Comparative Antipyretic Effect of Nagaradi Kwatha, Ghana Vati and Arishta in Wistar Albino Rats

Liju BS\(^1\), Seema MB\(^2\), Ravi Mandugaru\(^3\)

\(^1\)Lecturer, Department of PG studies in Rasashastra and Bhaishajya Kalpana, Sree Narayana Institute of Ayurvedic Studies and Research, Puthur, Kerala, India.  
\(^2\)Professor, Department of PG studies in Rasashastra and Bhaishajya Kalpana, SDM College of Ayurveda, Kuthpady, Udupi, Karnataka, India.  
\(^3\)Research officer, Department of Pharmacology and Toxicology, SDM Center for Research in Ayurveda and Allied Sciences, Udupi, Karnataka, India 574118.

Correspondence: Email: drseemasdm@gmail.com, Mobile: +919449534600

**ABSTRACT**

**Introduction:** Kwatha (Decoction) kalpana is one amongst the basic preparations in herbal pharmaceutics. Marketing these formulations is not possible because of its shorter shelf life and hence Nagaradi Kwatha is converted to Arishta (fermented product of decoction) and Ghana vati (solidified aqueous extract) form by using the method of Anukta paribhasha explained in the classical texts of Ayurveda. Nagaradi Kwatha is widely used in clinical practice as Jvaraghini (antipyretic). Nagaradi, Haritaki and Guduchi are the main ingredients, which helps in ama pachana here by relieves Jwara (fever). **Methods:** The pyrexia was induced by subcutaneous injection of 20% of Brewer’s yeast solution at a dose of 1ml/100g body weight. The group specific drugs were administered after 18th hour of yeast injection. The rectal temperatures were recorded by using digital Telethermometer before yeast injection and at hourly interval for 4 hours, 24 h after the yeast injection. **Results:** The results are significant indicators of the anti-pyretic activity of Nagaradi combination. The Arishta form of Nagaradi combination was significantly decreased the rectal temperature measured at 1st, 3rd, 5th, 8th and 24th after fever induction. **Conclusion:** It can be concluded that the Arishta form has better antipyretic effect than Kwatha and Ghana vati form of Nagaradi combination.

**KEYWORDS**

Antipyretic, Nagaradi Arishta, Nagaradi Ghana vati, Nagaradi Kwatha, Brewer’s yeast.

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Fever is a complex physiologic response triggered by infectious conditions such as urinary tract infections, meningitis, malaria common cold, and appendicitis or non infectious causes such as vasculitis, deep vein thrombosis. Increase of body temperature in febrile condition is regarded as a component of the complex host response to infection or inflammation that accompanies the activation of the immune system.\(^1\) Late phases of fever appear mediated by pro-inflammatory cytokines called endogenous pyrogens. Elevations in body temperature occur when concentrations of prostaglandin E2 (PGE-2) increase within certain areas of the brain.\(^2\) These elevations alter the firing rate of neurons that control thermoregulation in the hypothalamus. According to Acharya Charaka jwara (fever) is the santhupa of body, mind and indriyas (sense organs). Due to mitthya aharavaha jataragri (normal functioning of gastrointestinal tract) functions are impaired leading to ama. Thus the Ama is the main cause for jwara.\(^3\) The Nagaradi Kwatha\(^4\) found in Sahasrayoga in the context of Jwara Chikitsa contains the ingredients as drugs guduchi (Tinospora Cordifolia), hareetaki (Terminalia Chebula) and shunti (Zingiber officinale) possess main property like deepana, shrotoshodana and agnimandya nashaka respectively.\(^5\) Many research works carried out in this direction with single herb with Guduchi showing the anti pyretic effect in experimental study.\(^6\)

