Original Article

A Randomised Comparative Study To Compare The Outcomes In The Patients Of Chronic Venous Insufficiency Receiving Micronized Purified Flavonoid Fraction (MPFF) Before Surgical Intervention And Patients Not Receiving Micronized Purified Flavonoid Fraction (MPFF) Before Surgical Intervention

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INTRODUCTION

Chronic venous insufficiency (CVI) describes a condition that affects the venous system of the lower extremities, with an essential condition being persistent ambulatory venous hypertension casing various pathologies, including pain Oedema, skin changes and ulceration.[1-3]

Reports of prevalence of chronic venous insufficiency vary from < 1% to 40% in females and from < 1% to 17% in males. Prevalence estimates for varicose veins are higher, <1% to 73% in females and 2% to 56% in males.[4]

The manifestations of CVI may be viewed in terms of a well-established clinical classification scheme. The Clinical, Ethology, Anatomic, Pathophysiology (CEAP) classification was developed by an international consensus conference to provide a basis of uniformity in reporting, diagnosing, and treating CVI .[5]

Diagnostic modalities for Chronic venous sufficiency include duplex ultrasound scanning which is gold standard and first diagnostic test[i]. It is found to be over 98% sensitive and 93-97%.[6]

Micronized purified flavonoid fraction (MPFF) is a flavonoid-based venoactive drug, and is the only venoactive drug to demonstrate significant anti-inflammatory and venoprotective actions, which distinguishes this drug from other venoactive drugs to provide patients with rapid and substantial relief of symptoms. MPFF also provides a unique protection against complications by preserving the venous valves and walls. [7-8]

This study aims to look for the long term effect of Micronized purified flavonoid fraction (MPFF), an oral phlebotropic drug on the quality of life of patients suffering from Chronic venous

insufficiency post operatively if the drug is given before undergoing any surgical intervention.

METHODS

This study was conducted in Department of General Surgery, King George's Medical University, Lucknow, and patient admitted for CVI treatment after confirmation with Duplex Doppler US in standing position was enerolled.

Study was Comparative Randomized trial with Paralleled and open label having two arms. Patients randomized to a group by computer generated random number, after getting this number of patient were allocated to particular intervention by sequentially numbered opaque sealed envelope (SNOSE). The study Duration was 1 year and patients were followed up for 6 months.

Primary endpoints were to compare the outcomes of quality of life at 1 month,3 month and 6 month using two questionnaires between the both Groups, SF 36 – For general health being and Aberdeen varicose vein questionnaire (Disease specific). Secondary outcomes were to compare pain based on VAS scale, SSI.

Patient included were All patients age >15yr and Patient having C2, C3, C4, C5 on basis of CEAP classification of Chronic venous disorder. Patient were divided into two groups (A and B) and MPFF was Given to Group A Before the surgical intervention.

Generic Quality of life was compared on the basis of SF 36 questionnaire and followed up at baseline, 1 month, 3 month and 6 month and scores were assessed using RAND 36 Calculators available online.

Disease specific Quality of life (AVVQ) was compared with the manikin diagram and the total score was from 0 to 100, (patients with 0 points indicate best quality of life).

STATISTICAL ANALYSIS

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD. The variables are compared using independent t test and the P-value < will be taken as the significance level.

RESULTS

Comparison of disease specific (AVVQ) changes due in MPFF (Group A) and Non MPFF Group Patients (Group B) (Table 1.)

Mean value has been compared for Group A and Group B (table 1). Pre op Mean value of Group A was 0.939±1.603 while in Group B was 1.239±1.303 (p=0.4296). In 4th week mean value of Group A was 0.467±0.703 while for Group B was 0.583±0.423(p=0.4649). In 3rd month mean value of Group A was 0.145±0.396 while for Group B was 0.363±0.227(p=0.0113). In 6th month mean value of Group A was 0.167±0.566 while for Group B was 0.233±0.489(0.6307).

At 1 month, 3 month and 6 month the quality of life was better in group A but was statistically insignificant.

Table 1. Showing AVVQ

Comparison of AberdeenScore(n=30)	Group A		Group B		p-value
	Mean	SD	Mean	SD	
Pre op	0.939	1.603	1.239	1.303	0.4296
weeks	0.467	0.753	0.583	0.423	0.4649
3 months	0.145	0.396	0.363	0.227	0.0113
6 months	0.167	0.566	0.233	0.489	0.6307

Table 2. Social

SF 36 Questionnaire	P values	Intervals
physical functioning	0.3942	1 month
	<0.0001	3 month

	<0.0001	6 month
Role limitation due tophysical health	0.3048	1 month
	<0.0001	3 month
	<0.0001	6 month
Role limitation due toemotional problems	0.0003	1 month
	0.0044	3 month
	0.0142	6 month
Energy/ Fatigue	0.3969	1 month
	0.3245	3 month
	0.3972	6 month
Emotional well being	0.3373	1 month
	0.0494	3 month
	0.28995	6 month
Social functioning	0.3669	1 month
	0.3714	3 month
	0.3917	6 month
Pain	0.0975	1 month
	0.0770	3 month
	0.2228	6 month
General Health	0.0359	1 month
	0.2424	3 month
	0.0379	6 month

