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RESEARCH ARTICLE
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EFFICACY OF COMBINED CRYOTHERAPY AND INTRALESIONAL MEGLUMINE ANTIMONIATE (GLUCANTIME®) VS. CRYOTHERAPY AND INTRALESIONAL MEGLUMINE ANTIMONIATE (GLUCANTIME®) ALONE FOR THE TREATMENT OF CUTANEOUS LEISHMANIASIS

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Abstract

Introduction: Leishmaniasis is categorized into three different clinical forms that are: visceral, mucocutaneous, and cutaneous leishmaniasis (CL), of which the more frequent form is the cutaneous Leishmaniasis. There is a need for more effective and less time-consuming therapeutic methods for this condition.

Objectives: We ought to compare the efficacy of Intralesional meglumine antimoniate (Glucantime®) and cryotherapy combined whereas cryotherapy and Intralesional meglumine antimoniate (Glucantime®) alone for the treatment of cutaneous leishmaniasis**.**

Materials and Methods: A total of 258 (86 patients in each group) were observed. Patients were allocated in three groups that are A, B, and C. Group-A had the combination of Intralesional Glucantime and Cryotherapy fortnightly. Group-B patients received Intralesional Glucantime alone fortnightly. Group-C patients were treated with Cryotherapy alone fortnightly.

RESULTS: In Group-A the mean age was 31.37 years ± 10.99 SD. In Group-B mean age was 31 years ± 10.56 SD while in Group-C mean age was 32.50 years ± 10.50SD. In Group-A 61% of patients were male and 39% were female. In Group-B 58% of patients were male and 42% were female. In Group-C 59% of patients were male and 41% were female. Moreover, Group-A (Intralesional Glucantime and Cryotherapy) was effective in 98% patients, Group B (Intralesional Glucantime alone) was effective in 82% patients and Group C (Cryotherapy alone) was effective in 78% patients.

CONCLUSION: Our study concludes that it is more effective to use the combination of Intralesional Glucantime and Cryotherapy than either Intralesional Glucantime or Cryotherapy alone for the treatment of cutaneous Leishmaniasis.

Keywords: Efficacy, Intralesional Glucantime and Cryotherapy, Intralesional Glucantime, Cryotherapy, cutaneous Leishmaniasis

Introduction:

Some species of sandflies transfer a parasitic disease known as Leishmaniasis [1]. Leishmaniasis is categorized into three different clinical forms that are: visceral, mucocutaneous, and cutaneous leishmaniasis (CL), of which the more frequent form is the cutaneous Leishmaniasis [2]. It is most commonly introduced as a prolonged ulcer with indurated and erythematous fringes and is associated with lymphadenopathies [3]. Leishmaniasis is widespread globally in 88 countries with 1.3 million new cases reported per year in which 90% of cases occur in Algeria, Afghanistan, Brazil, Columbia, Iran, Peru, Syria, and Saudi Arabia [4]. There are approximately 21000-35000 cases of cutaneous Leishmaniasis reported annually in Pakistan [5]. In Pakistan, Khyber Pakhtunkhwa Province is having the highest rate of Leishmaniasis. Treatment for cutaneous Leishmaniasis (CL) is necessary to attain the revitalization and further stop transmission as well as a secondary bacterial infection [6]. Antimony compounds which include Glucantime (Meglumine antimoniate), and Pentostam (Sodium stibogluconate) have been used for the treatment of cutaneous Leishmaniasis (CL) patients in the majority of the countries [7]. The different methods of treatments for leishmaniasis also consist of cryotherapy with liquid nitrogen which is considered as an effective treatment [1,8]. These days, treatment of CL commonly involves a combination of cryotherapy with liquid nitrogen and Intralesional Glucantime for better results [9].

In practice, Glucantime drug is being used as Intralesional and systemic or locally for the treatment of cutaneous Leishmaniasis. This method has been reported to have better results but has considerable side effects. According to Rosiana Estéfane da Silva, the cure rate using Glucantime in different patients at six months was ranging from 67.7% to 77.7% [10].

In the treatment method using Cryotherapy, the liquid Nitrogen is applied to the diseased tissue for its destruction. According to Liliana López- Carvajal, in the treatment of CL through cryotherapy, the efficacies are in the range of 63.6% to 73.7% [11].

These days combination of Cryotherapy together with Intralesional Glucantime for the treatment of cutaneous Leishmaniasis is in use in many countries [12]. According to the studies conducted using this technique, the response rate of 18.4% has been recorded while using Cryotherapy alone whereas, the response rate while using the combination of both Glucantime and Cryotherapy for treatment is as high as 100% [13].The aim is to carry out a study in three groups using Intralesional Glucantime and Cryotherapy alone for the treatment of CL and a combination of both Glucantime and Cryotherapy for the treatment of CL. The study would also be beneficial, to assess the cost-effective treatment modality for Cutaneous Leishmaniasis. Such a study using the aforementioned techniques in three different groups has never been performed in the Country before.

Materials and Methods:

This randomized control trial was conducted in Department of Dermatology, Lady Reading Hospital Peshawar from February 2019 to August 2019 over a period of 6 months. Data was collected by non-probability consecutive sampling technique from 258 patients (86 in each group). The sample size calculation was done by WHO sample size calculation formula. Patients of either gender, age between 18-60 years, less than or equal to three lesions of less than twelve weeks duration with positive smear for LD bodies were enrolled in the study. Patients with history of hypersensitivity to antimonials, pregnant or lactating females, lesion size greater than 5cm, or patients on systemic therapy for cutaneous leishmaniasis were excluded from the study. The study was conducted after formal approval from the Hospital Ethical and Research Committee. All patients who present to Dermatology Unit LRH through OPD diagnosed as cutaneous Leishmaniasis based on history and clinical examination, fulfilling the inclusion criteria were included in the study. The purpose was explained to the patients, informed written consent from those who agree to participate in the study, demographic data like age, sex, and address was obtained. Patients were allocated randomly in three groups A, B, and C using the lottery method. Group-A had included those patients who receive a combination of Intralesional Glucantime and Cryotherapy fortnightly. Cryotherapy involved the application of liquid Nitrogen via a cotton swab for 10-25 seconds until the lesion and 1-2 mm of

surrounding normal tissue appear frozen. Then after thawing, Intralesional Glucantime was administered enough (0.5-3 ml of the solution for individual lesion depending on size). Group-B had included those patients who had received Intralesional Glucantime alone fortnightly. Group-C had included those patients who had treated with Cryotherapy alone fortnightly. The evaluation of the lesions was performed every four weeks until the resolution of the lesions. The findings were recorded in predesigned proforma and analyzed. The data was analysed using SPSS version 24. Frequencies and percentages were calculated for a categorical variable like gender and efficacy. Means and standard deviation were computed for a continuous variable like the age of patients. A Chi-square test was used to check the efficacy by comparing the intervention effectiveness in all three groups while keeping a p- value of <0.05 as significant . Efficacy in all the three groups was stratified among the age and gender to see the effect modification. The post- stratification chi-square test was applied keeping $P \leq 0.05$ as significant value. All the results were presented as tables and graphs.

