Ayurveda intervention for brass-induced heavy metal toxicity: A report from the single-arm pilot study

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Abstract

Background: Brass is a copper-zinc alloy that also contains additional elements, including lead. Industrial operations on brass produce dust and fumes that can be harmful to an individual’s health. Ayurveda recommends Dadima Svarasa and Triphala Churna for the management of symptoms caused due to brass toxicity.

Objective: To obtain preliminary evidence on the efficacy of Triphala Churna (powder mixture of three myrobalans) and Dadima Svarasa (pomegranate juice) in the management of brass-associated high serum level of copper, zinc, lead, and their harms through an open-label single-arm pilot study.

Materials and methods: A total of 20 workers with brass toxicity and increased level of one or more of the serum ions including copper, zinc and lead were prescribed. 5gm Triphala powder once daily and Dadima Svarasa 40 ml in two divided doses were administered daily for 28 days. Changes in serum concentration of heavy metals and common health problems like anorexia, headache, dizziness, weakness, nausea, nose irritation, eye irritation, epigastric pain, abdominal distention, chest pain, dyspnea, cough, lumbar pain, body ache, numbness, and occupational dermatitis were reported at baseline and end of the trial.

Results: Trial drugs were found to produce significant decrease in mean values of serum copper (p < 0.001) and serum lead (p < 0.001) whereas significant increase in mean values of serum zinc (p > 0.001) was observed. Significant relief was observed in nausea (p = 0.005), anorexia (p = 0.000), epigastric pain (p = 0.001), abdominal distention (p = 0.014), weakness (p = 0.005) and body ache (p = 0.005).

Conclusion: Triphala Churna along with Dadima Svarasa are safe and effective in the management of brass-associated high serum levels of copper and lead and their health hazards.

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1. Introduction

Among industrial workers, heavy metal toxicity has proven to be a major threat as it is associated with significant health risks. A variety of human activities such as urbanization and industrialization have resulted in serious environmental contaminations by heavy metals globally.

The brass industry of Jamnagar is one of the largest industries in India. The brass parts industries are mostly concentrated in and around the Jamnagar district which caters to the requirement of around 70% of the machine brass components of India and also exports to various countries [1].

Brass mainly consists of 60—the 70% copper (Cu) and 20—30% zinc (Zn). The amounts of zinc and copper are the responsible for the strength and versatility of the brass metal [2]. Lead, which is categorized as trace element and toxic metal, is used in the third highest quantity (up to 4%) to improve high machinability, strength and to improve casting characteristics of brass [3]. Chronic brass poisoning has been reported and is characterized by the appearance of anemia and green line at the base of the teeth (due to a large proportion of copper) along with palpitation, dyspnea on exertion, dyspeptic symptoms, anorexia and epigastric pains, nausea, vomiting, and colic [4].

Chelation therapy is the standard treatment to remove toxic metals by using chelating agents; [5] however, the chelating agents have a considerable risk of side-effects including renal failures, arrhythmias, tetany, hypocalcemia, hypotension, bone marrow depression, prolonged bleeding time, convulsions, respiratory arrest, etc. [6] The risk of such serious side-effects has led researchers...
to develop safer alternatives. Ayurveda-based antioxidants and herbal medicines may serve as a relatively safer and better alternative.