For the generic quality of Life SF 36 was compared (Table 2)-

- **Physical functioning scores** of the patients of Group A was increasing at a faster rate during the 1st month more than Patients of Group B. The mean score and p value of Group A and group B were compared for 3 and 6 months, they were coming almost similar as compared to group B.
- **Role limitation due to Emotional Problem** of the patients of Group A were similar during the 1st, 3rd and 6th month more than Patients of Group B
- **Role limitation due to physical Problem** scores of the patients of Group A were increasing at a faster rate at the 1st month more than Patients of Group B proving
- **Energy** scores of the patients of Group A are increasing at a faster rate during the 1 month 3 month and 6 month more than Patients of Group B
- **Emotional well-being** scores of the patients of Group A were increasing at a faster rate during the 1 month 3 month and 6 month more than Patients of GroupB
- **Social functioning** scores of the patients of Group A were increasing at a faster rate during the 1 month 3 month and 6 month than Patients of Group B proving

COMPARING THE SECONDARY OUTCOMES:

On Evaluation it was found that, 80% of patients had pain in the 1st month, 50% had pain in 3rd month and 10% in 6 month, while 20% of patients had SSI in 1st and 3rd month while in 6 month only 10% had SSI. 50% of patients was having edema in 1st month, 30% in 3rd month and 20% in 6 months(Table-3).

Table 4 shows that 80% of patients had pain in the 1st month, 50% had pain in 3rd month and 10% in 6 month, while 20% of patients had SSI in 1st and 3rd month while in 6 month only 10% had SSI. 50% of patients was having oedema in 1st month, 30% in 3rd month and 20% in 6 months.

Table 3- Evaluation of Pain Edema and SSI in Group A(MPFF) patients

N=30 Cases	1 month	3 months	6 months
Pain	80% (24/30)	50% (15/30)	10% (3/30)
Surgical site infection	20% (6/30)	20% (6/30)	10% (3/30)
Oedema	50% (15/30)	30% (9/30)	20% (6/30)

Table 4- Evaluation of Pain Edema and SSI in Group B (Non MPFF) patients.

N=30	1 month	3 months	6 months
Control			
Pain	80% (24/30)	60% (18/30)	30% (10/30)
Surgical site infection	24% (8/30)	24% (8/30)	21% (7/30)
Oedema reduction	50% (15/30)	40% (12/30)	36% (11/30)

DISCUSSION

The study was randomized control study to compare the quality of life outcome between two groups, Group A and Group B in which Group A iwas having patients who were taking MPFF (1000mg/OD) before any surgical intervention and Group B is having patient which has undergone surgery without having MPFF. Patient were randomized using sequentially numbered opaque envelope method. We have used Aberdeen varicose vein questionnaire and SF-36 questionnaire for comparison between the groups at intervals of 1 month, 3 month and 6 month. Patients completed follow up for complete 6 months are only included.

Kakkos et al in 2018[9]did a meta-analysis in which the main outcome measures were the individual and global symptoms, leg edema and redness, skin changes, QoL and evaluation of the overall effectiveness of the treatment by the physician, The effectiveness of MPFF compared with placebo was expressed as risk ratio (RR) or standardized mean difference (SMD) with 95% confidence interval (CI). Trial quality of evidence was graded using the GRADE system. They identified 7 trials, mostly with low risk of bias, involving 1,692 patients, Based on high quality evidence, MPFF is highly effective in improving leg symptoms, edema and quality of life in patients with CVD.

Martinez- Zapata et al in 2016[10]**,** did a Randomised, double-blind, placebo-controlled trials (RCTs) assessing the efficacy of rutosides, hidrosmine, diosmine, calcium dobesilate, chromocarbe, Centella asiatica, disodium flavodate, french maritime pine bark extract, grape seed extract and aminaRone in patients with CVI at any stage of the disease, Moderate-quality evidence shows that the phlebotonics group had greater risk of non-severe adverseevents than the placebo group (RR 1.21, 95% CI 1.05 to 1.41; I2
= 0; 3975 participants).
Belczak et al in 2014[11], included 136 patients with CVD (CEAP grades 2-5). They were randomly allocated into four groups to receive micronized diosmin + hesperidin, aminaphthone, coumarin + troxerutin, or placebo (starch), Pre op Mean value of Group A was 0.939±1.603 while for Group B was 1.239±1.303 (p=0.4296). In 4th week mean value of Group A was 0.467±0.703 while for Group B was 0.583±0.423(p=0.4649). In 3rd month mean value of Group A was 0.145±0.396 while for Group B was 0.363±0.227 (p=0.0113). In 6th month mean value of Group A was 0.167±0.566 while for Group B was 0.233±0.489(0.6307). Although there was significant difference found during the 3rd month of the study(p=0.0113) no difference was found at baseline and other intervals between both the group.
Study done by Saveljev VS et al[12]in 2008 in which 245 patients with varicose vein disease were taken and study group (n=200) received micronized diosmin (Detralex, 1000 mg/day) for 2 weeks before and 30 days after the surgical procedure found pain subjective symptoms and subcutaneous Haemorrhage were significantly lower in study group, the mean VAS score was 2.9 in the Daflon 500 mg group and 3.5 in the control group ($P<0.05$).
As we discussed & found out giving Daflon (MPFF-1000mg/OD) pre surgery has significant effect on overall quality of life as compared by SF-36 and AVVQ also there is significant reduction in the proportion of pain, Oedema and Surgical Site infection.

CONCLUSION

After following up to 6 month we have concluded that giving MPFF (1000mg/OD) to the patients pre operatively for 1 month, it reduces the Pain and Oedema and it also enhances the quality of life. Some domains of SF 36 and AVVQ showed advantages of having MPFF (1000mg/OD) before going into any surgical intervention for varicose vein. There is better and faster post-operative reduction of pain and oedema in the Study in Group A.

Although, there are some drawbacks regarding the compliance for the Drug and also not significant improvement in role limitation due to emotional problems and physical problems, despite all these giving MPFF (1000mg/OD) preoperatively has a significant effect on Quality of life of patients.

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