

Original Research Article

Effect of Ayurvedic interventions on toxemia of pregnancy & fetal outcome- A randomized placebo-controlled trial

Comment [f1]: Need to edit

ABSTRACT

Background- Toxemia of pregnancy is a common clinical condition affecting 8-10% pregnancies worldwide. It has adverse outcome both for mother and fetus. The management options are mainly targeted to prevent adverse outcomes associated to premature births, such as administration of antenatal corticosteroids and magnesium sulphate infusions.

Aim & objectives- The main aim of the study was to evaluate efficacy of Ayurvedic interventions in management of toxemia and in prevention of premature delivery as well as fetal hazards due to pre-eclampsia.

Methods-It was an open ended, parallel group, randomized placebo controlled clinical trial with equal allocation in both the groups. Sample size was 15 in each group. Trial group was administered Gokshura Siddha Yavagu and Dhatriyavaleha while control group was treated with similar looking placebo.

Results- Both ayurvedic parameters-Shotha, Avil mutrata& clinical features of toxemia have shown excellent relief while control group patients either show poor or no relief when assessed by USG scan and needed further treatment with induction of labor.

Conclusion-This study concludes that Ayurvedic interventions in the form of Gokshura siddha Yavagu and Dhatri Avleha can provide significant symptomatic relief ($p < 0.0001$) in toxemia of pregnancy and can also promote normal growth and development in fetus.

KEY WORDS- Toxemia of pregnancy, preeclampsia, Gokshura siddha yavagu, Ayurveda for preeclampsia, Shotha, USG scan

INTRODUCTION

Toxemia of pregnancy, now a day grouped as hypertensive disease of pregnancy, are group of disorder in late 2nd & third trimester of pregnancy with hypertension & edema being its core symptoms. Toxemia of pregnancy include preeclampsia and eclampsia. Preeclampsia is

characterized by hypertension (high blood pressure), headaches, protein in the urine, and swelling of the face, hands, and feet. It can progress to eclampsia, which is marked by onset of convulsions and can lead to brain injury, coma and death [1]. Preeclampsia occurs in around an average 4.6% of all pregnancies worldwide while eclampsia affects around 1.4% pregnancies [2]. Etiopathogenesis of toxemia of pregnancy is still not well clear but various hypotheses are formulated to explain its pathogenesis. However, there are various risk factors defined to increase risk of hypertensive diseases in pregnancy. These risk factors include primigravida (nulliparous), maternal age of ≥ 40 years, body mass index (BMI) ≥ 35 kg/m, multifetal pregnancy, inter-pregnancy interval of > 10 years, history of hypertensive disease in previous pregnancies or systemic diseases in mother like chronic kidney disease, autoimmune diseases, diabetes, or chronic hypertension [3,4]. Toxemia (preeclampsia) can result in various immediate as well as long-term health hazards in mother & fetus. In the mother, it includes increased risk (2-4 times higher) of chronic hypertension, cardiovascular morbidity & mortality, and around 1.5 times more risk of stroke. Fetal health hazards include risks of intra-uterine growth restriction (IUGR), preterm birth, oligohydramnios, placental abruption, fetal distress, and fetal death in utero [5,6,7]. There is also increasing data suggesting significant long-term cardiovascular sequel, including early onset hypertension, and an increased risk of ischemic heart disease and stroke in persons, who were exposed to maternal hypertension or preeclampsia during fetal life [8]. There are limited options for the prevention and management of fetal complications of preeclampsia. As preeclampsia is to blame for 1/5-1/3 of all preterm births, [9] the management options are mainly targeted to prevent adverse outcomes associated to premature births, such as administration of antenatal corticosteroids and magnesium sulphate infusions.

In Ayurveda, there are scattered references of toxemia like conditions in pregnancy. Kashyap Samhita has separate chapter for the management of various illnesses during pregnancy named as Antartvartani chikitsa Adhyay in Khil Sthan. In this chapter Acharya Kashyap has clearly mentioned onset of Shotha in pregnant female in sixth month of pregnancy [10]. In description of etiological factors of Shotha (edema), Garbha Sampidana (Fetal factors) is mentioned as one of internal causative factor for the pathogenesis of Shotha (edema) [11]. Pathogenesis of Shotha involves Vata pradhana three dosha which due to obstruction in srotas get further vitiated and produce swelling in various body parts. Acharya Sushruta has described use of Gokshura siddha Yavagu (Gruel medicated with Gokhsura) in sixth month of pregnancy [12]. Hence, on reviewing the Ayurvedic classics regarding Shotha (pre-eclampsia or oedema) in pregnancy, it is clearly mentioned that Shotha is produced due to fetal factors and mostly onset occurs during sixth month of gestation. In its management, for reduction of excessive accumulated water and improving fetal weight, use of Gokshura siddha Yavagu is advocated. In this present study, we have evaluated this very concept of Ayurveda for its efficacy and validity in present era.

