The effectiveness of local steroid injection for the treatment of breast-limited idiopathic granulomatous mastitis: A randomized controlled clinical trial study

Mohammad Yasin Karami (yasinkarami@gmail.com)
Shiraz University of Medical Sciences https://orcid.org/0000-0003-2307-5569

Vahid Zangouri
Shiraz Medical School: Shiraz University of Medical Sciences

Zahra Habibagahi
Shiraz Medical School: Shiraz University of Medical Sciences

Sedigheh Tahmasebi
Shiraz University of Medical Sciences

Aliyeh Ranjbar
Shiraz Medical School: Shiraz University of Medical Sciences

Mahdiyeh Sadat Seyyedy
Shiraz Medical School: Shiraz University of Medical Sciences

Somayyeh Hooshyar
Shiraz Medical School: Shiraz University of Medical Sciences

Masoumeh Ghoddusi Johari
Shiraz Medical School: Shiraz University of Medical Sciences

Alireza Golchini
Shiraz Medical School: Shiraz University of Medical Sciences

Elham Halimi
Shiraz Medical School: Shiraz University of Medical Sciences

Majid Akrami
Shiraz Medical School: Shiraz University of Medical Sciences

Abdolrasoul Talei
Shiraz Medical School: Shiraz University of Medical Sciences

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Abstract

Background: Idiopathic granulomatous mastitis (IGM) is a rare non-specific inflammatory breast disease and is usually considered a kind of autoimmune disease. There are several controversies regarding its standard treatment. We aimed to evaluate the efficacy of local corticosteroid injection for the treatment of breast-limited idiopathic granulomatous mastitis.

Methods: This randomized prospective clinical trial study evaluated the clinical response rate of local steroid injection to treat breast-limited IGM in women. The subjects received local steroid injection of long-action (LA) Betamethasone combined with standard systemic treatments (prednisolone, Methotrexate) (Combine therapy group), standard systemic treatments alone (Systemic group), or local steroid injection alone (LA Betamethasone, Injection group). Clinical benefits and recurrence rates were compared in the three groups.

Results: All of the patients were women, and their mean age was 34 years. The excellent clinical or radiological response was observed in 20/31 (64.5%), 24/38 (63.1%), and 17/30 (56.6 %) patients in the injection, combined, and systemic therapy groups, respectively. During the follow-up of 10 months in patients who received local steroid injection alone, recurrence was observed in six patients (16.4%, 6/31), and no side effects or injection steroid-related complications occurred. The local recurrence rate in systemic and combined therapy groups were 3.3 % (1/30) and 13.2 % (5/38) patients, respectively.

Conclusions: Our findings suggest that local betamethasone LA injection in breast limited IGM is as successful as current standard treatment and shortens the complete healing time compared to treatment with systemic therapy. Short time recurrence rate was not statistically significant among the groups. Local injection could be a beneficial option in the treatment of IGM.

Trial registration: The trial registry number was **IRCT20200608047694N1**. Registration date: **2020-07-21.**

Background

Idiopathic granulomatous mastitis (IGM) is a rare non-specific inflammatory breast disease. IGM can present as a painful irregular mass with skin appearance from redness to the fistula tract, which sometimes mimics breast abscess or carcinoma [1–3]. Clinical presentation of IGM can be variable. It is diagnosed with cytological or pathological evaluation and can be ruled out after other more common causes of breast mass [4, 5]. Different triggers are considered to cause IGM, such as infection, inflammation, and hormonal factors. It is more common in developing countries [6]. There is controversy regarding its treatment and there is no recommended treatment regimen. At present, the main treatment options include non-surgical and surgical treatment. Oral steroid therapy has been the most widely used non-surgical treatment for IGM and was considered to be the standard medical treatment, and the immunosuppressive treatment with methotrexate (MTX) or azathioprine is a therapeutic option. [7–10]

Surgery has been controversial because of poor wound healing, fistula generation, and recurrence of the disease [11]. Oral steroid therapy may result in side effects related to almost all the systems including hypertension, impaired glucose tolerance, and increased body weight, which are a serious challenge in ensuring treatment adherence. For minimizing the systemic side effects of oral steroids, topical corticosteroid therapy has become an option with a positive effect on IGM. [12] Topical steroids are absorbed through both normal and inflamed skin. Although topical steroids can be easily applied for the breast and the effect of topical steroid has been recently validated, in some IGM patients, no skin changes are available for diagnosis. Such cases present with pain, and MRI imaging evidence will confirm fullness in the breast tissue and IGM diagnosis. For this deep breast tissue involvement with IGM, topical steroids are not capable of reaching the target for the treatment of the IGM; thus, it is unclear whether steroid injection into the breast tissue affects deep IGM. Moreover, inflammation is often the result of a cascade reaction, and if not controlled early, symptoms may worsen, necessitating a longer therapeutic period. Hence, local corticosteroid (CS) injection has become a treatment of choice for IGM.

