ELSEVIER

Contraception 86 (2012) 413–418

Contraception

Original research article

The antifertility effectiveness of a novel copper-containing composite used in intrauterine contraceptive devices and the releasing behavior of cupric ions contained in the composite in rats

Xiangchi Peng[a,b], Shanshan Hu[a], Tianqing Meng[a], Jinping Suo[c], Chengliang Xiong[a,b,*]

[a]*Family Planning Research Institute, Tongji Medical College, HuaZhong University of Science and Technology, Wuhan 430030, P.R. China*
[b]*Center of Reproductive Medicine, Tongji Medical College, HuaZhong University of Science and Technology, Wuhan 430022, P.R. China*
[c]*State Key Laboratory of Mould Technology, College of Materials Science and Engineering, Huazhong University of Science and Technology, Wuhan 430074, P.R. China*

Received 26 November 2011; revised 24 January 2012; accepted 4 February 2012

Abstract

Background: This study was conducted to investigate the antifertility effectiveness of a novel copper-containing composite used in intrauterine contraceptive devices (IUDs) that contain cupric chloride/silicon dioxide/poly(vinyl alcohol) ($CuCl_2/SiO_2$/PVA) and the releasing behavior of cupric ions in the composite into the serum and uterine fluid in rats.
Study Design: Two hundred and forty sexually mature female Sprague–Dawley rats were randomly divided into six groups: sham-operated control group (n=20), bulk copper group (Cu group, n=40), SiO_2/PVA group (n=40), $CuCl_2/SiO_2$/PVA groups I (n=40, copper ion was released from IUD at a rate of 5–10 mcg/220 mm^2 per day) and II (n=40, copper ion was released from IUD at a rate of 10–20 mcg/220 mm^2 per day), and normal control group (n=20). IUD was inserted into the uterus of rats after acclimatization of 1 week .At different time points after implantation of the IUDs, cupric ion concentrations were measured in the serum and local uterine fluid in each group by flame atomic absorption, respectively. After 30 days of insertion, half of the rats in each group were mated with fertile male rats, and the antifertility rates were observed at 14 days of pregnancy. After the IUDs were removed, the remaining rats in each group were mated again to determine their fertility.
Results: Antifertility rates in the Cu group and $CuCl_2/SiO_2$/PVA groups I and II were 100%, and each of these rates was significantly higher than that in the other groups ($p<.05$). There were no differences in fertility restoration rates after the IUD was removed among the Cu group and the $CuCl_2/SiO_2$/PVA group ($p>.05$). No significant change in time dependence was found for the serum cupric ion concentrations in each group ($p>.05$), while the local uterine fluid cupric ion concentrations in the other groups were significantly lower than those in the Cu group ($p<.05$) and without a burst release of cupric ions in the initial days of application.
Conclusions: The novel copper-containing composite used in intrauterine contraceptive devices ($CuCl_2/SiO_2$/PVA composite IUD) had a low pregnancy rate and high contraceptive efficacy without a burst release of cupric ions in the initial days of application.

Keywords: Copper-containing intrauterine device (Cu-IUD); Novel copper-containing composite IUD; Cupric ion; Burst release; Antifertility effectiveness; Rat

1. Introduction

Intrauterine contraceptive devices (IUDs), especially copper-containing IUDs (Cu-IUDs), are increasingly being used worldwide as the most cost-effective contraception methods for birth control given their advantages of being long-lasting, highly efficacious, economical, safe and reversible [1]. However, the existing Cu-IUDs are not perfect. The most important adverse effects of Cu-IUDs are menorrhagia, intermenstrual bleeding, pelvic pain and other menstrual disorders. The side effects of Cu-IUDs are the main reasons for their discontinuation [2]. Results of domestic and foreign research reports showed a pregnancy rate of 0.81% for female subjects using TCu380A for a year. However, the expulsion rate in these cases was 6.32% [3], and 10% of the subjects had the TCu380A IUD removed because of bleeding

* Corresponding author. Center of Reproductive Medicine, Tongji Medical College, HuaZhong University of Science and Technology, Wuhan 430022, P.R. China. Tel.: +86 18986 172569; fax: +86 027 83692605.
E-mail addresses: clxiong@yahoo.com.cn, pxc1993pxc@163.com (C. Xiong).

0010-7824/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2012.02.001

and pain in the first year of use [4]. The discontinuation rate for female subjects at 5 years after the TCu380A IUD insertion was 50% [5]. To overcome these limitations, great efforts have been made to improve the material and structure of copper-containing IUDs. Nevertheless, these improvements have not settled the inherent disadvantages of Cu-IUDs. On the one hand, there still exist side effects associated with the burst release of copper in the first few days of usage [3–5]. On the other hand, the copper ion trapped in the corrosion product and deposited there was about 30%–40% of the total copper ions released [6], indicating that the effectiveness of cupric ions in the Cu-IUD is rather low.

