Journal of Clinical & Experimental Ophthalmology

Mohammad et al., J Clin Exp Ophthalmol 2019, 10:1
DOI: 10.4172/2155-9570.1000783

Research Article Open Access

Management of Different Types of Acute Idiopathic Orbital Inflammation Using Local Steroid Injection

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Received date: December 24, 2018; **Accepted date:** January 08, 2019; **Published date:** January 16, 2019

Abstract

Purpose: To assess the safety and efficacy of local steroid injection in the treatment of acute idiopathic orbital inflammation (AIOI).

Methods: This prospective non-comparative, interventional clinical study included 24 patients presented to the orbital outpatient clinic of Assiut University Hospital with AIOI in the period between April 2013 and April 2016. Diagnosis was based on the characteristic clinical and radiological picture after exclusion of other identifiable local or systemic causes. After a written consent, all patients were treated by local injection of 2-4 ml of a combined short and long acting steroid suspension under general anesthesia followed by a tight bandage and cold compression of 15 min were applied over the affected eye.

Results: Twenty out of the 24 patients (83.3%) have responded to local steroid injection with no recurrence for a follow up period ranging from 6-24 months (mean 11.06 months); 19 patients (79.2%) after a single injection and 1 patient (4.1%) after 2 injections. Three patients (12.6%) have responded to local steroid injection, but had a recurrent attack after a period of quiescence. They had complete cure after another injection with no recurrence within 6-9 months. One patient did not respond to the first steroid injection. She was advised to have a second injection but the patient refused and preferred the oral therapy. None of our patients suffered from any side effects except one who reported polyphagia and weight gaining following the injection.

Conclusions: Local steroid injection provides a safer and at least equally effective method in treating AIOI.

Keywords: Local steroid; Acute Idiopathic Orbital Inflammation (AIOI); Orbital pseudotumor

Introduction

Idiopathic orbital inflammation is defined as a benign, non-infective clinical syndrome characterized by features of nonspecific inflammatory conditions of the orbit without identifiable local or systemic causes [1]. The etiology and pathogenesis of orbital pseudotumor are unknown. The infection theory, the autoimmune theory, and the fibroproliferation theory have been suggested [2]. IOI can be classified according to the onset (acute, subacute, and chronic) [3], according to the localization (myositis, dacryoadenitis, anterior, posterior, and diffuse) [4], and according to the histopathology (classic, sclerotic, granulometous, vasculitic and eosinophilic) [2].

Diagnosis of acute IOI is based on the presence of symptoms and signs of acute orbital inflammation combined with the characteristic finding in the orbital imaging in the absence of any identifiable local or systemic cause [5]. Biopsy is better to be deferred to cases with atypical presentation or in cases with poor response to steroid therapy [6]. Orbital cellulitis, thyroid eye disease and other orbital inflammation, neoplastic and vascular disease should be rolled out [7,8].

Although oral corticosteroid is considered the mainstay of treatment of IOI, many reports have questioned its efficacy in controlling the disease. Failure of response or partial response, failure to reach cure with permanent damage, steroid dependence with prolonged therapy or recurrence after discontinuation of treatment have been reported [1,5,9]. A large list of side effects as well as contraindications have further limited its use [1,5,10]. Local steroid injection for management of IOI have been introduced as a safer method compared to systemic steroid [10].

Patients and Methods

This prospective non-comparative, interventional clinical study was carried out in the period between April 2013 and April 2017 after approval by the Ethical Committee of Assiut University with adherence to the principles outlined in the Declaration of Helsinki and after obtaining a written informed consent from all patients. The study included patients presented in the oculoplastic outpatient clinic of Assiut University Hospital with Acute Idiopathic Orbital Inflammation (AIOI). From each patient, a detailed history of the present illness was recorded as well as the past history (including history of previous similar attacks, history of diabetes mellitus, thyroid disease, collagen vascular disease or cancer, and history of trauma or infection). All patients were subjected to full ophthalmic examination (including visual acuity at time of presentation, slit-lamp examination, fundus examination, IOP measuring, testing of ocular motility, and examination of the orbit by inspection and palpation for detection of palpable masses). Proptosis was measured by Hertel

exophthalmometre. Ptosis was diagnosed based on the interpalpebral fissure height.