Some recent studies revealed that intra-lesion steroid injection is an effective treatment of IGM, and surgical resection is not required for most patients [13–18]. The optimal treatment modality remains unclear and also there is no randomized clinical study data on the application of steroid local injection compared with standard systemic therapy on IGM. We evaluated the effect of local corticosteroid injection for IGM compared to the systemic steroids and combined systemic and local injection treatments.

Methods

Study Design

Patients

This randomized single-blind parallel prospective clinical trial was designed to show the efficacy of local steroid injection in combination with systemic therapy, systemic therapy alone, and local steroid injection alone in the treatment of 165 females with primary IGM diagnosis who referred to the high-volume referral center for breast diseases in the south of Iran, (Breast diseases research center, Motahari Clinic, Shiraz University of Medical Sciences, Shiraz, Iran) and did not require surgical intervention between May 2020 and August 2020. The trial registry number was **IRCT20200608047694N1** (full trial protocol can be accessed here: https://www.irct.ir/trial/48903)

The ethics committee of Shiraz University of Medical Sciences approved the study protocol. The ethics committee reference number was IR.SUMS.MED.REC.1399.096. (https://ethics.research.ac.ir/EthicsProposalViewEn.php?id=135155)

The work has been reported in line with Consolidated Standards of Reporting Trials (CONSORT) Guidelines.

Inclusion criteria were breast limited IGM female cases aged18-65 years. Exclusion criteria were breast carcinoma or other malignancies, age under 18, large breast abscess which need surgical intervention, a high-risk factor for steroid therapy (Hypertension, Diabetes mellitus), patients who wished to get pregnant, and systemic diseases such as vasculitis, collagen vascular disease and sarcoidosis and associted extrammamary disease. Surgical treatment was preferred in patients who presented with extensive parenchymal involvement confirmed by radiologic examination. All patients who needed surgical intervention were excluded from the study.

Data on the length of the complaints and their relapsing nature, treatment for the same symptoms, duration of lactation, number of pregnancies, use of oral contraceptive or nicotine, and concomitant diseases were collected. We also noted the existence of inflammation and palpable masses, alterations in the nipples and breast skin, and fistulae in the breast examinations.

Core needle biopsy (CNB) with or without ultrasonography were done according to the clinical results on admission. All of the biopsy samples were subjected to Ziehl–Neelsen, periodic acid–Schiff, Gram staining to analyze the microbiological agents; also, tuberculosis and fungal analyses were done using culture methods. Thoracic imaging assessments, as well as purified protein derivative skin tests, were conducted for all patients. Systemic diseases like vasculitis, collagen vascular disease, and sarcoidosis were screened.

Breast ultrasound examinations and/or mammography were performed in all patients before CNB for clinical classification and determination of the extent of inflammation. Mammography was performed in patients suspected of having breast cancer but was not recommended for those who demonstrated a high probability of IGM because of the possibility of inflammation aggravation due to extrusion. Mammography was done by the Breast Imaging Reporting and Data System (BIRADS) criteria.

Granulomatous mastitis diagnosis was confirmed with histopathological results of multinucleated Langerhans-type giant cells, numerous epithelioid cells, lymphocytes, neutrophils, stromal cells in CNB specimens, and the existence of granulomatous inflammatory reaction with neither caseous necrosis nor any certain organisms in the specimens evidenced by fluid biopsy techniques at the beginning. [19, 20]

Ultra sound-assisted aspiration was done for cases who had an infected abscess at diagnosis or during the intervention follow-up. All patients with IGM and evidence of an abscess formation initially enrolled in the study were treated with 2 weeks of oral antibiotics (Ciprofloxacin 500 mg Po BD plus Metronidazole 250 mg Po TDS).

To prevent selection bias, blocked randomization was used to allocate the patients to three groups, and all of them were assigned to groups with the same probability. The size blocks were equal and consisted of three patients. The treatments were randomly assigned to the subjects in each block and the treatments were at least once in each block. Random Allocation Software will use for block randomization.

Participants in this single-blind study were familiar with three methods of IGM therapy. Furthermore, the observer who filled out the questionnaire was unfamiliar with the groups. Similarly, the data analyst was unaware of the study groups. However, the main researchers (surgeons) were made aware of the groups, and all treatments were carried out by the same surgeons.

