Review article

Dose-response meta-analysis of arsenic exposure in drinking water and hypertension

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ABSTRACT

Background: Based on the cross-sectional and cohort studies, exposure to As via drinking water can cause hypertension.

Methods: We searched PubMed, ISI WOS, and Scopus for relevant studies up to 1 January 2018 using related keywords. The meta-analysis was done on 10 studies (n = 28255) that report Odds Ratio for hypertension. The extracted ORs between As concentration and hypertension were pooled using random effect models. Study heterogeneity was analyzed using $I^2$.

Results: The estimated adjusted OR for association between As and hypertension was 1.44 (95% CI: 1.12, 1.84) with $I^2 = 71\%$. Dose-Response analysis showed a linear relationship between As and hypertension (OR = 1.0008 95% CI: 1.0003, 1.001). In general, by increase of each unit in arsenic concentration, odds of the hypertension would increase as 0.08%.

Conclusion: There was a significant relationship between As exposure and hypertension.

1. Introduction

Arsenic (As) is one of the natural toxic element of earth’s crust and classified as the carcinogenic to human by International Agency for Research on Cancer (IARC) [1,2]. Exposure to As through intake of food and contaminated drinking water is a serious threat to human health worldwide [3]. It was estimated that more than 200 million people are at risk for exposure to As via contaminated drinking water at concentrations higher than international standards [4]. Although WHO guideline set a limit of 10 μg/l for As, but according to the estimates, 30 million of human in Bangladesh and India drink water with As level above of 50 μg/l [5]. Chronic exposure to arsenic and drinking-water is a risk factor for lung, bladder and skin cancer [6]. Consumption drinking water containing high As concentrations (>500 μg/l) have also been positively correlated with risk of cardiovascular disease (CVD), including hypertension [7, 8, 9], ischemic heart disease [10,11] and carotid atherosclerosis [12] in a series of retrospective cohort studies in arsenic-endemic areas such Chile and Taiwan [7, 8, 9, 10, 11, 12]. A cross-sectional study in Bangladesh investigated relationship between hypertension and chronic As exposure through drinking water and identified borderline significant association between As and elevated systolic blood pressure. Moreover, As exposure (>50 μg/l) significantly positively associated with increased pulse pressure [13]. Experimental studies suggested several mechanism of arsenic on hypertension including, increased inflammation activity, oxidative stress, endothelial dysfunction and atherosclerosis [14,15].

Raised blood pressure is one of the major risk factor for CVD morbidity and mortality and accounts for 7.5 million deaths worldwide, approximately 12.8% of the total of all deaths [16]. About 57% of all stroke deaths and 24% of all coronary heart disease deaths in Eastern Asia are due to hypertension [17].
Considering that many people are exposed to As and hypertension is a major risk factor for coronary heart disease and ischemic as well as hemorrhagic stroke, further studies is require to elucidate association between As and hypertension. We conduct a dose-response meta-analysis that include relevant studies about As in drinking water and hypertension to pooling the results of the individual studies.

2. Method

2.1. Search strategy

In this study, three electronic databases including Medline (PubMed), Scopus, and ISI WOS were searched for paper title and/or abstracts in order to access English-language medical literature published up to 1 January 2018. We conducted searches using different combinations of keywords and MeSH terms including ‘blood pressure’ OR ‘hypertension’ OR ‘systolic’ OR ‘diastolic’ OR ‘hypertensive’ OR ‘BP’ arsenic OR ‘arsenate’ OR ‘arsenic’ OR ‘arsenical’ OR ‘arsenosis’ (Appendix 1). We checked duplicates papers and then deleted them. In addition, if the full text of paper was unavailable, we requested the paper from author via email. In cases where the author did not answer the email, papers were finally excluded from the study.

In accordance with the questions specified in advance, we conducted our search strategy, as follows: (a) P: Persons who exposed to arsenic in drinking water; (b) I: Arsenic; (c) C: Different levels of exposure to arsenic; (d) O: Hypertension.