The selection of Kashaya kalpanas for treatment purpose depends on various factors like roga, rogibhala, desha, kala, agni and vaya.\(^7\) Panchavridha kashaya kalpanas are the basic pharmaceutical preparation and most important form of kalpanas. These kalpanas cannot be preserved for longer duration. Among these, Kwatha can be preserved for 3 hours.\(^8\) Due to the advent of commercialization longer shelf life has become the need of hour, especially for the preparation of Kwatha (Decoction) which are highly perishable. Nagaradi Kwatha is one of the routinely practiced yoga in jwara which helps in the samprapti vighatana. Which contains Nagaradi, Haritaki and Guduchi as the ingredients in the ratio of 3:2:1 is commonly used in the form of decoction for fever in clinical practice. These Kwathas are available in market with preservatives and also in form of tablets prepared with the addition of different additives. Even though preservatives and additives are considered to be inert, one cannot expect the same result as that of freshly prepared Kwatha. Converting Kwatha into different dosage forms like Ghana vati, (solidified aqueous extract) Arishta (Self generated alcoholic liquid) may help to increase the shelf life without much change in the property of the particular formulation.\(^9\) Here Nagaradi Kwatha is converted into Nagaradi Arishta and Nagaradi Ghana vati by following the method of anuktha mama and anuktha paribasha respectively.\(^10\) However, jwarahara (Antipyretic) property of this formulation has not been reported till date. Considering this, study was undertaken to evaluate comparative anti-pyretic efficacy of Nagaradi Kwatha, Ghana vati and Arishta in experimental animals.
MATERIALS AND METHODS

Procurement and preparation of test drug

The raw materials i.e. Haritaki, Shunti and Guduchi were collected and authenticated from the S.D.M. pharmacy, Udupi, Karnataka, India. To prepare Nagaradi Kwatha Guduchi, Shunti, Haritaki are taken in the ratio of 3:2:1 respectively, boiled and reduced to 1/8th subjected to filtration. The same Kwatha is used for the preparation of Ghana vati by reboiling the Kwatha till it attains semisolid state, such paste is rolled into pills form of 500mg which further on drying shall be divided into ten equal parts of 45mg each and used for the study. The same prepared Kwatha is used for the preparation of Arishta by adding jaggery, Honey, Prakshepaka (powders of ingredients) and Dhakali pushapa by following Anukta muna of Sharanghadara Samhita and left for fermentation for the period of 45 days.

Dose selection and administration of the trial drug

The dose of Nagaradi Kwatha and Arishta for antipyretic effect in human is 48ml \cite{12,13}. Whereas the Ganavati form of test drug is 500mg. \cite{14} The dose of experimental animals was calculated by extrapolating the human dose to animal dose based on body surface area ratio by referring to the standard table of Paget and Barnes (1964). \cite{15} On this basis, the rat dose of Kwatha and Arishta was found to be 4.32 ml / kg body weight. The test drug was administered orally to animals with the help of oral catheter. The Trial drug Nagaradi Ganavati was administered at a dose of 45 mg / kg body weight by making small micro pellet administered with the help of oral catheter.

Experimental animals

Wistar albino rats (180-250g) of either sex were procured from Animal House attached to Pharmacology laboratory at SDM Centre for Research in Ayurveda and Allied Sciences, Udupi, Karnataka. The animals were kept under standard environmental conditions of room temperature (23 ± 2°C), relative humidity (55% ± 5%). The animals were housed in the colony cages (6 rats per cage). The animals were fed with rat pellet (Pranav Agro Ltd ‘‘Amrut’’ brand rat pellet) and water ad libitum. The institutional animal ethics committee was approved experimental protocol with the reference number (CPCSEA/2011-RS01). Six animals per group were used in each experiment. The animals were fasted for 18 hours before the commencement of the experiment but allowed free access to drinking water. All the experiments were carried out in accordance with the guidelines of Institutional Animal Ethics Committee.