The patients were allocated to the three study groups randomly. Combination therapy Group (N = 41, systemic treatment along with local steroid injection) received a local steroid injection into the breast weekly one to four times by the physician (betamethasone LA injection, each injection contained betamethasone Acetate (3 mg) and betamethasone disodium phosphate (3 mg/ml)) around and in the center of the mastitis or lesions using a 22-gauge needle and 5-ml syringe and also systemic oral corticosteroid and MTX as systemic therapy (Prednisolone PO 50 mg/day for two weeks, followed by a taper to 5 mg/day for 4 months: 25mg/day for 1 month followed by 12.5mg/day 1 month, then 10 mg/day for 1 month and 5 mg/day for 1 month + MTX 10 mg/week PO for 1 month then 15 mg PO per week until prednisolone was discontinued).

Systemic therapy alone group (N = 37, included systemic oral corticosteroid and MTX) received systemic therapy alone as aforementioned. Injection Group (N = 37) received a local steroid injection into the breast weekly one to four times by the physician (betamethasone LA injection alone).

Daily Calcium-D and folic acid supplements were administered for all the patients enrolled. Monthly, Liver Function tests (LFT), electrolytes (Na, K), and blood sugar were checked in all patients.

Follow-up

All the patients were followed once a week in the first month followed by once a month for five months for detecting the symptoms (pain and macroscopic breast appearance) and systemic and local side effects of the steroid (secondary infections, skin thinning, and hyperpigmentation, etc.). Follow-up information after treatment was obtained from an outpatient information system or by telephone interviews semi-annually in the tenth month.

Clinical improvement, including the closure of the fistula orifices, disappearance of inflammatory signs, and/or skin erosions, and healed skin ulceration was regarded as the primary outcome and the criteria to terminate the treatment. All patients were diagnosed and treated by three breast surgeons (Tahmasebi, Zangouri, and Karami).

Statistical analysis

The primary endpoint measure was the clinical response rate during six months, which was classified into “excellent control," "good control," "Fair control," "poor control," or "relapsed" when healing of the lesions was seen once; however, the symptoms returned.

Those with resolution of > 90 percent of the signs and symptoms without and with recurrence were regarded as excellent and good control, respectively. Those with marked reduction in the signs and

symptoms with recurrence were regarded as fair control. Patients with not a big resolution in signs and symptoms with persistant disease considered as poor response.

Symptoms were categorized into three items by surgeon examination and breast ultra-sonography as follow: Inflammatory items (Pain, Redness, Erythema, peu d'orange, skin thickening, axillary lymphadenopathy), Soft tissue items (Deep collections, tissue thickening, mass, skin dimpling, nipple retraction. This item considered mild when the collection was single with minimal inflammatory reaction around it, moderate when the collections were multiple in a single quadrant and severe when the collections could be seen in more than one quadrant), Cutaneous Destructive items (Thin red skin, superficial collection, Ulcer, fistula).

Systemic lymphadenopathy, arthralgia, arthritis and Erythema nodosum considered as extrammamary involvement (grade four).

The secondary endpoint measure was granulomatous mastitis recurrence in the ipsilateral on the contralateral breast at ten months post-intervention.

We compared clinical characteristics, primary and secondary endpoints in the three groups. Continuous and categorical variable differences among the 3 groups were analyzed using ANOVA and chi-square tests, respectively. SPSS software was used to analyze the data and a P-value less or equal to 0.05 was regarded as significant.

Sample Size

The minimum sample size required to compare outcomes in the three treatment groups was calculated with an error of 0.05 and a power of 80% as follows:$n = \frac{K \times \varnothing^2(\alpha,\beta,K-1)}{4 \times \left\{ \sum_{i=1}^{K} (\sin^{-1}\sqrt{\pi_{iA}} - \bar{A}_{\pi A} \right\}}$.

In this equation K is the number of groups, π_{iA} is the ratio in the groups and $\varnothing^2(\alpha, \beta, K-1)$ is a constant value that can be determined based on the error of the first, second type and the number of groups. Therefore, according to the results of other studies and considering the values of π_{iA}, (π_{1A} = 93%), (π_{2A} = 78%), (π_{3A} = 70%) and also $\emptyset^2$ (α, β, K- 1) = 10.90256, the sample size in each group was calculated as a minimum of 28 and a maximum of 31 individuals.

Results

Patients' characteristics

From May 2020 to August 2020, 118 breast-limited IGM out of the 165 patients diagnosed with IGM were enrolled in the study. Forty-seven patients did not meet the inclusion criteria or withdrew from the study.

Sixteen patients lost the follow-up period or discontinued their participation and were excluded from the trial analysis.

Of the 44 patients who did not meet the inclusion criteria, seven had extramamary systemic diseases (i.e. RA, SLE, etc.), seventeen patients had a history of surgical drainage, and twenty of them had needed surgical drainage or intervention due to severe abscess formation in the breast.

