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Research Article

Percutaneous Intramyocardial Septal Radiofrequency Ablation in Patients with Hypertrophic Cardiomyopathy

Fatema Tashrifwala*, Manisha Purushotham, Sai Krishna Bhushan, Mohammad Omer Khan, Ishaque Hameed

Department of Internal Medicine, DOW University of Health Sciences, Sindh, Pakistan

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ABSTRACT

Aim: In this study, we aimed to Meta-analyze all available data to provide a holistic, well-powered assessment of the effect of PIMSRA on LVOT gradient, LVEF, and anterior and posterior IVS thickness.

Methods: PubMed, Cochrane Central, Embase, and Scopus were systematically searched from inception till October 2022 for published clinical trials assessing the efficacy of PIMSRA in patients with HCM using the keywords "PIMSRA" OR "Percutaneous Intramyocardial Septal Radiofrequency Ablation" OR "Liwen procedure." Studies that reported change in either LVOT gradient, IVS thickness, or LVEF were selected. No time or language restrictions were applied. All case reports were excluded, and only clinical trials were included. The search and data extraction were carried out independently by two reviewers (MP, FT). A third reviewer (IH) was consulted to resolve discrepancies. All statistical analysis were conducted on Open Meta-analyst. Trials were pooled using a continuous random effects model (DL: DerSimonian-Laird), and results were presented with 95% Confidence Intervals (CIs). P value 75% regarded as substantial heterogeneity.

Results: All five studies reported a change in LVOT gradient from the baseline. Integrated analysis showed no significant change from baseline (MD:-69.506; 95% CI:-77.047, -61.966; P=0.089) (I^2=50.4%). Subgroup analysis based on follow-up revealed that there was no significant difference noted at 6 months according to data from 2 studies (MD:-65.351; 95% CI: -85.253, -45.450; P=0.181) (I^2=44.1%) however data from 3 studies at one year follow up did reveal a significant difference from baseline (MD:-71.010; 95% CI:-80.262, -61.758; P=0.047) (I^2=67.2%). Only three studies reported changes in LVEF from the baseline. Integrated analysis Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation showed a significant change from baseline at one-year follow-up in patients who underwent PIMSRA (MD:-1.760; 95% CI:-3.239, -0.282; P=0.047) (I^2=67.22%). The pooled analysis from four studies that reported anterior IVS thickness showed no significant change from baseline (MD:-9.707; 95% CI:-10.819, -8.595; P=0.095) (I^2=52.94%). Subgroup analysis based on follow-up revealed that there was no significant difference noted at 6 months (MD:-11.285; 95% CI:-12.825, -9.744; P=0.933) (I^2=0%) or at one-year follow-up (MD:-9.147; 95% CI:-9.837, -8.456; P=0.650) (I^2=0%) The combined analysis of the four included studies reporting posterior IVS thickness showed no significant change from baseline (MD:-8.859; 95% CI:-10.073, -7.644; P=0.119) (I^2=48.73%). Additionally, there was no significant difference noted in the subgroup analysis at 6 months (MD:-10.278; 95% CI:-12.133, -8.423; P=0.934) (I^2=0%) and at one-year follow-up (MD:-8.335; 95% CI:-9.880, -6.789; P=0.072) (I^2=69.14%)

Conclusion: This single-arm meta-analysis of 284 patients gathered from 5 clinical trials suggested that overall, after PIMSRA, LVOT gradient was reduced, and LVEF was slightly decreased. Additionally, no significant changes were observed in the anterior and posterior IVS thicknesses. Our results had substantial heterogeneity, which could be explained due to differences in the follow-up periods and studies with small sample sizes. It is important to note that even though no significant difference in follow-up was seen from the baseline at 6 months, there was indeed a significant difference noted at one year when assessing the outcomes of LVOT gradient. This could suggest that longer follow-up periods are imperative to truly observe the procedure's efficacy.

