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Cytotoxicity of six copper-bearing intrauterine devices on Chinese hamster ovary cells: the influence of frame, shape and copper surface area

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Objective *To evaluate the cytotoxicity of six commonly used copper-bearing intrauterine devices (Cu-IUDs) on Chinese hamster ovary (CHO-K1) cells and to investigate the influence of frame, shape and copper surface area of Cu-IUDs on cell toxicity.*

Methods *Cu-IUDs were incubated in 10% FBS-DMEM/F12 culture medium at 37 ℃ for 24 h. The extracts were analyzed by flame atomic absorption spectrometer and were then diluted into different concentrations with culture medium. Finally, cytotoxicity of these original and diluted extracts on CHO-K1 cells was detected by cell counting kit-8 (CCK-8) assay.*

Results *The viabilities of cells treated with the original extracts of six Cu-IUDs (TCu220C bulb, TCu220C, GCu220, GCu300, Yuangong Cu270 and Yuangong Ⅱ-300) were all below 10% and the cupric ion concentrations in these extracts were 28.22 mg/L, 31.80 mg/L, 92.80 mg/L, 99.74 mg/L, 114.90 mg/L and 119.20 mg/L, respectively. After these original extracts were diluted, significant differences in cytotoxicity were exhibited. IUDs with larger copper surface areas (GCu300 and Yuangong Ⅱ-300) showed more cytotoxicity than those with smaller areas (GCu220 and Yuangong Cu270) respectively; When different shapes of Cu-IUDs were compared, TCu220C bulb showed lower cytotoxicity than TCu220C, and GCu300 exhibited higher toxicity than Yuangong Ⅱ-300; TCu220C displayed significantly lower cytotoxicity than GCu220 due to their differences in frames.*

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Conclusion *We presented evidence on the cytotoxic effects of copper ions released from Cu-IUDs on CHO-K1 cells and found that shape, frame together with copper surface area of Cu-IUDs had obvious influence on the cytotoxicity.*

Key words: copper-bearing intrauterine device (Cu-IUD); Chinese hamster ovary (CHO-K1); cell counting kit-8 (CCK-8); cytotoxicity; extract concentration; influential factor

Copper-bearing intrauterine device (Cu-IUD) has been increasingly used in the world today since the 1960s[1]. The number of Cu-IUD users accounts for approximately two-thirds of worldwide IUD users[2] because of its long life span, rapid reversibility and high effectiveness[3-5].

The anti-fertility effect of Cu-IUD is mainly attributed to the uninterrupted release of cupric ions which leads to the inactivation of sperm[6-8]. A study of Wildemeersch[9] demonstrated that a minimal amount of cupric ion positioned in the upper part of the uterine cavity is sufficient to provide a high contraceptive effect. Araya et al.[10] also confirmed that cupric ion at a concentration of 8×10^{-6} mol/L significantly reduced spermatozoa motility after about 20 min. However, the entire genital tract is reported to be exposed to 25−80 μg/d of cupric ions released from an inserted Cu-IUD[11-12]. Arancibia et al.[4] has found that total copper concentrations released from TCu380A in uterine fluid were between 3.9 μg/ml and 19.1 μg/ml. It can be seen that the cupric ions released from Cu-IUDs are usually more than needed for contraception.

Meanwhile Cu-IUDs can also bring some side effects such as pelvic inflammatory disease, pain and bleeding[13-15]. Although the cause is still unclear, it has been believed that at least some of these side effects may be related to the burst release and overexposure of copper ion[16,17]. In our previous studies[17-19], the copper release behaviors of different kinds of Cu-IUDs have been investigated and it was found that there was a burst release during the first month for these Cu-IUDs. Many reports also indicated that overexposure of copper ion could produce a wide spectrum of effects on surrounding cells[20-23]. However, the cytotoxic effect of cupric ion released from Cu-IUDs and factors influencing the cytotoxicity were poorly studied.

A well-established mammalian cell line−Chinese hamster ovary (CHO-K1) cell has been employed to investigate the cytotoxicity of copper ions released from metallic copper and it was concluded that cells close to copper-baring materials were susceptible to cytotoxic effects[24,25]. As known to all, ovary is a part of the genital tract and it has been reported that cupric ions released from Cu-IUDs adversely affect genital tract[26], therefore CHO-K1 cell is an ideal model for cytotoxicity evaluation of Cu-IUDs. Cell Counting Kit-8 (CCK-