AIM & OBJECTIVE

The main aim of the study was to evaluate efficacy of Ayurvedic intervention in the form of Gokshura Siddha Yavagu and Dhatriyavaleha in management of toxemia and in prevention of premature delivery as well as fetal hazards due to pre-eclampsia.

MATERIALS AND METHODS

Study design and duration

It was an open ended, parallel group, randomized placebo controlled clinical trial with equal allocation in both the groups. **The study was approved by IEC.** Study duration was 15 days.

Participants

In present study, a total 34 patients fulfilling inclusion criteria were registered from the OPD & IPD of National Institute of Ayurveda, Jaipur, India and divided equally & randomly into 2 groups. Out of these 4 patients were lost to follow-up and they excluded from analysis. The criteria followed to include or exclude is described hereunder.

Inclusion criteria

- Pregnant females having 20 weeks onwards gestation and age between 15-45 years
- Hypertension: - Blood pressure ranging from 140/90 to 160/110 mm of Hg
- Mild generalized edema
- Weight gain ≥ 0.75 kg/week
- Proteinuria: - 300 mg/day or more

Urine for protein excluding mild toxemia in which it may not be present.

Exclusion criteria

Presence of severe preeclampsia, Anemia (Hb ≤ 6 gm%) with Hypo-Proteinemia, Epilepsy, Hypertension, Asthma, Tuberculosis, Diabetes mellitus, Thyroid Problem and Any Other Chronic Disease.

Interventions

1. Control group

The control group was given with placebo treatment. The placebo treatment included administration of plain Yavagu without any medication made from Mudga (green gram) in a dosage of 100 grams twice daily and placebo Avleha (linctus) made with mixing of madhu (honey) and ghrut (Cow's Ghee) in unequal quantity, administered in a dosage of

10 gm twice daily for 15 days, with milk in Apana kala for 15 days, later on continued under follow up till disease remission or delivery.

2. Trial group

Trial group patients were treated with Gokshura Siddha Yavugu 100gm twice daily and Dhatri avaleha 10gm twice daily with milk in Apana kala initially for 15 days, later on continued under follow up till disease remission or delivery.

Ingredients & Procedure of preparation of trial drug

Gokshura siddha Yavagu

Yavagu is prepared by following the description in SharangdharaSamhita,[13] 10 gm Gokshur churna (Powder of *Tribulus terrestris* Linn) was boiled in 640 ml of water & reduced to half then 50 grams of broken grains of mudga (green gram) is added & thick gruel prepared.

Dhatryavaleha

Dhatryavleha is prepared as per description in CharakaSamhita[14]. Contents are shown in table no. 1

Table No.1 showing various contents of Dhattravleha

S. No.	Name of drug	Scientific name	Part Used	Quantity
1.	Vanshlochana	<i>Bambusa arundinaceae</i> Retz.	Plant resin	160 g
2.	Sunthi	<i>Zingiber officinale</i>	Tuber	160 g
3.	Madhuyashti	<i>Glycyrrhiza glabra</i>	Roots	160 g
4.	Pippali	<i>Piper longum</i>	Fruits	1280 g
5.	Draksha	<i>Vitis vinifera</i> Linn.	Fruits	1280 g
6.	Sharkara	<i>Saccharum officinarum</i>	Sugar	4 kg
7.	Madhu	Honey	Whole	1280 g
8.	Amalaki	<i>Phyllanthus emblica</i> L.	Fruit juice	20480 ml

Outcome Measures

Outcome was assessed on the basis of pre-defined clinical and investigative parameters. They are as follows-

1. Clinical remission (subjective & objective)
2. Investigative remission (objective)
1. Clinical remission

Clinical remission was assessed on the basis of remission of various clinical symptoms & signs according to both ayurvedic as well as modern parameters.