2.2. Study selection

This study was conducted based on the criteria of the PRISMA guidelines [18]. Case-control and cross-sectional studies investigating the effect of As exposure through drinking water on hypertension were include. As was measured using laboratory technique. To simplify faster screening, first, the titles were judged, where clearly irrelevant papers were scraped. Then, the abstracts of the related studies were read to ensure that the basic subject of the article was relevant to As exposure and hypertension. Final screening of the studies was based on the full texts. We excluded studies that only measured As in the urine and keratin. The studies which had not reported the odd ratio (OR), mean or such parameter could be estimate from the published data, were excluded. In addition, case reports and letters to the editors were not included. The names of authors or titles of journals had no effect on the selection of papers.

2.3. Screening and data extraction

All potentially relevant publications were inserted in EndNote X8 software and reviewed independently by two authors (A. J and A. A). Discrepancies between authors were resolved by consensus with an expert (B. K). Two authors (R. M and M. G) screened the initial list of articles to identify articles that were irrelevant and, therefore, discarded from the list. To facilitate screening, articles were first judged based on their titles, where obviously irrelevant articles were discarded. Three authors then read the abstracts of the remaining articles (A. A and Y. M and MA. K) to ensure that the main subject of the study was related to arsenic exposure and hypertension. After the final evaluation, the authors extracted and recorded the required data, i.e., name of the first author, year of publication, country, sample size, study design, exposure and outcome measurement, crude and adjusted OR, and 95% confidence interval (CI). All the extracted data then entered into Excel software.

2.4. Quality assessment of studies

To assess the quality of included studies, we used the Newcastle-Ottawa quality assessment scale for check case-control and cross-sectional studies [19]. We assessed the quality of all relevant studies according to the type of study, sample size, participant’s selection, setting, representative of the sample (case or control group), comparability (case-control), method of ascertainment for cases and controls, valid and reliability of measuring exposure and outcome, identification confounding factors, matching of case and control group and appropriate statistical analysis. Finally, studies with high and medium quality were included in the analyses.

2.5. Statistical analysis

Higgins and Thompson’s I² was applied to determine the degree of heterogeneity between the studies. Applying random effect models the pooled associations (with uncertainty 95%) between As concentration and hypertension were presented as Odds Ratio (OR). R 3.6.0. The “meta” package was used to perform the meta-analysis.

In addition, we used a distributional approach [20] for dichotomization of continuous outcomes (systolic blood pressure) and estimating the OR. Actually, we considered systolic blood pressure as a surrogate for hypertension. To converting, we used sample sizes, means, and standard deviations in each group. It should be noted that the estimated ORs using distributional approach considered as crude summary measures. As a sensitivity analysis, the converted measures were pooled with the crude ORs using random effect models.

Moreover, using the “mvmeta” and “dosresmeta” packages, we tried to perform the dose-response meta-analysis to evaluate the relationship between As (μg/L) and hypertension. This way, two-stage random effects models (linear and cubic spline) were performed and the best model was chosen according to the AIC and BIC. Finally, publication bias was checked by applying eggar’s test and begg’s test.

3. Results

Up to 2018, 10 observational studies (Figure 1) with a total of 28255 men and women were included in the present study. Most of the studies included men and women with a wide range of age (15–79 years old). The studies had been published in five countries. More details about studies have been shown in Appendix 2.

3.1. Effect of exposure to arsenic in drinking water and hypertension

3.1.1. Crude OR

The pooled estimate of crude OR for the association of arsenic concentration and hypertension was illustrated in Figure 2. We estimated the crude OR as 1.33 (95% CI: 0.85, 2.08), that is not statistically significant. The I² statistics was estimated as 84%.

3.1.2. Total crude OR

In the studies of Richard. Ikwok [21], Khaled Hossein [22], and Saeed Dastgiri [23] odds ratio for hypertension has not been reported. Therefore, we used a distributional method to convert the summary measure. Systolic blood pressure considered as a marker (surrogate) for hypertension. Using the mean, sample size, and standard deviation, we calculated the crude odds ratio. As the sensitivity analysis to estimate the crude OR, we added the ORs were estimated from the three studies applying distributional method to the crude OR of section 3.1. For the association of arsenic concentration with hypertension we estimated the total crude OR as 1.62 (95% CI: 1.20, 2.18) (Figure 3). The I² statistics was estimated as 90%.