Three patients in the systemic therapy group suffered the side effects of prednisolone and discontinued the intervention. Eight patients lost the follow-up in three groups due to the COVID-19 pandemic.

Of the 69 patients who received the local injection, 5 developed disease progression after the fourth steroid administration (two in the combined therapy group and three in the Iinjection group); all these patients withdrawed and switched to oral steroid therapy that was tapered gradually over 40 days.

The **median age** of the study patients was **34** years. Breast feed and contraceptive use history are reported in Table 1. Breastfeeding period was higher in the injection and combined therapy groups than systemic treatment group patients (P = 0.048).

Table 1
Demographic and clinical presentation of breast-limited IGM patients at the beginning of the study.

Variable		Injection group (N = 31)	Combined Therapy group (N = 38)	Systemic Therapy group (N = 30)	*p*-value
Age (mean)		36.1	35.7	35.0	0.203
Median (range), years		34 (23–62)	34.5 (28–48)	34(24–50)	
Age category, n (%)		10(32.3)	4(10.5)	5(16.7)	
≤30 years		13(41.9)	24(63.2)	18(60.0)	
31–40 years		8(25.8)	10(26.3)	7(23.3)	
>40 years					
White Blood Cell (*10^3)		11.14 ± 3.20	9.742 ± 3.48	10.17 ± 3.47	0.310
C-Reactive Protein (CRP)		25.23 ± 12.65	23.81 ± 8.83	23.06 ± 12.63	0.753
Breast feeding time,(mean)		47.36 (19.12)	53.0 (23.1)	36.8 (19.0)	**0.048**
Taking contraceptives		12(38.7)	19(50)	13(43.3)	0.413
Yes		19(61.3)	19(50)	17(56.7)	
No					
Side, n (%)		15(48.3)	17(44.7)	16(53.3)	0.780
Right		16(51.6)	21(55.2)	14(46.6)	
Left					
Cutaneous	Yes	14(45.2)	16(42.1)	11(36.7)	0.792
Destruction	No	17(54.8)	22(57.9)	19(63.3)	
Soft tissue	Mild	21(67.7)	25(65.8)	16(53.3)	0.495
	Moderate	7(22.6)	12(31.6)	10(33.3)	
	Severe	3(9.7)	1(2.6)	4(13.3)	
Inflammatory	Mild	3(9.7)	9(23.7)	7(23.3)	0.581
	Mild to Moderate	17(54.8)	17(44.7)	15(50.0)	
	Severe	11(35.5)	12(31.6)	8(26.7)	
Grading of the severity of the disease	I	3(9.4)	5(13.2)	4(13.3)	0.962
	II	14(45.2)	17(44.7)	15(50.0)	

Variable		Injection group (N = 31)	Combined Therapy group (N = 38)	Systemic Therapy group (N = 30)	*p*-value
	III	14(45.2)	16(42.1)	11(36.7)	
	IV	0	0	0	

Figure 1 shows the allocation process throughout the trial.

Demographic, Inflammatory laboratory data and clinical presentation of breast-limited IGM patients at the beginning of the study are reported in Table 1.

Treatment And Outcome

The mean largest mass size was 37.16, 29.7, and 27.3 mm at the beginning of the study in the combined therapy, injection, and systemic therapy groups, respectively. (P = 0.039) The mean time of half remission was one month in the injection and combined therapy groups and 6.33 months in the systemic therapy group. (P = 0.001) The time to complete remission mean was 3.17 (range 1–6), 4.33 (range 1–6), and 6.37 (range 6–9) months in the injection, combined therapy, and systemic therapy groups, respectively. (P = 0.001) The initial response to local betamethasone LA injection was rapid in the combined and injection group. The mass lesion shrank significantly after four injections in these groups.

Ipsilateral or contralateral breast recurrence rate was assessed in all patients who completed 10 months of follow-up. IGM recurrence rate was 16.4% (6/31), 13.2% (5/38) and 3.3% (1/30) in the injection, combined, and systemic therapy groups, respectively.

