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Research Article

STUDY OF PIPPALI AS BIOAVAILABILITY ENHANCER OF LAUHA BHASMA IN MANAGEMENT OF HAEMOGLOBIN DEFICIENCY

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ABSTRACT

Introduction-Several drugs suffer from the problem of poor absorption or poor bioavailability due to *agnimandya* or *srotoavarodha*, hence are unable to give desire effect. *Lauha bhasma* is one of these drugs, which fails to give uniform results in the management of Hb deficiency. In such consequences there is need of a safe and effective bio availability enhancer. *Pippali* is one of the bio availability enhancers, which can increase absorption and utilization of *lauha bhasma*. This clinical trial was thus designed to assess the role of *Pippali* in enhancing the effect of *luaha bhasma* on Blood Hb level. **Objectives** - To evaluate efficacy of *pippali* as bio availability enhancer of *lauha bhasma* on blood haemoglobin level in adult healthy volunteers. **Material and Method-(i) Design**-Open, two arm, randomized and comparative clinical trial (ii) **Settings**-OPD registered volunteers, **Participants**-20 Consenting Healthy volunteers(15-60 years of age), of either sex, having Hb between 7-10 gm% in females and 8-12 gm% in males, **Intervention**-2 groups, Group A - *Louha Bhasma* 125mg b.d. with water after food and Group B - *Pippali* 1gm and *Louha Bhasma* 125mg b.d. with water after food twice a day, **Intervention Period** - 45 Days, **Outcome measures**-Blood Hb level. **Results**-Highly significant results were observed in Group A and Group B. Most effective result - 18.93% improvement in Hb level in Group B as compared to Group A (14.20%). **Conclusion**-*Pippali* enhances the efficacy of *lauha bhasma* in Hb deficiency.

INTRODUCTION

Many drugs including synthetic as well as herbal suffer from the low bio availability because of their poor lipid solubility or improper particle size or both. Bio availability refers to the rate and extent of absorption of the drug and ability to deliver the active ingredient to its site of action in sufficient amount to elicit desire pharmacological response (KD Tripathi, 2008). Therefore if bio availability of the drug is good it will more effective, e.g. drug administered through intravenous route are more effective than oral drug administration, because 100% bio availability is obtained through I.V. route.

A 'bio availability enhancer' is an agent capable of enhancing bioavailability and bio efficacy of a particular drug with which it is combined, without any typical pharmacological activity of its own at the dose used (Kritika Kesarwani and Rajiv Gupta 2004). Piperine is the world's first bioavailability enhancer (Atal CK 1979). Bose had reported an enhanced antiasthmatic effect of an Ayurvedic formula containing *vasaka* (*Adhatoda vasica*) when administered with long pepper (Boae KG 1929). Piperine increases *curcumin* bioavailability by almost ten-fold (Ankol DD *et.al*. 2009). This concept of 'bioavailability enhancers' is derived from the Ayurveda, as the group of *pippali* (*Piper longum* Linn.), *maricha (Piper nigrum* Linn.) and *shunthi (Zingiber officinale* Rosc.), popularly known as trikatu, is documented in several formulations for increasing its efficacy. These drugs have *dipana* property due to which they causes *agnivriddhi* (Sharangadhar samhita purva khanda 4/46) and *agni* is responsible for the drug absorption and its utilisation. Therefore it can be postulated as *dipana* drug acts as bio availability enhancer.

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Haemoglobin deficiency most of the times occurs due to iron deficiency, as Hb contains 65 % of total body iron (K. Sembulingam and Prema Sembulingam 2013). Iron deficiency is one of the most important health issues concerning global population. Nearly 50-80 percent of mothers suffer from anaemia due to iron-deficiency (United nations children fund 1984) while 83.9 percent girls of age between 12 and 18 years in rural India were found to be anaemic (Hellen kellar institute of girls 1996). Adolescent girls require continuous replacement of iron during menstruation (Brabin, L. and B. J. Brabin. 1992). Iron deficiency anaemia can result in a wide variety of adverse outcomes including diminished work or exercise capacity, impaired thermoregulation, immune dysfunction, GI disturbances, and cognitive impairment.

