Journal of Ayurveda and Integrative Medicine 13 (2022) 100585

Contents lists available at ScienceDirect

Journal of Ayurveda and Integrative Medicine

journal homepage: http://elsevier.com/locate/jaim

Original Research Article

Evaluation of efficacy and safety of adjuvant Ayurvedic therapy in patients with severe post-covid mucor-mycosis at a Government tertiary care hospital – A Case-Control study

Uma Shankar Prasad Adluri [a, *, 1], Srikanthbabu Perugu [b]

[a] M.D,D.N.B(Internal Medicine) B.A.M.S,M.Phil(Ayurveda), S.I.V.A.S Health & Research Institute, Sunshine Hospitals, Secunderabad, Telangana, India
[b] Principal I/C, Professor & HOD-Kayachikitsa, Dr. B.R.K.R Govt. Ayurvedic College, Erragadda, Hyderabad, Telangana, India

ARTICLE INFO

Article history:
Received 21 October 2021
Received in revised form
6 March 2022
Accepted 29 April 2022
Available online xxx

Keywords:
Post covid mucor mycosis
Ayurveda
Host response modification
Vataja vidradhi
Pancha Tikta Ghrita Guggulu
Adjuvant therapy

ABSTRACT

Background: In the wake of the unprecedented Mucormycosis epidemic following the delta variant run second wave of SARS COV-2, the Government of Telangana decided to utilize Ayurveda for its adjuvant immune-boosting role. Based on clinical assessment of patients, Mucor mycosis was identified as Vataja vidradhi and treatment was planned.

Objective: To assess the safety and efficacy of Ayurvedic regime as an adjuvant therapy in post covid mucor mycosis patients at Gandhi Hospital, the largest Government tertiary care center in Telangana.

Methods: In this prospective case control study, 77 patients with positive or probable post covid mucor mycosis were included. The varunadi kwatha regimen could be given in very few patients precluding its meaningful analysis. 65 patients received Pancha Tikta Ghrita Guggulu [PTGG] regimen. These patients were assigned into 2 groups; Intervention [A] group n = 36, who used PTGG for a mean duration of 34.1 days and Control [B] group [drop outs] n = 29 who used PTGG for a mean duration of 2.1 days. Objective parameters like biochemical changes and parameters like disease progression, recurrence, mortality rate, subjective and objective wellbeing, readmission, repeat surgeries, and persistence of symptoms were assessed before and after treatment. Statistical analysis was done using Mann Whitney, chi square and ANOVA test.

Results: The Intervention group mortality rate was ZERO where as it was 13.8% in control group. The statistical analysis showed significant improvement in all clinical parameters tested.

Conclusion: PTGG based regimen as adjuvant seemed to help across the entire spectrum of Mucormycosis. It was safe and tolerated very well with concomitant antifungal usage and in pre and post-operative patients, thus validating the host factor modification approach of Ayurveda and an integrative usage.

1. Introduction

SARS CoV-2 (Covid 19) infection has presented one of the greatest challenges to modern civilization as well as modern health care system across the world, affecting approximately 230 million people, as of date [1]. The emergence of variants of concern like the delta variant with its increased infectivity and increased pathogenicity affected a much larger population including younger individuals with lower risk factors across the globe. India being the country where the delta variant was first detected, bore an unprecedented and enormous brunt, stretching its health care system both in rural and urban areas beyond its maximum limits. India officially reported 33.9 million infections and 4.5 lakh deaths [2] while unofficial estimates give a much higher figure.

One of the dimensions of the 2nd wave of Covid pandemic that occurred in India was the occurrence of another epidemic of Mucormycosis; caused by ubiquitous fungus belonging to the family

Abbreviations: PTGG, Pancha Tikta Ghrita Guggulu.

* Corresponding author.
E-mails: aushankarp@yahoo.com, drperugu@gmail.com.

Peer review under responsibility of Transdisciplinary University, Bangalore.

[1] 12-5-188/7/1, Vijaypuri, Lalaguda Post, Secunderabad 500017, Telangana, India.

https://doi.org/10.1016/j.jaim.2022.100585

Mucorales, which thrives in patients with high blood glucose, acidosis and ischemic environments as in Diabetic keto acidosis, as well as in Immunosuppressive conditions like steroid/immune suppressant usage, hematological malignancies, organ transplantation, iron over load etc. It is also associated with penetrating wound injuries and natural calamities like tornados. Usually presenting with fever, nasal ulceration and necrosis of para nasal sinuses and bony walls, periorbital or facial swelling, reduced vision and ophthalmoplegia, headache etc … causing complications like loss of vision, intra vascular spread to cerebral venous sinuses and their thrombosis, cerebral abscesses and strokes with an overall mortality of 20–80%. Disease manifestation in the lungs as cavitory abscesses, gastro intestinal tract, kidneys and skin also is well documented. Management consists of withdrawal of the immune suppressant drugs, early and extensive debridement of necrotic areas, strict glycemic control and reversal of metabolic acidosis, intravenous Amphotericin B (preferably Liposomal) for a few weeks till clinical response, followed by oral antifungals for a prolonged period of time spanning over 3–6 months [3].

The reasons behind the emergence of the mucormycosis epidemic are many folds and still under investigation in India. But generally attributed to indiscriminate and overzealous usage of steroids, poor glycemic control prior to and during the Covid therapy, occurrence of severe cyclones in Indian summer facilitating the spread of spores etc. India reported a total of 45,300 cases of Mucor mycosis with 4330 deaths from January 2020 to October 2021 [4]. Thus, pushing its healthcare systems into an unprepared emergency due to lack of availability of the antifungals in required numbers. The treatment of a single patient of mucormycosis using liposomal amphotericin -b followed by posaconazole with surgery was estimated to cost between 14 to 18 lakhs (18.8- 25.6k US$) [5]. Hence this has put a huge economic burden on the health care sector additionally.

Telangana one of the southern Indian states reported nearly 2638 cases of post covid mucor mycosis [6]. The Government of Telangana decided to address the issue by utilizing the AYUSH systems for their adjuvant immune boosting role. An expert committee was formed to suggest necessary treatment protocols for mucor mycosis in Ayurveda and instructions were given to depute two separate teams at two designated nodal centers to treat and document the results [after obtaining due IEC permissions]in admitted patients with Ayurvedic medications as adjuvants. Consequently, two teams were constituted initially to study and evaluate mucor mycosis patients on Ayurvedic lines and then to suggest necessary treatment. The team at Gandhi Hospital, Secunderabad [the largest Government tertiary care hospital with around 1200 beds in Telangana] was entrusted to look into management of patients with severe disease as the hospital was designated nodal center for all patients with mucor mycosis with complications or co morbidities or Covid positivity, this paper aims to document the same.

Ayurveda the oldest traditional science on the Indian subcontinent dating back to more than 5000 years has described in explicate detail the principles underlying the causation and management of epidemics and pandemics. It's unique 'host centric' approach of evaluating and treating new and emerging infections by the principles of host factor modification (Dosha – Shodhana-Shamana based) rather than a 'germ centered' approach of modern bio medicine [7] offers several advantages in the peculiar circumstances of the present. Ayurveda's wisdom in choosing to modulate the limited varieties of host responses as against the innumerable number of pathogens (asankhyeyah krimayaha) each requiring an individual anti-microbial offers an extremely cost effective and patho-physiologically pragmatic approach in such scenarios.

