Chapter 8
Selenium: A Right Choice to Treat Arsenicosis in Bangladesh

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Contents

Abstract One half of the Bangladeshi population has been drinking arsenic contaminated water, drawn from the ground by tube-wells since 1993. More than 38,000 arsenicosis cases are reported. The present knowledge of the management of arsenicosis is limited, and specific treatment of chronic poisoning has not yet been identified.

With the approval of the ethical review board of the Bangladesh Medical Research Council (BMRC) double blind, randomized, placebo controlled trial with selenium intervention was carried out on 174 arsenicosis patients, irrespective of age and sex, for 12 months in a hyper-contaminated rural area of Bangladesh. In this study, melanosis decreased in 76% ($n = 67$, $p < 0.00$) of selenium treated patients and palmo-planter keratosis in 81% ($n = 67$, $p < 0.00$). For the selenium group arsenic content was decreased 38.2% ($p < 0.01$) in hair and 37.2% ($p < 0.00$) in nails. Overall symptoms improved 68% ($p < 0.00$) in the selenium treated group. There was no observed toxicity in a heart, kidney and liver function test. It was found that a dose of 100 μg of selenium as selenomethionine per day along with use of arsenic safe water for 12 months in chronic arsenic toxicity is a safe and effective treatment for arsenicosis.

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Abbreviations

BMRC	Bangladesh Medical Research Council
ECG	Electrocardiogram
HG-AAS	Hydride Generation Atomic Absorption Spectrometer
NAMIC	National Arsenic Mitigation information Center
SGPT	Serum Glutamic Pyruvate Transaminase
SPSS	Statistical Package for Social Sciences
WHO	World Health Organization

8.1 Introduction

Safe drinking water, sanitation and good hygiene are fundamental to health, survival, growth and development. Unfortunately, these basic needs are still a luxury for many of the poor people in a country like Bangladesh. From 1993, half of Bangladesh's population was drinking arsenic contaminated water drawn from the ground by tube-wells. More than 38,000 cases of arsenicosis have already been reported (Douglas 1999; Elizabeth 2000; Ganapati 2000; NAMIC 2005). Tondel et al. (1999) found that arsenic concentration ranged from 10 to 2,040 μg/L in tube-well, and crude prevalence rate was 29/100 Bangladeshi people. There was a significant dose response relationship ($p < 0.05$), regardless of sex (Tondel 1999). In econometric analysis, it was found that the burden of arsenicosis is on low-income, poor people (Milton et al. 2004; Anwar 2002). There is no known antidote. Avoidance of arsenic contaminated drinking water, chelating agents, retinoid, vitamins, balanced diet, spirulina, all these have tried with varying therapeutic results (Sato et al. 2000; Guha et al. 1998; Guha et al. 2001; Boyd et al. 1989; Thianprasit 1984; Khan and Ahmad 2002; Khan et al. 2001; Ahmad et al. 1998; Kosnett 1998; Huq et al. 2000; Misbahuddin et al. 2006)

Evidence from both laboratory and epidemiological studies suggests that arsenic obviously has an inhibitory effect on the antioxidant enzymes containing selenium by reacting with -SH group. This inhibitory impact has been observed in increased arsenic accumulation (Lin and Chiang 2000; Bates et al. 1992). Inorganic arsenic, once ingested, may lead to the production of reactive oxygen species (ROS) that can induce DNA damage, including single and double-strand breaks and nucleotide base modifications (Lynn et al. 2000; Shi et al. 2004; Liu and Jan 2000; Hei et al. 1998; Amundson et al. 1999). Selenium might be a suitable agent to reduce arsenic accumulation after chronic exposure for a number of reasons, i.e., there are a number of possible points and mechanisms for metabolic interaction between arsenic and selenium which include competition for the methyl donor, S-adenosylmethionine, competition for glutathione (GSH) and inhibition of glutathione reductase by a

