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Blood copper levels in Mexican users of the T380A IUD

Dolores De la Cruz[a], Angeles Cruz[a], Maricela Arteaga[b], Lourdes Castillo[b], Horacio Tovalin[c,*]

[a]Unidad Universitaria de Investigación en Cariología (University Cariology Research Unit), FES-Zaragoza, Universidad Nacional Autónoma de México, Mexico City, Mexico

[b]Laboratorio de Espectroscopía (Spectroscopy Laboratory), FES-Zaragoza, Universidad Nacional Autónoma de México, Mexico City, Mexico

[c]División de Estudios de Posgrado e Investigación (Graduate Studies and Research Division), FES-Zaragoza, Universidad Nacional Autónoma de México, Mexico City, Mexico

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Abstract

Objective: Copper T380A is one of the most commonly prescribed intrauterine devices (IUDs). However, there are few reports of its systemic health effects. This study evaluates the association between the use of T380A IUD and blood Cu levels in a group of Mexican users.
Methods: Eighty-six T380A users and eight nonusers were recruited. Blood Cu levels were measured using an atomic absorption spectrophotometic technique.
Results: In IUD users, mean blood Cu level was significantly higher than in nonusers, 216.63 vs. 107.47 μg/dL ($p \leq .001$), and above the normal blood Cu level range of 80–160 μg/dL. No significant difference in blood Cu levels was observed by age or length of time of IUD use.
Conclusions: The observed higher blood Cu levels among T380A user stands out in sharp contrast to previous reports of other types of Cu IUDs. Further research should evaluate if the observed levels are associated to toxic effects with the general population or special groups.

Keywords: Copper; T380A; Blood; Users; Mexican

1. Introduction

Copper intrauterine devices (Cu IUDs) are valuable birth control resources. Release of Cu from these devices is necessary for their contraceptive effects [1]. The Cu T380A is one of the most commonly prescribed IUDs; some of its advantages are fewer side effects in comparison with other method [2]. However, there are few reports of the T380A systemic side effects. The T380A is made of plastic with added barium sulfate for X-ray visibility, with a T-shape 36-mm height and 32-mm width. A copper wire twisted on its body and two copper sleeves on its arms, with a total Cu contact surface of 380 mm^2 [2].

Release and absorption rates have been evaluated for different CU IUDs. A study carried out by Hagenfeldt [3] did not find a significant difference in plasma Cu concentrations levels between Cu T120 and T130 users and nonusers, but observed an increment in endometrial Cu concentration. The same author [3] estimated a T120 and T135 annual Cu liberation of 10.3 mg/year (range=7.4–13.5 mg/year) and a 5% annual endometrial Cu absorption (about 0.5 mg per year), and for T200, a daily release of 45 μg, around 18 mg/year. Timonen [4] reported a daily release that ranged from 26 to 74 μg Cu/day for different IUDs, and Thiery and Kosonen [5] reported a release of 23 μg Cu/d after 10 years of insertion for T220 devices without calcareous deposits. In 1972, Oster [6] observed that Cu ions in uterus could cross over to blood, increasing about 1% blood Cu concentration in T200A users. Later, Anteby et al. [7] found a nonstatistical difference between the serum levels of Cu before and after insertion of the T200A IUD. Prema et al. [8] studied 24-h urinary Cu excretion and did not find differences between a control group and Cu IUD users.

Copper is an essential trace element found in small amounts in different cells and tissues. Copper exists in both oxidized, cupric (Cu^{2+}) or reduced (Cu^{+}) state [9]. Copper's function as a cofactor is required for structural and catalytic properties of a variety of important enzymes, such as cytochrome *c* oxidase, Cu-zinc superoxide dismutase, tyrosinase, dopamine beta-hydrolase and others. Once Cu is absorbed, it is stored in several tissues and organs, among which, liver, kidney, brain and bone have the largest amount and blood the lowest [10]. Bile is the main route for Cu

* Corresponding author. Tel.: +52 55 56 23 07 21.
E-mail address: htovalin@hotmail.com (H. Tovalin).