All patients were also subjected to orbital imaging (CT or MRI orbit), and the routine laboratory tests (complete blood count, C-reactive protein, and erythrocyte sedimentation rate). Specific tests to rule out other differential diagnosis were done in suspected case.

The diagnosis of Acute Idiopathic orbital inflammation was based on the presence of symptoms and signs of acute orbital inflammation associated with the characteristic findings in the orbital imaging in the absence of any identifiable local or systemic cause. Patients with sub-acute or chronic idiopathic orbital inflammation (more than 14 days) were excluded from the study. All cases that have an identifiable cause of orbital inflammation were also excluded. Also patients with lesions in the neuroimaging suspected to be neoplastic were excluded.

After a written consent, all patients were treated by local injection of combined short and long acting steroid suspension (this combination is commercially available, each milliliter of this suspension contain 2 mg betamethazone sodium phosphate and 5 mg beta methazone dipropionate). The type of anesthesia varied according to the age and the type of IOI. The dose of steroid used in the injection was 2-4 ml of the suspension according to the size and extent of the lesion. Following the injection, a tight bandage and cold compression of 16 min were applied over the affected eye. The eye bandage was removed 2 days post-injection and the patient was maintained on oral paracetamol twice daily for 2 weeks.

The treatment outcome was assessed according to the following items; the initial response, the final status of the disease, the occurrence of recurrent attack, and the presence of side effects. The initial response to treatment was recorded 3 days to 1 week post injection and graded according to the improvement of the clinical manifestation as good (improvement in all symptoms and signs), fair (improvement of most but not all symptoms and signs), or poor (minimal or no improvement). A follow up visits were arranged 2 weeks, 1, 3, and 6 months post injection to assess the final status of the disease.

A complete cure was defined as disappearance of all symptoms and signs of the condition. Partial cure was defined as disappearance of most of the symptoms and signs with residual manifestation. In case of partial response to the first injection within 1 month a second injection was made. A recurrence was defined as reappearance of the same manifestation as the previous disease after a period of quiescence with imaging showing a lesion similar to the previous attack. Recurrent cases were treated with another injection in the same protocol. During each follow up visit, the patients were asked to report side effects (e.g. gastric troubles, weight gain) and were subjected to visual acuity test, slit lamp examination and IOP measurement, as well as measuring blood glucose level and blood pressure to detect any local or systemic side effects.

Results

During the period of the study, twenty four patients with a final diagnosis of acute idiopathic orbital inflammation that met the inclusion criteria were included in the study. Their age ranged from 2.6 to 62 years (mean equal 36.06 years). Of these 24 patients, 18 were females and 6 males (3:1). The disease was unilateral in 23 patients (the right orbit was involved in 14 patients while the left orbit was involved in 9 patients) while one patient had bilateral involvement (Fig 2). According to the clinical presentation and the neuro-imaging study, the patients were classified to 4 subtypes; acute isolated dacryoadenitis (10 patients), acute isolated myositis (10 patients), and combined myositis and dacryoadenitis (4 patients).

The symptoms and signs varied among the 3 groups. In patients with dacryoadenitis, Periorbital swelling was the most presentation (90%) followed by pain (70%) and palpable lacrimal gland (60%). Other manifestations included S-shape deformity of the upper eye lid, conjunctival congestion and erythema of the skin. In myositis group, the most common presenting manifestations were pain (90%) and proptosis (70%). Conjunctival redness (60%), limited ocular motility (40%) and Diplopia (30%) were also present. Patients with combined myositis and dacryoadenitis had symptoms and signs similar to the previous 2 groups.

Table 1 summarizes the treatment and follows up of patients with different types of acute IOI. All patients with acute dacryoadenitis were treated by local intra-lesional injection of a steroid within the substance of the lacrimal gland under general anesthesia except for one pediatric patient. The dose of steroids ranged from 2-3 ml according to the size of inflamed gland in the CT (7 patients received 2 ml, 2 patients treated with 3 ml, and 1 patient with bilateral involvement received 2 ml for each side).