Taking Diabetic keto acidosis as the commonest and central pathology leading to mucor mycosis, the authors identified Vataja Pramehas including Madhumeha [8, NidanaSthana 4/44], as the closest correlate to diabetic keto acidosis and decided to pursue the suppurative conditions described in the context of prameha by the name of' 'Prameha Pitikas [8, Nidanasthana 4/48], and zeroed upon Vataja variety of Vidradhi described by Vagbhata [9, Nidanasthana 11/6] as being the closest match to mucor mycosis The treatment protocols of vatajavidradhi were explored from different classics, their practical applicability in a non ayurvedic emergency setting, safety diseases vis a vis the usage of drugs with narrow therapeutic margin like amphotericin and imidazoles, and dosage requirements for a potential life threatening discussed minutely before finalizing the regime. Two regimens were proposed based on the above principles with Varanadigana kashayam [9, Sutrasthana 15/21–22] and Pancha Tikta Ghrita Guggulu (PTGG) [10, Guggulu prakaran pg. 880] being the chief drugs, each supported by common medications of Nisaamalaki, Kaishoraguggulu, Vasantakusumakararas, Shilajith capsules, Triphalachurnam or Gandharvahastadi erandathailam.

2. Materials and methods

2.1. Study design

A four arm, open-labeled, prospective case control study was planned after obtaining institutional ethical committee clearance (wide letter no: No. IEC/DRBRKRGAC/2020-21 dated 24/05/2021) Informed consent was obtained from all the participants prior to enrollment.

It was planned to divide participants in two major groups to be treated prospectively for up to 45 days with 2 interventions, namely intervention I (Varunadi and common Ayurvedic Medicines) and intervention II (Pancha tikta ghrita guggulu and common ayurvedic regimen) used as adjuncts to available Modern medical Management and the results will be evaluated, but as the number of patients meeting criteria for intervention 1 was only 4, it could not be analyzed meaningfully and hence was dropped from analysis.

Therefore, here we present a Two Arm Prospective Case Control Study of intervention II (Panch tikta ghrita guggulu and common ayurvedic regimen) used as an adjunct to Bio-medical care, consisting of 65 patients divided in two groups. Group A comprising of patients who had taken Pancha Tikta Ghrita Guggulu (PTGG) and common ayurvedic regimen as advised and continued treatment for more than 8 days with mean usage duration of 34.08 days. This group was taken as Intervention group. Group B consists of dropout patients who had not taken Pancha Tikta Ghrita Guggulu and common ayurvedic regimen as advised and discontinued the treatment within 7 days with mean usage duration of 2.14 days. Group B was taken as Control group. Data of both the groups are analyzed and results were drawn (Fig. 1).

2.2. Study site and population

Patients who were admitted to Gandhi hospital, Secunderabad in mucor mycosis unit (ICU and ward) between the period 28th May 2021 to 28th July 2021 with probable or proven mucor mycosis on clinical or radiological or microbiological grounds and willing to take adjuvant Ayurvedic therapy were included in the study.

2.2.1. Duration

The maximum duration of the intervention was 45 days and the period of follow up was 60 days.

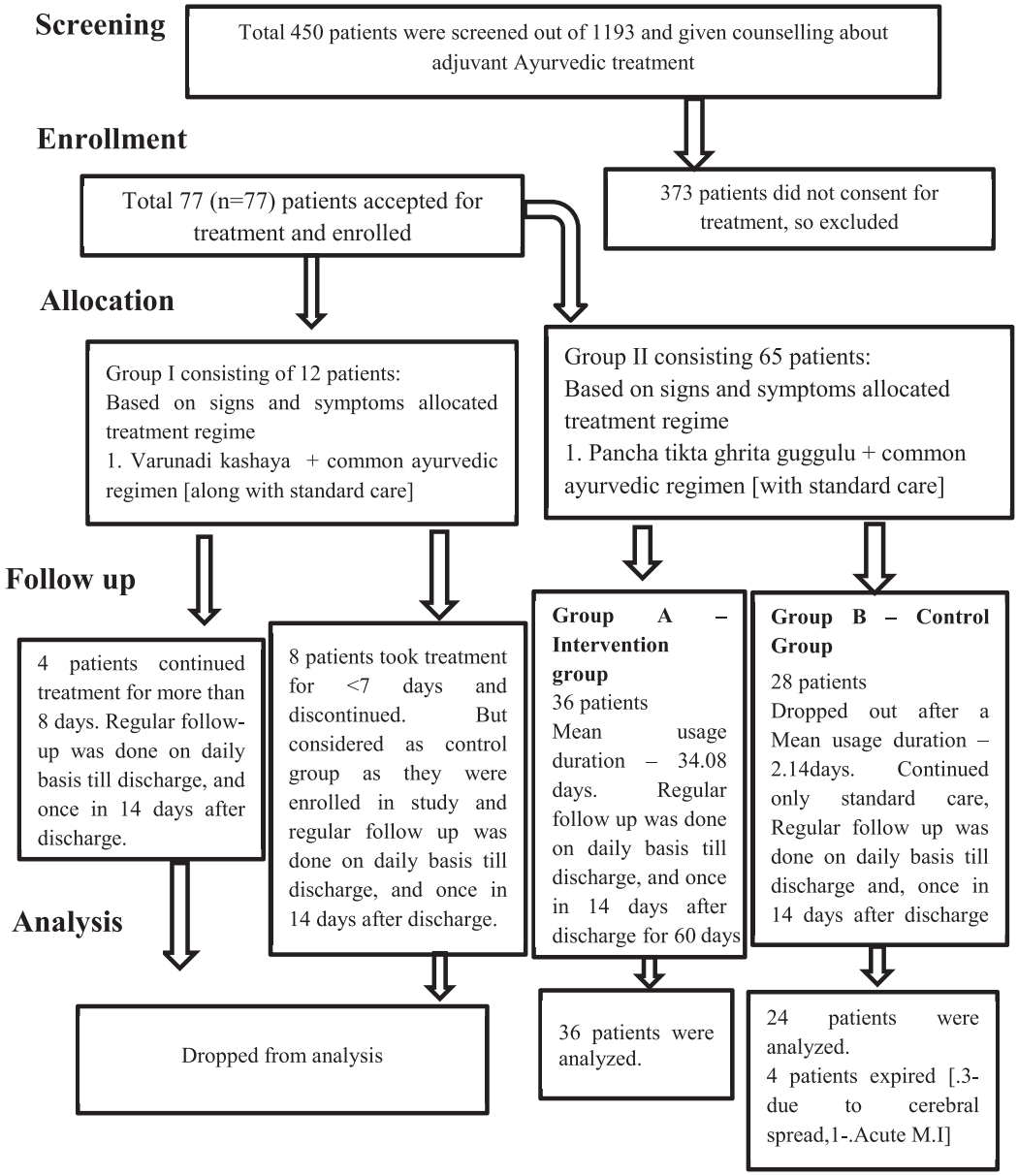

Fig. 1. Showing studying design.

2.3. Inclusion criteria

- Age more than 18 years men and non-pregnant women.
- Recent Covid positivity in RT PCR/RAPID ANTIGEN/CT SCAN.
- Mucor mycosis probable/proven based on clinical/radiological/histological/microbiological grounds.
- Who have used Ayurvedic medicines more than 7 days without interruption
- Non-responders or poor responders to modern medical treatment at evaluation were preferred.
- Rapid progression of disease was preferred.

For Varunadi Kashaya Group

- Early phase of sophavastha [swelling without suppuration] or late phase of sinus venous thrombosis.
- Not on Amphotericin B.
- No surgical intervention done(post-operative) or planned.

For Pancha Tikta Ghrita Guggulu Group

- Intermediate or Late presentation.
- Rakta or pitta involvement or lung involvement.
- Using Amphotericin-B.
- Post-operative or planned for surgery.

2.4. Exclusion criteria

- Less than 18 years of age.
- Pregnant women.
- Known case of Liver failure, Acute Kidney Injury, Chronic Kidney Disease
- Allergic to any Bhallataka product.