Keywords: Hypertrophic Cardiomyopathy (HCM), Percutaneous Intramyocardial Septal Radiofrequency Ablation (PIMSRA), Left ventricular Outflow Tract (LVOT), Left Ventricular Ejection Fraction (LVEF), Anterior Interventricular septum (IVS) thickness, Posterior IVS Thickness, Efficacy

***Correspondence:** Fatema Tashrifwala, Department of Internal Medicine, DOW University of Health Sciences, Sindh, Pakistan, E-mail: fatema.tashrifwala12@gmail.com

ABBREVIATIONS

HCM: Hypertrophic Cardiomyopathy; LVOT: Left ventricular Outflow Tract; US: United States; CMRI: Cardiovascular Magnetic Resonance Imaging; LVEF: Left Ventricular Ejection Fraction; ASA: Alcohol Septal Ablation; PIMSRA: Percutaneous Intramyocardial Septal Radiofrequency Ablation; IVS: Interventricular Septum; NYHA: New York Heart Association; CI: Confidence Interval; MD: Mean Deviation

INTRODUCTION

Hypertrophic Cardiomyopathy (HCM) is an autosomal dominant intrinsic disease of the myocardium characterized by asymmetric hypertrophy and stiffness of the left ventricle along with the systolic anterior motion of the mitral valve, leading to a Left Ventricular Outflow Tract (LVOT) obstruction. It affects one in five hundred people worldwide and is the most common genetic heart disease in the US (Zhou M, *et al*., 2022). The reduced volume of the heart chambers with a reduced capacity of the heart to pump blood results in a decreased stroke volume. LVOT obstruction is present in about one-third of the patients. The symptoms include exertional dyspnea, exercise intolerance, orthopnea, peripheral edema, and syncope (Marian AJ and Braunwald E, 2017). Diagnostic modalities include echocardiography, Electrocardiogram (ECG), and Cardiovascular Magnetic Resonance Imaging (CMRI). Identification of the HCM phenotype can be made by family screening and genetic testing in affected individuals (Qian D, *et al*., 2021; Tuohy CV, *et al*., 2020). The treatment goals are to reduce the severity of symptoms and prevent sudden cardiac death, particularly in young adults. Pharmacological treatment

revolves around β-blockers or non-dihydropyridine calcium-channel blockers with the newer generation of drugs, including Mavacamten, Perhexiline, and Trimetazidine. Evaluation and follow-up are done by LVOT gradient, Left Ventricular Ejection Fraction (LVEF), and myocyte hypertrophy measured by Interventricular Septum (IVS) thickness (Waldman CB and Owens A, 2021). In patients who are refractory to maximum dosage (about 40%) or have intolerance to drugs, surgical options like septal myectomy and trans-catheter mitral valve repair may be considered. The downside to these is the need for a sternotomy. Minimally invasive procedures which can instead be done are high-intensity focused ultrasonography and radiofrequency ablation, or Alcohol Septal Ablation (ASA), which come with their own risk of complications with chances of occurrence ranging from 0.5%-5% (Liu L, *et al*., 2018). The suitability of ASA is limited by septal coronary anatomy and the risk of alcohol being injected into the wrong site. Advancements in techniques have now led to the use of Percutaneous Intramyocardial Septal Radiofrequency Ablation (PIMSRA) as a promising technique for such patients. This technique uses a radiofrequency electrode needle inserted under guidance into the hypertrophied IVS to achieve ablation (Tuohy CV, *et al*., 2020; Zuo L, *et al*., 2020). Trials have shown reductions in IVS thickness and LVOT gradients along with improvement in New York Heart Association (NYHA) functional classification following PIMSRA, but these studies have been limited by small sample sizes, thus being underpowered to reliably demonstrate any significant differences in outcomes. In this study, we aimed to meta-analyze all available data to provide a holistic, well-powered assessment of the effect of PIMSRA on LVOT gradient, LVEF, and anterior and posterior IVS thickness.

