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A Comparative Study to Evaluate the Efficacy of Panchtikta Ghrita and Bisphosphonate in the Management of Postmenopausal Osteoporosis (Asthikshaya): A Study Protocol

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Abstract---Background: *Asthikshaya* is a disorder related to bone degeneration. It is similar to osteoporosis. A disturbance in bone remodeling is the underlying mechanism for decrease in normal bone density. Osteoporosis is caused due to low bone mass, and micro architectural breakdown of bone tissue. In India, Osteoporosis is an emerging public health problem with increasing numbers of elderly. Women are more prone as compared to men. Risk of Osteoporosis even increases at the stage of menopause, which is physiological transition period of hormonal imbalance. Aims and objectives: To compare the efficacy of *Panchtikta Ghrita* and Bisphosphonate in the management of Postmenopausal osteoporosis (*Asthikshaya*). Methodology: For proposed study, Postmenopausal women will be assessed for BMD by organizing special camp for assessment of BMD, Recruitment of women having T^{sc} score -2.5 to -1 subjects will be randomly divided into two groups. Group A will be given *Panchtikta Ghrita* in the dose of 15 ml orally on empty stomach for 90 days and Group B will be given *Bisphosphonate* (as a standard drug) in dose of 70 mg orally once weekly on an empty stomach for 90 days. The record of assessment will be taken at zero day, 30th day, 60th day and 90th day.

Keywords---asthikshaya, bisphosphonate, BMD, panchtikta ghrita.

Introduction

Osteoporosis is defined as a skeletal disease, caused due to micro-architectural deterioration of bone tissue resulting in bone fragility results in increased risks of fractures.^{1,2} In India, Osteoporosis is an emerging public health problem with increasing numbers of elderly.³ Women are more prone compared to men.⁴ This risk even increases at menopause, which is physiological transition period of hormonal imbalance. Usually, average age of menopause is around 50 years, with limits between 45 and 55. Postmenopausal osteoporosis affects over one third of all postmenopausal women with increasing morbidity and mortality because of its association with fractures.^{5,6} According to menopausal Society, *Bisphosphonates* is a first line of drugs therapy in Osteoporosis or who are at high risk of fractures.⁷ Osteoporosis is diagnosed on the basis of T-score of BMD.⁸

Asthi kshaya is a degenerative disorders mentioned in *Ayurvedic* literatures where there is *Kshaya* of *Asthi dhatu*. In Osteoporosis is a condition there is a decrease in bone mass which leads to the fragility and fracture of bones. Hence *Asthi kshaya* may be compared to Osteoporosis. According to the principal of *Ashrayashrayi bhava*, *Vata prakopa* is the *nidan* of *Asthi kshaya*.⁹ *Asthi dhatu* and *Vata dosha* are inversely proportional to each other i.e. when the later is increased the former decreases. The *lakshanas* of *Asthi kshaya* described in different *Samhitas* are *Asthi shool*, *toda*, *sandhishaitilya*, *kasha-roma-nakha-danta vikara*, *dourbalya* and *rukshata* etc.^{10,11,12,13}

According to Ayurveda, *Asthi kshaya* is caused due to imbalance of *Vata dosha* which is advised to be treated with the herbs having *Katu* (bitter) and *Tikta* properties.¹⁴ *Panchatikta Ghrita*¹⁵ is one such formulation having a combination of five main drugs with *katu* and *tikta* properties. It is a combination of *Azadirachta indica* (*Nimba*), *Trichosanthes dioica* (*Patola*), *Solanum surattense* (*Kantakari*), *Tinospora cordifolia* (*Guduchi*), and *Adhatoda vasica* (*Vasa*).

Rationale of the study

Post menopause is an unavoidable phase in female's life cycle and its major impact is on bones. According to Ayurveda, Old age is considered as the *Vata* dominant phase. This study will focus on *Asthi kshaya* in relation to *vata vriddhi*, having *Ashrya-Ashriyi Sambandh*. *Tikta* rasa dravya are specifically *Vayu* and *Akash* mahabhuta pradhan,¹⁶ hence *Panchatikta ghrita* is selected. According to modern medicine, *Bisphosphonate* is selected as a standard control which is known source of calcium.¹⁷

Aim and Objectives

Aim: To compare the efficacy of *Panchatikta Ghrita* and Bisphosphonate in the management of Postmenopausal osteoporosis (*Asthi kshaya*).