3.1.3. Adjusted OR

The pooled estimate of adjusted OR for the association of arsenic concentration and hypertension was depicted in Figure 4. We estimated the OR as 1.44 (95% CI: 1.12, 1.84), that is statistically significant. The I² statistics was estimated as 71%.
3.1.4. Dose-response association between arsenic concentration and hypertension

Using “dosresmeta” function in R package we investigated the linear relationship between As and hypertension (Figure 5). The result indicated that the OR of the association between arsenic concentration and hypertension would be 1.0008 (95% CI: 1.0003, 1.001). Actually, the OR of the hypertension would increase as 0.08% for each unit increase in arsenic concentration (microgram per liter).

3.1.5. Assessment of publication bias

The egger’s tests indicate that there is no publication bias in the present study (P value = 0.92). Additionally, the begg’s test indicate no publication bias (P value = 0.83).

4. Discussion

In this meta-analysis, association between arsenic exposure and the prevalence of hypertension was measured. The common unit of μg/L was used for measurement arsenic concentration. However, the “exposure” definition varies among the studies, since there is discrepancies on how to display the exposure duration and what amount of arsenic constitute an exposure. The present meta-analysis included 10 articles carried out on cross sectional and case-control (total sample size 28255), that suggested convincing evidence on the association between As exposure through drinking water and hypertension. It should be noted that hypertension definition was differ between the selected studies. Guha Mazumder et al. [24], Zhang et al. [25], Xin Li et al. [26], Kwok et al. [21], Islam et al. [13], and Hossain et al. [27], have followed the WHO...
protocol for the measurement of blood pressure and Hypertension was
defined as a systolic blood pressure (SBP) of 140 mm Hg or greater
and/or a diastolic blood pressure of 90 mm Hg or greater; while Hall et al.
[28], Dastgiry et al. [29], and Mahram et al. [30] provided no definition
for the hypertension.

Results of this meta-analysis indicate that chronic arsenic exposure is
likely to be associated with hypertension. The pooled adjusted OR for
association between As and hypertension was 1.43 (95% CI: 1.11, 1.84).
The P values for homogeneity for arsenic and hypertension were signif-
cicant at \( P < 0.01 \). The I\(^2\) was 90% for arsenic concentration studies.

We investigated linear association between As and hypertension, that
OR for relationship between As and hypertension would be 1.0008 (95%
CI: 1.0003, 1.001). In fact for each unit increase in As concentration OR
for hypertension would be increase as 0.08%.

In the study conducted by Zhang et al. [25] effect of long-term
exposure to low-level arsenic in drinking water on blood pressure was
surveyed. They found a positive effect between arsenic exposure and
hypertension. In their study, association between arsenic exposure and
hypertension was evaluated in relation with age, gender, Body Mass
Index (BMI), alcohol consumption and smoking. After adjusting of this
parameters, the odds ratios showed a 1.45-fold (95%CI: 0.63–3.35) in-
crease in the group with \( >30–50 \) years of arsenic exposure and a
2.95-fold (95%CI: 1.31–6.67) increase in the group with \( >50 \) years
exposure. According to their funding despite the lower level of arsenic
exposure, the risk of hypertension increases by the years of arsenic
exposure (\( p < 0.001 \)).

Xin Li et al. [26] investigated the prevalence of hypertension and
arsenic exposure in Inner Mongolia, China, with the emphasis on the
assessment of low-level exposure. Adjustment of the possible con-
founders of gender, age, cigarette smoking, alcohol consumption, BMI,
CAE, and diabetes was done. Based on their result, low-level arsenic
exposure (10–50 \( \mu \)g/L) was not statistically associated with hyperten-
sion. (\( OR = 1.417; \) 95% CI: 0.767, 2.618).