Study design

Animals were kept under fasting for 18 hours before the commencement of the experiment. Initial rectal temperatures of all the animals were recorded by digital Tele thermometer. The pyrexia was induced by subcutaneous injection of 20% of Brewer’s yeast solution at a dose of 1ml/100g body weight \cite{16}. The group specific drugs were administered after 18th hour of yeast injection. Group I rats were administered with distilled water 1ml /kg body weight and served as normal control. Group II rats were administered with paracetamol 100mg / kg body weight and served as reference standard. Group III, IV & V rats were administered with the Nagaradi Kwatha, Ghana vati & Arishta respectively. The rectal temperatures were recorded by using digital telethermometer before and after fever induction and at hourly interval for initial 4 hours followed by 24 h after the yeast injection.

Statistical Analysis

The data was expressed as Mean ± SEM and analyzed by one way ANOVA followed by Dunnet’s multiple comparison t-test using Graph Pad Prism 3. A p <0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Paracetamol showed significant (p<0.01) antipyretic effect during 2nd and 4th h after drug administration, whereas the Arista form of test drug showed significant antipyretic effect at 1st, 3rd & 4th hour after drug administration (p<0.01). The Ganavati and Kwatha form of test drug was significantly reduced rectal temperature measured during 1st & 24th h and 2nd & 4th h respectively after drug administration (Table 1).

Nagaradi Kwatha is classically used for generalized fever and the use is well established in Ayurvedic practice. The present study is mainly focused on the effect of different dosage forms of the Nagaradi dravya combination such as Kwatha, Ganaavati, and Arishta for their anti pyretic effect. Brewer’s yeast is a fungi containing lipo-poly saccharide, which is a cell wall component of gram negative bacteria. It binds with macrophages and releases cytokines, interleukin -1 etc into the blood circulation, leading to antigen-antibody reaction. Then it crosses blood brain barrier and releases arachidonic acid mediated by the enzymes phospholipase, prostaglandin E2 synthase, and cyclo-oxygenase. The synthesis and release of PGE2 into anterior hypothalamus results in pyrexia. In the present study the pyrexia was induced by subcutaneous injection of 20% Baker’s yeast at a dose of ml/100g body weight and the rats with rectal temperature above the basal temperature was recruited for the study. The Pyrexia was achieved after 18h after yeast injection. Later the test drugs and vehicle to control group were administered by oral route with the help of syringes attached with oral catheter. There after the rectal temperature was measured repeatedly at an interval of 1st, 2nd, 3rd, 4th, and 24th h. The present study was mainly focused on the short term evidence and of antipyretic activity of the test formulations and hence the rectal temperature was measured at initial four consecutive hours followed by 24h time intervals.

The rectal temperatures of control group rats were continuously raining throughout the experimental period. The standard drug paracetamol administered rats showed remarkable reduction in the rectal temperature during 2nd, 3rd and 4th h of reading and found to be statistically significant in comparison to control group rats. Similar pattern of hourly reduction in temperature is
seen in Kwatha group. The test drug Arishta form has found to be highly effective and decreased the rectal temperature significantly in comparison to control group rats. The analysis of the results obtained clearly indicates that all the test group drugs have significant anti-pyretic activity. Comparison among the test formulations revealed that Arishta form of test drug has significant (p<0.01) anti-pyretic activity. In fact Kwatha and Ghana vati group produced moderate and statistically significant reduction in the rectal temperature followed by injection of yeast suspension.

Table 1. Effect of test drugs on rectal temperature (°C) at different time interval in Brewer’s yeast induced pyrexia in experimental animals