number of arseno-glutathione complexes. Moreover, both selenium and arsenic interact extensively with sulfhydral (-SH) groups in tissues; it is possible that arsenic elimination is delayed in Se-deficiency because there could be more target -SH groups for arsenic to react with because Se intake is low (Kenyon et al. 1997). There is evidence that low Selenium intake may influence the development of arsenicosis (Islam et al. 2004). In an animal study, it was observed that the cytotoxic effect of arsenic can be prevented through dietary supplementation by selenium in mice, which is of significance in protecting against the widespread toxicity observed in humans (Biswas et al. 1999; Nasir et al. 2004), but multicentral trial of selenium in humans is lacking. In 1989 a clinical trial in China among the smelter workers exposed to arsenic showed that the chromosomal aberration rate of cultured lymphocytes in workers was lowered by 46.1% after treatment with selenium (150 μg/day for 21 days; Hu 1989). There were no soil selenium maps of Bangladesh though Spallholz et al. (1978) had measured in 25 samples from Jessore district of Bangladesh and found less amount of selenium in soil, which automatically produces low selenium containing crops. In a developing country and largely agrarian Bangladesh villages, animal protein intake is low, with fruits and vegetables often proving to be poor sources of selenium where arsenicosis is occurring and excessive selenium excretion owing to selenium/arsenic complexion may add to the likehood of arsenic being more toxic and carcinogenic over time (Spallholz et al. 1978, 2004). So, interest was found to conduct a clinical trial with selenium intervention among arsenicosis patients in Bangladesh.

8.2 Materials and Methods

Arsenicosis patients were selected from 11 villages having a population of 19,000 of Shahpur union, under Chatkhil Upazilla, of District Noakhali. The area is a hyper-contaminated arsenic zone (British Geological Survey 1999). From a total population 560 probable arsenicosis patients, screened with the help of local elites and a field team, were invited to a health camp. The patients were selected clinically by the dermatologist and confirmed by positive spot urine examination by a digital arsenitor (positive indicates an arsenic concentration 1 ppb or more).

All adults, male and female, with a history of exposure to arsenic contaminated drinking water from shallow tube-well for more than 6 months and presenting signs/symptoms of arsenicosis were included in the study. Exclusion criteria included patients not exposed to arsenic, no clinical feature of arsenicosis, patient refusal to give consent, patients not having arsenic in urine, patients having concurrent illness like malaria, tuberculosis, or history of smoking (Yes or No), alcoholics (drinking more than 2 pegs) or taking hepatotoxic drug. Pregnant and lactating mothers were also excluded. Finally, 174 patients, irrespective of age and sex, were selected. An identification number was assigned to one of the three treatment groups “A” or “B” randomly following a computer generated number.

The study was approved by the ethical review board of the Bangladesh Medical Research Council (BMRC). Prior to entering the study each patient signed an informed consent form and were assured of their right to withdraw from participation. The information were kept strictly confidential and used only for research purposes. The study was a part of research work leading to a PhD.

A baseline survey was conducted which included information about age, gender, height, weight, socio-economic status, water use data, drinking water source, cooking water source, number of tube wells, duration of use and skin manifestation of arsenicosis with duration. Samples of water from the tube well were collected for arsenic estimation. In 10% randomly selected cases, 24 h food recall surveys were conducted for the estimation of arsenic in consumed food. Urine and blood samples were collected before and at the end of 4, 8 and 12 months. Only scalp hair and finger nail samples were collected at the beginning and at the end of study period. All the collected samples were labeled properly by including the identification number, date of collection and nature of the specimen. All the samples were transported to Dhaka within 24 h in frozen containers and were stored at −20°C until analysis.

Treatment Procedure: The arsenicosis patients were assigned randomly to group 'A' or group 'B'. Each group of participants was provided the drugs, identical in appearance and blindly coded as 'A' and 'B', respectively. The drugs were delivered to each participant in a sealed air tight plastic bottle of same color and size. Only code number was written on each bottle. The bottles were packed earlier with 15 tablets of the respective group of drugs by the pharmacists who kept the code confidential. Neither the investigator nor the patients knew the intervention groups. Each patient was instructed to visit the treatment camp monthly for the drug. While receiving the drug, the patient had to bring the previously used containers in order to check the compliance. Each patient was instructed to swallow one half of the tablet daily with a glass of water. Any failure to take the drug for 1 day was recorded and instructed to take a double dose the next day. The trained field workers regularly visited the patients at home to ensure compliance. The overall supervision, both in clinic and field, was maintained by the principal investigator over 12 months. None of the patients were allowed to drink arsenic contaminated water throughout the study period. All the study subjects drank boiled surface water throughout the study period. A local office-cum clinic was set up and a registered medical officer was recruited to monitor the treatment of patients. After the laboratory analysis was complete, the drug codes were decoded and data were analyzed along with clinical, biochemical and social data. After decoding, intervening drugs were found to be 'A' for Selenium and 'B' for Placebo.