Two studies from Bangladesh [13] and Romania [31] didn’t show
significant association between arsenic exposure and hypertension. The
study in Bangladesh found that arsenic exposure was strongly associated
with increased pulse pressure and this association was stronger in resi-
dents with longer duration of high arsenic exposure (\( OR = 3.54, \) 95% CI:
1.46–8.57). In general, systolic or diastolic hypertension were not asso-
ciated with any amount or duration of arsenic exposure in subjected area.
In Romania study although effect of arsenic exposure on hypertension
was more modest, but non-significant, adjusted odds ratio for average
arsenic concentration in association with HBP was found (\( OR = 1.36; 
95% CI 0.68–2.39; p = 0.300 \)).

The studies of Kwok et al. [21], Khaled Hosein et al. [27], Hall et al.
[28], Mahram et al. [30], Dastgiry et al. [29], and Mazumder et al. [24],
showed evidence of increased association of hypertension in participants
in arsenic endemic area.

Lalita.N. Abhyakar [14] evaluated the association between arsenic
exposure from drinking water and hypertension. In this paper that
included 11 cross sectional studies, the pooled OR for hypertension
comparing the highest and lowest arsenic exposure categories was 1.27
(95% CI: 1.09,1.47). In this systematic review they found positive effect
between arsenic and the prevalence of hypertension. In another study
Abir et al. [32] conducted a meta-analysis on the association between
chronic As exposure and hypertension in 2012. In this paper eight studies
were analysed. This meta analysis suggested possible association be-
tween chronic exposure to As and hypertension. The results of our study
are similar to those reported by Abir et al. Similar to Abir et al., a random
effects model was used in conducting this meta-analysis.
The limited number of studies, heterogeneity across studies, in appropriate adjustment for related confounders, need for standard hypertension definitions, and individual assessment of arsenic exposure can be mentioned as possible limitation in integral interpretation of arsenic exposure and hypertension. The exact mechanism through which long term exposure to arsenic may damage the human vascular system is not clearly understood. Based on the previously conducted studies, in both humans and animals, arsenic promotes oxidative stress and inflammation [28,33,34]. These processes may accelerate endothelial cell damage, increased platelet adhesion, and reduced vasodilation. This can define the main mechanism of arsenic-related hypertension. In addition, some Kidney disease may result in Kidney dysfunction, which finally mediates arsenic-hypertension associations [28,35]. The ten studies that included in present paper, have shown that impact of As on hypertension varied with factors such as age, body-mass index, sex, cigarette smoking, nutrition, monthly income, marital status and baseline hypertension rates [3,13,21, 22, 23,26,28,30,31,36]. Although this study specified that arsenic in drinking water is associated with hypertension, for better understand and illustrating more specific dose-response relationships, larger studies are needed.

4.1. Limitations and strengths

In this paper we perform converting summery measure in the studies did not have OR for systolic and diastolic, just they have mean. This is a strength of the current study. Conducting a dose-response meta-analysis investigating the association between As concentration and hypertension can be mentioned as another strength point of this study as the novelty. In fact, applying dose-response meta-analysis approach, we estimated a weighted pooled estimate based on each unit increase in arsenic concentration. High variability of hypertension measurements could be considered as a main limit. Moreover, in this study the author did not search the grey literature. Roughly high heterogenicity could be another limitation and affect the results. This heterogenicity could be due to the study designs, different statistical models, and different variables entered in the models.

5. Conclusions

The present dose-response meta analysis identified relationship between As exposure through drinking water with hypertension. Based on the obtained results, for each unit increase of the As concentration (microgram per liter) hypertension would increase 0.08%. However due to small number of studies, methodological limitations as well as limitations in study quality, establishing causal relationship between arsenic exposure and hypertension was main challenges.

Due to widespread exposure to arsenic and high prevalence of hypertension in global level which is a well-known risk factor for cardiovascular disease and one of the main causes of morbidity and mortality, conducting high quality prospective studies with proper measures for assessment of arsenic exposure is needed.

Declarations

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Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

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