Results:

In the present study age distribution among three groups was analysed as shown in table no.1. In Group-A 56 (65%) patients were in the age range 18-30 years, 30 (35%) patients were in the age range 31-60 years. The mean age was 31.37 years with SD ± 10.99. In Group-B 58 (68%) patients were in the age range 18-30 years, 28 (32%) patients were in the age range 31-60 years. The mean age was 31 years with SD ± 10.56. In Group-C 57 (66%) patients were in the age range 18-30 years, 29 (34%) patients were in the age range 31-60 years. The mean age was 32.50 years with SD ± 10.50 as shown in table no. 2. The frequency of age from 18-60 years has been shown in graph no. 1. Whereas the frequencies of age in individual groups A, B, and C have been shown in graphs no 2, 3, and 4 respectively.

Gender distribution among the three groups was analysed as in Group- A 52 (61%) patients were male and 34 (39%) patients were female. In Group- B 50 (58%) patients were male and 36 (42%) patients were female. In Group- C 51 (59%) patients were male and 35 (41%) patients were female that has been shown in table no. 3. The frequency and percentage of gender has been displayed in graph no. 6 and 7 respectively.

Efficacy among the three groups was analyzed as Group-A (Intralesional Glucantime and Cryotherapy combined) was effective in 84 (98%) patients and was not effective in 2 (2%) patients. Group-B (Intralesional Glucantime alone) was effective in 71 (82%) patients and was not effective in 15 (18%) patients. Group-C (Cryotherapy alone) was effective in 67(78%) patients and was not effective in 19(22%) patients that have been shown in table no. 5. In graph no. 8 and 9, the frequency and percentage of the efficacy of individual groups have been shown in graph no. 8 and 9 respectively. In table no. 7, the chi-square test was applied on efficacy which yielded a value of .0005 that shows the result is very significant.

Stratification of efficacy concerning age has been shown in table no.8. In Group-A, Intralesional Glucantime and Cryotherapy combined for 18-30 years patients was effective for 55 patients and not effective for only 1 patient. In Group-A, Intralesional Glucantime and Cryotherapy combined for 31-60 years patients was effective for 29 patients and not effective for 1 patient. In Group-B, Intralesional Glucantime only for 18-30 years patients was effective for 49 patients and not effective for 7 patients. In Group-B, Intralesional Glucantime only for 31-60 years patients was effective for 22 patients and not effective for 8 patients. Similarly, in Group-C, Cryotherapy alone for 18-30 years patients was effective for 47 patients and not effective for 9 patients. In Group-C, Cryotherapy alone for 31-60 years patients was effective for 20 patients and not effective for 10 patients. A Chi-square test was applied for stratification of efficacy w.r.t. the age which has been shown in table no. 9 which yielded a result of .033 for 18-30 years patients and .011 for 31-60 years patients. Stratification of efficacy w.r.t. age for 18-30 years patients and 31-60 years patients have been shown in graph no. 10 and 11 respectively. Stratification of efficacy concerning gender has been shown in table no.11 and 12. In Group-A, Intralesional Glucantime and Cryotherapy combined for male patients was effective for 51 patients and not effective for only 1 patient. In Group-A, Intralesional Glucantime and Cryotherapy

combined for female patients was effective for 33 patients and not effective for 1 patient. In Group-B, Intralesional Glucantime only for male patients was effective for 42 patients and not effective for 8 patients. In Group-B, Intralesional Glucantime only for female patients was effective for 29 patients and not effective for 7 patients. Similarly, in Group-C, Cryotherapy alone for male patients was effective for 43 patients and not effective for 8 patients. In Group-C, Cryotherapy alone for male patients was effective for 24 patients and not effective for 11 patients. A Chi-square test was applied for stratification of efficacy w.r.t. gender which has been shown in table no. 13 which yielded a result of .034 for male patients and .009 for female patients. Stratification of efficacy w.r.t. gender for male patients and female patients has been shown in graph no. 12 and 13 respectively.

TABLE NO. 1: AGE DISTRIBUTION

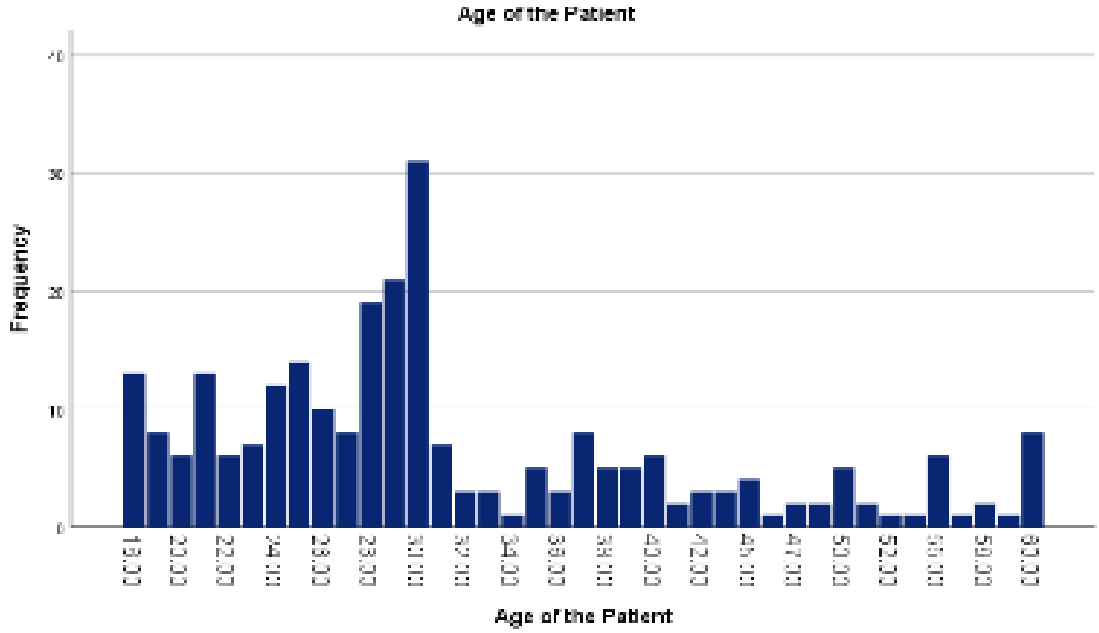
(n=258)