2.5. Intervention

Regimen 1:

1. **Varanadi Kashayam**: [9, Sutrasthana 15/21–22] [Vaidyaratnam Oushadhasala Pvt. Ltd.] 15 ml with 45 ml of luke warm water (morning one hour. before food and at night)
2. **Nishamalaki Vati**: [9, Chikitsasthana 12/5] 500 mg morning one hour before food and night 500 mg, at night. [Government Indian Medicines Pharmacy (Ayurveda), Hyderabad.]
3. **Vasantakusumakara Ras**: [11, rasayanadhikar 73/134] [Shree Dhootapapeshwar Ltd.] 125 mg 1 tablet early morning one hour before food and 1 tab. at night.
4. **Capsule Shilajit** [12 and 9, Chikitastanam 12/34] [Dabur]: 500 mg 1 capsule, morning one hour before food and one capsule at night.
5. **Kaishora Guggulu**: [13] [Shree Dhootapapeshwar Ltd.] 500 mg morning one hour before food and 500 mg at night.
6. **Gandharva Hastadi Erandam** [14] [Vaidyaratnam Oushadhasala Pvt. Ltd.] **or Triphalachurnam**: [15] [Government Indian Medicines Pharmacy (Ayurveda), Hyderabad.] One teaspoon or 5 g respectively 1 h after dinner.

Regimen 2:

1. **Pancha Tikta Ghrita Guggulu** [10, Guggulu prakaran pg. 880] [Shree Dhootapapeshwar Ltd]: 1–3 g morning one hour before breakfast and 2–6 g, night at bedtime with water.
2. **Nishamalaki Vati**: 500 mg Morning one hour before breakfast and night 500 mg, at bedtime.
3. **Vasantakusumakara Ras**: 125 mg 1 tablet early morning one hour before breakfast and 1 tab. at bedtime.
4. **Capsule Shilajit**: One capsule 500 mg morning one hour before breakfast and one cap at night.
5. **Kaishora Guggulu**: 500 mg I hour before breakfast and 500 mg at bedtime.
6. **Triphala Churnam (or Gandharva Hastadi Erandam)**: 5 g or 1 tea spoon respectively with luke warm water, 1 h after dinner

2.5.1. Rationale of treatment

Fig. 2.

2.5.2. Dietary considerations

As it was impractical to suggest special diets for patients who were in a modern medical hospital, all the patients were advised not to take abhishyandi food like eggs, curd and bananas which were being supplied, and to take laghu and ushna (light and hot) food, and to drink luke warm water, if possible, to aid in aama pachana [digestion of inflammatory intermediates [7].

2.6. Assessment criteria

2.6.1. Subjective parameters

Pain as per Visual Analog Scale [16], Subjective wellbeing, and clinical improvement at 7 days and end of treatment were recorded and analyzed.

2.6.2. Objective parameters

The objective parameters that were recorded and analyzed were –

- Disease Progression occurrence of disease in a new, previously un-involved area clinically or on CT scan]
- Disease Recurrence [at same site],
- Death [during or after hospitalization],
- Persistence of symptoms,
- Re-admissions [at same or any other hospital],
- Repeat surgeries,
- Objective wellbeing,
- CT Scans [before and after]
- Nasal endoscopies.

2.7. Outcome

2.7.1. Primary outcome

To evaluate the effect of Ayurvedic therapy as an adjuvant in the management of severe post covid mucor mycosis.

2.7.2. Secondary outcome

To evaluate safety of Ayurvedic drugs as adjuvants in the severe cases of post covid mucor mycosis through the help of investigations like complete blood picture (CBP) (for marrow toxicity), liver function tests (LFT) (Hepato-toxicity), Serum Creatinine (Renal toxicity).

2.8. Statistical analysis

Statistical analysis was carried out using SPSS 20 version. For subjective parameters Wilcoxon Signed Rank test and Mann–Whitney Test and Pearson Chi-square test and for objective parameters Independent sample paired t test, and to compare both the groups ANOVA test [one-way] were carried out. A p-value of <0.05 was considered significant.

3. Observation & results

3.1. Demographic and health profile of patients

In the present study among 65 patients 51 (78%) were male and 14 (22%) were female. The relatively high incidence of severe disease in males was seen in other centres of the state as well. The mean BMI was between 22 and 23 also reflecting the catabolic effect of the disease and diabetes or the low socio-economic group affected. The mean occurrence of the first mucor symptom was 18 days after the first day of covid. The average CT-severity score was between 11 and 14.5 reflecting a moderate to severe disease. Among the study group 72%(47/65) of patients received steroids, but majority hospitals did not document the steroid dose used in the discharge summaries. But is assumed to be much higher than prescribed limits from contemporary experience. The average HBA1C was between 9.6 and 10.2 at admission and mean duration of diabetes was 39 months, although the figure could be much higher in reality due to the low educational status of most patients and consequent low check-up rates. The onset of denovo-diabetes was noted as more than 30%. In the study group around 68%(44/65) patients had ocular involvement and 38.5% (25/65) had cerebral involvement and 10.8%(7/65) patients had pulmonary involvement. The high incidence of eye and CNS reflect the selection of severe cases as planned (Figure 4).

3.2. Effect of treatment on subjective parameters

Considering the effectiveness of treatment in reducing pain (assessed using Visual Analog Scale) statistically significant improvement was found in the group A after treatment. Thus the study was found effective in reducing the pain (see Tables 1 and 2).

The results suggest a significant reduction in most of the clinical parameters with the Ayurvedic intervention including sensorium, pain and swelling, while there was no significant improvement in