No significant difference was observed in the ipsilateral or contralateral recurrence rate between the injection and the two other groups ($P = 0.154$) during the follow-up period of 10 months. All 69 patients in the injection and combined therapy group had received a full four dose of LA betamethasone injection. Excellent and good control were observed in 28 (90.3%), 34 (89.4%), and 23 (76.6%) patients in the injection, combined, and systemic therapy groups, respectively. (P = 0.511) (Table 2, Fig. 2)

Table 2
Clinical outcomes of the patients with breast limited IGM

Variable		Injection group (N = 31)	Combined Therapy group (N = 38)	Systemic Therapy group (N = 30)	*p*-value
IGM description in breast ultrasound, N (%)	Single Collection	20(64.5)	24(63.2)	19(63.3)	0.899
	Multiple Collection	8(25.8)	10(26.3)	6(20)	
	Diffuse Mastitis	3(9.6)	4(10.5)	5(16.6)	
Size of the largest mass ,Mean and SD (range), mm		29.7 ± 12.5 (10–70)	37.16 ± 14.6 (16–75)	27.3 ± 12.49 (8–46)	**0.039**
Relapse rate during treatment		0(0)	2(5.26)	4(10.52)	**0.036**
Time to half remission Mean (range), Month		1(0)	1(0)	6.33(6–9)	**0.001**
Time to complete remission Mean (range), Month		3.17(1–6)	4.33(1–6)	6.37(6–9)	**0.001**
Recurrence, n (%), Ipsilateral or contralateral		6(16.4)	5(13.2)	1(3.3)	0.154
Response to Treatment	Excellent Control*	20(64.5)	24(63.2)	17(56.7)	**0.511**
	Good Control **	8(25.8)	10(26.3)	7(23.3)	
	Fair Control ***	3(9.7)	2(5.3)	2(6.7)	

IGM, idiopathic granulomatous mastitis

*Resolution of > 90 percent of the signs and symptoms (complete initial control of disease without recurrence)

**Resolution of > 90 percent of the signs and symptoms (complete initial control of disease with 1–2 recurrence)

***Marked reduction in the signs and symptoms (partial initial control of disease with 3–4 recurrence)

& not a big resolution in signs and symptoms (fair initial control of disease with persistent disease)

Variable		Injection group (N = 31)	Combined Therapy group (N = 38)	Systemic Therapy group (N = 30)	*p*-value
	Poor Control [&]	0	2(5.3)	4(13.3)	
IGM, idiopathic granulomatous mastitis					
[*]Resolution of > 90 percent of the signs and symptoms (complete initial control of disease without recurrence)					
[**]Resolution of > 90 percent of the signs and symptoms (complete initial control of disease with 1–2 recurrence)					
[***]Marked reduction in the signs and symptoms (partial initial control of disease with 3–4 recurrence)					
[&] not a big resolution in signs and symptoms (fair initial control of disease with persistent disease)					

Four patients in combined therapy group and three patients in systemic therapy group had systemic side effects. No side effects of local steroid injection such as skin thinning, hyperglycemia, hypertension, and secondary infection were observed during or after the treatment.

Discussion

IGM is a rare chronic inflammatory benign disease of the breast with a different clinical presentation and controversial optimal treatment modality. Recently observed more in Middle Estern breastfeeding women. [21] The main etiologies of this disease are unknown. Autoimmunity to proteins and some microorganisms, or breastfeeding reactions are suspected etiologies [12, 22].

Surgery had an elevated full remission rate along with a relatively low recurrence rate but avoided as much as is feasible for cases concerning surgical scarring and immunosuppressive agents are preferred in the treatment of IGM. However, the systemic corticosteroids have several side effects[23], [24], [25]

In our center, oral steroids are mainly used when patients develop systemic symptoms. Furthermore, immunosuppressive treatment with methotrexate is used when the disease progresses during oral steroid treatment alone. Based on the lengthy course and high dose of oral steroid therapy, side effects are unavoidable and have become a serious challenge in ensuring treatment adherence.

Recent investigations suggest topical or local injection steroids for better cosmetic outcomes and also if patients intend rapid remission. [13, 26, 27]

To the best of our knowledge and review of literature, few studies suggest local injection as an alternative treatment of surgery or systemic steroids and MTX therapy.[14, 18]

In the present study, we tried to compare the effectiveness of local steroid injection, combined systemic immunosuppressive administration and intralesional corticosteroid injection and systemic immunosuppressive administration alone.

In our study, We show that local steroid injection are as effective as systemic immunosuppressive administration.

Recently, one study [13] suggests that intralesional steroid injection was an effective treatment for IGM compared with systemic steroid treatment, active observation and surgical resection. These treatment modalities are amongst the commonly reported treatment options for IGM.

Surgery has unfortunate cosmetic outcomes, tardy scar healing, and high relapse rates. For this reason, systemic steroid treatment has been the common treatment in IGM[12, 26, 28, 29].

Systemic steroid therapy has longterm disease control but patients experience various side effects such as weight gain, hirsutism, diabetes mellitus, and Cushing's syndrome lead to limitations in treatment.[30]

Recentely, some studies suggest the use of topical treatment and local steroid injection in IGM.