AGE (Years)	GROUP-A (Intralesional Glucantime and Cryotherapy)		GROUP-B (Intralesional Glucantime alone)		GROUP-C (Cryotherapy alone)	
	No.	%	No.	%	No.	%
18-30	56	65%	58	68%	57	66%
31-60	30	35%	28	32%	29	34%
Total	86	100%	86	100%	86	100%
Mean ± SD	31.37 year ± 10.99		31 year ± 10.56		32.50 year ± 10.50	

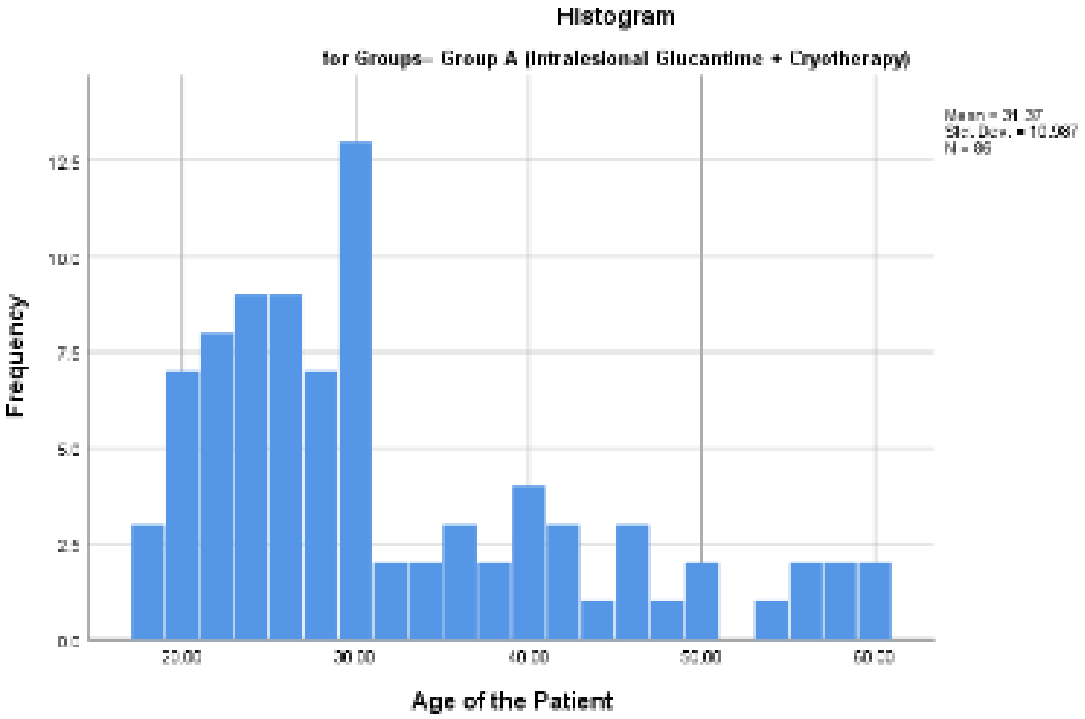
TABLE NO. 2: MEAN AND SD OF AGE

	Distribution of groups		Statistic
Age of the Patient	Group A (Intralesional Glucantime + Cryotherapy)	Mean	31.3721
		Std. Deviation	10.98667
		Minimum	18.00
		Maximum	60.00
	Group B (Intralesional Glucantime)	Mean	31.0000
		Std. Deviation	10.55518
		Minimum	18.00
		Maximum	60.00
	Group C (Cryotherapy)	Mean	32.5000
		Std. Deviation	10.50126
		Minimum	18.00
		Maximum	60.00

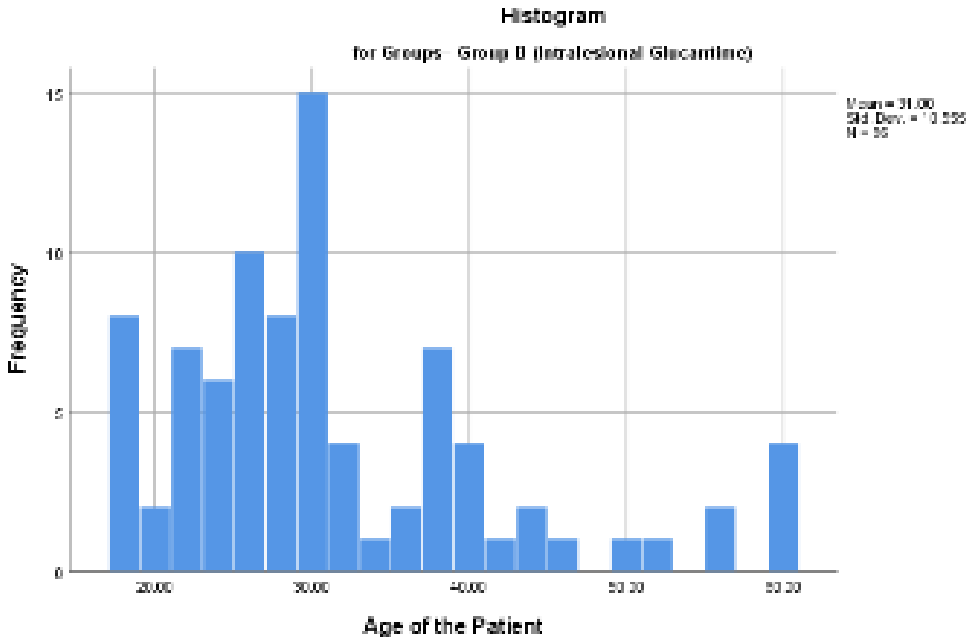
GRAPH NO. 1: FREQUENCY OF AGE FROM 18-60 YEARS