8.2.1 The Intervention Agents

(A) Selenium commercially sold in the market as a solid tablet form, named 'Selenium' (Manufactured by Schiff and distributed by Schiff products, Salt Lake City, UT, USA 84104) packed in a sealed bottle. Each tablet containing 200 μg selenium as yeast rich L-selenomethionine, without any artificial color or preservatives.

(B) Placebo preparations containing potato starch in each as a tablet form which is identical in appearance and color to the selenium tablet (manufactured by The Acme laboratories Ltd, Dhanmondi, Dhaka, Bangladesh).

8.2.2 Analysis of Biological Samples

All biological samples of hair, nails and urine were digested in high purity acids and pretreated with reductants prior to analysis for estimation of arsenic using continuous flow hydride generation with Atomic Absorption Spectrophotometer (HG-AAS) (Buck Scientific, USA, and Model 210 VGP).

8.2.3 Other Biochemical Parameters

For other biochemical parameters, such as random blood glucose, serum alkaline phosphatase, and serum alanine transaminase, estimation has been done with a clinical chemistry analyzer (Microlab 300, The Netherlands). Urine was examined for the presence of albumin and microscopically examined for any cast and RBC which denotes as abnormal findings. Electrocardiogram (ECG) was done in selective cases when there was high blood pressure (either >160 in systolic or >90 in diastolic or in combination) or high pulse rate (>100/min) found in physical examination.

8.2.4 Statistical Analyses of the Data

Data analyses were carried out using Statistical Package for Social Science (SPSS) (version 12.0 for windows, SPSS Inc, Chicago, USA). Results were expressed as mean ± SD (standard deviation) and in graphical forms after log transformation to make the data normal. The statistical analyses Pearson Chi-square test (χ^2), and Student two-tailed paired t-test were performed. Differences were considered significant with $*p < 0.05$.

8.2.5 Clinical Outcome Evaluation

The patients were examined in every follow-up visit by the same dermatologist, and severity of keratosis, melanosis, leucomelanosis and other clinical variables were recorded in the checklist without going through the records. Primary outcome measures for this study included changes in arsenical skin lesions (incidence of new lesions and improvement of old lesions), as assessed by clinical examination and secondary outcome measure included changes of arsenic levels in hair, nails and urine.

Skin lesions related to arsenic tend to occur on certain parts of the body (particularly palms, soles, and trunk), and the efficacy of the intervention as indicated by prognosis of severity of lesions (particularly melanosis, leucomelanosis and keratosis), was evaluated as grade l = mild, grade ll = moderate and grade lll = severe (WHO 2002) and recorded in the checklist at each follow-up visit.

8.3 Results

In this study, out of 174 patients selected, 33 patients could not complete the 1 year study periodic follow-up, so the dropout rate was 18.9%. Among the study subjects, 112 (64.3 %) were young adult female and the rest were male. The majority of the subjects had five or more family members and showed that the mean BMI was 20.3 ± 3.5 kg/m^2, 94% of male subjects and 89% of female subjects had suffered from arsenicosis for more than 4 years (Fig. 8.1).

As all our study subjects were from the same homogenous environment, it was found that am average of 45.45 μg/L of total arsenic was taken by each subject daily through their food chain, and an average of 243 μg/L through drinking contaminated shallow tube well water. About 33.3% subjects were drinking contaminated water initially, but eventually this rate dropped down to zero. More than 94% cooked their meals with surface water, which was found safe from arsenic. But more than 87% were drinking arsenic contaminated water from shallow tube well water for 21.1 ± 11.4 years (range 11.5–35.6 years) (Table 8.1).

The selenium treated group showed significant improvement of their physical and clinical signs and symptoms after intervention. Marked changes were observed in the severity scores compared to their pre-treatment values.

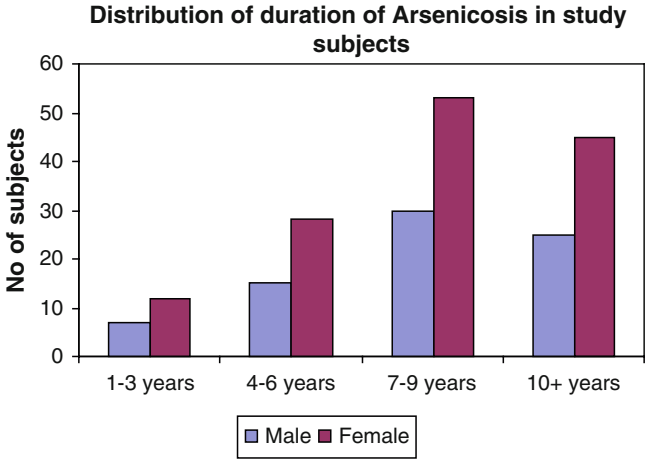

Fig. 8.1 Duration of arsenicosis in study subjects

Table 8.1 Percent distribution of source of water use

	Drinking		Cooking	
Source of water	Selenium	Placebo (%)	Selenium	Placebo (%)
Deep tube well	6.9	10.3	3.4	1.1
Shallow tube well	86.2	87.4	2.3	2.3
Pond	4.6	2.3	94.3	96.6
Filter/boiling	2.3	0.0	0.0	0.0

