Efficacy of Pippali in vardhamana and fixed dosage pattern in primary hypothyroidism – A randomized clinical trial

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ABSTRACT

Introduction: Hypothyroidism is an endocrine condition. The signs and symptoms of Hypothyroidism match with the descriptions of several conditions like Vataja Shotha, Rasa Pradoshaja Vikara or a disorder Agni. In the current study two different dosage forms i.e., Vardhamana (Increasing & Decreasing pattern) and fixed Dosage to evaluate its efficacy on Primary Hypothyroidism.

Materials and methods: 40 patients randomized into two groups Escalating and Fixed were administered Vardhamana Pippali in two dosage forms for 19 days. Serum T3, T4, and TSH were assessed at baseline and on the 20th day along with the assessment of clinical score through Zulewskis’s clinical score for measuring tissue hypothyroidism. The total pippali administered in both groups was 69 g.

Results: The mean levels of TSH were 9.52 ± 3.97 mIU/ml, 10 ± 6.02 mIU/ml, and 10.21 ± 8.49 mIU/ml at baseline, 20th day and 40th day respectively in group A. In group B it was 9.21 ± 3.72 mIU/ml, 8.23 ± 4.62 mIU/ml, and 9.15 ± 6.47 mIU/ml at baseline, 20th day and 40th day respectively. The mean Zulewski’s clinical score was 3.67 ± 1.49, 2.28 ± 1.32, and 2.06 ± 1.25 at baseline, 20th day, and 40th day respectively, suggesting minimal efficacy on the 20th-day and 40th-day respectively.

Discussion: Zulewski’s clinical scores were statically non-significant in both the groups on the 20th-day respectively, suggesting minimal efficacy of the interventions. But subjects administered with Vardhamana Pippali exhibited better long-lasting effects suggesting sustained effects of the drug.

Conclusion: Pippali is efficacious in reducing the signs and symptoms of Primary Hypothyroidism and also has a positive impact on the Thyroid profile but is more effective when administered in Vardhamana dosage compared to fixed dose.

1. Introduction

Thyroid disorders are the most common disorders of the endocrine glands with an estimated 42 million people suffering from thyroid disorders in India. The prevalence of hypothyroidism in urban India is 10.95% with a greater incidence in females and elderly persons [1]. The signs and symptoms of the initial stages of Hypothyroidism are vague and are often missed in its early stages and instead treated for infertility, hyperlipidemia, depression, etc. In the primary stage, the signs and symptoms are wide-ranging but later on affect the different systems of the body and worsen the condition of the patient. Hence, Hypothyroidism is an important public health issue. The contemporary management of Hypothyroidism is through replacement with synthetic thyroxin i.e., Levothyroxine sodium. The major risk of Levothyroxine sodium therapy is over-replacement, anxiety, muscle wasting, osteoporosis, and atrial fibrillation [2] (see Fig. 1).

Hypothyroidism doesn’t bear direct reference in Ayurvedic literature, but the signs and symptoms can be understood and assessed based on the involved Dosha (Humors), Dushya (Tissue elements), Sthana (Site), and Srotas (Channels). The signs and symptoms match with the descriptions of several conditions like Vataja Shotha [3] characterized by non-pitting edema—a feature of myxedema, Rasa Pradoshaja Vikara [4] characterized by loss of appetite, heaviness, fatigue, etc. Further analysis of the condition in

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0975-9476/© 2022 The Authors. Published by Elsevier B.V. on behalf of Institute of Transdisciplinary Health Sciences and Technology and World Ayurveda Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
light of the principles of Dosha and Dushya indicates the predominance of vitiated Kapha and Vata Dosha along with Rasa Dhatu. Thyroid hormones act on nearly every cell in the body. They increase the basal metabolic rate, help in protein metabolism, synergize with growth hormone, etc. In Ayurveda parlance, this is attributed as the function of Agni. Hypometabolism is the characteristic feature of hypo functioning of Agni. Hypo-functioning Agni leads to the manifestation of Ama (An intermittent by-product of faulty metabolism). Owing to the Antigenicity of the Ama, in most Autoimmune disorders; it acts as a precursor. Further hypo-functioning Agni affects the Ojus (essence of body tissues) a key factor in maintaining homeostasis of immune system. Hypothyroidism is one of the Autoimmune disorders; Agni plays a major role in its pathogenesis and the manifestation of symptoms. Hence one can interpret the pathogenesis of hypothyroidism in the context of Ayurveda, in which the role of Agni is foremost and through its management, normal functioning of the thyroid gland may be achieved.