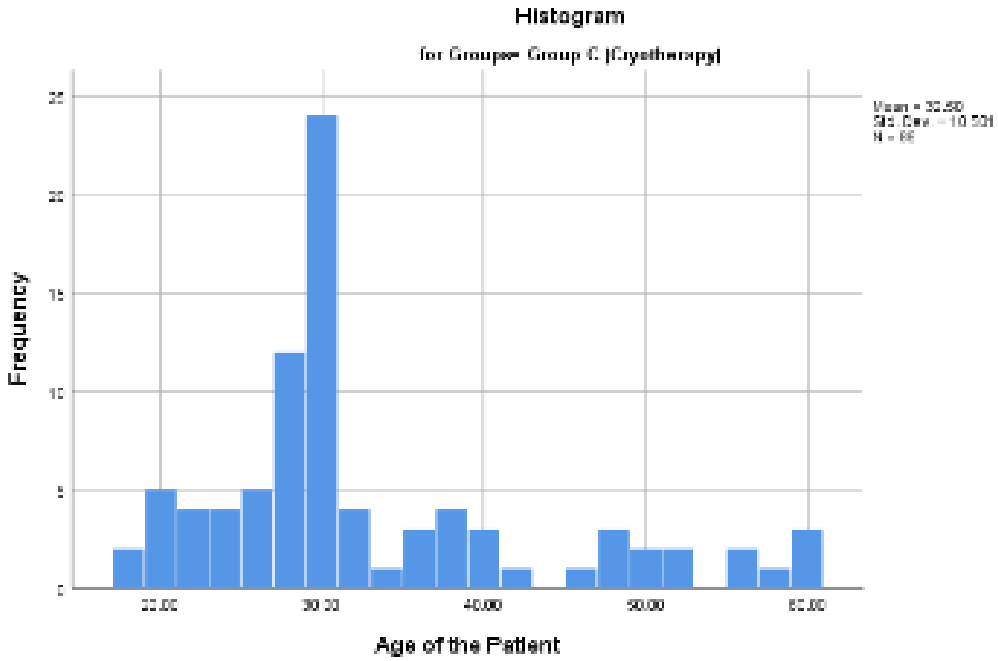
GRAPH NO. 2: FREQUENCY OF AGE FOR GROUP-A



GRAPH NO. 3: FREQUENCY OF AGE FOR GROUP-B



GRAPH NO. 4 FREQUENCY OF AGE FOR GROUP-C



GRAPH NO. 5: FREQUENCY OF 3 GROUPS

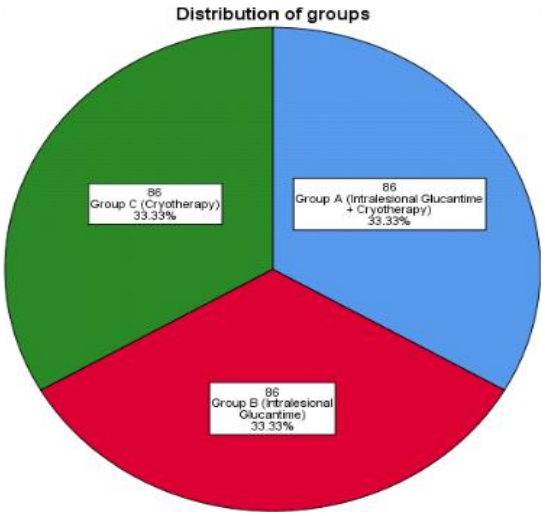


TABLE NO. 3: GENDER DISTRIBUTION

(n=258)

Gender	GROUP-A (Intralesional Glucantime and Cryotherapy)		GROUP-B (Intralesional Glucantime alone)		GROUP-C (Cryotherapy alone)	
	No.	%	No.	%	No.	%
Male	52	61%	50	58%	51	59%
Female	34	39%	36	42%	35	41%
Total	86	100%	86	100%	86	100%

GRAPH NO. 6: FREQUENCY OF GENDER

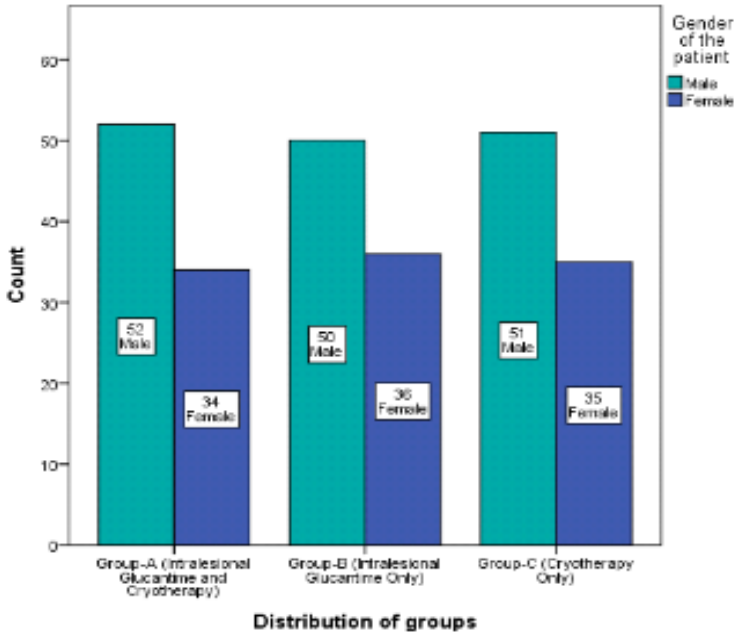


TABLE NO. 4: GENDER DISTRIBUTION W.R.T. FREQUENCY AND PERCENTAGE

		Distribution of groups						
		Group-A (Intralesional Glucantime+ Cryotherapy)		Group-B (Intralesional Glucantime)		Group-C (Cryotherapy)		Subtotal
		Count	%	Count	%	Count	%	Count
Gender	Male	52	61	50	58	51	59	153
	Female	34	39	36	42	35	41	105
	Subtotal	86	100	86	100	86	100	258