Table 8.2 Distribution of skin changes before and after intervention in study subjects

	Selenium (69)[a]		Placebo (72)[a]	
Skin sign	Before (%)	After (%)	Before (%)	After (%)
Grade I (mild)				
Diffuse melanosis/suspicious spotty pigmentation on trunk/limb	14.5	50.7	16.9	21.1
Mild thickening of palms/soles	19.0	49.2	21.2	21.2
Suspicious spotty depigmentation on trunk/limb	33.3	24.2	38.0	38.0
Grade II (moderate)				
Definite spotty pigmentation on trunk/limb, bilateral	30.4	36.2	26.8	22.5
Definite spotty depigmentation over trunk/limb, bilateral	48.5	50.0	39.4	35.2
Severe diffuse thickening of palms/soles	30.2	41.3	34.8	34.8
Grade III (severe)				
Definite spotty pigmentation on trunk & limb, bilateral	55.1	13.0	56.3	56.3
Definite spotty depigmentation over trunk & limb, bilateral	18.2	25.8	22.5	26.8
Mucosal pigmentation in tongue or oral mucosa	0.0	0.0	0.0	0.0
Large nodules over thickened palm/soles	50.8	9.5	43.9	43.9
Diffuse verrucous lesions with crack and fissure on soles	15.9	10.1	6.9	6.9
Non-healing ulcer, e.g., Bowen's disease, etc.	2.9	0.0	2.9	0.0
Gangrene of palm or sole	2.9	2.9	0.0	0.0

[a]Figures in parentheses are number of patients; % = percentile

The severity of melanosis and keratosis reduced to almost normal skin in many subjects after intervention. The melanosis was reduced 76% in severe grade ($n = 67$, $\chi^2 = 32.13$, $p < 0.00$) of selenium treated group after intervention, but very little change was found in Placebo group ($n = 72$, $\chi^2 = 0.59$, $p < 0.74$). The severity of keratosis in the palm and soles was reduced by 81% in severe grade of selenium intervention group ($n = 67$, $\chi^2 = 27.27$, $p < 0.00$), but no changes were observed in placebo group ($n = 72$, $\chi^2 = 0.00$, $p < 1.00$) (Table 8.2). The symptoms like anorexia, nausea, vomiting, weakness, dizziness, etc., reduced from 100% to 31.9%

(68% reduction, $p < 0.00$) in selenium intervention group but there was only 2.8% reduction in the placebo group.

The Arsenic concentration in nails reduced significantly (83.1%) after intervention in Selenium treated group ($n = 55$, $t = 2.708$, $p < 0.00$) but very little change was observed in the placebo group ($n = 61$, $t = -0.191$, $p < 0.85$). The Arsenic concentration of hair was also reduced (61.8%) significantly after intervention in the selenium treated group ($n = 60$, $t = 5.269$, $p < 0.00$), but also found a 33.7% reduction in the placebo group ($n = 67$, $t = 4.672$, $p < 0.00$) (Table 8.3).

The concentration of arsenic titer in urine also found significant reduction (42.4%) after intervention in selenium group ($t = 6.653$, $p < 0.00$), and a 41.1% reduction in the placebo group ($t = 7.493$, $p < 0.00$). The trend of arsenic excretion in urine found in selenium group was linear (Fig. 8.2).

The serum selenium concentration was found to be 1.792 ± 0.293 µg/L in study subjects, but after intervention the concentration rose to 62.4% only in the selenium treated group ($t = -2.079$, $p < 0.04$) with no change in the placebo group.