Owing to the predominance of Kapha and Vata Dosha along with deranged metabolism, Pippali which mainly possesses Vata–Kaphahara with Agni deepana (Bio-fire enhancer) and Rasayana (Rejuvenating) properties seems to be promising in Hypothyroidism. Studies suggest Vardhamana Pippali Rasayana acts by correcting Agni, does purification of microchannels by exerting Vata kaphahar property, and by increasing supply and assimilation of micronutrients to tissues in Hypothyroidism [5] (Singh et al., 2015). The Rasayana property of Pippali further augments the therapeutic effects and as the clinical picture of Hypothyroidism is similar to conditions indicated for the administration of Vardhamana Pippali [6] the current study was structured to evaluate the efficacy of pippali in different dosage patterns i.e., Vardhamana (Increasing & decreasing) and fixed dosage form, where the total quantity of
Pippalis administered i.e., 300 Pippalis (69 g) and timespan of treatment in both forms were same.

2. Materials and methods

2.1. Study design

A randomized uncontrolled comparative clinical study. Randomization was done by using randomization software from www.randomizer.org. The study population was composed of subjects diagnosed with Primary Hypothyroidism selected from OPD, IPD, and special camps conducted at Sri Sri College of Ayurvedic Science and Research Hospital, Bengaluru, with a timespan from March 2018—December 2019. Ethical clearance was obtained from the institutional ethical committee (SSIEC/56/2018) before the initiation of the research work. Informed written consent in language suitable to the patients was obtained from all enrolled participants.

2.2. Sample size

In the current study the sample size was based on a previous thesis “Comparative study of Pippali prayoga and shodhana purvaka shamana chikitsa in management of Dhatvagni Vikruti (Hypothyroidism)” by Dr. Chanchal Gupta, Gujrat Ayurveda University, Jamnagar. The optimal sample size was estimated using the standard principles & methods [20]. Using the effect size calculated from the above study for efficacy of pippali in TSH (1.24), for an allocation ratio of 1, it was estimated that a sample size of at least 20 patients in each group (including 30% dropout) will be required to detect a two-tailed significant difference of $\alpha = 0.05$ with an estimated 95% power. Hence total sample size was 40.

2.3. Inclusion criteria

❖ Subjects in the age group of 18—60 years.
❖ Serum $T_3$ ($< 80$ ng/dL) $T_4$ ($< 5.10$ µg/dL) and TSH ($> 4.20$ mIU/dL) levels which indicate Subclinical or Overt Hypothyroidism
❖ Subjects who were under Levothyroxine Sodium orally were withdrawn for 14 days (t1/2 of thyroxin = 6.2—7.5 days [7]) were included in the study.
❖ Subjects willing to give written consent.

2.4. Exclusion criteria

❖ Subjects who had undergone any type of thyroid surgery.
❖ Subjects diagnosed with cardiac disorders, morbid obesity, uncontrolled diabetes, and carcinomas.

❖ Subjects suffering from congenital or secondary hypothyroidism.
❖ Serum TSH levels more >20 µIU/dL.
❖ Pregnant and lactating women

2.5. Diagnostic criteria

The diagnosis was made based on the presence of signs and symptoms of Hypothyroidism [8] with Ser. TSH values > 5.0 mIU/ml [9] with or without the decrease in serum $T_3$ and $T_4$ concentration.

2.6. Laboratory investigations

Thyroid profile (Ser. TSH, Total $T_4$, and $T_3$).

2.7. Preparation of drug

Dried Pippali (Piper longum) fruits were procured and finely powdered at the Sri Sri Tattva pharmacy. Three pippali is the starting dose of heena matra vardhamana pippali Rasayana. Hence 3 small pipplis were weighed which accounted for 0.69 g. The powder was then weighed as per the day-wise dosage (19 days) and packed in small air-tight packets (Table 1).

2.8. Intervention

Escalating group

❖ 0.69 g Pippali Churna, equivalent to 3 Pippalis was administered on day one on empty stomach in the morning with 50 ml of Ksheera (milk) as anupana.
❖ The dosage of Pippali Churna was gradually increased by 0.69 g per day till the 10th day.
❖ It was reduced by 0.69 g per day till the 19th day.
❖ A total of 300 pippalis (69 g of churna) were administered in 19 days.