A. Ayurvedic Parameters

- Dosha vridhi assessment
- Dhatu kshaya assessment
- Mala kshaya assessment
- Sroto dushti assessment

B. Modern parameters

i. Assessment of remission

- Ankle circumference for pedal edema
- Weight
- Blood pressure

ii. Assessment of fetal wellbeing by USG scan

a. During pregnancy

Fetal heart rate

b. After delivery

Anthropometric measurements- weight, length, head circumference, chest circumference, abdominal circumference & mid upper arm circumference

2. Investigative remission

Assessment for mother

- Urinary protein
- Kidney function test- Blood urea, creatinine

Assessment of fetal wellbeing

- USG

The results were categorized into excellent, good, partial & no remission according to following criteria.

Excellent remission/ ER > 75% relief in signs and symptoms

Good remission/GR - 50-75 % relief in signs and symptoms

Partial remission / PR - 25-50% relief in signs and symptoms.

No remission / NR < 25% relief in signs and symptoms.

Sample size, Randomization & Blinding

Sample size was calculated on the basis of expected effect size and previous studies. Total calculated sample size was 14 in each group. In the present study 34 patients were enrolled, out of which 30 patients (15 in each group) completed the trial.

Randomization was used for enrollment & assignments of participants to the intervention. The random allocation sequence was generated using table of random number by supervisor of the study while assignment in to groups was done by separate person.

The present study was single blind and participants were blinded for the type of intervention they were given.

OBSERVATION AND DISCUSSION

This study included a total of 34 patients out of which 4 patients were lost to follow-ups. Thus, the data of results consists for 30 patients only.

Socio-demographic characters- The mean age of females was 23.2 years with maximum (73.33%, no.22) being in the age group of 15-25 years. Most of the females were of low socio-economic status with household monthly income of less than Rs5000. Most females (18) were from Muslim community, 60 % of total. This may be due to location of sample collection area being Muslim populated area. Both groups were compared for their demographic characteristics and were found to be similar in most of the characteristics.

Obstetric characters: Females who were married before the age of 18 years (n-14, 46.67%) and had conception within first year after marriage (n-23, 76.67%) were maximum in our study. First pregnancy associated with toxemia was maximum with 24 females (80%) being primigravidae. Gestational period of more than 30wk was significantly associated with pre-eclampsia (n-22, 73.33%) compared to gestational period between 20-30wk (n-7, 26.67%).

Personal history: Previous history of pregnancy induced hypertension (PIH) was positive in multi gravidae females in 4 females out of 6 i.e. 66.67%. Most females were of Vata-Kaphaja prakriti (n-20, 66.67%) followed by Vata-Pittaja prakriti in 23.33% (n-7). Most were having Krura Koshtha (n-24, 80%), and habits of eating spicy foods as well as junk foods (n-21, 70%).

Family history: History of pre-eclampsia, hypertension, diabetes mellitus and obesity were most common with 23 females having positive history for these diseases in their parents.

Effect on Ayurvedic parameters -Efficacy of the treatment assessed on Ayurveda parameters revealed mild effect in control group while excellent to good response in trial group by drug. (Table no.2)

Effect on various signs & symptoms- Regarding maternal morbid features, trial group patients have shown excellent relief while control group patients either show poor or no relief and needed further treatment with induction of labor. Edema and hypertension were 2 essential criteria present in all patients but protein urea was inclusive but not essential. (Table no.3)

Effect on fetal wellbeing & outcome- Trial group showed 100% relief with significance in fetal & neonatal morbidity as well as outcome parameters where as in placebo group there was no relief observed as not significant in these parameters. (Table no.4)

Statistical analysis of signs and symptoms of control group have revealed increase in problem while significant reduction of both sign and symptoms

Table no.2 showing effect of treatment on ayurvedic parameters in both the groups