GRAPH NO. 7: PERCENTAGE OF GENDER

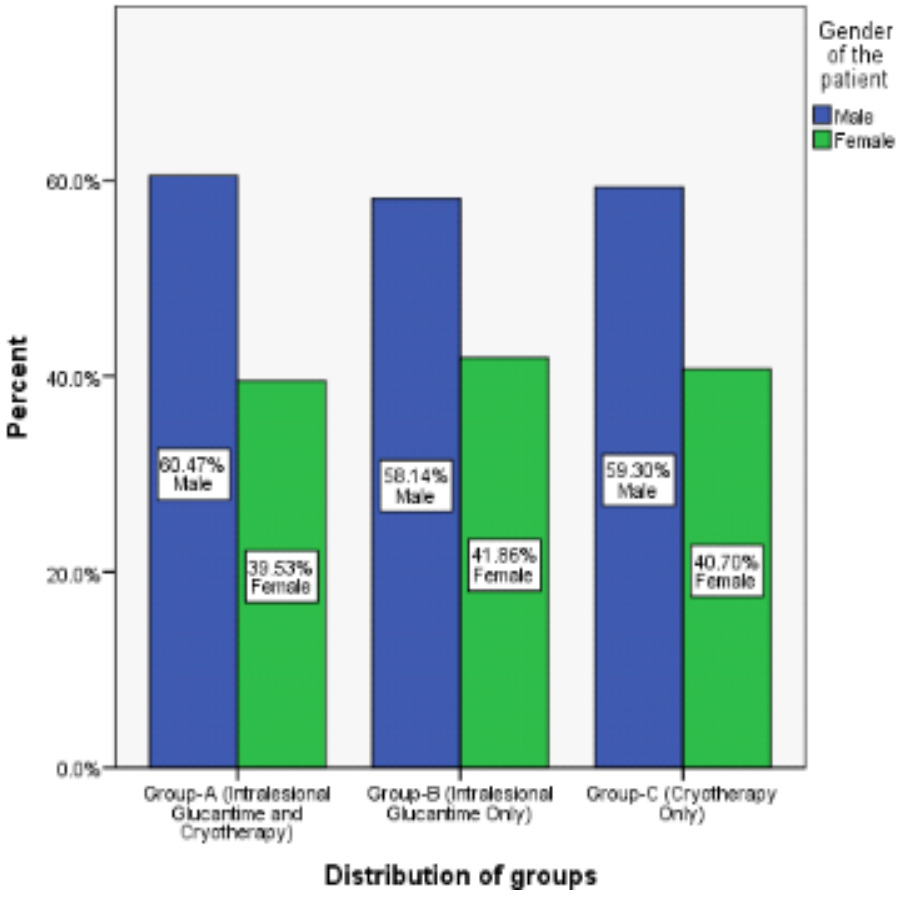


TABLE NO. 5: EFFICACY (n=258)

Efficacy	GROUP-A (Intralesional Glucantime and Cryotherapy)		GROUP-B (Intralesional Glucantime alone)		GROUP-C (Cryotherapy alone)		P-Value
	No.	%	No.	%	No.	%	
Effective	84	98%	71	82%	67	78%	
Not Effective	2	2%	15	18%	19	22%	
Total	**86**	**100%**	**86**	**100%**	**86**	**100%**	**.0005**

GRAPH NO. 8: FREQUENCY OF EFFICACY

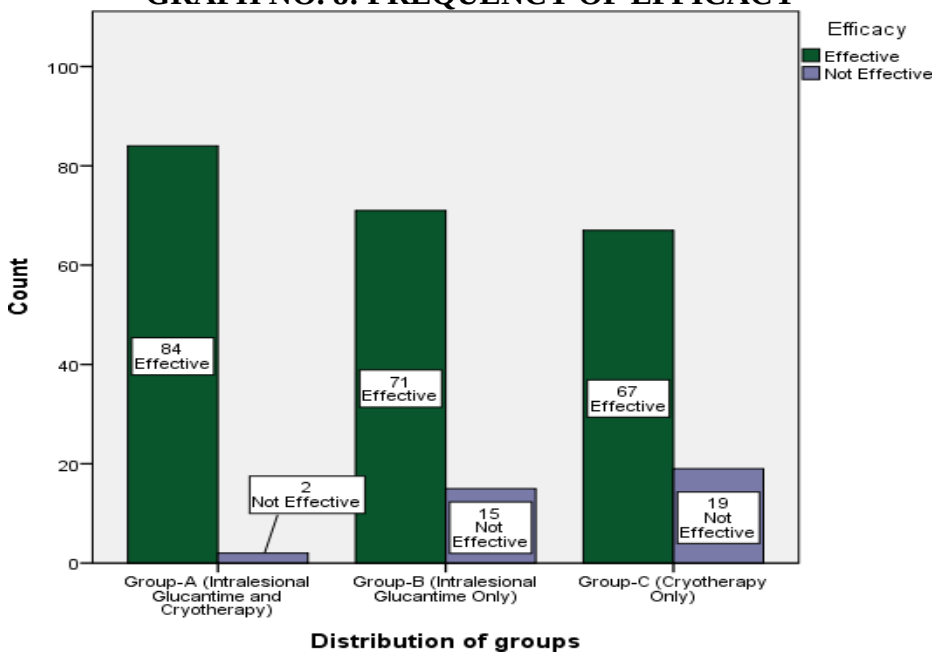


TABLE NO. 6: EFFICACY OF 3 GROUPS

		Distribution of groups			
		Group-A (Intralesional Glucantime + Cryotherapy)	**Group-B (Intralesional Glucantime)**	**Group-C (Cryotherapy)**	**Total**
		Count	Count	Count	
Efficacy	**Effective**	84	71	67	222
	Not Effective	2	15	19	36
Total		86	86	86	258

GRAPH NO. 9: PERCENTAGE OF EFFICACY

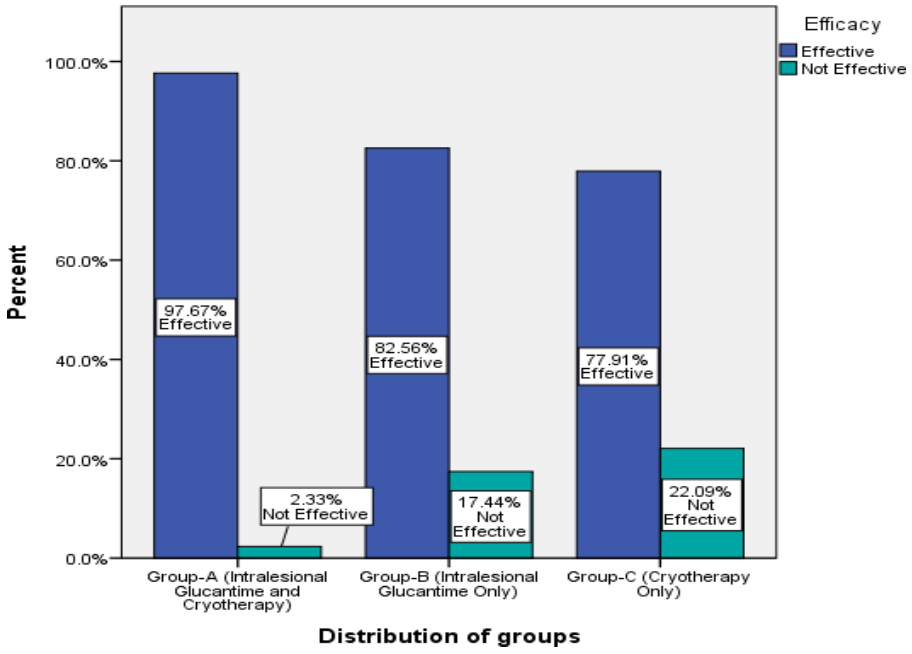


TABLE NO. 7: CHI-SQUARE TEST FOR EFFICACY

Pearson Chi-Square Tests		
		Distribution of groups
Efficacy	**Chi-square**	15.302
	Df	2
	Sig.	**.000***
*. The Chi-square statistic is significant at the .05 level.		