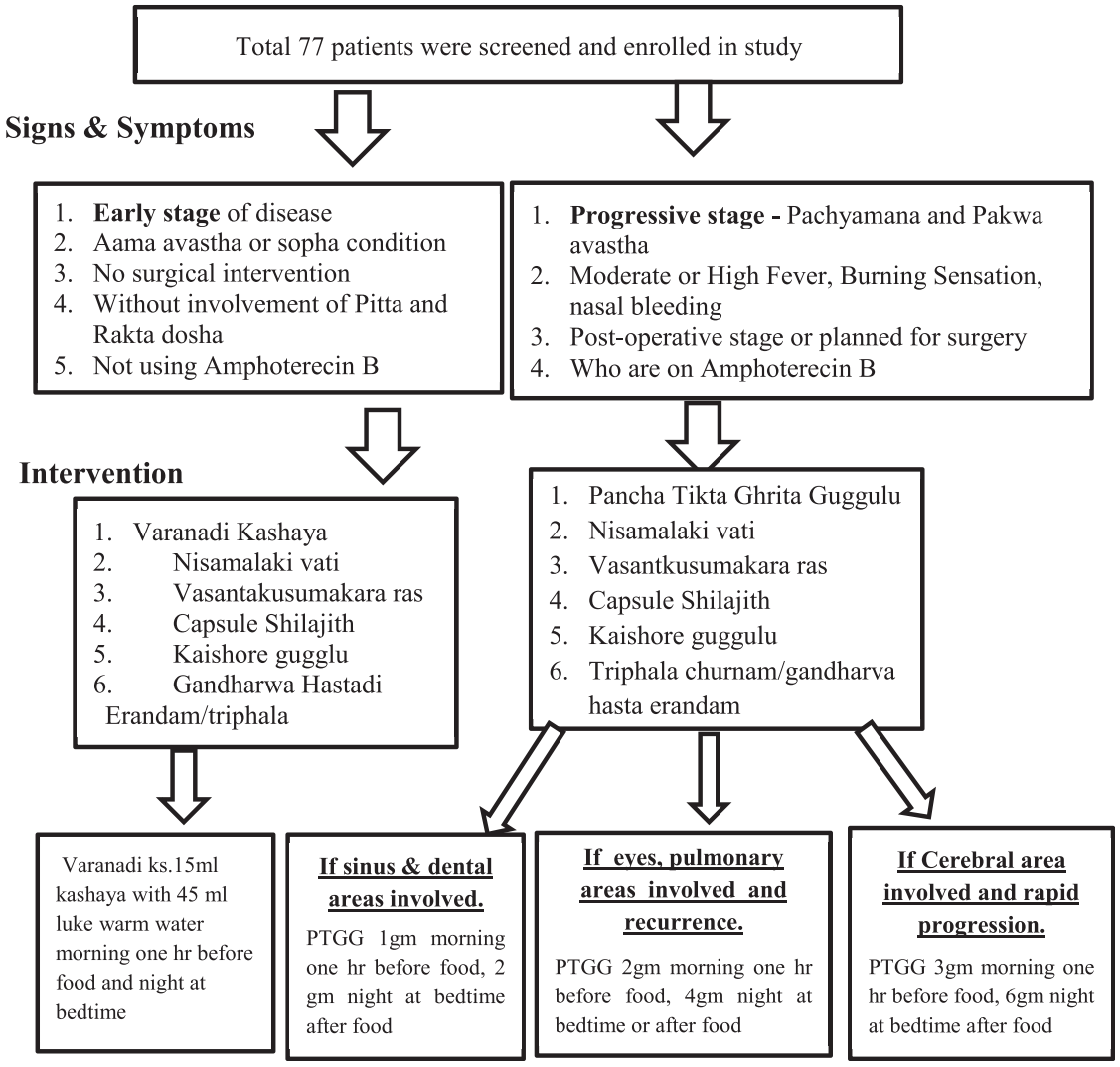

Fig. 2. Showing the rationale of treatment given in this study.

Table 1
Shows comparative analysis of VAS scale for pain in both groups.

Groups	Visual analog scale (Mean ± SD)		Within group comparison (Wilcoxan signed ranked test)
	BT	AT	
Group A	5.47 ± 1.540	1.72 ± 1.427	Z = 5.271 **p = 0.0001***
Group B	5.00 ± 2.00	4.66 ± 2.224	Z = 1.256 p = 0.209
Between Group comparison (Mann Whitney test)	Z = 1.589 p = 0.112	Z = 5.123 **p = 0.000***	

vision, proptosis, ocular pain and muscle power. The symptoms of cough, sputum, fever etc. could not be analyzed due to the insufficient numbers.

3.3. Effect of treatment on objective parameters

The analysis suggests a significant reduction of Alkaline phosphatase [ALP] and Gamma glutamyl transferase [GGT] after treatment and a mild increase in serum creatinine in both groups after treatment (Tables 3 and 4).

To compare the effectiveness of treatment before and after in both groups, Pearson Chi-Square test and ANOVA [One-way] Test was done. The test showed significant results in all 8 parameters (Figs. 3 and 4). So, the treatment was found effective in reducing all important end points like mortality, recurrence, progression, repeat surgeries, readmissions etc.

3.4. Recurrence after treatment

Recurrence rates were significantly lower in patients of Intervention group than any other groups. While contemporary non-

Table 2
Showing the distribution of patients in various clinical parameters after treatment (analyzed by Mann Whitney test).

Degree of severity of Pain after treatment								
	NA	Increase	Same	Percent decrease				Total
				25%	50%	75%	100%	
Group A – intervention PTGG	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (19.4%)	11 (30.6%)	16 (44.4%)	36 (100.0%)
Group B – control	5 (17.2%)	1 (3.4%)	5 (17.2%)	1 (3.4%)	11 (37.9%)	5 (17.2%)	1 (3.4%)	29 (100.0%)
P = 0.000*S								
Degree of severity of Swelling after treatment								
	NA	Increase	Same	Percent decrease			Complete improv.	Total
				25%	50%	75%		
Group A – intervention PTGG	8 (22.2%)	0 (0.0%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	10 (27.8%)	15 (41.7%)	3 (100.0%)
Group B – control	2 (6.9%)	1 (3.4%)	7 (24.1%)	0 (0.0%)	7 (24.1%)	9 (31%)	3 (1.3%)	29 (100.0%)
P = 0.005*S								
Ophthalmoplegia after treatment								
	NA	Partial	Same	Percent decrease				Total
				25%	50%	75%	100%	
Group A – intervention PTGG	21 (58.3%)	0 (0.0%)	5 (13.9%)	4 (11.1%)	5 (13.9%)	1 (2.8%)	2 (5.6)	36 (100%)
Group B – control	0 (0.0%)	1 (3.4%)	8 (27.6%)	15 (51.7%)	2 (6.9%)	2 (6.9%)	1 (3.4%)	29 (100%)
p = 0.0121* S								
Paralysis/muscle power after treatment								
	NA	Incoordination	Same	Percent increase				Total
				25%	50%	75%	100%	
Group A – intervention PTGG	30 (83.3%)	1 (2.8%)	2 (5.6%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	0 (0.00%)	36 (100%)
Group B – control	24 (82.8%)	0 (0.00%)	4 (13.8%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.4%)	29 (100%)
p = 0.352 NS								
Proptosis after treatment								
	NA	50% increase	Same	Percent decrease				Total
				25%	50%	75%	100%	
Group A – intervention PTGG	23 (63.9%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	2 (5.6%)	2 (5.6%)	6 (16.7%)	36 (100%)
Group B – control	13 (44.8%)	1 (3.4%)	5 (17.2%)	0 (0.00%)	3 (10.3%)	5 (17.2%)	2 (6.9%)	29 (100%)
p = 0.500 NS								
Altered sensorium after treatment								
	NA	Comatose	Stupor	Drowsy	Restless	Conscious		Total
Group A – intervention PTGG	29 (80.6%)	0 (0.00%)	1 (2.8%)	1 (2.8%)	0 (0%)	8 (22.4%)		36 (100%)
Group B – control	22 (75.9%)	2 (6.9%)	0 (0%)	2 (6.9%)	1 (3.4%)	1 (3,4%)		29 (100%)
p = 0.005* S								
Cough & Sputum after treatment								
	NA	25% decreased	50% decreased	75% decreased	100% decreased	Total		
Group A – intervention PTGG	29 (80.6%)	0 (0.00%)	0 (0.00%)	2 (5.6%)	5 (13.9%)	36 (100%)		
Group B – control	27 (93.1%)	1 (3.4%)	1 (3.4%)	0 (0.00%)	0 (0.00%)	29 (100%)		
p = 0.111 NS								
Color of Sputum after treatment								
	NA	Same	White	Scanty White	50% reduced	100% reduced	Total	
Group A – intervention PTGG	31 (86.1%)	0 (0.00%)	1 (2.8%)	1 (2.8%)	0 (0.00%)	3 (8.3%)	36 (100%)	
Group B – control	27 (93.1%)	1 (3.4%)	0 (0.00%)	0 (0.00%)	1 (3.4%)	0 (0.00%)	29 (100%)	
p = 0.084*S								
Nasal discharge after treatment- persistence								
Symptoms	NA	same	50% dec.	Complete improv	Total			
Group A – intervention PTGG	29 (80.6%)	0 (0.0%)	0 (0.0%)	7 (19.4%)	36 (100%)			
Group B – control	22 (75.9%)	4 (13.8%)	2 (6.9%)	1 (3.4%)	29 (100%)			
p = 0.039*S								
Fever/Burning after treatment								
	NA	Complete improv	Total					
Group A – intervention PTGG	36 (100.0%)	0 (0.00%)	36 (100%)					
Group B – control	28 (96.6%)	1 (3.4%)	29 (100%)					
'p = 0.265 NS								
Numbness after treatment								

Table 2 (*continued*)

Degree of severity of Pain after treatment									
	NA	Increase	Same	Percent decrease				Total	
				25%	50%	75%	100%		
	NA	same	Percent decrease			Complete improvement		Total	
			50%		75%				
Group A – intervention PTGG	29 (80.6%)	0 (0.00%)	1 (2.8%)		0 (0.00%)	6 (16.7%)		36 (100%)	
Group B – control	23 (79.3%)	4 (13.8%)	1 (3.4%)		1 (3.4%)	0 (0.00%)		29 (100%)	
P = 0.015*S									
Occular pain after treatment									
	NA	Same	Percent decreased				Post exenteration	Total	
			25%	50%	75%	100%			
Group A – intervention PTGG	12 (33.3%)	2 (5.6%)	0 (0.00%)	5 (13.9%)	2 (5.6%)	14 (38.9)	1 (2.8%)	36 (100%)	
Group B – control	11 (37.9%)	3 (10.3%)	1 (3.4%)	5 (17.2%)	7 (24.1%)	1 (3.4%)	1 (3.4%)	29 (100%)	
p = 0.074 NS									
Vision after treatment									
	NA	Same	25% Better	50% Better					
Group A – intervention PTGG	25 (69.4%)	10 (27.8%)	1 (2.8%)	0 (0.0%)					
Group B – control	18 (62.1%)	10 (34.5%)	0 (0.0%)	1 (3.4%)					
p = 0.620 NS									

Note: NA-when the clinical feature was not found even before the treatment. * S = significant. NS = Not Significant.