Objectives

- To correlate the clinical findings of *Asthi kshaya* mentioned in *Samhita* with Postmenopausal Osteoporosis.

- To study the efficacy of *Panchtikta Ghrita* on BMD in Postmenopausal Osteoporosis (*Asthikshaya*).
- To study the efficacy of Bisphosphonate on BMD in Postmenopausal Osteoporosis(*Asthikshaya*).
- To compare the efficacy of *Panchtikta Ghrita* and Bisphosphonate on BMD in Postmenopausal Osteoporosis (*Asthikshaya*).

Case Definition: A postmenopausal woman with BMD (by Quantitative calcaneal ultrasound) T score between -2.5 to -1.

Research Question: Whether *Panchtikta Ghrita* is more effective than Bisphosphonate in Postmenopausal Osteoporosis (*Asthikshaya*)?

Hypothesis

- Null Hypothesis: *Panchtikta Ghrita* has no effect on Postmenopausal Osteoporosis (*Asthikshaya*) in comparison with Bisphosphonate.
- Alternative Hypothesis: *Panchtikta Ghrita* is more effective than Bisphosphonate in Postmenopausal Osteoporosis(*Asthikshaya*).

Study type

Trial design: A Randomized open label Controlled clinical trial.

Methodology

Place of Study: This study will be conducted in Mahatma Gandhi Ayurved College Hospital & Research Centre, Wardha.

Registration Number: Registered for CTRI, Registration no. is Awaited.

Composition & characteristics of trial drug:^{18,19,20,21,22}

Table 1
Contents of Panchtikta Ghrita

Sr. No.	Name of the Drug/ Botanical Name	Rasa	Guna	Virya	Vipaka	Karma
1.	Nimba (<i>Azadirachta indica</i> A Juss)	Tikta, Kashaya	Laghu, Snigdha	Sheeta	Katu	Laghu, grahi, hridya, kshata- kshayaghna
2.	Vasa (<i>Adhatoda vasica</i> Nees)	Tikta, Kashaya	Laghu, Ruksha	Sheeta	Katu	Hridya, prameha, kushtha, Kshayaghna
3.	Patola (<i>Trichosanthes dioica</i> Roxb.)	Tikta,	Laghu, Ruksha	Ushna	Katu	Tridoshashamaka, vrishya, rochana- deepana,
4.	Guduchi (<i>Tinospora cordifolia</i> (Willd)	Tikta, Kashaya	Guru,, Snigdha	Ushna	Madhura	Tridoshashamaka, rasayana, balya, deepana, Vatahara, Kshayaghna
5.	Kantkari	Katu,	Laghu,	Ushna	Katu	Grahi,

<i>(Solanum indicum Tikta Linn.)</i>	<i>Ruksha, Tikshna</i>	<i>hridaya,pachni, Agnimandyajeeta</i>
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Eligibility Criteria

Inclusion criteria

- Postmenopausal women of age group between 55 to 65years.
- Postmenopausal women with BMD (by Quantitative calcaneal ultrasound) T score between -2.5 to -1.
- Postmenopausal women with controlled NIDDM, Hypertension and/or Dyslipidemia.

Exclusion criteria

- Females with BMD (t-score) above -1.
- Women with Menopause caused due to hysterectomy.
- Patients with Rheumatoid arthritis, Gouty arthritis and any chronic systemic disorders.
- Known case of Hyperparathyroidism, Tuberculosis of bone Osteomalacia and any genetic disorder.
- Patient with CKD (Chronic Kidney disease).

Withdrawal criteria

- Patient unwilling to continue the treatment.
- If any types of adverse effect seen.