Textbooks of Ayurveda, the traditional system of medicine of India, mentioned the traditional way of removing toxins from the body using herbs as antidotes. Poisons/toxins are termed as Visha in Ayurveda [7]. Information about toxic and poisonous substances originated from metals, minerals, herbs/foods, or animal products along with their pathophysiology and management are described in detail in classical Ayurvedic texts [8]. Metal toxicity falls under the Shhavara Visha (inanimte poison) category in Ayurveda and Charaka categorized management for Visha into twenty-four categories [9]. Anupana manjari, an exclusive Ayurvedic text on managing adverse effects of drugs, recommends the use of Paaka Dadima Phala Svarasa (juice of ripe pomegranate) for the poisonous effect of Pinga (brass) in particular and Triphala Churna for the symptoms caused by Trihatri (a combination of three metal) i.e., Naga (lead), Vanga (tin), and Yashada (zinc) [10]. Pomegranate is one of the most commonly available and frequently consumed fruit across the globe. Triphala is an Ayurvedic herbal formulation composed of varied proportion of three myrobalans. Ayurvedic Formulary of India recommends the use of Triphala which contains dried fruits from three herbal plants in equal proportions i.e., Terminalia chebula Retz (Haritaki), Terminalia bellirica Roxb (Bibhitaki), and Emblica officinalis Gaertn (Amalaki) [11].

The aim of the present study was to obtain preliminary evidence on the efficacy of Triphala Churna and Dadima Svarasa in the brass toxicity.

2. Materials and methods

2.1. Study design

An open-label, interventional, single-arm pilot study was designed to achieve the study objectives. The study protocol was approved by the Institutional Ethical Committee (vide letter no. PGT/7/-A/ethics/2018–19/3399 dated: 14-02-2019). The study was conducted according to good clinical practices (GCP) guidelines and registered in the Clinical Trial Registry, India (vide CTRI Reg. No. CTRI/2019/03/017973). Informed consent was obtained from each of the patients prior to enrollment.

2.2. Study site, sampling, and selection of participants

This study was conducted from August – October 2020 in brass industries of Jamnagar, Gujarat, India located in Dared village, M.P. Shah Industrial Area, Hapa Industrial Area, and Shankar Tekri. Based on the operation of brass units in Jamnagar, brass clusters are engaged in three different operations, viz., casting, machining, and electroplating. Casting units include foundry and extrusion [12]. The potential community-dwelling brass industrial workers were targeted through an observational study that is reported elsewhere. The selection criteria for study participants is briefly described here. One thousand brass industry workers were selected randomly and interviewed. The level of exposure of brass was accessed through a standard questionnaire designed to collect information about the working hours in exposed areas such as brass dust, fumes, minute brass particles, etc. at their workplaces. Three hundred and twenty two participants with a high level of brass exposure, irrespective of their working units in the factory, with symptoms/health complaints related to heavy metal poisoning were listed and further screened for eligibility. Among these sampling frames of 322 workers, 20 randomly selected workers were referred to the institute hospital, for further screening of toxicity of copper, zinc, and lead. Among these participants, the ones with high serum levels for at least one of the heavy metals – copper, zinc and/or lead, were provided with clinical counselling and were enrolled in the study.

2.3. Inclusion criteria

Workers having age more than 18 years who were working for more than 3 years and had high level of brass exposure with increased serum levels of any one of the three i.e., copper (>140 µg/dL) [13], zinc (>120 µg/dL) [14], and lead (>30 µg/dL) [15,16] were included for the study.

2.4. Exclusion criteria

Workers having diagnosis of uncontrolled systemic and life-threatening diseases with serum levels, two times of upper normal ranges of copper (>280 µg/dL), zinc (>240 µg/dL), and lead (>70 µg/dL), severe anemic condition (Hb < 7 g/dL) and impaired psychological health were excluded from the study. All the screened individuals having high serum level of lead (>70 µg/dL) were referred to chelation therapy. However, among these individuals, those who refused to seek chelation therapy and were willing to provide consent for Ayurvedic treatment at their own risk were included in the present study.

2.5. Study procedure

The participants who fulfill the inclusion criteria were registered and examined for the baseline characteristic wherein demographic profile, medical history, data from general and systemic examinations were recorded and outcomes were analyzed. Intervention was provided to each participant for 28 days. At the end of the trial, participants were subjected to primary and secondary outcome analysis.