Table 3
Showing the effect of treatment on various bio-chemical parameters [analyzed by paired T test and Mann-Whitney test].

Parameter	Group A – Intervention PTGG			Group B – Control		
	Before treatment (Mean ± SE Mean)	After treatment (Mean ± SE Mean)	P value	Before treatment (Mean ± SE Mean)	After treatment (Mean ± SE Mean)	P value
Hb	10.64 ± 0.42	10.67 ± 0.33	0.95: NS	11.91 ± 0.48	10.52 ± 1.15	0.27: NS
TLC	10.05 ± 0.96	8.95 ± 0.57	0.16: NS	7.48 ± 0.78	11.13 ± 1.41	0.12: NS
CRP	66.87 ± 10.54	48.90 ± 9.95	0.26: NS	71.80 ± 19.31	149.00 ± 1.15	0.72: NS
Bilirubin	0.55 ± 0.03	0.60 ± 0.09	0.21: NS	0.32 ± 0.15	0.98 ± 0.19	0.13: NS
SGPT	39.71 ± 7.14	25.35 ± 3.50	0.12: NS	26.40 ± 5.57	33.00 ± 7.61	0.15: NS
Creatinine	0.88 ± 0.06	**0.93 ± 0.09**	**0.04*S**	1.26 ± 0.25	**1.31 ± 0.43**	**0.04*S**
ALP	143.85 ± 22.42	**117.01 ± 24.23**	**0.02*S**	127.28 ± 3.44	128.0 ± 1.12	1.23: NS
GGT	149.92 ± 44.32	**104.22 ± 24.36**	**0.03*S**	20.00 ± 21.36	**66.00 ± 1.12**	**0.03*S**

*Significant (P > 0.05). S = significant. NS = Not significant.

study patients at the same institution reported above 20% recurrence rates across all groups [mild, moderate and severe], the control group reports a 20.7% recurrence, with PTGG based intervention group showing only 2.8%, which was statistically highly significant on the ANOVA and Chi-square test for equality of variances.

3.5. Progression of the disease

Patients who used PTGG regime for more than 7 days showed no progression [0%] against the comparison group [24.1%] which was also found to be statistically significant on both tests.

3.6. Mortality rate

The most striking benefit seen in the PTGG intervention group, was with regards to the decreased rate of mortality. The hospital recorded a general mortality of 16.3% [194 out of 1190 admissions] which although was above the reported national average, in view of the severity and other co-morbidities in this patient subset was far lower than international figures for the disease [20–50% for rhino-cerebral. Death due to cerebral spread and CVA were the leading causes, followed by post-op deaths. Considering the fact that the PTGG intervention group had very high ocular and cerebral involvement or CNS complications, the group had no mortality [0%] reported in the entire follow up period of 3 months and also in the post follow up period of 3 months. The comparison group reported 13.8% mortality [4/29] in the same period [3 deaths due to continued cerebral spread with CVA, 1 due to acute onset SOB, presumed to be Acute Myocardial Infarction]. The benifit was found to be significantly higher in the intervention group as compared to the comparision group or even the non study patients.

3.7. Re-admission

Although the readmission rates were 11.1 in study group and 31.8 in comparison group, in reality 2 of the 4 readmissions in study groups were due to false alarm due to MRI done by both patients after discharge, (with no-prior MRI for comparison), which showed some residual disease. Clinically both patients were much better and admitted only by virtue of MRI findings, and discharged shortly. Hence use of PTGG regimen showed significant reduction in need for readmissions, seen on analysis as well.

3.8. Repeat surgeries

The need for repeat surgeries was 13.9% (5/36) in the study group as against 31% (9/29) in the comparison group and this difference was statistically significant.

Table 4
Showing Distribution of patients in various clinical outcomes after treatment [analyzed by Pearson Chi-Square test].

	Group A – Intervention PTGG (%)	Group B – Control (%)	P value
Subjective wellbeing after treatment			P = 0.00*S
Worse	–	27.6*	
Same	5.6	48.3*	
Better	52.8**	24.1*	
Much Better	41.7**	–	
Presence of persistent symptoms			P = 0.01*S
Yes	11.1	48.3	
No	88.9	51.7	
Repeat surgeries			P = 0.02*S
Yes	13.9	31.0	
No	86.1	69.0	
Disease progression after treatment			P = 0.02*S
Yes	0	24.1	
No	100.0	75.9	
Disease recurrence after treatment			P = 0.02*S
Yes	2.8	20.7	
No	97.2	79.3	
Death during treatment			P = 0.02*S
Yes	0	13.8	
No	100.0	86.2	
Readmission			P = 0.02*S
Yes	11.1	31.0	
No	88.9	69.0	
Objective assessment			P = 0.00*S
Worse	–	27.6	
Same	5.6	48.3	
Better	52.8	24.1	
Much Better	41.7		

*Significant: P < 0.05. NS = Not Significant. S = Significant.

3.9. Persistence of symptoms

Persistent symptoms like pain or discharge from surgical/disease site after completion of treatment was seen in 11.1% [4/36] in comparison to 48.3 [14/29] in the other group. The difference was statistically significant by both the tests.

3.10. Subjective wellbeing

In the study group 94.6% of patients reported subjective wellbeing in overall quality of life, appetite, energy levels and decrease in pain and swelling with 41.7% among them reporting being "much better" in contrast to 24.1 % of comparision group who felt "better". This was statistically significant in both tests.

4. Discussion

4.1. Need for adjuvant therapy

Adjuvant therapy of Ayurveda was necessitated on multiple grounds like pathophysiological appropriateness in view of the primary role of immune deficiency in the disease, non-availability of anti-fungal, the high cost of antifungals etc.

4.2. Ayurvedic considerations and diagnosis

Many experts have opined Mucor-Mycosis to be correlated with different disease entity described in Samhitas of Ayurveda. They are enumerated along with explanation of the authors for not accepting the possibility. The Primary reasons for all of them in common being, them not having any corelation with prameha [Diabetes] and the fact that they are not described as life threatening diseases.

Dusta Pratisyaya and puti nasya: [8, ChikitsaSthana 26/110–113] described under nasagataroga as a consequence of long-term neglect of peenasa [rhinitis] was not seen in post covid mucor mycosis. No spread of the disease to other parts from the nose has been described in classics. Nasal discharge which is an essential feature of Dustapeenasa was uncommonly seen in patients.

Raktaja Pratisyaya [17 and 8, ChikitsaSthana 26/114]: The rarity of clinical features of pitta and rakta and of blood-stained nasal discharge, apart from its spread to other areas, all go against this diagnosis.

Krimi: [18, 7 kruminidana 7/7–10] The description of krimis in all the texts classically refers to ecto parasites, nematodes, cystodes or maggots, although invisible microscopic krimis are described. If accepted, the most apt description would be abhyantara kaphaja krimis. But the clear description of their taking origin in amasaya and migrating to other places, gross morphological description and color of the krimis described, do not match with mucor.