Case no.	Diagnosis	Steroid dose	No. of inj.	Initial response	complication	Follow up	Final status
1	Unilat. dacryoadenitis	2 ml	1	Good within 3 days	None	12 m	Complete cure within 2 weeks, with no recurrence
2	Unilat. dacryoadenitis	2 ml	1	Good within 1 week	None	12 m	Complete cure within 2 weeks, with no recurrence
3	Unilat. dacryoadenitis	2 ml	1	Good within 1 week	None	11 m	Complete cure within 2 weeks, with no recurrence
4	Unilat. dacryoadenitis	2 ml	1	Good within 3 days	None	14 m	Complete cure within 2 weeks, recurrent attack after 6 months, received another injection
6	Unilat. dacryoadenitis	2 ml	1	Good within 1 week	None	24 m	Complete cure within 2 weeks, with no recurrence

6	Unilat. dacryoadenitis	2 ml	1	Good within 1 week	None	11 m	Complete cure within 2 weeks, with no recurrence
7	Bilat. dacryoadenitis	4 ml	1	Good within 1 week	polyphagia	6 m	Complete cure within 2 weeks, with no recurrence
8	Unilat. dacryoadenitis	3 ml	1	Good within 1 week	None	6 m	Complete cure within 2 weeks, with no recurrence
9	Unilat. dacryoadenitis	2 ml	1	Good within 1 week	None	8 m	Complete cure within 2 weeks, with no recurrence
10	Unilat. dacryoadenitis	3ml	1	Good within 3 days	None	6 m	Complete cure within 2 weeks, with no recurrence
11	myositis	2 ml	1	Good within 3 days	None	12 m	Complete cure within 2 weeks, no recurrence during follow up
12	myositis	3 ml	1	Good within 3 days	None	14 m	Complete cure within 2 weeks, no recurrence during follow up
13	myositis	3 ml	1	Good within 1 week	None	12 m	Complete cure within 4 weeks, no recurrence during follow up
14	myositis	4 ml	2	Good within 1 week,	None	6 m	After initial response, failed to reach a cure after 1 month. A biopsy followed by 2nd injection
15	myositis	3 ml	1	Fair within 1 week	None	16 m	Complete cure within 1 month, no recurrence
16	myositis	4 ml	1	Good within 3 days	None	10 m	Complete cure within 2 weeks, no recurrence during follow up
17	myositis	4 ml	1	Good within 3 days	None	16 m	Complete cure within 2 weeks, no recurrence during follow up
18	myositis	2 ml	1	Poor after 1 week	None	6 m	No improvement to 1st injection, patient refused 2nd injection, maintained on oral steroid
19	myositis	3 ml	1	Good within 3 days	None	9 m	Complete cure within 2 weeks, no recurrence during follow up
20	myositis	4 ml	2	Fair within 1 week	None	6 m	Complete cure within 1 month, recurrence after 3 months, 2nd injection was given
21	Combined myositis and dacryoadenitis	4 ml	2	Good within 1 week	None	12 m	Complete resolution after 2 weeks, recurrence of the condition 3 months later, a 2nd injection was given
22	Combined myositis and dacryoadenitis	4 ml	1	Good within 3 days	None	7 m	Complete resolution after 2 weeks, no recurrence during follow up period
23	Combined myositis and dacryoadenitis	4 ml	1	Good within 3 days	None	6 m	Complete resolution after 2 weeks, no recurrence during follow up period
24	Combined myositis and dacryoadenitis	4 ml	1	Good within 4 days	None	6 m	Complete resolution after 1 month, no recurrence during follow up period

Table 1: All injections were given perimuscular within the vicinity of the inflamed muscle. Response to treatment was graded as poor (minimal or no benefit), fair (significant but limited improvement), or good (marked improvement). Complete cure means disappearance of all symptoms and signs of the disease.