2.6. Investigational drug/intervention

All study participants received Triphala Churna powder 5 gm/day orally before 8 am prior to consumption of any food items and Dadima Svarasa (juice) 40 ml twice daily (after breakfast at 8 am and evening snacks at 8 pm) for 28 days. Dadima Svarasa was prepared from its fruit Dadima (Punica granatum Linn.) as per standard procedure in the departmental laboratory and 0.1% sodium benzoate, a United States Food and Drug Administration approved preservative [17] was added to the juice [18]. Triphala Churna was prepared by adding an equal quantity of T. chebula Retz. (Haritaki), T. bellirica Roxb. (Bibhitaki), and E. officinalis Gaertn. (Amalaki) procured from the institutional pharmacy. Along with the intervention, participants were also advised to take precautionary measures to minimize further exposures.

2.7. Outcomes

2.7.1. Primary outcome

Changes in the serum levels of copper, zinc, and lead were the primary outcomes of interest. The copper, zinc, and lead levels were assessed by using inductively coupled plasma-optical emission spectrometry (ICP-OES) under optimized conditions in all acid digested blood samples. The calculated samples were nebulized manually downstream to the plasma and therefore, the concentrations were automatically determined using the quality calibration graph prepared within the same plasma conditions [19].
2.7.2. Secondary outcome

Common health symptoms as per WHO guideline were the secondary outcomes. These symptoms were anorexia, headache, dizziness, weakness, nausea, irritation in eyes and nose, epigastric pain, abdominal distention, chest pain, dyspnea, cough, lumbar pain, body ache, numbness, and occupational dermatitis [20]. Grading of common symptoms was adopted from common terminology criteria for adverse events [21].

2.7.3. Safety outcome

Study participants were instructed to report any spontaneous adverse events during the trial period. Levels of Hb, FBS, SGPT, SGOT, and serum creatinine were assessed at the end of the trial. Primary, secondary, and safety outcomes were measured at baseline and at the end of the trial.

2.8. Statistical methods

The collected data was entered and coded in MS Excel (version 2013; 15.0.4420.1017) and statistically analyzed using SPSS (version 26.0). Continuous data were presented in mean and standard deviation and categorical data as frequencies and percentages. Paired t-test was performed to analyze parametric data like laboratory investigations and heavy metal analysis. Wilcoxon signed-rank test was applied to assess non-parametric data like change in grade of symptoms. The test results were considered significant when p-value < 0.05 and confidence interval at 95%.

3. Results

A total 1000 workers had been surveyed. Among them, 652 workers were excluded because they did not belong to high exposure group, 5 workers declined to participate and 21 workers were having diseased conditions. 322 screened individuals eligible for study, 20 were randomly selected for the study. Four participants did not complete the study. Participants who dropped out after the baseline visit were excluded from the analysis (Fig. 1).

The mean age of the study group was 42.5 ± 7.4 years with 10 participants (50%) belonging to 44–56 years age group and 9 (45%) belonging to the 31–43 years age group. Majority of the workers were literate (n = 16; 80%). Thirteen workers (65%) were vegetarian and adopted regular dietary habit i.e timely intake of breakfast, lunch and dinner. Eighteen workers (90%) complained about poor appetite. The baseline mean value of serum copper (153.31 ± 19.98) and serum lead (49.23 ± 21.77) was higher than normal ranges whereas the mean value of serum zinc was slightly below (72.3 ± 9.01) to normal range. Among 20 selected workers, 11 (55%) workers were from casting units whereas rest of the workers (n = 9; 45%) were from machining units (Table 1).

3.1. Primary outcome

The study data indicate that a significant decrease was observed at the end of the trial in the mean values of serum copper (p < 0.001) and serum lead (p < 0.001) whereas a significant increase in the mean value of serum zinc (p < 0.001) from the baseline. (Table 2).

3.2. Secondary outcome

It was observed that anorexia and generalized weakness were the most frequently occurring health problems (n = 16) followed by body ache (n = 15), and nausea (n = 12). The other health problems observed among the participants were epigastric pain, dizziness, chest pain, and skin-related complaints found in 11 workers. Numbness was found in 7 workers followed by abdominal distention (n = 6) and headache (n = 6). Shortness of breath was reported by 5 workers, cough by 2 workers (Table 3).