Asthi majjagata Kusta [18, kustanidanam 49/29]: Asthimajjagatakusta is described as happening only if origin of kusta in twak, rakta, mamsa, lasika is neglected (anupakranta) and not as an original manifestation i.e., there should be preceding skin manifestation for a long period of time.

Visarpa: [8, ChikitsaSthana 21/25] Although acute in onset, rapidly spreading and life threatening, known to involve only rakta-lasika-rasa-mamsa; but not known to involve asthi, majja.

Vata Rakta [9, nidanasthana 16/7]: Predominantly involves joints. It begins in feet or hands and spreads like aakhuvisha i.e.; very slowly.

Athimantha [17, UttaraTantra 6/11]: although many ocular features and rapidity match the description, it is not known to spread to other organs and is strictly a netra roga [ocular disease].

Why VatajaVidradhi:

Mucor mycosis including the post covid variety has shown a very strong association with uncontrolled diabetes mellitus and Diabetic Keto Acidosis (DKA).

DKA has been clearly described in samhitas as vataja avastha of prameha or Madhumeha [urine with color, taste and consistency of honey] [8 NidanaSthana 4/44] and prameha-pitikas are closely described as complications of madhumeha. Vidradhi is described as a variety of pramehapitika-where in doshas are based in bone (Asthi samashrita) or mahamula [deep seated] and is characterized by rapid liquefaction (seeghra vidaha or paka). Repeated mention of spoilt food, alcohol is made in nidana as an oblique reference to fungus, apart from raktapradushakara bhavas (in this case steroids and other drugs). Vidradhi is clearly described as a disease that can happen externally and, in internal organs as well as in marmas [Siras being a pradhana marma] which also correlates with the multi-system presentation of Mucormycosis. Although it is more common in mamsala areas [9, nidanasthana, 11/1–6] [areas with soft tissues and muscle] and with dushtamedodhatu [vitiated adipose tissue] as is seen in prameha.

The features of vataja vidradhi such as severe pain,black or reddish hue, variegated surface or variegated origin (udgama), rapidly spreading (sarpana), suppuration (prapaka) also lend a strong co-relation.

4.3. Criteria for selection of drug [19]:

Drug was selected mainly based on following parameters.

1. **PTGG** [9, chikitsasthanam 21/57–61] selected as it is specifically indicated in vidradhi and vrana [post-operative wound healing] [roga pratyanika]; in severe vata vyadhi and is rakta prasadana [dosha pratyanika]; is prameha hara even in vataja pramehas

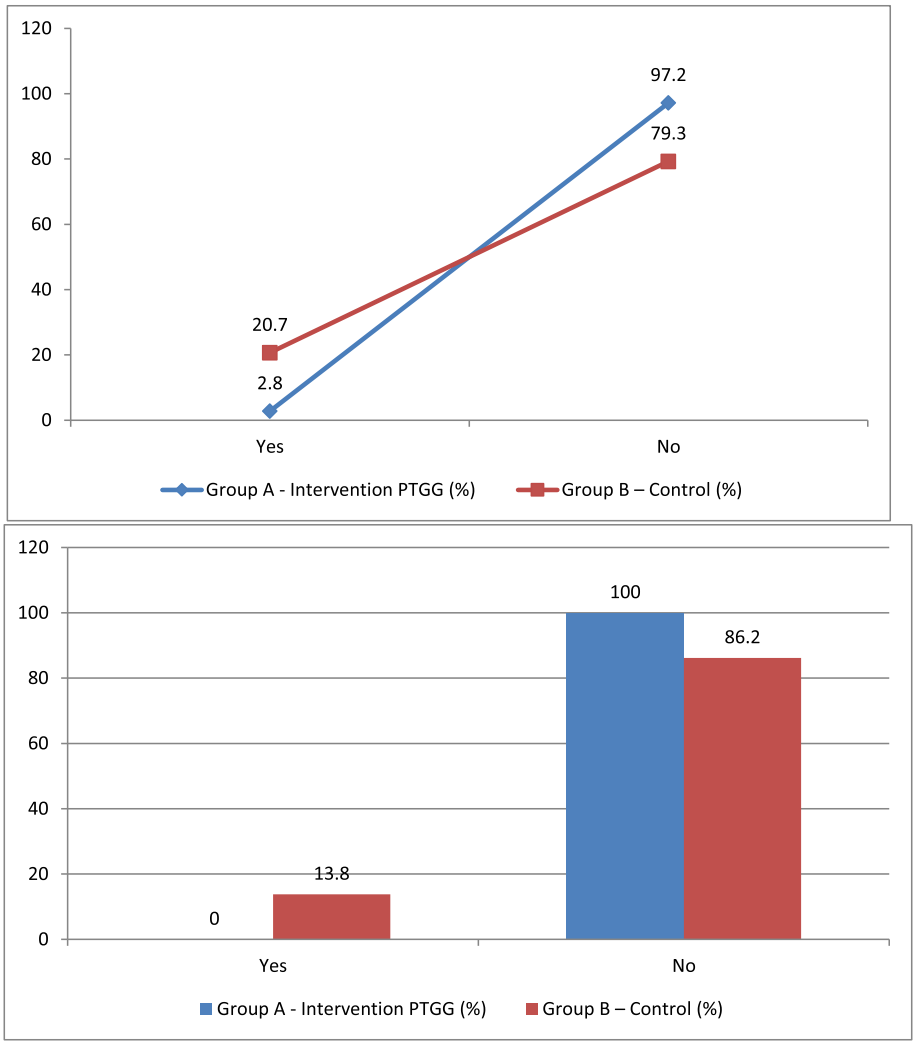

Fig. 3. Showing disease recurrence [above] and mortality in both groups [below].

[advanced stage of diabetes mellitus] as it is a sneha preparation, Visha hara due to pancha tiktas [could counteracts steroid and anti-fungal toxicity], specifically indicated in urdhwa jatru rogas [disorders of head and neck] and in asthigata vata [vata in bone] a very common site of mucor, and due to it being sroto rodha hara [clears blocked channels]thus may counteracts the vaso-occlusive property of mucor, and cholestatic jaundice caused by Imidazoles and is described in section on vata vyadhi [prakarana vishe-shatwam]. It is noteworthy that most of the symptoms of mucor mycosis (hanu bheda – splitting pain in lower jaw, akshi bheda – splitting pain in eyes, danta bheda – splitting pain in teeth, mukha sosha – dryness of mouth ghrana nasha – anosmia, karna shula-pain in ears, vartma stambha – ptosis, akshivyudasa-opthalmoplegia, timira–blindness, shankabheda–splitting pain in temples, shirahsula-headache), [31] or complications. (pak-shaghata-Hemiplegia) are all vata based [8, sutrasthana 20/11]. It is also helpful in bony repair and regeneration being a tikta rasa ghrita kalpana [ghee processed with bitter herbs]

2. **Varanadi kwatha**: [9, SutraSthana 15/21–22] varunadi was selected for being disease specific – extensively used in multiple ways in abhyantara vidradhi. (In-accessible suppurative disorders), dosha specific-in vata, kapha and ama doshas and site specific in head region. And in view of its ushna and teekshna gunas it was avoided in patients with rakta or pitta involvement, and on amphotericin B [having a similar profile] and in later stages of abscess due to its ability to liquefy.
3. The other drugs were selected due to their indications in vataja avastha of prameha and in vidradhi, while triphala was selected for anulomana and offset toxicity of bhallataka if any.

4.4. Need for two interventions

The sudden surge in cases of a rare disease with the whole country being unprepared to face it with adequate anti-fungals and ENT surgeons needed different approaches if patients got ampho-tericin-b and/or surgical debridement, the proportion of which wasnt clear at the start of this study Hence for patients recieving amphotericin -b and /or surgery a milder regimen with raktapra-sadaka property was planned ,while for those not recieving them a more aggressive regimen with varunadi kashayam was planned, a rakta-prasadaka one [PTGG].