Signs & symptoms based on Ayurvedic parameters	Group A (Placebo Group)				Group B (Trial Group)			
	Means of no. of S/S				Means of no. of S/S			
	BT	AT	Relief in %	P value	BT	AT	Relief in %	P value
DOSHA								
1. Vatavruddhi	4.0	3.20	20.0	0.21NS	4.80	2.30	52.1	0.05
2. Pitta vruddhi	2.8	2.00	28.6	0.32, NS	3.20	0.53	83.4	0.001
3. Kaphavruddhi	2.0	2.00	0.00	-	2.00	0.26	87.0	0.001
DHATU								
1. Rasa kshay	1.50	1.30	13.4	0.21,NS	1.73	0.26	85.0	0.001
2. Rakta kshay	1.80	1.60	13.4	0.21,NS	1.20	0.20	83.4	0.001
3. Mamsa kshay	1.50	1.20	20.0	0.35NS	1.40	0.13	90.7	0.001
4. Meda kshay	0.70	0.30	57.1	0.05, S	0.47	0.00	100	0.0001
5. Asthi Kshay	0.65	0.48	26.2	0.34,NS	0.47	0.00	100	0.0001
6. Majja Kshay	1.00	1.00	0.00	-	0.80	0.00	100	0.0001
MALA								
1. Mutra kshay	1.00	0.80	20.0	0.35, NS	0.92	0.00	100	0.0001
2. Purish kshay	0.80	0.30	62.5	0.044,S	0.70	0.00	100	0.0001
STROTAS								
1. Rasavaha dushti	4.30	4.00	20.0	0.35	4.80	1.80	62.50	0.01
2. Annavaha dushti	2.20	2.00	13.4	0.21,NS	3.40	0.20	99.94	0.0001
3. Mutravaha dushti	1.80	1.50	20.0	0.35, NS	1.80	0.00	100	0.0001
4. Udakavaha dushti	1.80	1.50	20.0	0.35NS	1.90	1.50	22.05	0.35, NS

Table no. 3 showing efficacy of Drug on Sign & symptoms of toxemia

Clinical features	Group A					Group B				
	Mean of s/s BT	Mean of s/s AT	Mean difference	Relief in %	P value	Mean of s/s BT	Mean of s/s AT	Mean difference	Relief in %	P value
Edema	1.4	1.46	-0.06	0.00	0.92	1.53	0.20	1.33	86.9	0.001
Hypertension	1.2	1.3	-0.10	0.00	0.92	1.87	0.33	1.54	82.4	0.001
Proteinuria	0.13	0.33	-0.20	0.00	0.92	1.00	0.86	0.14	14.0	0.69
Vertigo	1.13	1.06	0.07	6.20	0.84	1.20	0.27	0.93	77.5	0.001
Headache	1.06	1.33	-0.27	0.00	0.92	1.40	0.33	1.07	76.4	0.001
Epigastric pain	0.53	0.20	0.33	62.3	0.04	0.93	0.06	0.87	93.5	0.0001

	3	20	0	00	2	13.3	2	100
Fetal distress	3	20	0	00	2	13.3	2	100

DISCUSSION

Toxemia of pregnancy is ill understood disease with wide range of presentation and severity. Most cases of pre-eclampsia get unnoticed and can contribute to morbidity as well as mortality among pregnant females and their progeny. Early diagnosis with prompt correction of various derangements in toxemia can lead to prevention of fetal distress, intrauterine growth failure and can result in better outcome on the part of newborn. Ayurveda has described use of healthy diet, life style and some drugs for the management of this condition for better fetal outcome. The present study signifies the role of Ayurveda in toxemia of pregnancy.

Age is an important factor which influences the incidence of toxemia of pregnancy. Young females with first pregnancy around 20 years or all pregnant females over 30 years have an increased risk of preeclampsia[15]. In present study most females were primigravida and in the age group of 15-25 years. The results are similar to various previous studies[16,17]. The reason behind high incidence among young females may be the most common age of conception in our country is this age group. Most females were in 31-35 weeks of gestation and belongs to low socio-economic strata. The findings are in concordance to previous reported facts[18]. Most participants have positive family as well as past history for pre-eclampsia, which are similar to findings of Sonia et al.[19] Most females were of Vata-Kaphaj prakriti and Krur koshta. These findings are in accordance to Ayurvedic principles wherein it clarifies that in pathogenesis of Shotha, Vata dosha is root cause. Thus, vata predominant prakriti and Krura koshta persons will be more prone to this type of disorder. The same is reflected by highest score of Vata among all the three dosha in both the groups.

On assessing results for improvement, trial drug group showed better improvement in most of the parameters with excellent remission in 9 out of 12 parameters including edema, hypertension, headache, epigastric pain, nausea, vomiting, blurring of vision and vertigo; while in placebo group only epigastric pain show good remission and all other parameters showed either poor remission or no remission, not significant. In trial group, only dyspnea shows poor remission and proteinuria & sleeplessness show no remission. These results indicate that trial drug can reduce various clinical features of toxemia of pregnancy mainly edema & hypertension, however, it did not show effect on proteinuria. The results may be attributed to various pharmacological actions of trial drugs discussed vide infra.