Lauha bhasma is being prescribed to treat anaemia (*pandu*) (Rasratna samucchaya 5/139) owing to its haematinic activity (Pandit S *et.al*. 1999& PK Sarkar *et.al*. 2007). *Lauha bhasma* increases blood haemoglobin level according to *samanya-vishesha siddhanta*, (Charaka Samhita Sutra sthan 1/44) in absence of *pratibadhaka hetus.* In clinical practice uniform predictable results dose not occurs with *lauha bhasma* because of *pratibadhaka hetus* such as status of *agni*, *aam*, status of *koshtha*, status of *dosha-dushya*, status of patient, etc. All these *pratibadhaka hetus* ultimately manifests into *agni mandya.*

Pippali has *deepana* (Charak Samhita Sutra sthan 4/9) and *yogavahi* property meaning it enhances the absorption of drug co-administered with it (Charak Samhita Chikitsa sthan 3/38). Recent researches also have proved the bio enhancer activity of piperine (Atal CK *et.al*.1981), major chemical constituent of *trikatu*. Hence formulations containing *Lauha bhasma* plus *trikatu* like *navayasa lauha*, *yagaraja*, *Tapyadi lauha*, etc. are being prescribed in iron deficiency anaemia. *Pippali* is bioavailability enhancer and having 62.8mg/100gm iron content (National Institute of nutrition).

Therefore the present trial was planned to evaluate the role of *pippali* as a bio enhancer of *lauha bhasma* in haemoglobin deficiency.

Hypothesis

The efficacy of *lauha bhasma* can be better when used with *deepana* and *srotoshodhana* (bioavailability enhancing) drugs like *pippali* due to increase in absorption and better utilization of *lauha bhasma*. If this hypothesis stands good then it will pave the way for a low cost and effective management for Hb deficiency.

Aims and objectives

To evaluate efficacy of *pippali* as bio availability enhancer of *lauha bhasma* in management of haemoglobin deficiency.

MATERIALS AND METHODS

***Study Design*-**An open, two arm, randomized and comparative clinical trial was designed to test the hypothesis of the current work.

***Study Population*-**20 consenting apparently healthy volunteers of 15-60 years of either sex were enrolled for this trial after screening them as per the inclusion criteria. Volunteers were randomly divided into 2 groups, each group having 10 volunteers.

***Study Setting*-**Selected volunteers were registered in the Out Patient Department of National Institute of Ayurveda, Jaipur (N.I.A. OPD) for the clinical trial.

***Study Period*-**12/9/2014 to 27/1/2015

Volunteers Inclusion criteria

Haemoglobin between 7-10 gm% in females and 8-12 gm% in males.

Volunteers exclusion criteria

- Pregnant ladies.
- Patients suffering from malignant diseases like leukaemia.
- Patients suffering from serious diseases such as Ischemic heart disease (IHD), congestive cardiac failure (CCF), Diabetes mellitus (DM), renal disorders, acute and chronic blood loss, bleeding disorders, haemoglobinopathies.
- Patients suffering from chronic disorders like Rheumatoid arthritis (RA), hypothyroidism, and hyperthyroidism.
- Anaemia due to causes other than iron deficiency.
- Patients that have recently taken iron supplement therapy.

Volunteers discontinuation / withdrawal criteria

- Any Adverse/ Serious adverse event is encountered, where continuation of study poses medical risk to the Volunteer.
- Volunteers not complying with the protocol.
- Volunteers not turning up for assessment in time.
- Volunteers expressing desire to withdraw.

Trial Drug

API directs that dried fruit of *Piper longum* Linn. is the botanical source of the drug *pippali* (API). There is no controversy regarding the botanical identification of the *pippali*. Hence in the present study fruits of *Piper longum* Linn. was selected as the trial drug. It was collected by the scholar herself from Kochi, Kerala, after due botanical authentication (Identification no-(*Piper longum* Linn.-RUBL211473). Powder was prepared by pulveriser. This powder was passed through sieve size 80. This powder was packed into soft gelatine capsules of 500mg each.

Lauha bhasma was purchased from the GMP certified company named Krishna Gopal Ayurved Bhawan, Kalra. *Lauha bhasma* was packed into soft gelatine capsules of 125mg each by a capsule filling machine.

Both the drugs were subjected to pharmacognostical and phytochemical investigations for quality assurance and found to be quality drugs for use.

Dose, Duration & Administration

Group A: *Louha Bhasma* - 125mg, 1 capsule of 125mg, with water after food twice a day for 45 days

Group B: *Piper longum* dry fruit powder-1gm, 2 capsules of 500mg each and *Louha Bhasma* - 125mg, 1 capsule of 125mg, with water after food twice a day for 45 Days.

Criteria of Assessment

The enrolled volunteers were assessed for Blood Hb % at baseline and after the end of the trial i.e. on 46th day.

Observations

Blood Hb % of the volunteers were assessed and recorded before and after treatment. The values are given in Table 1.