Sample size

Based on previous studies the minimum sample size calculated is 22 in each of the groups with α -value = 0.05, α -value = 0.01 and 90% power of the study. So the sample size is calculated by using following formula. (Reference article- Munshi R, Joshi S, Panchal F, Kumbhar D, Chaudhari P. Does Panchatikta ghritha have anti-osteoporotic effect? Assessment in an experimental model in ovariectomized rats. J Ayurveda Integr Med. 2019 Nov 7:S0975-9476(19)30033-6.)

$$k = \frac{n_2}{n_1} = 1$$

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_1 = \frac{(1.03^2 + 1.03^2/1)(1.96 + 1.28)^2}{1^2}$$

$$n_1 = 22$$

$$n_2 = K * n_1 = 22$$

$\Delta = |\mu_2 - \mu_1|$ = absolute difference between two means

σ_1, σ_2 = variance of mean #1 and #2

n_1 = sample size for group #1

n_2 = sample size for group #2

α = probability of type I error (usually 0.05)

β = probability of type II error (usually 0.2)

z = critical Z value for a given α or β

k = ratio of sample size for group #2 to group #1

In consideration of 10% dropout, 30 participants will be assigned in each group. Criteria for discontinuing or modifying allocated interventions: Subject will be removed from the study, if any unwanted side effects appears or subject is diagnosed with any major illness during study.

Follow up

During treatment, patient will be called on 30th, 60th and 90th day for confirmation of regular medication and for assessing *Asthishool* (pain in bones), *Sandhishool* (pain in joints), *Katishool* (low backache) and *Keshapatan* (HairFall). BMD, Serum Alkaline Phosphatase(ALP), Serum 25(OH)D levels and Lipid profile will be done on baseline & on 90th day

Outcomes

Primary outcomes include evaluation of effect of *Panchtikta Ghrita* on Postmenopausal Osteoporosis by Bone mineral Density (BMD) assessment after and before treatment. Secondary outcomes involve evaluation of effect of Total Serum Alkaline Phosphatase(ALP), Serum 25(OH)D levels and Lipid profile and subjective parameters.

Table 2
Interventions table

Group	Group A	Group B
Sample size	30	30
Intervention	Panchtikta Ghrita With Lukewarm water	Bisphosphonate (Alendronate) With water
Dose	15 ml PO once a day	70 mg PO once weekly
Follow Up period	30 th , 60 th , 90 th day	30 th , 60 th , 90 th day
Total study duration	90 days	90 days

Schematic diagram of Study methodology

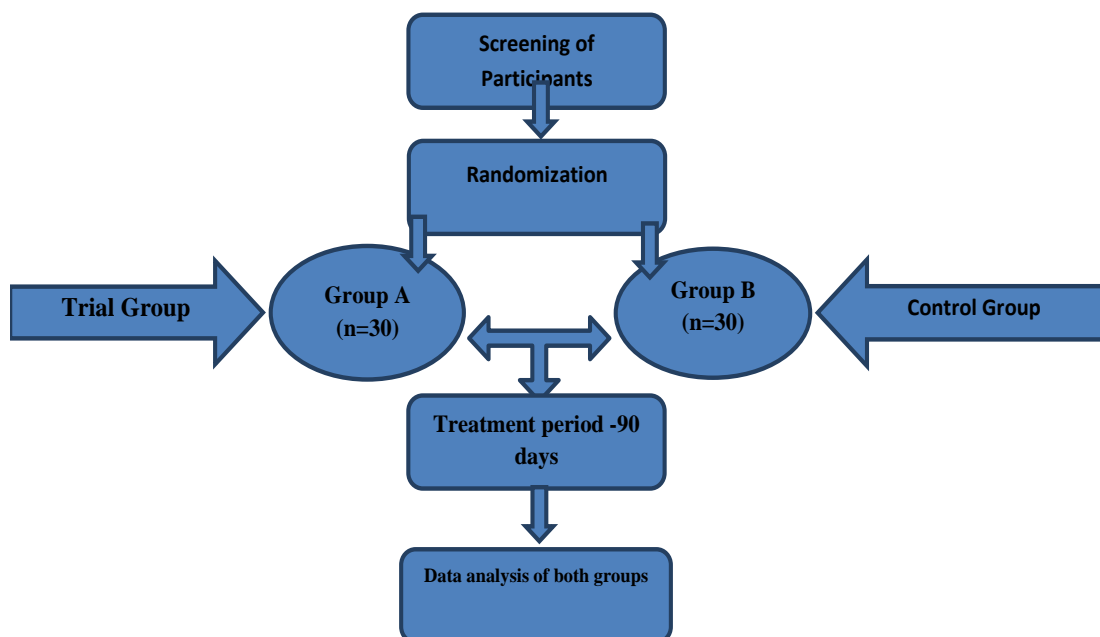


Table 3
Study schedule

Day	0	30	60	90
Time point	Visit 1	Visit 2	Visit 3	Visit 4
Allocation & Informed consent	*			
Medication to group A	*	*	*	*
Medication to group B	*	*	*	*
BMD (Bone Mineral Density)	*			*
Total Serum Alkaline Phosphatase(ALP)	*			*

Serum 25(OH)Dlevels	*	*
Lipid profile	*	*

Time duration: The treatment duration for the patients is 90 days.