All the 10 patients (100%) experienced good initial response (3 of which within 3 days and 7 within 1 week). They had complete cure with disappearance of the signs and symptoms within 2 weeks (Figure 1). None of the patients had experienced any local or systemic side

effects except for one patient with bilateral dacryoadenitis (Figure 2) who reported polyphagia and weight gaining. One of the patients (No. 4 in Table 1) had a recurrent attack 6 months after the injection. The clinical and radiological pictures were similar to the previous attack. A second intralesional steroid injection was given. There was a good response within 3 days after the injection and a complete cure was achieved within 2 weeks post injection. The patient reported no recurrent attack for a period of 9months.

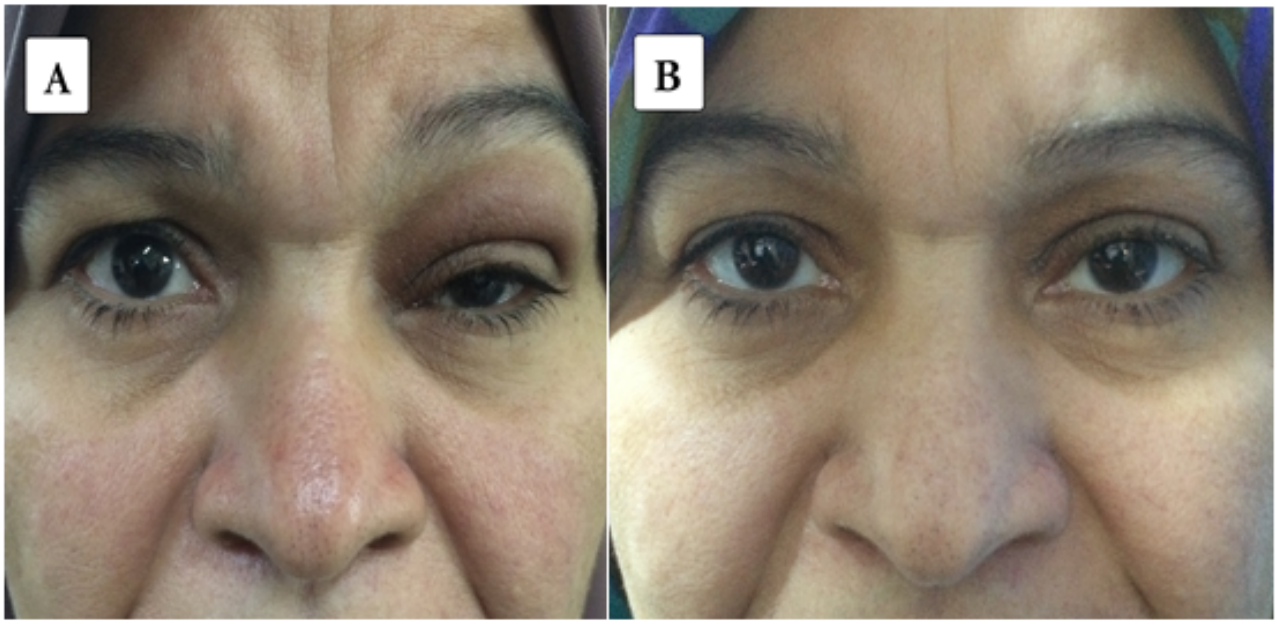

Figure 1: Acute isolated dacryoadenitis; A) Gross photography of patient No. 10 in Table 1 showed periorbital edema, ptosis and erythema of the overlying skin. B) The same patient 2 weeks post injection with complete disappearance of the manifestations