MATERIALS AND METHODS

PubMed, Cochrane Central, Embase, and Scopus were systematically searched from inception till October 2022 for published clinical trials assessing the efficacy of PIMSRA in patients with HCM using the keywords "PIMSRA" OR "Percutaneous Intramyocardial Septal Radiofrequency Ablation" OR "Liwen procedure". Studies that reported change in either LVOT gradient, IVS thickness, or LVEF were selected. No time or language restrictions were applied. All case reports were excluded, and only clinical trials were included. The search and data extraction were carried out independently by two reviewers (MP, FT). A third reviewer (IH) was consulted to resolve discrepancies. All statistical analysis were conducted on Open Meta-analyst. Trials were pooled using a continuous random effects model (DL: DerSimonian-Laird), and results were presented with 95% Confidence Intervals (CIs). P value <0.05 was considered significant. Subgroup analysis according to time at follow-up was done. Heterogeneity was evaluated using Higgins I^2, with I^2>75% regarded as substantial heterogeneity.

The initial search yielded 72 potential studies. After exclusions, 5 trials remained for analysis (Zhou M, *et al*., 2022; Qian D, *et al*., 2021; Tuohy CV, *et al*., 2020; Zuo L, *et al*., 2020; Liu LW, *et al*., 2019). The detailed literature search is highlighted in the PRISMA Flow Chart. The characteristics of the included studies have been summarized in *Table 1*.

RESULTS AND DISCUSSION

All five studies reported a change in LVOT gradient from the baseline (*Figure 1A*). Integrated analysis showed no significant change from baseline (MD:-69.506; 95% CI:-77.047, -61.966; P=0.089) (I^2=50.4%). Subgroup analysis based on follow-up revealed that there was no significant difference noted at 6 months according to data from 2 studies (MD: -65.351; 95% CI; -85.253, -45.450; P=0.181) (I^2=44.1%) however data from 3 studies at one year follow up did reveal a significant difference from baseline (MD:-71.010; 95% CI:-80.262, -61.758; P=0.047) (I^2=67.2%).

Only three studies reported changes in LVEF from the baseline (*Figure 1B*). Integrated analysis showed a significant change from baseline at one-year follow-up in patients who underwent PIMSRA (MD:-1.760; 95% CI:-3.239, -0.282; P=0.047) (I^2=67.22%).

The pooled analysis from four studies that reported anterior IVS thickness showed no significant change from baseline (MD:-9.707; 95% CI:-10.819, -8.595; P=0.095) (I^2=52.94%). Subgroup analysis based on follow-up revealed that there was no significant difference noted at 6 months (MD:-11.285; 95% CI:-12.825, -9.744; P=0.933) (I^2=0%) or at one-year follow-up (MD:-9.147; 95% CI:-9.837, -8.456; P=0.650) (I^2=0%) (*Figure 1C*).

The combined analysis of the four included studies reporting posterior IVS thickness showed no significant change from baseline (MD:-8.859; 95% CI:-10.073, -7.644; P=0.119) (I^2=48.73%). Additionally, there was no significant difference noted in the subgroup analysis at 6 months (MD:-10.278; 95% CI:-12.133, -8.423; P=0.934) (I^2=0%) and at one-year follow-up (MD:-8.335; 95% CI:-9.880, -6.789; P=0.072) (I^2=69.14%) (*Figure 1D*).

Table 1: Characteristics of included studies

Included studies	Year	Characteristics of patients					Number of participants	Follow up
		Age in years	Gender	NYHA class	LVOT gradient	IVS thickness		
Zhou M, *et al*., 2022	2022	33-61	M-125 F-75		>50 mmHg		200	1 year
Qian D, *et al*., 2021	2021				>50 mmHg	15-25 mm	30	1 year
Zuo L, *et al*., 2020	2020	15-79	M-20 F-10	Chest pain, syncope, NYHA Class III/IV	>50 mmHg		30	1 year
Liu L, *et al*., 2018	2018	24-57	M-13 F-2	Chest pain, syncope, NYHA Class III/IV			15	6 months
Liu LW, *et al*., 2019	2019			Two NYHA class II and Seven NYHA class III cases			9	6 months