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial</th>
<th>After 18h of yeast injection</th>
<th>1h</th>
<th>2h</th>
<th>3h</th>
<th>4h</th>
<th>24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyacetamol</td>
<td>37.9±0.04</td>
<td>38.18±0.29</td>
<td>39.03±0.10</td>
<td>39.26±0.12</td>
<td>38.75±0.22</td>
<td>38.95±0.15</td>
<td>37.58±0.19</td>
</tr>
<tr>
<td>Kwatha</td>
<td>37.95±0.16</td>
<td>38.93±0.06</td>
<td>38.86±0.11</td>
<td>38.10±0.10**</td>
<td>37.71±0.17</td>
<td>38.26±0.14*</td>
<td>37.51±0.16</td>
</tr>
<tr>
<td>Ghana vati</td>
<td>37.98±0.19</td>
<td>38.68±0.13</td>
<td>38.45±0.20*</td>
<td>38.66±0.15</td>
<td>38.65±0.14</td>
<td>38.58±0.11</td>
<td>37.53±0.14**</td>
</tr>
<tr>
<td>Arishta</td>
<td>37.23±0.09</td>
<td>38.73±0.14</td>
<td>38.2±0.073**</td>
<td>38.66±0.31</td>
<td>37.83±0.21**</td>
<td>37.6±0.13**</td>
<td>38.4±0.21</td>
</tr>
</tbody>
</table>

Data expressed in Mean ± SEM, *p<0.05, **p<0.01 in comparison to normal control.

On the basis of present the study Arishta form showed significant effect compared to other dosage forms, even when it is compared with standard drug. It may be due to the qualities of self generated alcohol better known by the term Madhya guna attributed to the Nagardi yoga by the samskaras during Arishta preparation. Madhya gunas like snaksmya (enter in to minute pores), teekshna (cleans the channels of the body), vyanu vinas (drugs that spread throughout the body without first getting digested), ushna (hot), laghu (light) help in the faster absorption of the drug, which in turn increases its efficacy. This may be the reasons for the better anti-pyretic activity profile in Arishta form of Nagaradi yoga when compared to Kwatha and Ghana vati. Ghana vati on the other hand is a solid dosage form, where as Arishta and Kwatha are liquid dosage forms. While considering the mode of drug action, liquid dosage form is likely to have faster absorption than solid dosage forms. Here for Ghana vati, experimental results showed significance in 24th hr reading than the readings in the initial hours. This delayed action may be due to longer the disintegration time (2 hours) taken by the vati (solid dosage form).

Paracetamol (Acetaminophen) is generally considered to be a weak inhibitor of the synthesis of prostaglandins (PGs) in the peripheral tissues, but more active on cyclo-oxygenase in the brain. However, the in vivo effects of Paracetamol are similar to those of the selective cyclooxygenase-2 (COX-2) inhibitors. Paracetamol also decreases PG concentrations in vivo, but, unlike the selective COX-2 inhibitors. The Nagaradi combination has shown significant anti-pyretic activity and the probable mechanism of action may be as follows. Among the likely mechanisms is inhibition of formation of endogenous pro-inflammatory molecules like PGE and cytokines; or blocking of their receptors. The drug may also act by down regulating the thermoregulatory circuits or by enhancing the formation and release of endogenous anti-pyretic factors enumerated above.

CONCLUSION

From the present study, it can be concluded that the Arishta form of Nagaradi combination has high degree of anti-pyretic action as compared to Kwatha and Ganavati. The anti-pyretic effect of Arishta form of Nagaradi combination was comparable with that of reference standard paracetamol. Thus the study provides evidence for the presence of anti-pyretic activity in the Nagaradi combination in the Arishta form. The specific reason behind the formulation is need to explore in the further experimental model.

CONFLICTS OF INTEREST

Nil

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ABOUT AUTHORS

Liju BS MD (Ayu) is Lecturer at Department of PG studies in Rasashastra and Bhaishajya Kalpana, Sree Narayana Institute of Ayurvedic Studies and Research, Puthur, Kerala.

Seema MB MD (Ayu) PhD is Professor at Department of PG studies in Rasashastra and Bhaishajya Kalpana, SDM College of Ayurveda, Kuthpady, Udupi, Karnataka.

Ravi Mandugaru MSc (Medical pharmacology) is Research officer at Department of Pharmacology and Toxicology, SDM Center for Research in Ayurveda and Allied Sciences, Udupi, Karnataka.

GRAPHICAL ABSTRACT


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