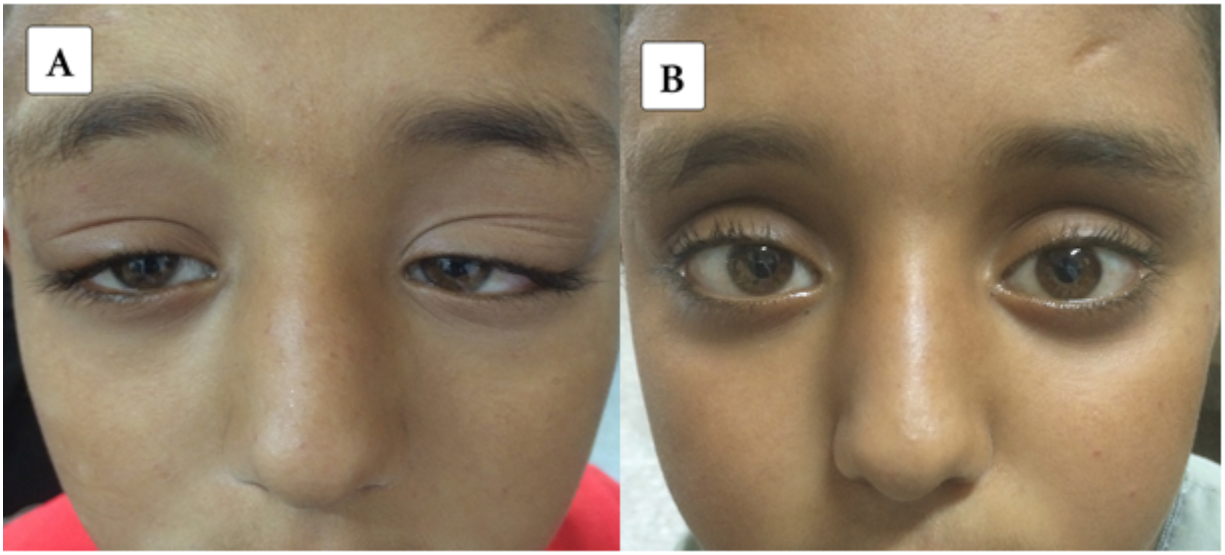

Figure 2: Bilateral acute isolated dacryoadenitis; A) Gross photograph of patient No. 7 in Table 1 showed bilateral periorbital edema, S-shape deformity & ptosis of the upper eye lid. B) The same patient 1 month post-injection showed complete resolution.

All patients with acute myositis were treated by local peri-muscular injection of a steroid in the vicinity of the inflamed muscle under general anesthesia. The dose of steroids ranged from 2-4 ml according to the number of muscles involved, the size of the inflamed muscle as well as the extent of lesion to the surrounding structures in the CT (2 patients received 2 ml, 4 patients treated with 3 ml and 4 patients with 4 ml).

In our study, 7 out of 10 patients (70%) experienced good initial response within 1 week. Six out of the 7 patients reached the complete cure within a period ranged from 2-4 weeks. The last patient with an initial good response had partial cure with residual manifestations after 1 month of the injection. A follow up CT was obtained that showed a similar lesion with the same criteria to the previous lesion. Surgical exploration was performed and a biopsy for histopathology was taken that revealed chronic non-specific inflammation with fibrosis. A second injection was carried on with good response 3 days after the injection and complete cure within 2 weeks.

Two patients had fair response (No. 15 & 20 in Table 1); 1 patient had persistence of the retro-bulbar pain and the other patient had persistent proptosis. They have reached the complete cure within 1 month of the injection. Unfortunately, one of them (NO. 20) had a recurrent attack 3 months later, CT scan showed recurrence with the same picture of the previous attack. The patient received another perimuscular injection of 4 ml steroid. The response to the second injection was good with complete resolution after 2 weeks.

One patient had poor response after 1 week of the injection with persistence of the clinical signs for over 1 month. After consulting the patient for a second injection, the patient refused and she was maintained on oral steroid at a dose of 60 mg daily. None of our patients had experienced any systemic or local side effects.

All the 4 patients with combined myositis and dacryoadenitis were treated by injection of 4 ml of steroid (2 ml injected within the substance of the lacrimal gland and 2 ml at the region of the inflamed muscle). A good response within 1 week was observed and the 4 patients had complete cure after 2 weeks. One of the patients (No. 21) had a recurrent attack of pain and swelling three months later. CT disclosed the same picture as the previous attack. A 2nd injection of 4 ml of steroid in the same pattern as before was given to the patient; there was good response within 3 days and complete cure within 2 weeks. No recurrence after a follow up period ranged from (6-12) months (Figure 3).