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Table 1
Blood Cu levels in T380A users and nonusers

Group	Blood Cu, μg/dL (μmol/L)				
	N	Mean	SD	Minimum	Maximum
Users	86	217.36[a] (34.12)	±21.32	178 (27.95)	277 (43.49)
Nonusers	8	107.47 (16.87)	±16.30	89 (13.97)	134 (21.03)

[a] *t* Test, p≤.001.

excretion, while urine represents a minor route [11,12]. The daily recommended Cu intake is 1.5–3 mg/day [13,14]. Food Cu concentrations are variable, chocolate and liver being among the highest in concentration, followed by cereals and fruits.

In the general population, a mean serum Cu concentration of 80 μg/dL with an upper range of 150 μg/dL [15,16] and a whole blood Cu concentration with a mean value of 110 μg/dL have been reported [16,17]. Although Cu is an essential element, it can become toxic for cells when present at high concentrations; as it is the case with cadmium and lead, Cu could displace metal ions such as calcium and magnesium [18]. In addition, the Cu^{2+} as other redox active metals can be toxic by generating free hydroxyl radicals [19,20]. Free hydroxyl radicals resulting from catalytic Cu can bind to DNA and result in DNA strand breaks and DNA base modifications [21].

Toxic symptoms such as gastrointestinal symptoms have been reported at a serum level of 200 μg/dL and whole blood concentration above 287 μg/dL [16]. Hepatic symptoms appear at blood levels above 798 μg/dL [22]. Very high Cu levels can cause acute toxicity, and an oral dose of 200 mg/kg/day is considered fatal [23]. Individuals with Wilson's disease, an autosomal recessive disease, do not adequately metabolize and eliminate Cu and have a progressive accumulation of Cu in the brain, kidneys and liver [24].

In an effort to provide more information on Cu absorption in T380A IUD users, a group of users and nonusers was studied with the aim to measure their blood Cu levels and to evaluate potential Cu toxic effects.

2. Material and methods

The study was approved by the Research Committee of the Facultad de Estudios Superiores-Zaragoza, Universidad Nacional Autónoma de México (UNAM).

2.1. Study population

Volunteers were recruited among women who attended a general hospital located in Mexico City. Cases were healthy women 15–45 years old who have been using the T380A IUD for at least 1 month. Controls were healthy women from the same age group not using any type of birth control method. Verbal and printed information about the study was provided to the hospital clients, and those who accepted to participate received and signed an informed consent. Women taking any kind of medication or vitamin supplements were excluded from this study.

2.2. Blood sample collection and analysis

Blood was collected in heparinized sample vials by a nurse and kept in refrigeration until analysis. Blood samples were processed as described by ACF [25]. Briefly, blood was lysed with 1% Triton X-100 solution (Sigma-Aldrich, St. Louis, MO, USA). Blood Cu was chelated with ammonium pyrrolidine dithiocarbamate (Sigma-Aldrich). Copper chelates were extracted with methyl isobutyl ketone (Merk & Co., Whitehouse Station, NJ, USA), and analyzed by an atomic absorption spectrometer Perkin-Elmer 3110 (Perkin-Elmer, Boston, MA, USA).

2.3. Data collection and statistical analysis

A questionnaire about demographics, length of time of IUD use, diet and health information was administered by trained interviewers. Length of time of IUD use was measured by counting the number of months since IUD insertion. Age and IUD use subgroups were created using the values of the first, second and third quartiles as cut-points.

Student's *t* test was used to compare mean values of cases and controls, while ANOVA was used to compare blood Cu levels among age subgroups and to compare the Cu levels among subgroups of length of IUD use. The statistical software SPSS 10 (SPSS, Chicago, IL, USA) was used to analyze the data.

3. Results

Ninety-four women participated in the study, 86 were T380A users and 8 were controls. The mean ages for the cases and controls were 27.41±6.62 and 23.2±4.34 years old, respectively. No difference between the groups was found related to consumption of foods with relatively high Cu content such as chocolate, cereals, vegetables and fruits. Mean length of IUD use was 25±1.12 months with a minimum of 2 months and a maximum of 124 months.