Table no. 1 Observations of the change in Hb%

Volunteer	Group A		Volunteer	Group B	
	BT	AT		BT	AT
1	9.1	11.9	1	8.1	9.1
2	10	11.3	2	7.6	8.2
3	10	11	3	10	11.9
4	10	10.6	4	10	10.7
5	11.3	11.7	5	9.3	9.7
6	10.5	13	6	9	10
7	8.7	11.9	7	10	12.4
8	10	11.4	8	9.4	12.4
9	10.8	11	9	9.4	12.7
10	8.8	9	10	9	12.3

BT-Before Treatment, AT-After Treatment

RESULTS

The recorded values were subjected to statistical analysis for their significance and results. Statistical analysis was conducted by Graph pad prism-6 software. For obtaining results in individual group (before and after treatment) paired 't' test while for intergroup comparison unpaired 't' test was applied. Obtained results are given in Table no. 2 and Table no. 3.

Table No.2 Effect of trial drugs on Haemoglobin level

Group	Mean		D	Change in %	S.D.	S.E.	T	P	R
	B.T.	A.T.							
A	9.92	11.28	1.36	14.20	1.1097	0.3509	3.8753	0.0037	H.S.
B	9.18	10.94	1.76	18.93	1.1635	0.3679	4.7834	0.0009	H.S.

BT-Before Treatment, AT-After Treatment, D-Difference, SD-Standard Deviation, SE-Standard Error, P-P value, R-Result, HS-Highly Significant

Table no 3 Inter group comparison (Unpaired 't' test)

	Group A (Diff. mean)	Group C (Diff. mean)	P	R
Hb %	1.36	1.76	0.4417	N.S.

Diff. mean- Difference mean, P-P value, R-Result, NS-Non Significant

DISCUSSION

Both the groups showed statistically highly significant results. Quantitatively the most effective result (change in % 18.93) was seen in Group B *(pippali* with *lauha bhasma)* whereas the change in percentage in Group A (*lauha bhasma*) was 14.20%. The results were in compliance with expected hypothetical outcome of this trial i.e. *pippali* will increase the efficacy of *lauha bhasma*.

Lauha bhasma contains iron and it effectuated increase in iron level of body on the basis of *dravya samanya siddhanta*. Hb contains most of the body iron (65%), therefore increase in iron can lead to increase in Hb%. *Samanya vishesha siddhanta* says '*samanyam vriddhi karanam,*' i.e. similar attributes will effectuate in an increase of similar attributes in the body. Chakrapani explains that such an increase is possible only when there is absence of *pratibadhaka hetus*. Therefore volunteers having *agnimandya (pratibadhaka hetu)* did not showed significant increase in haemoglobin.

Pippali is a bio availability enhancer hence when administered along with *lauha bhasma* it increases the iron absorption, transportation and utilization and ultimately increases in Hb%.

Probable mode of action

The mode of action of medicinal substances in *Ayurveda* is explained by *Charaka* (Charak Samhita Sutra sthan 26/13). The medicinal substances can act on the basis of their *guna (rasa, virya, vipaka, guna)* and their *prabhava*.

- Iron absorption hampers due to the *agnimandya* which leads to formation of *aam* and *srotorodha* and vice a versa.
- *Pippali* is said to be *dipana* (Charak Samhita Sutra sthana 4/9). Piperine causes reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply (Annamalai AR *et. al*.) owing to its *katu rasa* and *ushna virya*, hence it is also *aampachaka* leading to increased intake iron with proper digestion. Due to *ushna virya* and *tikshna guna* it has bio energetic and thermogenic effect (Atal CK *et.al*. 1985).
- *Srotorodha* occurs due to vitiated *doshas* and *amaa*. Pippali is very *dipana* and *pachana* drug render to digest *ama* in the body and it is also have *ushna*, *tikshna* property due to which *srotoshodhana* takes place. Piperine causes modifications in GIT epithelial cell membrane permeability, leading to better absorption and transport of iron (Khajuria A *et.al*. 2002).
- *Pippali* is one the *rasayana dravyas* (Charak Samhita Chikitsa sthan 1-3/47), which nourishes all *dhatu* including *rakta dhatu* (Hb %).
- *Pippali* have *yogavahi* (Charak Samhita Vimana sthan 1/16) and *Sukshma* properties, due to which it goes to deep tissues and takes the drug to deep tissue administrated along with it, so it facilitates absorption, transport and utilization of iron administered along with it.

CONCLUSION

The present study indicates that *pippali* increases bio availability of *lauha bhasma* and consequently its pharmacological action.

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