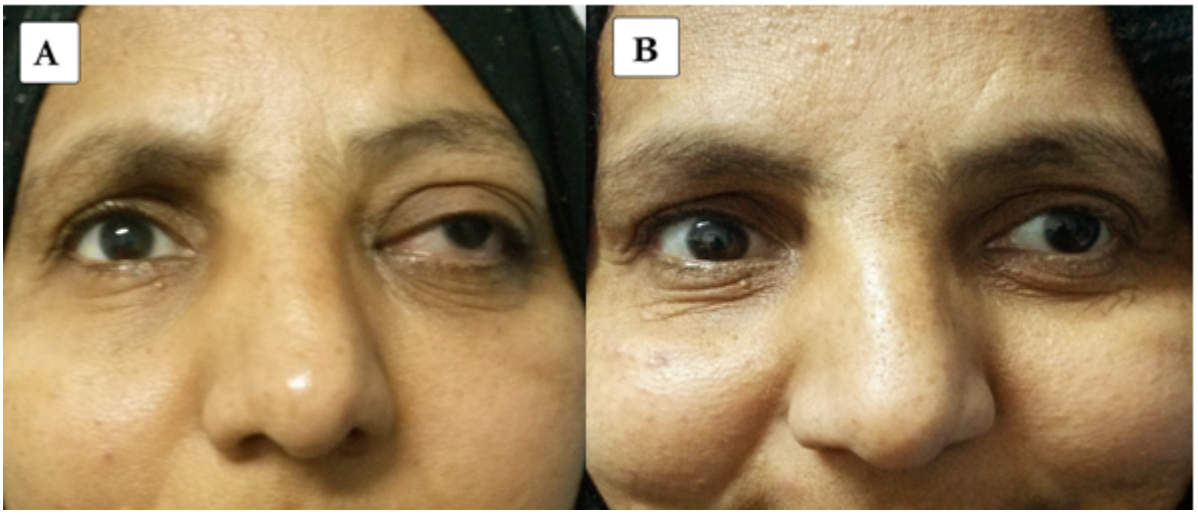

Figure 3: Acute isolated myositis; A) gross photograph of patient No. 3 Table 1 (3, 4) showed left proptosis, periorbital edema, conjunctival congestionand ptosis (the exotropia was reported to present since birth). B) The same patient 4 weeks post injection with disappearance of the previous signs. C) T2 weighted MRI axial view showed left marked enlargement of the right lateral rectus involving the tendon with extension of the lesion to the surrounding tissues blurring the muscle edges. D) CT axial view showed marked reduction in the size of the lateral rectus 4 weeks post injection.

Discussion

The most recent definition of idiopathic orbital inflammation is a benign, non-infective syndrome characterized by manifestation of nonspecific orbital inflammation without any identifiable local or systemic causes [1]. Idiopathic orbital inflammation is the third most common orbital disease, following Graves' orbitopathy and lymphoproliferative diseases. It accounts for 4.7% to 6.3% of orbital disorders [1,3].

Idiopathic orbital inflammation can affect literally any age group [1,11]. In our study, the age of the patients ranged from 2.6 to 62 years with mean age of (36.06) years. There was an obvious female predominance with overall female to male ratio (3:1). Generally, idiopathic orbital inflammation is a unilateral disease, but bilaterality is reported in many studies [3]. In this study, almost all patients had unilateral involvement except one patient (4.16%) had bilateral disease.

Diagnosis of idiopathic orbital inflammation is considered a challenge for the ophthalmologists. This is due to the high variability of clinical picture. Unfortunately, idiopathic orbital inflammation lacks a worldwide accepted protocol for diagnosis. The role of biopsy in the diagnosis as well as the corticosteroid therapeutic test has been controversial [2,9,11].