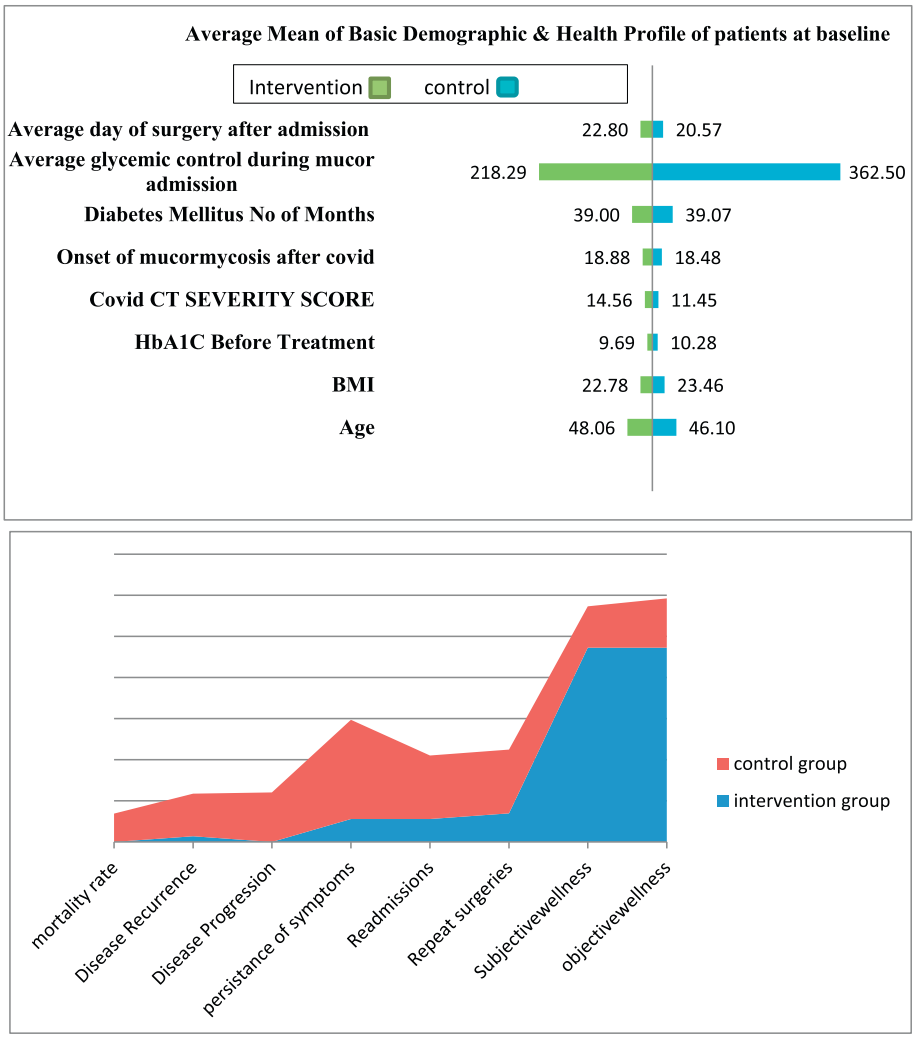

Fig. 4. Showing baseline demographic data [above] and important clinical outcomes [below].

4.5. Sample size and mean duration differences

Varanadi Kashaya group had a low sample size and lesser mean duration due to the following reasons.

The initial phase with low amphotericin -b availability and low surgical rates coincided with maximal patient reluctance to be on ayurvedic adjuvants due to multiple factors like-apprehension of side-effects with combined use, perception that using ayurveda might not enable them to get surgery and anti-fungals, ushna nature of the drug in hot summer, frequent nil per oral orders for diagnostic nasal endoscopy etc. the nature of the drug to produce paka [liquefaction] if given in later stages of disease, and inaccessibility of region for drainage, extensive use of surgery and amphotericin -b later on precluded its use. Despite these varunadi showed a lot of promise in the chronic stages of chronic sinus venous thrombosis and in very early phases; but as the sample size was too low, it was excluded from analysis.

In case of PTGG the good response of the few initial hesitant seekers, made sure that it was sought by a good number of patients, despite having to take high number of tablets [250 mg*9 g = 36 tabs] and despite some of the factors mentioned earlier persisting.

4.6. Control/Comparision group

Due to multitude of reasons as discussed in sec. 6 there was large number of defaulters in follow up of the controls. The same reasons also led to significant drop-out in intervention group as many patients felt using ayurvedic medicines could deprive them of a surgery or amphotericin- B, but the initial relationship established with the Ayush team ensured a follow-up in his group. As the mean duration of therapy was only 2.14 days, it was decided to use this group as the control group for comparison. Although the planned duration of therapy was 45 days due to dropping out after using for atleast 8 days, the mean duration was 34.18 days in study group.

4.7. Lab parameters

Despite the constraints discussed in sec. 6 the parameters showed an considerable improvement in CRP and LFT in majority of patients, with reduction of ALP and GGT [elevation presumed to be due to imidazole toxicity]. The difference was statistically significant. It is presumed to be due to visha hara and kamala and sroto

rodha hara effect of PTGG. There was a marginal rise in serum creatinine, presumably due to use of amphotericin -b and a marginal drop in hemoglobin, (although all other cell lines remained normal) presumably due to the chronic inflammatory state of the disease or poor nutrition. There was a significant improvement in the average blood glucose levels of the subject group than the comparison group despite similar degree of modern medical intervention, presumably due to the prameha hara effect of the PTGG regime. Due to Institutional non-availability of MRI which would have been a gold standard, CT scans were done which showed a very good improvement but are not included in the analysis. Nasal endoscopies could not be studied due to prevalent working conditions described.

4.8. Adverse events

In general, both regimen were well tolerated by the participants and no serious adverse events were seen, despite the high dosages used. PTGG regimen caused nausea and vomiting in 3 patients, which was reversible with time or with suitable anupana. One patient reported severe itching, needing discontinuation of drug; but the itching did not recur on self-reintroduction by patient and was presumed to be due to posaconazole. One patient reported of epistaxis after 36 days usage, which on evaluation was found to show a pattern consistent with Vitamin K deficiency and responded well to its management by supplementation of vitamin k.

Varunadi regimen patients reported nausea and vomiting, features of liquefaction with consequent increase in fever, pain etc needing discontinuation due to intra-cerebral location of abscess in one patient while one patient reported rashes also needing discontinuation.

5. Significance of the study

In challenging circumstances against a severe life-threatening disease, with a severely compromised modern medical management [where average time to surgery from admission was 22 days, average sugar levels were much above accepted levels, and amphotericin-B was either un-available or sub-optimal] and non-usage of shodhana therapies like rakta-mokshana, the results of this study are very encouraging. It emphasizes the need to further explore the Host response modification approach of Ayurveda.

This is also the first of its kind, wherein Ayurveda was used and studied in a severe life-threatening disease with positive results. It provides the economic template for cost-effective Integrative management, as at an additional cost of Rs. 5700 per patient, it may be possible to cut down the duration of the expensive anti-fungals.

6. Challenges and limitations of the study

The study was conducted during the height of the pandemic and in a modern medical Institute with no integrative infrastructure and consequently placed a lot of challenges. Sub-optimal support of ground staff along with unprecedented work-load led to poor co-ordination between teams, patients being referred to multiple institutions spread across the city, poor educational status of patients leading to apprehensions regarding combined use, an inherent bias for surgery and anti-fungals due to social media blitz-krieg and a notion that opting for Ayurveda could delay or deny surgery leading to significant drop-outs from therapy and follow-up. Inaccessibility to local lab, sudden discharges without mutual co-ordination led to low lab sampling, Constant rotation of associated investigators, Hot and humid weather conditions and poor research infrastructure were the different kind of challenges faced.