Note: NYHA: New York Heart Association; LVOT: Left Ventricular Outflow Tract; IVS: Interventricular Septum

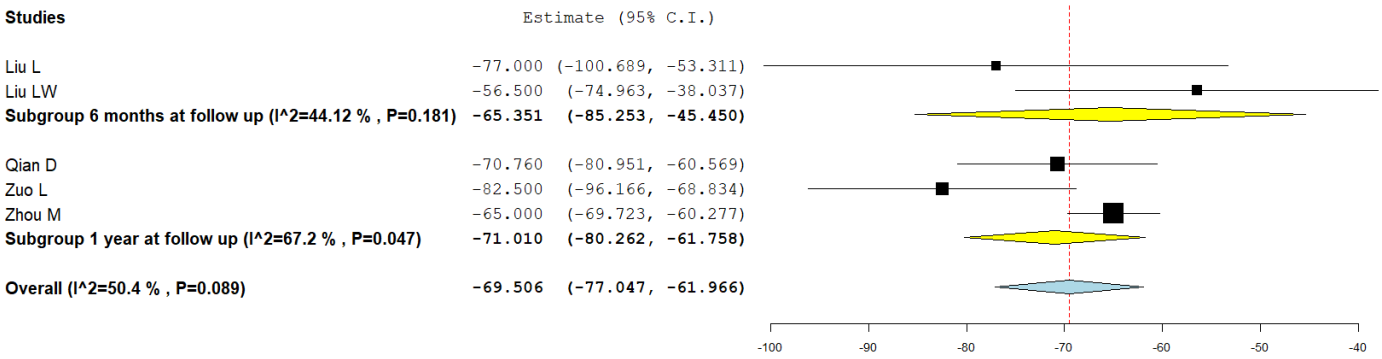

Figure 1A: Change in Left Ventricular Outflow Tract (LVOT) gradient

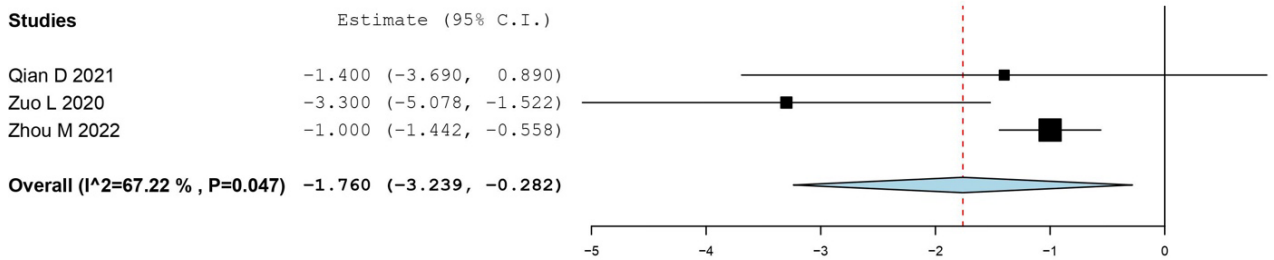

Figure 1B: Change in Left Ventricular Ejection Fraction (LVEF)