Significant reduction in grading was observed in nausea (p = 0.005), anorexia (p < 0.001), epigastric pain (p = 0.001), abdominal distention (p = 0.014), generalized weakness (p = 0.005), and body ache (p = 0.005). No statistically significant changes were observed in lumber pain (p = 1.000), headache (p = 0.083), dizziness (p = 0.157), numbness (p = 0.083), chest pain (p = 0.083), shortness of breath (p = 1.000), cough (p = 0.317), occupational dermatitis (p = 0.083), nose irritation (p = 1.000), and eye irritation (p = 1.000) (Table 3).

3.3. Safety outcome

No statistically significant changes were observed in Hb (p = 0.09), FBS (p = 0.795), SGPT (p = 0.375), SGOT (p = 0.06), and

Table 1

| S. No. | Socio-demographic variables | N (%) |
|-------|-----------------------------|-------|
| 1.    | Age (yrs.) | Mean ± S.D | 42.5 ± 7.4 |
|       | Range       | 18–67 |
| 1.    | Sex         | Male | 20 (100%) |
|       |            | Female | 0 (0%) |
| 3.    | Religion    | Hindu | 19 (95%) |
|       |            | Muslim | 1 (5%) |
| 4.    | Education   | Illiterate | 4 (20%) |
|       |            | Literate | 16 (80%) |
| 5.    | Working units | Casting | 11 (55%) |
|       |            | Machining | 9 (45%) |
| 6.    | Types of diet | Vegetarian | 13 (65%) |
|       |            | Mixed | 7 (35%) |
| 7.    | Dietary Habits | Regular | 12 (60%) |
|       |            | Irregular | 8 (40%) |
| 8.    | Appetite    | Poor | 18 (90%) |
|       |            | Moderate | 2 (10%) |
| 9.    | Copper (µg/dL) (n = 16) | Mean ± S.D | 153.31 ± 19.98 |
|       |            | Range | 70–140 µg/dL |
| 10.   | Zinc (µg/dL) (n = 16) | Mean ± S.D | 72.31 ± 9.01 |
|       |            | Range | 80–120 µg/dL |
| 11.   | Lead (µg/dL) (n = 16) | Mean ± S.D | 49.23 ± 21.77 |
|       |            | Range | >30 µg/dL |

Fig. 1. Participants flow diagram.
Table 2
Effect of the intervention on blood serum heavy metal analysis of copper, zinc, and lead (n = 16).

| Heavy metal | BT Mean ± S.D | AT Mean ± S.D | p     |
|-------------|--------------|--------------|-------|
| Copper (70–140 µg/dL) | 153.31 ± 19.98 | 139.06 ± 22.37 | <0.001* |
| Zinc (80–120 µg/dL) | 72.31 ± 9.01 | 87.31 ± 7.73 | <0.001* |
| Lead (>30 µg/dL-Exposure >80 µg/dL- Chelation Therapy) | 49.23 ± 21.77 | 38.64 ± 23.15 | <0.001* |

Paired t-test. BT- Before treatment, AT- After treatment, S.D- Standard Deviation.

* p < 0.05 (Level of significance).

Table 3
Effect of the intervention on workers of brass industries (n = 16).