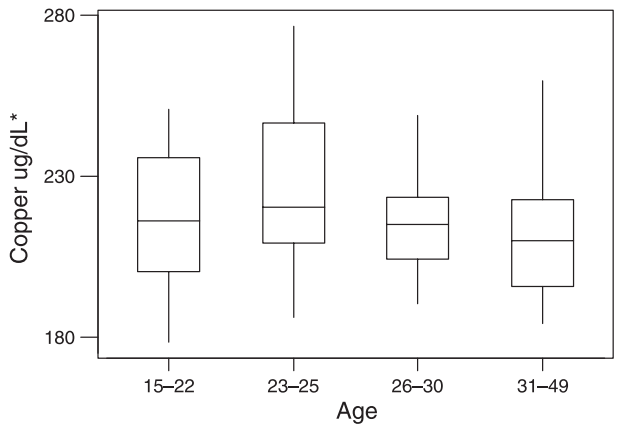

Fig. 1. Blood Cu levels (μg/dL) in T380A users by age group. *CU mean ± SD μg/dL (μmol/L) by age groups: 15–22=217.06 (34.07)±21.85; 23–25=226.73 (35.60)±26.30; 26–30=215.09 (33.77)±14.87; 31–39=211.25 (33.17)±19.36.

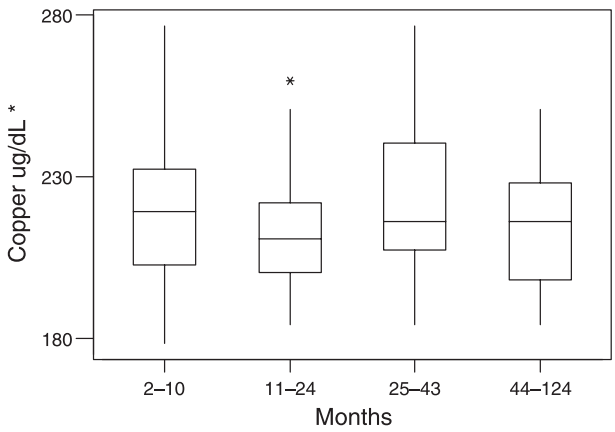

Fig. 2. Blood Cu levels (μg/dL) in T380A users by length of time (months) of IUD use. *CU mean ± SD μg/dL (μmol/L) by months of use: 2–10=219.35 (34.4)±23.34; 11–24=212.59 (33.37)±18.40; 25–43=221.71 (34.81)±24.20; 44–124=216.39 (33.97)±19.86.

Mean blood Cu level was significantly higher for cases (IUD users) than for controls (nonusers). In fact, the blood Cu level found in cases was twofold higher than that observed in controls (Table 1).

No significant differences were found in blood Cu concentrations when stratifying by age groups or length of time of IUD use (Figs. 1 and 2). Blood Cu concentrations by age group are not reported for controls due to small sample size.

4. Discussion

According to Hagenfeldt [3], there was no significant increase of plasma Cu among T120 and T135 users as compared with controls. However, we found a significant increase in blood Cu levels among T380A users as compared with nonusers. Contrary to Hagenfeldt's [26] findings, in this study, Cu absorption has an observable effect in the metabolism of Cu in the body. In this case, the observed difference might be due to a greater Cu contact area, since the T380A has a 90% greater contact area than the T200A.

As previously mentioned, Oster [6] suggested that formed cupric ions are absorbed by the endometrial tissue and that IUD use could lead to a 1% increment in blood Cu levels. Based in our results, we can estimate that the blood Cu levels of T380A users increased about 35% over the highest normal level reported and became almost 100% higher than mean blood Cu concentration of nonusers. Considering the potential of the T380A to produce high blood Cu concentrations, it is interesting to note that our results were not associated with age and length of time of IUD use. These findings may be an indication of a constant Cu release rate from IUDs and that Cu metabolism in the body has adapted to the situation.

Even though the control group was small, it was a valid comparison group given that its mean blood Cu level were within the range of reported normal values [16] and data variability was small (coefficient of variation=15.17%).

Our results show a significant difference in blood Cu levels between T380A users and nonusers, a twofold above the population values and higher than values reported previously for T120, T135 and T220 users. Blood Cu levels in this study were higher than levels related with gastrointestinal symptoms and a slight alteration of indicators of liver function reported by Araya et al. [27]. It is also important to note that the use of the T380A by special risk groups as Wilson's disease patients [28] may increase the Cu-related damage to their health. Although the T380A IUD is an invaluable birth control resource, potential side effects due to Cu absorption need further evaluation.

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