In a randomized study by Cetin et al [26], the efficiency of the topical and systemic steroid treatment was similar in IGM. Although cases responded later to topical treatment, with a mean recovery period of 22 weeks with topical treatment compared to 11.7 weeks on systemic therapy. In the same study, The lack of systemic side effects in topical treatment (2.4% vs. 38.2%) increased the compliance of the patients with the topical therapy. They demonstrated that systemic, topical, and combined therapies had no superiority, and topical therapy was among first-line treatment because it had fewer side effects and more compliance than systemic therapy.

In a study by Altintoprak et al.[12] clinical improvement in 28 IGM patients occurred in an average of 8.3 weeks without topical steroid-related side effects, mean follow up of 37.2 months showed success rate of over 90% in long-term.

There is no reported randomized prospective clinical trial study that compared systemic therapy with local injection for IGM treatment. To the best of our knowledge, our study is the first prospective randomized trial to assess the efficacy of local corticosteroid injection and systemic use. Four studies suggested an injection of steroids into the breast cavity; all studies showed good clinical and radiological response without complications. [13, 15, 17, 18]

In Kim et al.'s study [16], they compared intralesional triamcinolone (2–4 cc, 40mg/ml) injected once every 1 or 2 weeks with or without oral steroid (10 mg/daily) administration, and this was repeated until the resolution of symptoms and ultrasonography findings considered as treatment goal and treatment stopped afterwards. Intralesional Triamcinolone injection was an effective treatment modality for IGM. The recurrence rate was zero in the above-mentioned study.

In a retrospective non-randomised study by Toktas et al[18], the combination of steroid injection and topical steroid therapy in IGM showed same results as first line therapy which is systemic steroid therapy in patients with non-complicated IGM. Local steroid injection may even be more effective than systemic treatment in term of pooled analysis of complete and partial reponse rate, respectively (93.5% vs 71.9%).

In our study, the excellent and good response rate in the local injection group (90.3%) and combined therapy group (89.4%) were more than the systemic group (80%).

The Mean size of the largest mass in the combined therapy group was larger than other groups, significantly. Breastfeeding reactions is one of the suspected etiology of IGM. The mean breast feeding time in combined therapy group patients was more than two other groups. These two issues may affect response rate to the treatment in this group.

A low recurrence rate is an important treatment goal. The relapse rate during treatment of the injection alone group was zero, relapse in combined and systemic therapy groups was 2 (5.2%) and 4 (13.3%) during the first 5 month period which considered as poor control.

To date, surgery is one of the best treatment options with a low recurrence rate and high complete remission (CR) rate. [24, 31] The meta-analysis of the CR and recurrence rate revealed overall estimates of 94.5% (95% CI 88.9%, 98.3%) and 4.0% (95% CI 1.5%, 8.4%), respectively.[24]

The CR rates and recurrence rate of IGM cases treated with oral steroids ranged from 30.8%[32] to 100.0% [33, 34] and from 0.0%[34] to 46.2%[35], respectively. The pooled estimates for CR rate and recurrent rate of steroids were 71.8% (95% CI 67.1%, 76.3%) and 20.9% (95% CI 9.2%, 16.1%), respectively.[24]

In our study, CR rate and recurrence rate of systemic therapy patients were 56.6% and 3.3%, respectively.

Two studies [12, 36] reported a CR rate of 100% for IGM patients treated with topical steroids. The recurrent rates were 10.7% and 18.2%, respectively. The pooled estimate for CR rate and recurrence rate of topical steroids were 98.8% (95% CI 93.3%, 99.8%) and 14.3% (95% CI 5.4%, 26.6%).[24]

In our study, CR rate of combined therapy and local injection group were 63.1% and 64.5%, respectively. The recurrence rate of combined therapy and local injection groups were

13.2% and 16.4% respectively.

The results of our clinical study indicated that local steroid injection alone and in combination with systemic therapy could quickly control the symptoms and be effective as systemic therapy alone to treat IGM.

The efficacy of local injection steroid therapy was validated for breasr limited IGM of the breast in our study. The optimal steroid, dosage, and injection site remain unclear. Different steroids should be injected in future studies to find the optimal steroid dosage. Although young women have dense mammary

glands, administering CS into the gland tissue is difficult, but we suggest intralesional injection in the palpable mass and normal breast tissue in patients with IGM under sonography giude.

We selected the intralesional and also four spaces around the mastitis lesion as the injection site because steroids in this site could be absorbed by the breast tissue and would thereby have a rapid effect. In this study, the effectiveness of local betamethasone injection was verified.