Recruitment: Patients who fulfill inclusion criteria will be enrolled and randomly recruited in two groups by lottery method.

Data collection Method: The demographic data (age, sex, nationality) will be recorded at the time of enrolment. Patient will be investigated at baseline & on completion of treatment i.e. on 90th day

The follow-up during treatment will be of every 15th day for medication adherence and adverse event if any. All information will be recorded in the structured CRF

Objective Criteria

- BMD (Bone Mineral Density)
- Total Serum Alkaline Phosphatase(ALP)
- Serum 25(OH)D levels
- Lipid profile

Subjective Criteria

- *Asthishool* (pain in bones)
- *Sandhishool* (pain in joints)
- *Katishool* (low backache)
- *Keshapatan* (Hair Fall).

Data management: The data coding will be done by principle investigator.

Statistical Method: Descriptive and analytical statistics will be done. The normality of data will be tested by Shapiro-Wilk test. If the data followed normal distribution parametric tests (independent sample t-test) will be used and if the data does not follow normal distribution non-parametric test (Mann Whitney U test) will be used.

Ethics and dissemination: Institutional Ethics committee has approved the study. The IEC approval no. is MGACHRC/IEC/October- 2020/138.

Consent assent: Patient will be given detail information regarding intervention in his own language. Then written consent will be taken from patients before starting the study. During study the confidentiality will be maintained.

Dissemination policy: Data will be disseminated in the form of paper publication and presentation. Authorship eligibility guidelines and any intended use of professional writers. Informed consent material Informed.

Discussion

Numerous studies established for *Asthikshaya* like Two animal studies are on ovariectomised rats and steroid-induced osteoporosis, Other human study is on osteopenia of male & female, In another two studies, Natural calcium is taken as intervention in postmenopausal osteoporosis. This study will be focused on only postmenopausal osteoporotic women to compare the effect of *Panchatikta ghrita* & Bisphosphonates, the firstline treatment of postmenopausal Osteoporosis treatment.

Asthikshaya is one of the degenerative disorders mentioned in *Ayurveda* where there is *Kshaya* of *Asthi dhatu*. In Osteoporosis, there is a decrease in bone mass which leads to the fragility and fracture. Hence *Asthikshaya* may be compared to Osteoporosis. *Vata prakopa* is the *nidan* of *Asthikshaya*, according to the principal of *Ashrayashrayi bhava*.²³ *Asthi shool, toda, sandhishaithilya, kasha-roma-nakha-danta vikara, dourbalya and rukshata* etc are the *lakshanas* of *Astikshaya* described in different *Samhitas*.^{24,25,26,27}

Due to imbalance of *Vata dosha* *Asthikshaya* occurs which is advised to be treated with the herbs having *katu* (bitter) and *tikta* properties.²⁸ All the five ingredients of *Panchatikta Ghrita* (*Azadirachta indica* (*Nimba*), *Trichosanthes dioica* (*Patola*), *Solanum surattense* (*Kantakari*), *Tinospora cordifolia* (*Guduchi*), and *Adhatoda vasica* (*Vasa*)) has *katu* and *tikta* properties. Description about Ghrita is available in Ayurvedic literatures, Ghrita having *Brimhana* property which is useful specially for *Asthikshaya*. *Panchatikta Ghrita* is indicated in 80 types of *Vata vikar*, so it can be helpful in *Asthikshaya* by strengthening the bone. Few of the related studies were reviewed²⁹⁻³³.

Conclusion

Conclusion will be mentioned after the deliberate and analyzing data.

Source of Funding: Self

Conflict of Interest: Nil.

Trial Registration: Name of Registry- Clinical trial registry- India

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