Table 1

| Day | Number of pippalis | Wt. in grams |
|-----|--------------------|--------------|
| 1   | 3                  | 0.69         |
| 2   | 6                  | 1.38         |
| 3   | 9                  | 2.07         |
| 4   | 12                 | 2.76         |
| 5   | 15                 | 3.45         |
| 6   | 18                 | 4.14         |
| 7   | 21                 | 4.83         |
| 8   | 24                 | 5.52         |
| 9   | 27                 | 6.21         |
| 10  | 30                 | 6.90         |

Table 2

Course of vardhamana Pippali.

| Ascending pattern | Descending pattern |
|-------------------|--------------------|
| Day | Number of pippalis | Wt. in grams | Day | Number of pippalis | Wt. in grams |
|-----|--------------------|--------------|-----|--------------------|--------------|
| 1   | 3                  | 0.69         | 11  | 27                 | 6.21         |
| 2   | 6                  | 1.38         | 12  | 24                 | 5.52         |
| 3   | 9                  | 2.07         | 13  | 21                 | 4.83         |
| 4   | 12                 | 2.76         | 14  | 18                 | 4.14         |
| 5   | 15                 | 3.45         | 15  | 15                 | 3.45         |
| 6   | 18                 | 4.14         | 16  | 12                 | 2.76         |
| 7   | 21                 | 4.83         | 17  | 9                  | 2.07         |
| 8   | 24                 | 5.52         | 18  | 6                  | 1.38         |
| 9   | 27                 | 6.21         | 19  | 3                  | 0.69         |

2.9. Observation on chronicity.

| Chronicity Escalating group | Fixed group | Total | Percentage |
|-----------------------------|-------------|-------|------------|
| Newly detected              | 6           | 10    | 16         | 44.44      |
| Chronicity > 1 year         | 3           | 5     | 8          | 13.88      |
| Chronicity > 2 years        | 6           | 12    | 18         | 33.33      |
| Chronicity > 3 years        | 1           | 1     | 2          | 2.77       |
| Chronicity > 5 years        | 2           | 2     | 4          | 5.55       |
2.9. Assessment criteria

21 (58.33%) of them had a sedentary lifestyle followed by 13 related to Information technology which were 7 (19.4%) in number. 14 (38.8%) subjects were housewives followed by ones with jobs in the age group of 31–40 years and 27 (75%) of them were females. 14 (38.8%) subjects were housewives followed by ones with jobs related to Information technology which were 7 (19.4%) in number. 21 (58.33%) of them had a sedentary lifestyle followed by 13 (36.11%) having moderate physical activity daily. 16 patients (44.44%) were newly diagnosed through screening camps or vague complaints whereas a total of 12 patients (33.33%) presented with a known history of hypothyroidism for more than 2 years. Kapha–Pitta prakruti was mainly observed in 28 (77.77%) patients and Kapha–Vata prakruti in 3 (8.33%) patients. 5 (13.88%) patients had Pitta Vata Prakruti. 22 subjects (61.11%) predominantly consumed food with Madhura and katu rasa dominance whereas 5 of them (13.88%) were said to consume food with Madhura rasa (Sweet taste) dominance. Observation on chronicity is provided in Table 2.

4. Results

The mean levels of TSH were 9.52 ± 3.97 mIU/ml, 10 ± 6.02 mIU/ml, and 10.21 ± 8.49 mIU/ml at baseline, 20th day, and 40th day respectively in Escalating group. In Fixed group it was 9.21 ± 3.72 mIU/ml, 8.23 ± 4.62 mIU/ml, and 9.15 ± 4.67 mIU/ml at baseline, 20th day and 40th day respectively.

The mean levels of Ser. T3 was 108.29 ± 24.44 ng/dl, 100.37 ± 20.52 ng/dl, and 102.86 ± 20.59 ng/dl at baseline, 20th day, and 40th day respectively in Escalating group. In Fixed group it was 102.34 ± 15.95 ng/dl, 114.44 ± 25.01 ng/dl, and 117.57 ± 31.74 ng/dl at baseline, 20th day and 40th day respectively.

The mean levels of Ser. T4 were 7.19 ± 2.09 ng/dL, 7.08 ± 2.18 ng/dL, and 7.005 ± 2.34 ng/dL at baseline, 20th day and 40th day respectively in Escalating group. In Fixed group it was 7.25 ± 1.57 ng/dL, 7.89 ± 1.70 ng/dL, and 7.84 ± 1.52 ng/dL at baseline, 20th day and 40th day respectively.