In addition to high efficiency and low recurrence rates, the side effects of local corticosteroid therapy should be considered. Although the exact amount of systemic absorption and the side-effects associated with local injections remain unclear, the effects associated with oral CS use could also occur with local CS injection [37]. To minimize possible side-effects, we used up to four injections (28 mg of betamethasone, comparable to 233 mg of prednisone and equivalent to a 1-week oral dose of prednisone for a 70-kg patient) during the whole therapeutic cycle and used injection steroids as a follow-up treatment. Since a vast majority of IGM patients were healthy young women and a low dosage was used in our study, the risk of systemic side-effects was significantly reduced.

In the limitation section of this super selective study that might result in treatment allocation bias,short patient follow-up times was one of the pitfalls. short term follow up might have an impact on the recurrence rates.

A trials with a larger sample size and alternative steroid administration can provide a comprehensive understanding of the efficacy and treatment-related side effects of local steroid injections in limited breast IGM.

Conclusion

Local steroid injection therapy controls severe symptoms more quickly and shortens the treatment time compared to systemic treatments alone. Local betamethasone injection alone effectively treats IGM and would be considered as a first-line treatment option.

Abbreviations

Idiopathic granulomatous mastitis (IGM)

long-action (LA)

methotrexate (MTX)

corticosteroid (CS)

Core needle biopsy (CNB)

Breast Imaging Reporting and Data System (BIRADS)

Liver Function tests (LFT),

Declarations

Ethics approval and consent to participate

The research performed in accordance with the Declaration of Helsinki. The ethics committee of Shiraz University of Medical Sciences approved the study protocol. The ethics committee reference number was IR.SUMS.MED.REC.1399.096. (https://ethics.research.ac.ir/EthicsProposalViewEn.php?id=135155)

The written consent was obtained from all study participants.

Consent for publication

The written informed consent for publication was obtained.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

MYK and VZ and ZH carried out the experiment. AG, AR and MSS wrote the manuscript with support from MYK, VZ, MGJ, SH and E.H. MA and ART helped supervise the project. MYK and ST conceived the original idea. H.I. supervised the project. All authors read and approved the final manuscript.