| Body Systems       | Complaints          | Reported in participants (n) | Baseline score [median (IQR)] | EOT score [median (IQR)] | p     |
|--------------------|---------------------|------------------------------|-------------------------------|--------------------------|-------|
| Gastrointestinal   | Nausea              | 12                           | 2 (1.25–2)                    | 1 (1–1)                  | 0.005*|
|                    | Anorexia            | 16                           | 3 (3–3)                       | 1 (1–1.75)               | <0.001*|
|                    | Epigastric pain     | 11                           | 2 (2–2)                       | 1 (1–1)                  | 0.001*|
|                    | Abdominal distention| 6                            | 2 (2–2)                       | 1 (1–1)                  | 0.014*|
| Musculoskeletal     | Weakness            | 16                           | 2 (2–2)                       | 1 (1–1)                  | 0.005*|
|                    | Bodyache            | 15                           | 2 (1–2)                       | 1 (1–1)                  | 0.005*|
|                    | Lumbar Pain         | 2                            | 1 (1–1)                       | 1 (1–1)                  | 1.000 |
| Neurological        | Headache            | 6                            | 1.5 (1–2)                     | 1 (1–1)                  | 0.083 |
|                    | Dizziness           | 11                           | 1 (1–1)                       | 1 (1–1)                  | 0.157 |
|                    | Numbness of hands   | 7                            | 2 (1–2)                       | 1 (1–2)                  | 0.083 |
| Respiratory         | Chest pain          | 11                           | 1 (1–2)                       | 1 (1–1)                  | 0.000 |
|                    | Dyspnea             | 5                            | 1 (1–1)                       | 1 (1–1)                  | 1.000 |
|                    | Cough               | 2                            | 1.5 (1–0)                     | 1 (1–1)                  | 0.317 |
| Local complaint     | Occupational Dermatitis | 11               | 2 (2–2)                       | 1 (1–2)                  | 0.083 |
|                    | Nose irritation     | 3                            | 1 (1–1)                       | 1 (1–1)                  | 1.000 |
|                    | Eye irritation      | 6                            | 1 (1–1)                       | 1 (1–1)                  | 1.000 |

EOT- End of treatment, IQR- Inter Quartile range.

* p < 0.05 (Level of significance).
Effect of the intervention on biochemical and hematological parameters (n = 16).

| Parameters       | BT Mean ± S.D. | AT Mean ± S.D. | p* |
|------------------|----------------|----------------|----|
| Hb               |               |                |    |
| 14.25 ± 1.24     | 14.00 ± 1.38   | 0.090          |    |
| FBS              | 98.43 ± 33.86  | 100.06 ± 38.64 | 0.795|
| SCPT             | 26.62 ± 9.21   | 24.75 ± 8.91   | 0.375|
| SCOT             | 22.31 ± 4.28   | 20.12 ± 4.48   | 0.06 |
| Serum creatinine | 1.11 ± 0.12    | 1.16 ± 0.10    | 0.240|

* Paired t-test, p < 0.05 (level of significance).

4.1. Limitations of the study

This single-arm clinical trial study design has some limitations. Without control, it is difficult to assess the impact of interventions. The sample size of the present study was small and included workers from casting and machining units only. Hence, this study may not be generalized to the workers of other units of brass industry and other industries. Confounding effect of the precautionary measures was also not analyzed due to the absence of control group. Furthermore, a single-center trial may not be generalized to another geographical location and cultural groups. The generalizability of the studied findings is therefore, limited to the selected characteristics of participants.

Based on the encouraging result of the present study, future randomized control trials may be planned adopting classical guidelines considering the specific Aushadha Sevana Kala (time of administration) referred by Anupana Manjari, freshly prepared pomegranate juice, and Triphala Churna prepared from different ratios of the three ingredients quoted by different Ayurveda texts.

5. Conclusion

This single-arm pilot study supports the traditional usage of Dadima Phala Svarasa (juice of ripe pomegranate) and Triphala Churna for heavy metal toxicity. Both drugs appeared safe for internal administration and in combination, can be considered as the alternative option for the management of heavy metal toxicity of brass. However, the finding needs further confirmation through good design randomized controlled trials.

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Conflict of interest

None.

Author contributions

Vivek Kumar Patel: Methodology, Formal analysis, Investigation, Writing- original draft preparation. Kalpesh Panara: Methodology, Formal analysis, Supervision, Writing - reviewing and editing. Rabinarayan Acharya: Conceptualization, Supervision, Funding acquisition, Writing - reviewing and editing.

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