In our study, the diagnosis of acute IOI was based on the presence of symptoms and signs of acute orbital inflammation together with the characteristic features in radiological study after exclusion of other possible differential diagnosis. We did not include the histopathology as a criterion for diagnosis of IOI and biopsy was deferred to cases poorly responding to steroid. This diagnosis protocol was also adopted by most of the recent IOI studies. Mombaerts et al. [12], Yuen et al. [1],Tsai et al. [13], Partab et al. [14], Ariatti et al. [15] and Mohammad et al. [10] have made the diagnosis of IOI based on the same previous

protocol. Bijlsma et al, reviewed 60 patients with clinical and radiological features with IOI, and recommended that surgical biopsy should be restricted to easily accessible cases with high suspicion for malignancy or resistant to corticosteroid [6].

We also did not include the therapeutic corticosteroid test as a criterion for diagnosis because several studies showed that not all cases of IOI showed adequate response to steroid. Mombaerts et al. reported 22% of their cases with no or poor response to steroid therapy [9]. Furthermore, other orbital diseases rather than IOI, even malignant ones, may show a similar initial response to steroid resulting in a misdiagnosis [9,16].

Although oral corticosteroid is considered the mainstay of treatment of IOI, many reports have questioned its efficacy in controlling the disease. Failure to respond to oral corticosteroid was reported by Mombaerts et al. [9], Partab et al. [14], Ariatti et al. [15], and Chirapapaisan et al. [16], by 22%, 36%, 60%, and 18% of the patients respectively. In addition to poor response, the disease recurrence was reported to affect many patients even after a favorable response to steroid. Mannor et al, reported a recurrent attack in (66.6%) of their patients [17]. Mombaerts et al. reported (40.7%) of their cases to have a recurrent attack either during tapering (18.6%) or after discontinuation (22.2%) of treatment [9]. Chirapapaisan et al. [16] and Siatkowski et al. [18], have reported recurrence in 20.4%, and 16% of their cases respectively.

In some cases, the disease became steroid dependent in which a trial of gradual withdrawal of steroid is accompanied by flaring of the inflammatory manifestation which led to prolonged oral therapy for months or even years. Yuen et al reported 21.6% of their cases to have steroid dependent IOI half of which did not achieve a complete cure [1]. Garrity et al. reported 4 patients requiring maintenance dose of steroid for a period ranged from 1- 6 years [19]. Hatton et al. reported 3 patients with steroid dependent IOI with 4 to 6 relapses during steroid taper [20].

Another obstacle faces the treatment using systemic corticosteroids that is the safety. IOI patients require prolonged treatment with gradual tapering over a period of weeks to months before cure is achieved. This exposes the patients to a large list of complications either ocular or systemic which renders the prolonged therapy difficult (steroid intolerance). Yuen et al reported steroid intolerance in 4 patients (6.2%) of their cases for which steroid had to be stopped [1]. Mannor et al. reported 6 patients treated with oral steroid and developed adverse reactions [17]. Garrity et al. [19] and Hatton et al. [20] also reported different side effects affecting their patients. Moreover, systemic steroid is contraindicated in a considerable number of patients especially in elders with uncontrolled diabetes mellitus or hypertension which led to the introduction of steroid sparing immunosuppressant which have their own list of side effects and contraindication [1,10,14,16].

This was the base upon which the local steroid injection was introduced By Mohammad (2003) in the treatment of IOI. He aimed at achieving high concentration within the inflamed tissue without having any undesirable systemic side effects [21].

In our study, we adopted local steroid injection in the treatment of AIOI. Twenty out of the 24 patients (83.3%) have responded to local steroid injection with no recurrence for a follow up period ranging from 6-24 months (mean 11.06 months); 19 patients (79.2%) after a single injection and 1 patient (4.1%) after 2 injections. Three patients (12.6%) had a recurrent attack after a period of quiescence following the injection. They had complete cure after another injection with no recurrence within 6-9 months. One patient did not respond to the first steroid injection, refused further injection and preferred the oral therapy.