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Figures

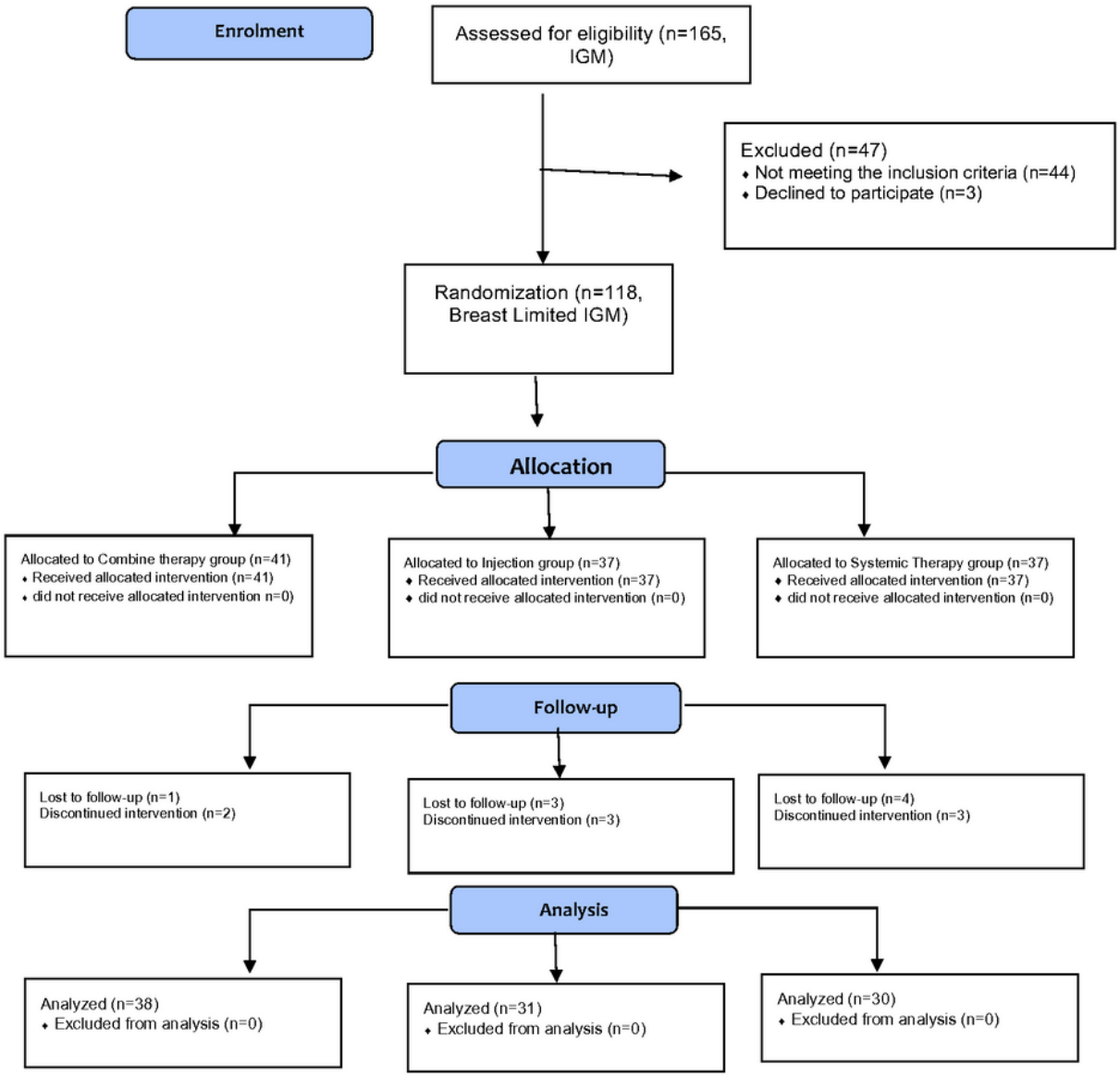

Figure 1

The CONSORT diagram showing the allocation process throughout the trial

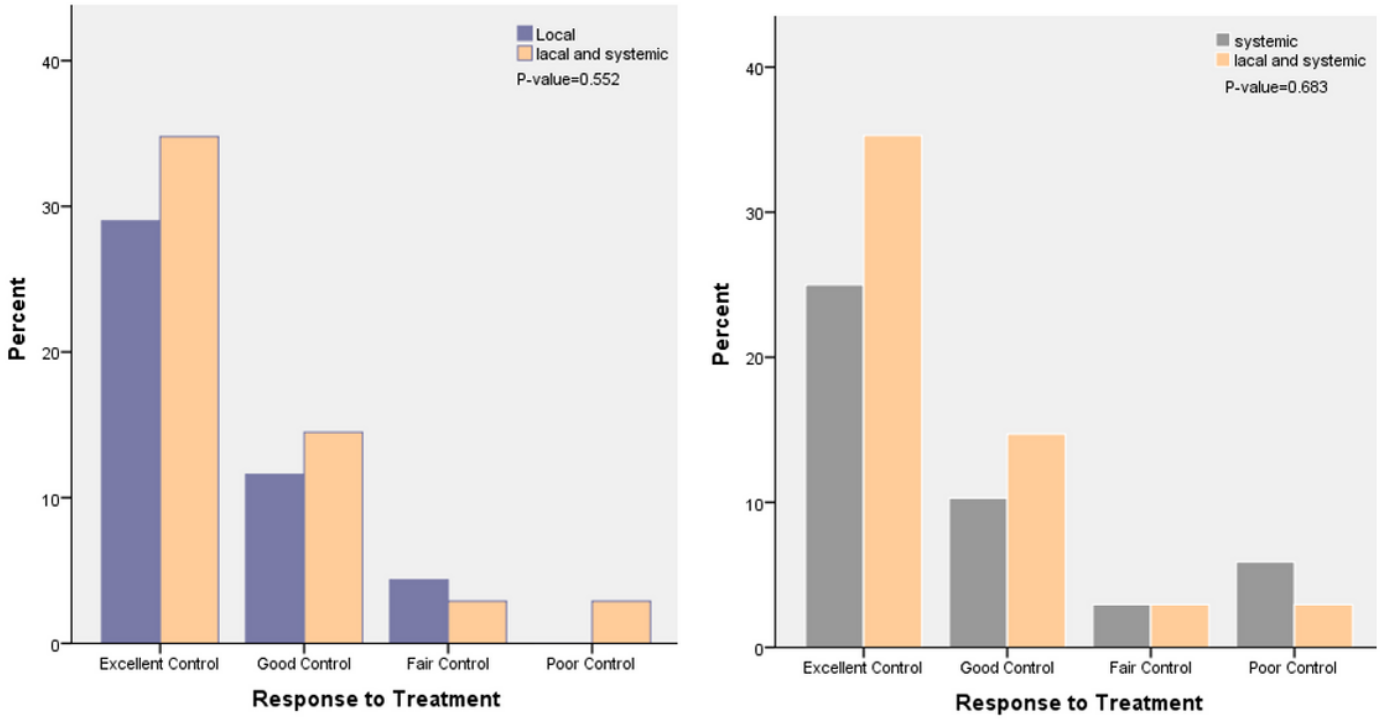

Figure 2

The Comparison of the treatment response between groups

Supplementary Files

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- CONSORT2010Checklist.doc