TABLE NO. 8: STRATIFICATION OF EFFICACY W.R.T. AGE (n=258)

AGE	EFFICACY	GROUP-A	GROUP-B	GROUP-C	P-value
18-30 years	Effective	55	49	47	**.033**
	Not effective	1	7	9	
Total		**56**	**56**	**56**	
31-60 years	Effective	29	22	20	**.011**
	Not effective	1	8	10	
Total		**30**	**30**	**30**	

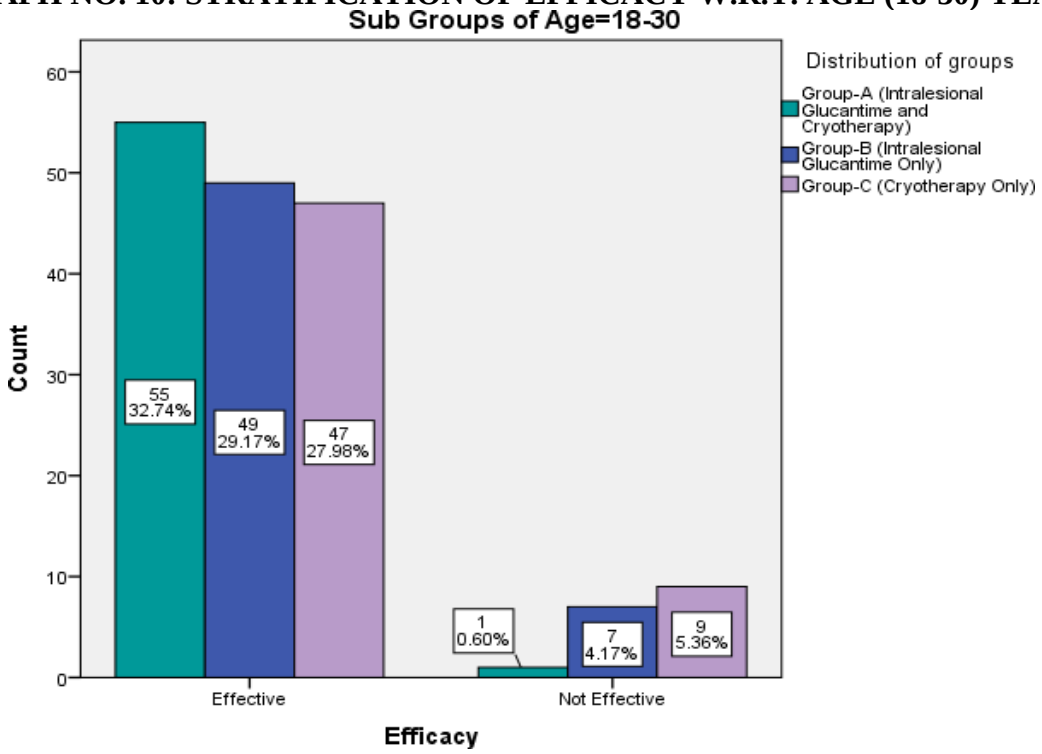
TABLE NO. 9: CHI-SQUARE TEST FOR EFFICACY W.R.T. AGE

Pearson Chi-Square Tests				
				Distribution of groups
Sub Groups of Age	**18-30**	**Efficacy**	Chi-square	6.806
			Df	2
			Sig.	**.033***
	31-60	**Efficacy**	Chi-square	8.940
			Df	2
			Sig.	**.011***
*. The Chi-square statistic is significant at the .05 level.				

TABLE NO. 10: STRATIFICATION OF EFFICACY W.R.T. AGE IN 3 GROUPS

Crosstab						
Count						
Sub Groups of Age			**Distribution of groups**			**Total**
			Group-A (Intralesional Glucantime and Cryotherapy)	**Group-B (Intralesional Glucantime Only)**	**Group-C (Cryotherapy Only)**	
18-30	**Efficacy**	**Effective**	55	49	47	151
		Not Effective	1	7	9	17
	Total		56	56	56	168
31-60	**Efficacy**	**Effective**	29	22	20	71
		Not Effective	1	8	10	19
	Total		30	30	30	90
Total	**Efficacy**	**Effective**	84	71	67	222
		Not Effective	2	15	19	36
	Total		86	86	86	258