To avoid the burst release of copper during the first few days, a novel cross-linked composite was developed. It was based on poly(vinyl alcohol) (PVA) and contained cupric ions, but not metallic copper [7]. Briefly, two issues for the new material are addressed: the effectiveness of polymers in reducing the initial burst in cupric ion release and the amount and pattern of continuing release. It is reported that in vitro tests for toxicity [8] and antibirth tests of male canine with the composite have already been accomplished [9]. The result indicates that this new material is very promising on histocompatibility and antibirth effectiveness. However, there is no relevant reporting of antibirth effectiveness and the release behavior of cupric iron compounds in female animals.

As a logical extension of our previous work, in this paper, we report on the antifertility effectiveness of a novel copper-containing composite IUD and its release rate of cupric ions in the serum and uterine fluid in female rats to provide preclinical data for the clinical application of this novel Cu-IUD.

2. Materials and methods

2.1. Materials

2.1.1. Animals

Sexually mature female and male Sprague–Dawley (SD) rats, 10–12 weeks of age (Grade SPF, Certificate SCXK 2008-0004 and SCXK 2004-0007) were obtained from the animal facility of the institute (Wuhan University Lab Animal Center, Wuhan, China) and allowed to acclimatize for 1 week before starting the experiment. Animals were bred under specific pathogen-free conditions and barrier maintained during the experiment (12-h light/dark cycle, 22°C ±1°C, 50%±5% relative humidity). Drinking water and conventional feed were provided ad libitum. The experiment was approved by an independent Ethical Committee on Animal Experimentation and conducted in compliance with all applicable provisions of the national laws, i.e., the Experiments on Animals Decree and the Experiments on Animals Act.

2.1.2. IUD component materials

The IUD component materials were provided by the Department of Materials Science and Engineering of Huazhong University of Science and Technology and Wuhan People's Health Medical Device Co., Ltd. IUD component materials of bulk copper group is in the form of a cylinder with a diameter of 2 mm and a length of 5 mm which is part of the copper tubes of TCu380A. IUD component materials of the silicon dioxide (SiO_2)/PVA group, the cupric chloride ($CuCl_2$)/SiO_2/PVA group I (copper ion was released from IUD in the uterus at a rate of 5–10 mcg /220 mm^2 per day) and the $CuCl_2$/SiO_2/PVA group II (copper ion was released from IUD in the uterus at a rate of 10–20 mcg/220 mm^2 per day) were provided by the Department of Materials Science and Engineering of Huazhong University of Science and Technology. Component materials of these IUDs are in the form of a cylinder with a diameter of 2 mm and a length of 5 mm.

2.1.3. Instrumentation

Cupric ion concentrations were determined by flame atomic absorption spectrophotometry (AA-300, Perkin Elmer, Norwalk, CT, USA). The detection limit of the atomic absorption spectrophotometry for cupric ion is 0.077 ppm (10 mcg/L) [10]. All experiments were performed in triplicate, showing a reproducibility of more than 93%.

2.2. Methods

2.2.1. Animal treatment

Two hundred and forty sexually mature, female SD rats were randomly divided into six groups: sham-operated control group (SO group, n=20), bulk copper group (Cu group, n=40), SiO_2/PVA group (n=40), $CuCl_2$/SiO_2/PVA groups I (n=40, copper ion was released from IUD at a rate of 5–10 mcg/220 mm^2 per day) and II (n=40, copper ion was released from IUD at a rate of 10–20 mcg/220 mm^2 per day), and normal control group (NC group, n=20). Firstly, we randomized by phone to the Director of Animal Research Center in Tongji Medical College, Huazhong University of Science and Technology. A computer program generated a randomization schedule. Two hundred and forty sexually mature SD rats were stratified by different body weight at an increment of 10 g, and rats were then classified into six groups by random digit. Rats in the Cu, SiO_2/PVA and $CuCl_2$/SiO_2/PVA groups were anesthetized with 3% thioethamyl (45mg/kg ip), then each corresponding material (please refer to Section 2, paragraph 2) was inserted into the caudal portion of the left uterine horn and secured to the uterine wall via operations including laparotomy and uterotomy. Rats in the SO group underwent the same operations without insertion of material into the uterine horn. During the experiment, animals were examined daily for any clinical signs and general abnormal appearances of the skin, awareness, motor activity, posture, muscle tone, reflexes and autonomic features. The body weights of rats were recorded before the experiment and once every 7 days after the treatment.