The mean Zulewski’s clinical score was 3.67 ± 1.49, 2.28 ± 1.32, and 2.06 ± 1.25 at baseline, 20th day, and 40th day respectively in Escalating group. In Fixed group it was 3.83 ± 1.20, 2.50 ± 1.42, and 3.44 ± 1.33 at baseline, 20th day, and 40th day respectively. Both the groups did not show difference in Zulewski’s clinical score with an overall p value of 0.551, but group B showed a highly significant

### Table 3

**Zulewski’s score assessment.**

|                               | Escalating group | Fixed group  |
|-------------------------------|-----------------|--------------|
|                               | Baseline | 20th day | 40th day | Baseline | 20th day | 40th day |
| Diminished sweating           | 8        | 4        | 6        | 8        | 5        | 7        |
| Dry skin                      | 5        | 5        | 5        | 6        | 6        | 6        |
| Parasthesia                   | 8        | 3        | 4        | 9        | 8        | 8        |
| Weight increase               | 14       | 14       | 11       | 15       | 15       | 15       |
| constipation                  | 15       | 2        | 1        | 17       | 2        | 1        |
| Hoarseness                    | 0        | 0        | 0        | 0        | 0        | 0        |
| Impairment of hearing         | 0        | 0        | 0        | 0        | 0        | 0        |
| Slow movement                 | 9        | 5        | 5        | 4        | 3        | 4        |
| Coarse skin                   | 1        | 1        | 1        | 0        | 0        | 0        |
| Cold skin                     | 3        | 1        | 1        | 10       | 6        | 10       |
| Per orbital puffiness         | 2        | 1        | 0        | 0        | 0        | 0        |
| Delayed ankle jerk            | 0        | 0        | 0        | 0        | 0        | 0        |

### Fixed group

- A fixed dosage of 3.6 g Pippali churna was given with 50 ml of Ksheera (milk) as anupana in the morning on empty stomach for 19 days.

2.9. Assessment criteria

- The degree of clinical hypothyroidism was estimated using the score developed by Zulewski et al. according to which Euthyroidism is indicated by a score of 0—1 point, Borderline hypothyroidism by 2—5 points, Clinical hypothyroidism by > 5 points [10].
- Ser. TSH, T3 and T4 levels

#### 2.9.1. Assessment schedule

0th, 20th, and 40th day (follow up).

3. Statistical analysis

The data obtained was systematically arranged and statistical analysis was performed, using the paired and unpaired t-test for comparing the parameters within and between the groups respectively with the help of SPSS software IBM SPSS Statistics for Windows, Version 20.0, Armonk, New York: IBM Corp.

3.1. Observations

36 subjects completed the study, among which 13 (36.11%) were in the age group of 31–40 years and 27 (75%) of them were females. 14 (38.8%) subjects were housewives followed by ones with jobs related to information technology which were 7 (19.4%) in number. 21 (58.33%) of them had a sedentary lifestyle followed by 13

### Table 4

**Comparison of parameters within the groups.**

| Parameter            | Group        | N  | Mean-baseline | S.D. | Mean-20th day | S.D. | p-value | Mean-20th Day | S.D. | Mean-40th Day | S.D. | p-value |
|----------------------|--------------|----|---------------|------|---------------|------|---------|---------------|------|---------------|------|---------|
| Zulewski’s Score     | Escalating   | 18 | 3.67          | 1.49 | 2.28          | 1.32 | 0.001   | 2.28          | 1.32 | 2.06          | 1.259| 0.331   |
|                      | Fixed        | 18 | 3.83          | 1.20 | 2.50          | 1.42 | 0.000   | 2.50          | 1.42 | 3.44          | 1.33 | 0.000   |
| Ser. TSH (mIU/ml)    | Escalating   | 18 | 9.52          | 3.97 | 10.00         | 6.02 | 0.670   | 10.00         | 6.02 | 10.21         | 8.49 | 0.856   |
|                      | Fixed        | 18 | 9.21          | 3.72 | 8.23          | 4.62 | 0.173   | 8.23          | 4.62 | 9.15          | 4.67 | 0.112   |
| Ser. T3 (ng/dL)      | Escalating   | 18 | 108.29        | 24.44| 100.37        | 20.52| 0.045   | 100.37        | 20.52| 102.86        | 20.59| 0.371   |
|                      | Fixed        | 18 | 102.34        | 15.95| 114.44        | 25.01| 0.060   | 114.44        | 25.01| 117.57        | 31.74| 0.075   |
| Ser. T4 (ng/dL)      | Escalating   | 18 | 7.19          | 2.09 | 7.08          | 2.18 | 0.522   | 7.08          | 2.18 | 7.005         | 2.34 | 0.458   |
|                      | Fixed        | 18 | 7.25          | 1.57 | 7.89          | 1.70 | 0.046   | 7.89          | 1.70 | 7.84          | 1.52 | 0.853   |
result with a p-value of 0.00 compared to group A with a p-value of 0.33.

Overall, there was no difference in TSH values with a p-value of 0.054. Similarly, there was no difference between the groups with p values 0.85 and 0.11 respectively.

