicated that IPSI could provide a good alternative to SCs for patients with a risk of developing cortisol-related side effects. It also can be used in patients suffering from resistant and recurrent nasal polyps [35]. However, recent evidence suggested that IPSI might be associated with nasal dryness and crusting, which were not observed in this study.

Current findings suggest that IPSI should not be considered as the only treatment approach for CRSwNP. Other treatment approaches should also be considered in treating CRSwNP such as nasal saline irrigation, nasal spray, allergen immunotherapy, and biologics treatment [36]. In addition, the underlying causes of CRSwNP should also be considered before any treatment plan. Signs of anatomical abnormalities, genetic, and

environmental factors can significantly alter treatments outcomes and the recovery time if not considered [37]. Besides, there are number limitations and weaknesses associated with IPSI that could impact procedure effectiveness, such as the requirement for specialized surgical training and other equipment for the procedure. In cases with persistent nasal polyps or high recurrence rate of polyp's growth, the side effects associated with repeated IPSI are not well understood. It is suggested by several studies that repeated IPSI might result in aggravated signs of nasal septal perforation or adrenal suppression [18,22,38].

The current practice is to use SCs which showed effective approach in treating signs and symptoms of CRSwNP. However, the efficacy and safety characteristics of SCs remain questionable in many cases treated with this approach [14]. Patients are usually exhibiting varied responses to corticosteroids administration. In most cases, individuals might experience short relief of signs but ultimately suffer from a recurrence of the disease. Prescribing higher dosages or prolonged usage of steroids may provide benefit to some individuals, while others might experience considerable adverse effects that exceed the advantages of the procedure [11]. Moreover, corticosteroids are mostly used to address signs and symptoms of the disease but not the underlying causes of CRSwNP [39]. These conditions could involve infectious agents or allergic reactions that require a distinct treatment regimen. The absence of a comprehensive treatment approach can result in patient's frustration and dissatisfaction with the method of treatment which may result in temporary improvements and not a complete clinical cure [40].

The current findings also shed light on the potential concession between the treatment efficacy of the steroids administration and the side effects associated with their use. Although SCs are commonly reported to generate acceptable clinical results in terms of polyp size reduction, olfactory function, and quality of life, continuous administration of steroids could impose significant damage to multiple systems. The benefits associated with IPSI are to provide a localized steroid effect with lower systemic absorption and less impact on organs. Hence, it can be considered a safer alternative for patients at risk of corticosteroid-related complications. The treatment of choice for such cases should be steered by the early-mentioned patient-specific factors and the degree of the severity of polyposis, risk of steroid complications, and the overall clinical outcome.

There are a number of limitations to the study that require comment on. First, the follow-up period was limited to three months. A longer follow-up approach could help in assessing the efficacy of each treatment approach, the incidence of polyp recurrence, and other adverse effects that might emerge at later stages. Second, the study utilized serum cortisol levels as a marker of systemic steroid absorption. Addressing this point should be followed by assessing specific endocrine markers for a comprehensive evaluation of the adrenal function status. Third, the study did not include biomarkers that are designed to assess the level of inflammation or immune hyperactivity in the methodology of assessing treatment outcomes. These markers, such as cytokine levels or nasal biopsy histopathology, could provide further significant information that is essential to understand the whole picture of the disease. Future research with larger cohorts, longer follow-up, and additional inflammatory markers is needed.

5. Conclusions

The study showed that IPSI and SCs generated the required clinical efficacy in reducing polyp size, improving olfactory function, and enhancing quality of life. Best clinical outcomes were reported in patients who followed the SCs approach compared to IPSI. However, those patients displayed higher systemic steroid absorption. Further research is necessary to fully reveal the long-term efficacy, safety, and optimal dosing of various treatment plans.

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