As a consequence of the pandemic driven resource crunch, there were some technical limitations like non-availability of matched controls, lack of institutional MRI which is the usual gold standard,nasal endoscopic non-correlation,lack of universal testing etc. The duration of the intervention was based on logistics only, but it needs to be emphasized that, as mucormycosis is a chronic disease, long term medications and follow up will be needed to prevent late recurrences.

7. Future scope of the work

This study showed very promising results and in the long run serves as a pilot study for more rigorously planned randomised clinical trials to evaluate the host response modification approach of ayurveda not only in mucormycosis but in other infections as well. In the short run it gives enough ground for using ayurveda as adjuvant for patients with severe or recurrent mucor mycosis to reduce mortality and morbidity. it also sets a template for judicious integration not only in challenging times but in healthier times as well. it also enlists the issues that could be faced by future attempts to integrate two systems of medicine,and thus helps for better planning for policy makers.

8. Conclusion

The study gave clinically and statistically significant results based on the principle of identifying mucor-mycosis as vata-pradhana vidradhi. Pancha tikta ghrita guggulu based regimen seemed to help across the entire spectrum of mucor mycosis including ocular, cerebral and pulmonary, apart from mild and moderate cases. It produced significant reduction in progression, recurrence of the disease and reduced mortality significantly, and thus reduced the need for re-admissions and repeat surgeries, and also gave subjective and objective wellbeing. It was tolerated very well by pre and post-operative patients and seemed to reduce the toxicity of posaconazole and amphotericin-B as well and so was safe for concomitant use despite the higher dosages used, the study seeks to emphasize the importance of host response modification-based approach of Ayurveda against the germ based approach of Modern medicine and also gives evidence for their thoughtful concomitant usage even in life-threatening disease. It sets the template for future research not only in mucor-mycosis, but for the direction of health planning in India and world at large by virtue of its pathophysiological appropriateness and cost-effectiveness.

Sources of funding

This study was funded by Department of AYUSH, Ministry Of Health and Family Welfare, Government of Telangana, India. Letter No: 446/c/2020, Office of Director, Department of AYUSH, Telangana State, Secunderabad.

CRediT author statement

Adluri Uma Shankar Prasad: Conceptualization, Methodology, Investigation, Data-collection and supervision, Writing-original draft and Review, Supervision, Project administration. **Srikanth Babu Perugu:** Methodology, Resources, Writing-reviewing, Supervision, Project administration, Funding acquisition.

Conflict of interest

The authors have no conflicting interest to disclose.

Acknowledgments

The Authors acknowledge the contributions of the following in this study.

Dr. V.S. Alagu Varsini, IAS, Commissioner, Department of AYUSH, Telangana State for her initiation, planning, overall supervision, mentorship, administration, Financial and all round support for this study, without which this study would not have happened.

Dr. Akash Chandra Tripathi, M.D. Ayurved (BHU), Director: Chandra Prakash Ayurved Sansthan, Varanasi/Gorakhpur for his immense contribution in Conceptualizing of this study.

The Participating investigators, **Dr. Sunitha Kotla**, Post graduate in Dept. of Kaya Chikitsa, **Dr. Lavanya Gali**, House surgeon, **Dr. Rambabu Salana**, Post graduate in Dept. of Shalakya, **Dr. Shiva Boora**, Post graduate in Dept. of Shalakya; and the other post-graduates, all from Dr. BRKR Govt Ayurvedic Medical College, Hyderabad for their tremendous contribution in providing and care of study patients and data collection.

Dr. Ashutosh Kumar Pathak, M.D (Ay.), Ph.D, Assistant Professor, Department of Rachana Sharir. Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University for his support in manuscript preparation and data analysis.

Dr. (Mrs) E. Naga Mallika, MVSc.Ph.D.FMRC, Associate Professor, Department of Livestock Products Technology, NTR College of Veterinary Science, Gannavaram, Andhra Pradesh for her valuable support in statistical analysis and visualization of the paper.

Mr. Mir Wajahat Ali for their contribution towards Formal analysis of the study and software support.

Mr. Varada .C and his team for their support in creating the visualizations for this paper, despite their hectic schedule.

The Staff of Gandhi Hospital and the Dept. of E.N.T in particular for their Support.

Dr. K Anasuya, P.G professor-A.D[Ay]i/c for her overall support.

References

[1] https://covid19.who.int/. [Accessed 15 September 2021].
[2] https://covid19.who.int/region/searo/country/in. [Accessed 29 September 2021].
[3] https://www.uptodate.com/contents/mucormycosis-zygomycosis [accessed 29.09.21]. Author: Gary M Cox, Section Editor:Carol A Kauffman, Deputy Editor: Keri K Hall.
[4] https://www.indiatoday.in/india/story/over-45-000-cases-of-mucormycosis-reported-in-country-1830590-2021-07-21/. [Accessed 9 October 2021].
[5] Ibrahim AS, Edwards Jr JE, Bryant R, Spellberg B. Economic burden of mucormycosis in the United States: can a vaccine be cost-effective? Med Mycol 2009;47(6):592–600. https://doi.org/10.1080/13693780802326001.
[6] https://www.tribuneindia.com/news/ludhiana/only-three-mucormycosis-cases-in-10-days-lowest-so-far-316315/. [Accessed 9 October 2021].
[7] Adluri Uma Shankar Prasad, Tripathi Akash Chandra. Understanding COVID - 19 pandemic – a comprehensive Ayurvedic perspective. J Ayurveda Integr Med 2022;13(1):100348. https://doi.org/10.1016/j.jaim.2020.08.001. ISSN 09759476.
[8] Sharma PV, editor. Charaka Samhita of Agnivesa. 9th ed. Varanasi: Chaukambha Viswabharati; 2018.
[9] Murthy KRS, editor. Astanga Hridaya of Vagbhata. 1st ed. Varanasi: Chaukambha Publications; 2014.
[10] Krishnanand Maharaj. Ras Tantra Sar Va Siddha Prayoga Sangraha (Hindi) Krishna Gopala Ayurved Bhavan; Ajmer. 17th ed. 2006.
[11] (Hindi commentary). In: Mishra SN, editor. Bhaishajya Ratnavali of Sen Govind Das (Sanskrit) Varansi. 1st ed. Varanasi: Chaukhamba Surbharati Prakashan; 2005.
[12] Gupta V, Keshari BB, Tiwari SK, Narasimha Murthy KH. A comparative study of *Shilajatu and Asanadi Ghana Vati* in the management of *Madhumeha* w.s.r. to type-2 diabetes mellitus. Ayu 2016;37:120–4.
[13] Murthy PHC, editor. Sharangadhara Samhita of Sharangadhara, Madhyama kanda, chapter 7, verse 70-81. 2nd ed. Varanasi: Chaukambha Sanskrit Series; 2007.
[14] Sharma S, editor. Shashileka Sanskrit commentary of Indu, Astanga Samgraha of Vagbhata, Chikitsasthana; Vidradhi vriddhi chikitsitam: chapter 15, verse 25. 1st ed. Varanasi: Chaukhambha Sanskrit Series; 2006.
[15] Kamat SD, editor. Bhava Prakasha nighantu of Bhavamisra, Chapter Hareetakyadi varga, verse 42-43. 1st ed. Varanasi: Chaukambha Publications; 2009.
[16] https://www.physio-pedia.com/Visual_Analogue_Scale. [Accessed 15 September 2021].
[17] Panigrahi H, editor. Susrutha Samhita of Susrutha, Uttara Tantra, Chapter 24, verse 13. 1st ed. Varanasi: Chaukambha Orientalia; 2014.
[18] Tripathi B, editor. Madhavanidana of Sri Madhavakara. Varanasi: Chaukambha Surbharathi Prakashan; 2006.
[19] Mahadevan L. M.D, Ph.D. Director & Chief Consultant of Sri Sarada Ayurveda Vaidya Sala Derisanamcope, Kanyakumari. Personal Communications.