On Ayurvedic parameters, trial drug showed excellent remission in pitta & kapha dushti, all dhatu and mala kshaya as well as Annavaaha & Mutravaha srotodushti symptoms. It shows good remission in pacifying Vata and improving Rasavaha srotodushti symptoms. Only Udakavaha srotodushti did not show any remission. These improvements are attributed to balya, grahi,

tarpana and vatanashaka properties of Yavagu,[20] mutrala [21](Diuretic) and Shothhara[22](Anti-inflammatory) properties of Gokshura, which is a best drug for mutrakrichha (dysuria) & vata hara (vata pacifying)[23]. Dhatri Avleha is very good rasayana drug used to pacify Pitta and treat various ailments which are common in pregnancy & preeclampsia like pandu (anemia), kamla (jaundice) and kasa (cough)[24]. Also, most drugs in Dhatri Avleha are either Madhur rasa or Madhura vipaka and thus have rasayana properties. Thus, Dhatri avleha is useful for improving pandu (anemia in pregnancy) and its rasayana properties improve status of dhatu Kshaya in toxemia of pregnancy.

Mode of action of interventions

1. Gokshura siddha Yavagu (Gruel medicated with Gokshura)

Gokshura .(*Tribulus terrestris* Linn)

Gokshura is proven to have potent diuretic property [25] which helps in reduction of both, edema as well as blood pressure in preeclamptic females. Gokshura also possesses strong anti-oxidant/adaptogenic,[26] and anti-inflammatory[27] properties which are useful to break the pathogenesis of toxemia.

Mudga(*Vigna radiata*)

Mudga is good source of various amino acids which can be easily assimilated into body.²⁸ It is useful in hypo-albuminemia, improve blood concentration of albumin and thus also help in reducing edema, excessive water retention as well as weight. Mudga is also known to have anti-oxidant, anti-hyperglycemic, anti-hypertensive, angiotensin-I converting enzyme inhibitory activities,[29] hypoglycemic, hypolipidemic and hepatoprotective properties [30]. These properties of Mudga make it suitable protein supplement in cases of toxemia of pregnancy to improve hypoalbuminemia, hypertension as well as edema.

Dhatri Avleha

Various contents of Dhatri avleha have anti-oxidant, adaptogenic, anti-hypertensive, diuretic, immunomodulatory, cardio-protective, antiemetic, anti-inflammatory properties which are helpful in pacifying various symptoms of toxemia as well as breaking its pathogenesis.

Amalaki (*Phyllanthus emblica* L.) is one the best rasayana (rejuvenative) drug and best vayasthapan (anti-ageing) drug.[31] It possesses anti-oxidant,[32] anti-inflammatory,[33] anti-hypertensive,[34] cardio-protective and immune-modulatory properties[35] which are useful to treat various manifestations of toxemia.

Pippali(*Piper longum*) is well known for its bio-availability enhancing properties [36] which promotes absorption of various nutrients as well as improve availability of various drugs at the

place of action[37] Pippali also possesses various properties like anti-oxidant,[38] anti-inflammatory[39]and vasodilatory activities;[40] which are useful in toxemia.

Draksha (*Vitis vinifera* Linn.) possesses good anti-oxidant, anti-inflammatory actions⁴¹ and it is known to inhibit angiotensin converting enzyme and thus producing anti-hypertensive action[42] These actions are useful in breaking pathogenesis of toxemia.

Shunthi (*Zingiber officinale*)possesses anti-oxidant,[43]anti-inflammatory,[44] ACE inhibitory & anti-hypertensive properties[45] which are useful to break pathogenesis. It also possesses antiemetic and anti-nausea actions which are very useful for symptomatic relief in toxemia[46]

Madhuyashti(*Glycyrrhiza glabra*) also possesses anti-oxidant & anti-inflammatory properties[47].

Madhu (honey) is well known for its potent anti-oxidant,[48] anti-inflammatory,[49] immunomodulatory[50] properties. Honey contains many minerals and micronutrients like calcium, iron, magnesium, phosphorus, vitamins B1, B2 and enzymes[51] which are useful in pre-eclampsia.

Thus, on the basis of these properties, it may be understood that Gokshura siddha yavagu and Dhatri Avleha have broken the pathogenesis of toxemia and produced symptomatic relief in pregnant females and also promoted normal growth of fetus.

CONCLUSION

This study concludes that Ayurvedic intervention in the form of Gokshura siddha Yavagu and Dhatri Avleha can provide symptomatic relief in toxemia of pregnancy and can also promote normal growth and development in fetus. However, as this study was conducted on a small sample size; a study with large sample size is needed to verify these results.

NOTE:

The study highlights the efficacy of "Ayurveda" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of

knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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