Agnibala (Digestive Strength) was reduced in all the subjects in Escalating group and Fixed Group. The pre and post mean score of Agnibala was 8.7 and 6.8 in Escalating group and 8.4 and 7.0 in Fixed Group respectively. It was analyzed by using a self-assessment tool to estimate Agnibala (Digestive Strength) (Singh A et al., 2017) [11] (See Tables 3–5).

5. Discussion

5.1. Discussion on incidence and etiology

Previous studies performed over larger populations indicate a higher prevalence of hypothyroidism in the age group of 46–54 years (13.11%) [1]. The age-wise increase in prevalence is probably due to thyroid autoimmunity [12] resulting in early gland atrophy [13]. It is well-established that women are affected approximately six times more frequently than men with hypothyroidism [14]. The higher prevalence in housewives could be attributed to the sedentary lifestyle, calorie-rich food with a very low energy expenditure resulting in an impaired metabolism. Also increased stress levels mainly observed in businessmen and the ones working as I.T. professionals might act as triggers for autoimmune response resulting in agenesis of thyroid hormones. Physical exercise is widely recognized to increase metabolism by increasing the ATP turnover by more than 100-fold [15]. Hence the relationship between metabolism and physical activity can be demonstrated attributing to the higher prevalence of Hypothyroidism in patients with a sedentary lifestyle. Kaptha-related Prakriti individuals appear to have a greater tendency for acquiring Hypothyroidism. The Madhura–Amal–Lavana Rasas aggravate Kaptha Dosh, mainly because of their Snigdhatawa (Oilyness) and Abhishyandatvam (moistening) resembling the properties of Kaptha Dosh [16], which might have lead to the Agnimandya (Reduced Bio - fire) resulting in the pathogenesis of the disease indicated by a higher incidence in subjects consuming them.

5.2. Discussion on results

The Zulewski’s Score indicated a reduction in the signs and symptoms of Hypothyroidism with a mean of 2.28 ± 1.32 in Escalating group and 2.50 ± 1.42 in Fixed Group respectively on the 20th day (mean 2.50 ± 1.33). Overall, both groups exhibited no difference with p-value <0.051 on the 40th day. This might be due to better absorption of the active components of Pippali when administered in the Vardhamana dosage pattern.

The Ser. TSH, T3, and T4 values didn’t show any statistically significant differences between and within the groups p < 0.054, p < 0.629, and p < 0.989 respectively. Ser. TSH values of the group administered with Vardhamana Pippali showed an increasing trend that might not comply with the efficacy. From the chronicity front in both the groups’ drug naive patients and patients with a history of hypothyroidism < 2 years responded better than patients with a history of hypothyroidism more than 2 years. It has been suggested that patients with severe hypothyroidism show irregularity of TSH secretion [19] which might be a factor for the apparent increase, indicating the role of chronicity of the disease in the overall thyroid profile.

6. Conclusion

Hypothyroidism can be considered under the purview of Dhaturwagni Madyojanayu vyadhii, where the metabolism at the level of Dhatu (tissues) is hampered. A sedentary lifestyle, calorie-rich food with a very low energy expenditure can be held responsible for disturbed metabolism. Pippali was more efficacious when administered in Vardhamana (Increasing & Decreasing pattern) rather than a fixed dosage. Pippali administered in Vardhamana form has a sustained and long-lasting effect, lowered the incidence of relapse of signs and symptoms, and better acceptance; though being Teekshna (sharp) and Ushna (hot) in potency.

7. Recommendations

Further studies can be done on a larger sample size. Assessment can be performed based on free T4 and T3 levels. Also to assess the impact on autoimmune pathology of the thyroid, Antithyroid antibodies like Thyroid peroxidase Antibody (TPOAb), Thyroglobulin antibody (TgAb), Thyroid-stimulating immunoglobulin antibody
(TSI), and Thyroid-stimulating hormone receptor binding inhibitory immunoglobulin (TBI) can be evaluated.

8. Limitations

The major limitation to the present study was the duration of the study. As Pippali was used as standalone and was used in avara dose the study duration was limited to 20 days.

Source of funding

None.

Conflict of interest

None.

Author contributions

Shrey Bhavin Shah: Conceptualisation, Investigation, Data curation, Writing-original draft, Visualization. Umesh Chikkanna: Conceptualisation, Methodology, Validation, Data curation, Writing- review & editing, Visualization, Supervision. Gopal Krishna Guttal: Conceptualisation, Investigation, Data curation, Writing-original draft, Visualization, supervision. Neelkanta J. Sajjanar: Conceptualisation, Methodology, Validation, Data curation, Writing- review & editing, Visualization, Supervision.

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