GRAPH NO. 10: STRATIFICATION OF EFFICACY W.R.T. AGE (18-30) YEARS



GRAPH NO. 11: STRATIFICATION OF EFFICACY W.R.T. AGE (31-60) YEARS

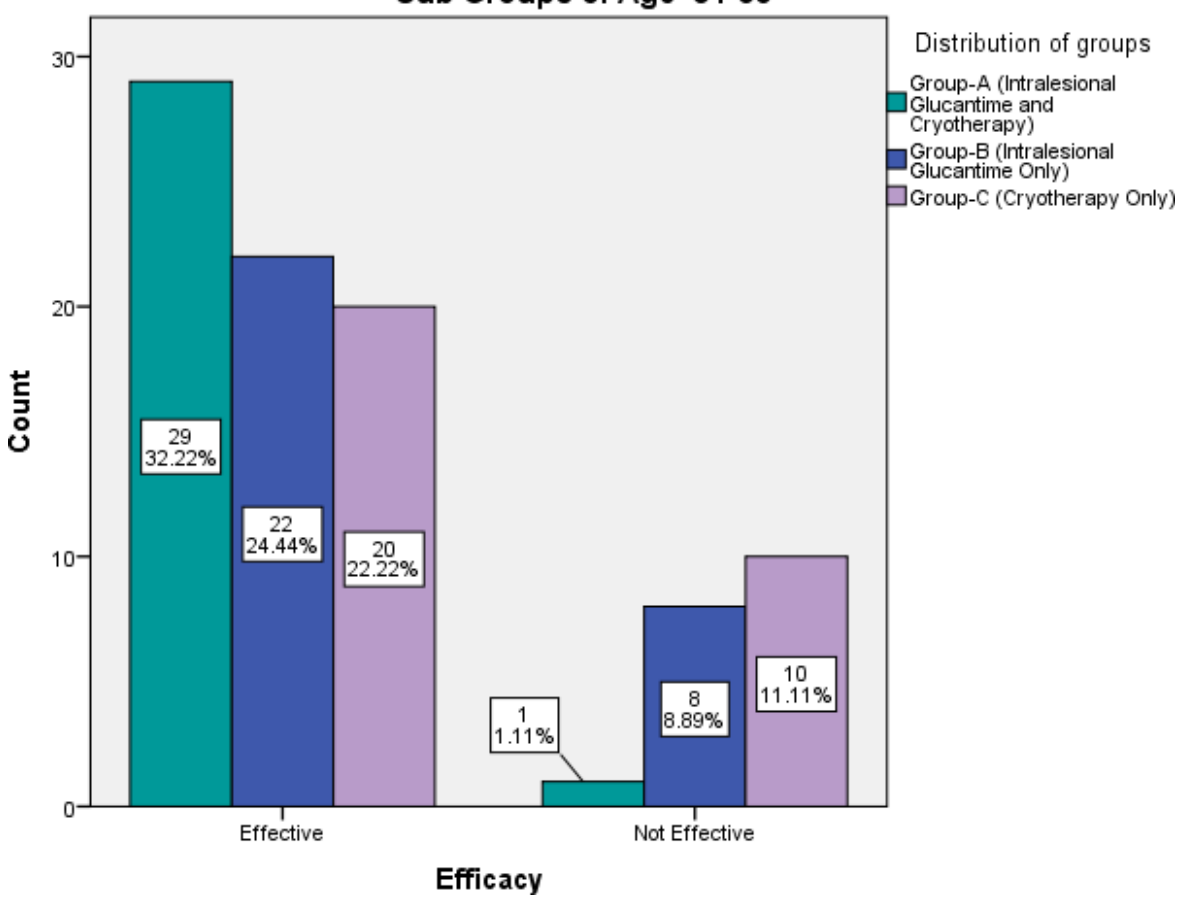


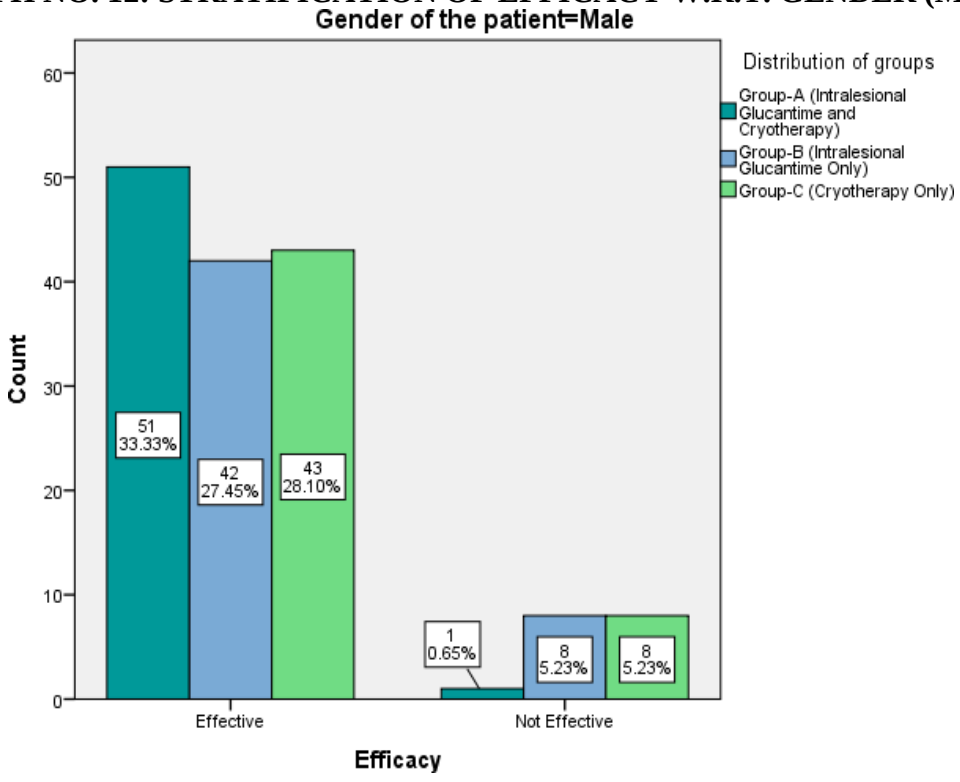
TABLE NO. 11: STRATIFICATION OF EFFICACY W.R.T. GENDER (n=258)

GENDER	EFFICACY	GROUP A	GROUP B	GROUP C	P-value
Male	Effective	51	42	43	.034
	Not effective	1	8	8	
Total		52	50	51	
Female	Effective	33	29	24	.008
	Not effective	1	7	11	
Total		34	36	35	

TABLE NO. 12: STRATIFICATION OF EFFICACY W.R.T. GENDER IN 3 GROUPS

Efficacy * Distribution of groups * Gender of the patient Crosstabulation						
Count						
Gender of the patient			Distribution of groups			Total
			Group-A (Intralesional Glucantime and Cryotherapy)	Group-B (Intralesional Glucantime Only)	Group-C (Cryotherapy Only)	
Male	Efficacy	Effective	51	42	43	136
		Not Effective	1	8	8	17
	Total		52	50	51	153
Female	Efficacy	Effective	33	29	24	86
		Not Effective	1	7	11	19
	Total		34	36	35	105
Total	Efficacy	Effective	84	71	67	222
		Not Effective	2	15	19	36
	Total		86	86	86	258

GRAPH NO. 12: STRATIFICATION OF EFFICACY W.R.T. GENDER (MALE)



GRAPH NO. 13: STRATIFICATION OF EFFICACY W.R.T. GENDER (FEMALE)