The response to the injection was quite fast in most patients within 3-7 days with relief to the pain and swelling. Most patients reached cure within 2 weeks. This rapid response decreased the morbidity time and allowed the patients to early return to their normal life. Patients with poor response to local injection or having recurrent attacks did not show any different clinical or radiological picture than other patients although the low number of patients in this category did not allow us to adequately analyze those cases.

In the literatures, the number of studies reporting the use of local steroid injections in the treatment of IOI was very few and in the form of case series or case reports. In his study, Mohammad used local steroid injection in the treatment of 47 patients with idiopathic orbital inflammation. He focused on the acute type of IOI. He reported dramatic initial response to local steroid injection with complete cure within 1-4 weeks in all his patients. During the follow up, 2 of his patients had a recurrent attack after a period of quiescence of 9 and 14 months. A second injection was given, with complete cure within 2 weeks. None of his patients experienced any local or systemic side effects [10].

Leibovitch et al. used local steroid injection in treatment of 10 patients with idiopathic orbital inflammations. They restricted their study to the anterior forms of IOI (dacryoadenitis, myositis, combined dacryoadentis and myositis, and anterior orbital mass). The number of injections was based on the clinical response of each patient; ranging from single injection in 6 patients. They reported complete resolution in 8 patients (80%) within a period ranging from 1 week to 20 weeks. One patient showed partial improvement with residual diplopia in downgaze. The last patient did not show response to the first injection and refused further injections. They reported no recurrences over a mean follow up of 9.8 months (range 3-24 months). The only reported side effect was an isolated episode of nausea and vomiting 1 hour post injection [22].

A number of case reports about the use of local steroid injection in the treatment of IOI were published. Garrity et al. reported the use of retrobulber injection of triamcinolone in treatment of 2 patients with idiopathic myositis with good response to the therapy, but the disease recurred after 4 months [19]. Skaat et al reported the use of a mixture of triamcinolone and dexamethazone for local injection in the treatment of persistent atypical idiopathic dacryoadenitis [23].

Comparing our results to the previous 2 large studies revealed similarity regarding some points; all the three studies reported better outcome in patients with idiopathic dacryoadenitis than other forms of IOI. This could explain why the final outcome in Mohammad's study seems to be better than Leibovitch's and our results, because his study included higher number of dacryoadenitis patients (70% of his patients) compared to 40% and 41.6% in leibovitch's and our study.

There was low recurrence rate in the three studies (ranged from 0-12.6%) but the relative short follow up periods in most cases may question this outcome as recurrence of IOI was reported in previous studies to occur years after the initial treatment. The follow up period should be expanded to correctly assess this point.

The use of a long acting betamethazone as the injection steroid in our study and Mohammad's made the number of steroid injections

fewer and the duration to reach cure shorter compared to the intermediate acting triamcinolone used my Leibovitch (some of their patients required up to 4 consecutive injections along the treatment course which extend up to 20 weeks). All the three studies did not report any local or systemic side effects to the injection apart from one patient in leibovitch's study who had an episode of nausea and vomiting [23] and one of our patients who reported polyphagia and weight gaining after the injection.

Because the technique is relatively new with few reported studies, several questions have not yet been answered neither by our nor other studies. This include the proper dose of the injected steroid; how to individualize this proper dose for every patient and the maximum dose that can be safely used. Also the use of the second injection; whether to give it routinely in all patients to avoid the recurrence or to spare it to patients with inadequate response and what is the cutoff point after which a second injection should be given.

In addition, the low rate of recurrence of the condition after local injections has not allowed us to adequately analyze these cases and what could cause the recurrence. The suggested etiologies include lower dose of injected steroid than necessary, the severity of the disease that required more than one injection or just a second reactivation of the disease. Further studies with a more proper design; a higher number of patients and expanded period of follow up is needed in the future to answer the previous issues.

Conclusion

In conclusion, the previous reports about the use of local steroid injection in treatment of IOI in addition to reports on local steroid injection in the treatment of other orbital lesions without any serious local or systemic side effects may strongly support the safety profile of local injections compared to systemic steroid. This may shift the treatment of idiopathic orbital inflammation into the more safe and, at least, equally effective local injections.

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