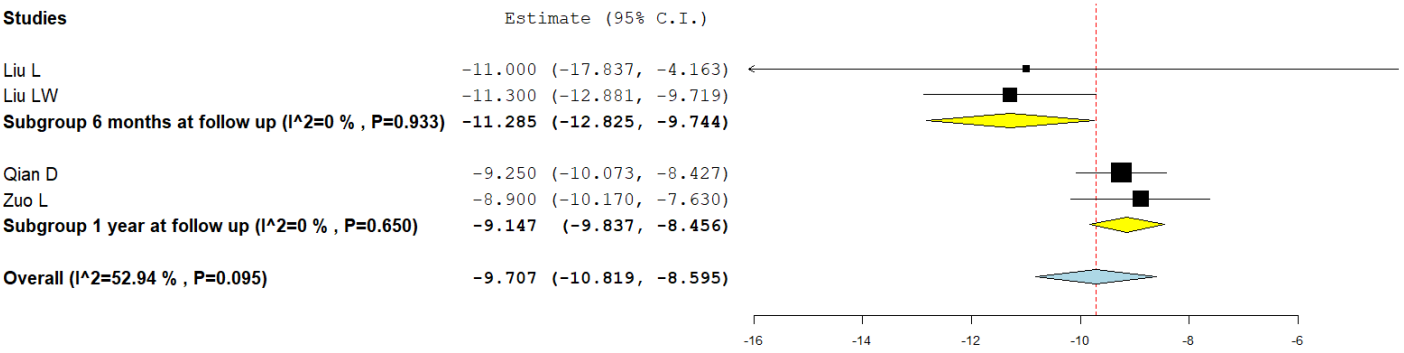

Figure 1C: Change in anterior Interventricular Septum (IVS) thickness

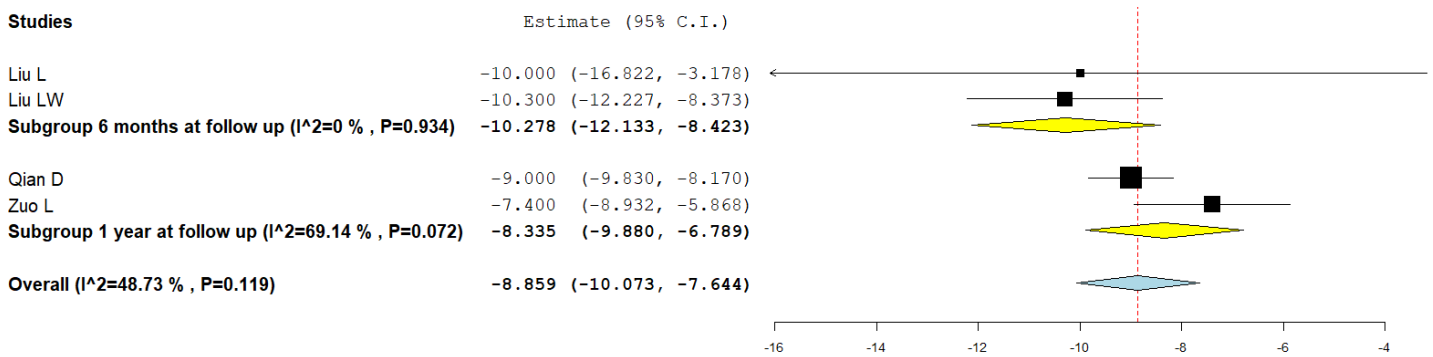

Figure 1D: Change in posterior Interventricular Septum (IVS) thickness

CONCLUSION

This single-arm meta-analysis of 284 patients gathered from 5 clinical trials suggested that overall, after PIMSRA, LVOT gradient was reduced, and LVEF was slightly decreased. Additionally, no significant changes were observed in the anterior and posterior IVS thicknesses. Our results had substantial heterogeneity, which could be explained due to differences in the follow-up periods and studies with small sample sizes. It is important to note that even though no significant difference in follow-up was seen from the baseline at 6 months, there was indeed a significant difference noted at one year when assessing the outcomes of LVOT gradient. This could suggest that longer follow-up periods are imperative to truly observe the procedure's efficacy.

Our meta-analysis had some limitations. The number of studies and the sample size available for analysis was limited, and most patients were of Chinese origin. Furthermore, no studies have evaluated the long-term effects on cardiac conduction due to the scar tissue formed following ablation. Therefore, further studies with long-term follow-up having large sample sizes from different patient populations and ethnicities should be done to demonstrate the effectiveness of PIMSRA with more statistical power. Outcomes measuring procedure safety, such as intraoperative and postoperative complications, should also be recorded and compared with a control group.

AUTHOR DECLARATIONS

Author contribution

All authors had access to the data and a role in writing the manuscript. All authors have reviewed the manuscript and approved it in its current form.

Code availability

Followed PRISMA guidelines and Software used was Open Meta analyst.

Availability of data and material

Transparent.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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