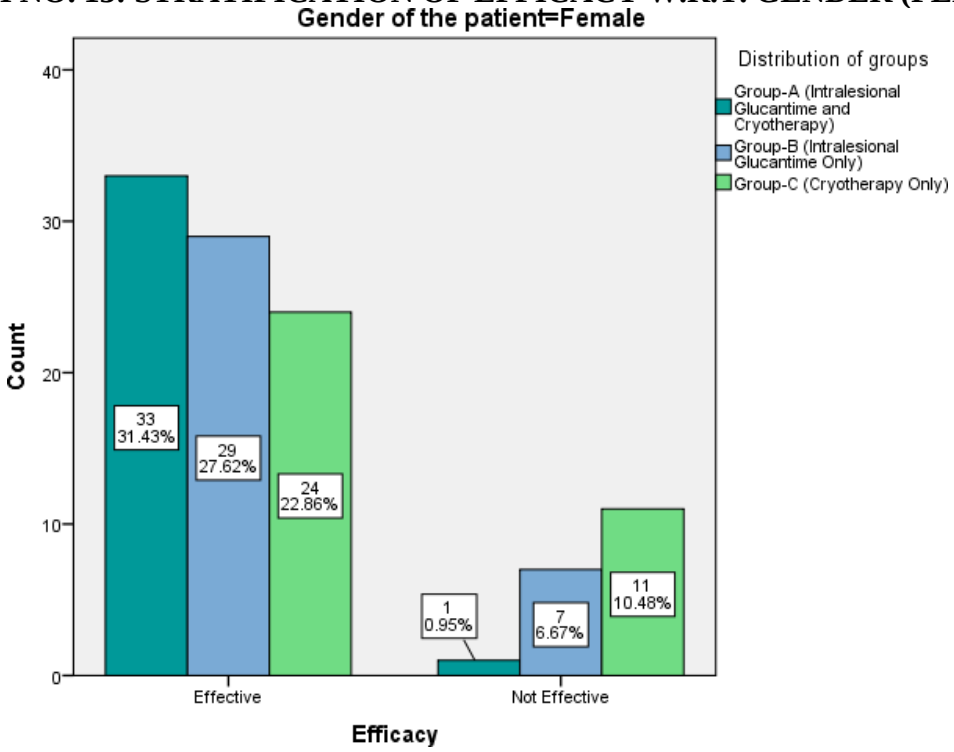


TABLE NO. 13: CHI-SQUARE TEST FOR EFFICACY W.R.T. GENDER

Pearson Chi-Square Tests				
				Distribution of groups
Gender of the patient	**Male**	**Efficacy**	Chi-square	6.736
			Df	2
			Sig.	**.034***
	Female	**Efficacy**	Chi-square	9.511
			Df	2
			Sig.	**.009***
*. The Chi-square statistic is significant at the .05 level.				

DISCUSSION

Leishmaniasis is a parasitic disease that is transmitted by some species of sandflies [12]. It is presented into three clinical forms: cutaneous leishmaniasis (CL), mucocutaneous and visceral, of which the more frequent form is the cutaneous Leishmaniasis [7,10,12,13]. It is most commonly presented as a chronic ulcer with indurated and erythematous borders and is associated with lymphadenopathies [7].Worldwide, Leishmaniasis is prevalent in 88 countries with 1.3 million new cases reported per year in which 90% of cases occur in Afghanistan, Algeria, Brazil, Colombia, Iran, Peru, Saudi Arabia, and Syria [4].In Pakistan, approximately 21,000-35,000 cases of cutaneous Leishmaniasis are reported annually [3]. In Pakistan, Khyber Pakhtunkhwa Province is having the highest rate of Leishmaniasis. Our study shows that in Group-A mean age was 31.37 years with SD ±10.99. In Group-B mean age was 31 years with SD ± 10.56 and in Group-C mean age was 32.50 years with SD ± 10.50 In Group-A 61% of patients were male and 39% of patients were female. In Group-B 58% of patients were male and 42% of patients were female. In Group-C 59% of patients were male and 41% of patients were female. Moreover, Group-A (Intralesional Glucantime + Cryotherapy) was effective in 98% patients, Group-B (Intralesional Glucantime alone) was effective in 82% patients and Group-C (Cryotherapy alone) was effective in 78% patients. Similar results were observed in another study carried out by Asilian A et al.,[13] in which patients were divided into three groups: Group 1,100 patients with 149 lesions were treated with cryotherapy plus intralesional MA; Group 2,200 patients

with 230 lesions were treated with cryotherapy; Group 3, 100 patients with 160 lesions were treated with intralesional MA. These groups were followed for 6 months after the end of treatment. The results showed a complete cure in 90.9% of cases in Group 1, 57.15% of cases in Group 2, and 55.63% of cases in Group 3. The difference between Group 1 and the other groups was statistically significant ($P < 0.05$). They had concluded that combined cryotherapy and intralesional MA is more effective than either cryotherapy or intralesional MA alone for the treatment of CL.

In another study carried out by Bhatti MZ et al.[5] had reported that a total of 76 patients were randomly divided into two equal groups A and B. Patients in group A were given combined intra-lesional meglumine antimoniate and cryotherapy weekly for 06 weeks and patients in group B were given cryotherapy alone weekly for 06 weeks. At the end of 06 weeks of the treatment, a direct skin smear test for Leishmania donovani bodies was performed to determine intervention efficacy. In another study carried out by Leibovici V et al. [12]had reported response rates of 55.63% for glucantime, 57.15% for cryotherapy, and 41.4% for combined therapy (glucantime plus cryotherapy). Gurei et al.18 in a clinical trial compared the efficacy of intra- lesional sodium stibogluconate (pentostam) with cryotherapy in the treatment of CL. A total of 92% of cases who received pentostam and 78% of those who received cryotherapy were clinically cured at the end of the three-month follow-up period. In another study carried out conducted by Estéfane da Silva R et al. [7] had reported that the cure rate using Glucantime in different patients at six months was ranging from 67.7% to 77.7%. In another study carried out conducted by Vélez ID et al. [4] had reported that In the treatment method using Cryotherapy, the liquid Nitrogen is applied to the diseased tissue for its destruction. In the treatment of CL through cryotherapy, the efficacies are in the range of 63.6% to 73.7%. In another study carried out conducted by Noor SM et al. had reported that these days combination of Cryotherapy with Intralesional Glucantime for the treatment of CL is in use in many countries. According to the studies conducted using this technique [1,5,7] the response rate of 18.4% has been recorded while using Cryotherapy alone whereas, the response rate while using the combination of both Glucantime and Cryotherapy for treatment is as high as 100%.

CONCLUSION

Our study concludes that a combination of Intralesional Glucantime and Cryotherapy is more effective than either Intralesional Glucantime or Cryotherapy alone for the treatment of cutaneous Leishmaniasis.

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