There was no substantial organopathy found in kidney function test, liver function test and random blood glucose before and after intervention in study population. Liver function test showed that there was no abnormality in serum glutamic pyruvate transaminase (SGPT) level before and after intervention in

Table 8.3 Shows distribution of concentration of Arsenic (As) in nail and hair of study subjects

Parameters	Group	Before	After	*p*-value
As concentration in nail µg/kg as mean ± SD	Selenium (55)[a]	0.314 ± 0.522	0.052 ± 0.608	<0.00
	Placebo (61)[a]	0.222 ± 0.540	0.235 ± 0.582	<0.85
As concentration in hair µg/kg as mean ± SD	Selenium (60)[a]	0.123 ± 0.442	0.047 ± 0.560	<0.00
	Placebo (67)[a]	0.608 ± 0.442	0.403 ± 0.493	<0.00

[a]Figures in parenthesis are sample numbers; µg/kg = microgram per kilogram

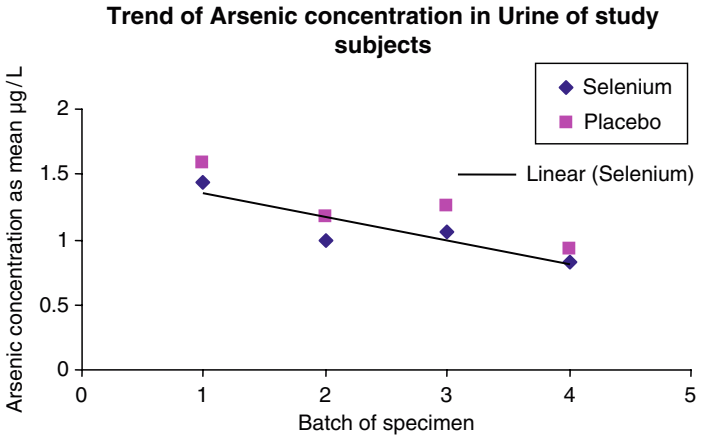

Fig 8.2 Trend of arsenic excretion in urine of selenium group

study subjects, but only 23.1% of cases had a high level of alkaline phosphatase before intervention which, after intervention, 74% reversed under the selenium group and no changes were found in the placebo group, respectively. There was no significant change in the blood glucose level of the study population after intervention ($p < 0.06$).

8.4 Discussion

In this study, it was observed that all the study subjects had multiple clinical presentation and there were gradual improvement of clinical sign and symptoms, including skin changes, after intervention. The severity of melanosis and keratosis was reduced to almost normal skin in many subjects. The severity of melanosis and keratosis was reduced by 76% and 81% respectively in selenium group after intervention but very little changed in placebo group. This study was similar to the findings by Wang et al. in China where they administered 100–200 μg selenium/day for 14 months and observed 75% and 55% reduction in clinical signs like keratosis and melanosis respectively (Wang et al. 2001). Rabbani in Bangladesh showed 63.3% improvement in planter keratosis, and a 59.7% decrease in melanosis (Rabbani et al. 2003).

A urinary concentration of total arsenic is a reliable indicator of arsenic consumption because urine is the primary route of elimination of most absorbed arsenicals (Vahter 1994). In this study, after 12 months of treatment with selenium and consumption of arsenic safe water, urinary concentration of total arsenic dropped to 50% of the pretreatment value in all groups. This drop was likely to be related to sudden cessation of arsenic consumption accomplished by taking boiled pond water. However, the peak excretion levels did not reach a constant level or a plateau at the end of the 12 month period; this indicates that treatment time might have to be prolonged to reach a maximum excretory threshold level.

In this study, the concentration of arsenic in scalp hair was significantly reduced in the selenium group. The reduction in placebo treated groups is likely to be related to the introduction of arsenic-free water. In contrast, reduction of arsenic load in hair after intervention with 200 μg/day selenium for 14 months in Mongolia found the hair arsenic content of selenium patients decreased by 73%, whereas placebo patients dropped 52% (Yang et al. 2002). In this study, the present observations support the findings by Tseng, in Taiwan, Guha in India and Yang in Mongolia that a supply of arsenic safe water alone is not sufficient to detoxify individuals exposed to arsenic for a prolonged period (Tseng et al. 1968; Guha et al. 1998; Yang et al. 2002). The findings suggest that prolonged exposure to toxic levels of inorganic arsenic may induce changes in the body that are reversible by preventing further exposure to arsenic and supplementation with selenium with a therapeutic safe dose. We found that a combination of 100 μg of selenium as selenomethionine and arsenic-safe water per day for 12 months is a safe, effective, and cheap, but needs more multicentral trials before advising mass use in combating arsenicosis in

Bangladesh. More study is also necessary for estimation of selenium in different foods and soil mapping in Bangladesh.

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