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5. Author(s)

1. I Chi
M Acosta
2. G Alvarado, R Rivera
3. J Bandaragoda
ID Betancourt

6. Contributing Organization(s)

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**Is the Copper T 380A Device Associated with an Increased Risk of
Removal due to Bleeding and/or Pain?
--An Analysis--**

I-cheng Cui*, Gaston Farr, Karen Thompson
Family Health International; Post Office Box 13950;
Research Triangle Park Branch; Durham, North Carolina 27709 USA

Manuel Acosta
Hospital Maternidad Lima; Lima, Peru

Gloria Alvarado, Roberto Rivera
Instituto de Investigacion Cientifica; Durango, Mexico

J. Bandaragoda
Family Planning Association; Colombo, Sri Lanka

Jose Delgado Betancourt
Clinica Del Paso; Villahermosa, Tabasco, Mexico

Abstract

Previous studies have consistently shown that the family of the Copper T 380 devices is more effective in preventing accidental pregnancies than the inert, as well as most other, if not all, copper devices. However, a number of these studies also reported a higher removal rate due to bleeding and/or pain for the TCu 380A than for other devices. The programmatic importance of these findings prompted us to analyze the international multi-center randomized clinical trial datasets to examine this question on the new TCu 380A (ParaGardTM) recently marketed in the U.S. Our results, while confirming the inherent superior efficacy of the TCu 380A, did not reveal a significantly higher removal rate because of bleeding and/or pain among TCu 380A users than among users of the comparative devices, which included the Lippes Loop D, the TCu 200, the TCu 220 and the Multiload Cu 250 devices.

*To whom correspondence should be addressed.

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Introduction

Previous studies have consistently shown that the family of the Copper T 380 devices* is more effective in preventing accidental pregnancies than inert devices, as well as most other, if not all, copper intrauterine devices (1,2,3,4,5). Expulsion rates for the TCU 380 devices have generally been comparable to those of other copper devices.

Reported removal rates of the TCU 380 devices due to bleeding and/or pain vary greatly. Higher rates for these devices than for the TCU 200 (2,6), the TCU 300 (1), the MLCu 375 (5), the TCU 220C and Mahua** (7) IUDs were reported in a number of studies from the US as well as from developing countries. Overall continuation rates of this newer device have thus been similar to those reported for other devices, despite its higher efficacy rates (2,8,9).

Some clinical trials, on the other hand, have reported no significant differences in removal rates due to bleeding and/or pain between the TCU 380 devices and the Lippes Loop C (3), the TCU 200 (10) and the MLCu 375*** (11). In Apelo et al.'s study the TCU 380Ag showed a lower removal rate at three years than the Cu7, although the difference was not statistically significant (12).

Although the new TCU 380A (ParaGardTM)**** has only been marketed in the US since June 1988, more than 8 million TCU 380A IUDs have been distributed in over 69 countries in recent years (13). Because of its generally acknowledged high efficacy, this device has the potential to be widely used. Experience of Family Health International (FHI) in studies of this new TCU 380A spans more than five years in over 25 research sites worldwide. We feel that it is of programmatical importance to examine this international clinical trial dataset to determine if the higher removal rates for bleeding and/or pain among TCU 380A users reported in some earlier studies (1,2,5,6,7) would be replicated.

Materials and Methods

The multi-center randomized clinical trials have been initiated under the auspices of FHI since 1984. Healthy and sexually active women aged 18-40 were candidates for admission. Those with uterine abnormalities, evidences of pelvic inflammatory disease (PID) and anemia, and those with a history of ectopic pregnancy, severe PID and menorrhagia or hypermenorrhea were excluded from entering the study.

The women's socio-demographic characteristics, reproductive, menstrual, contraceptive and medical histories, and desire for additional children were ascertained and recorded at admission on the standardized case

*Include the TCU 380Ag and the TCU 380 without a ball.

**A Chinese-made double-coil stainless steel ring.

***While the removal rates for bleeding and/or pain were similar between users of the TCU 380A and those of the MLCu 375, the former group was associated with a higher incidence of pelvic pain (11).

****Marketed and distributed in the U.S. by GynoPharma, Inc., Sommerville, New Jersey.

record form. Pelvic examination was performed immediately before IUD insertions. At each center, the TCU 380A and a comparative IUD (usually the device type which had been commonly used at the center) were randomly assigned and inserted by trained insertors. The women were blinded to the types of the IUDs inserted.

For centers to be included for this analysis, they must have achieved a 12-month follow-up rate of 80% or higher by the cut-off date of June 30, 1989. Four study sites (two in Latin America and two in Asia) were included for analysis. All four sites had completed admissions by May, 1987. The study population totaled 1181 insertions, all performed at least 42 days after the patient's last pregnancy ended (including 31 insertions performed in nulligravid women).

IUD performance in terms of accidental pregnancy, expulsion and removal for medical and personal reasons was ascertained at follow-up visits, scheduled at three, six and 12 months post-insertion. Gross cumulative life-table rates for these termination events by device type were calculated using the Tietze-Potter method (14) and compared between the two device types within each center by the log-rank method (15). When necessary, the rates were adjusted for age and parity of the women using Person's method (16).

Findings

Table I presents the numbers of women enrolled, the IUD types studied and their respective 12-month follow-up rates at each of these four centers.

Table I: Number of women recruited and twelve-month follow-up rates by IUD type at four centers: FHI comparative clinical trials of the TCU 380A and selected IUDs, 1984-1987

Center	IUD types studied	No. of women recruited	% with 12 months FU
A	TCu 380A vs TCu 200	150 vs 147	90.5 vs 91.7
B	TCu 380A vs TCu 220	143 vs 154	97.8 vs 96.7
C	TCu 380A vs MLCu 250	150 vs 150	97.1 vs 98.6
D	TCu 380A vs LLD	146 vs 141	84.2 vs 87.2

Table II shows that at each center, patients randomized to receive either the Cu 380A or the comparative device had similar characteristics. The only exception was that at Center D; TCU 380A users reported a higher incidence of previous induced abortion than the users of the Lippes Loop D ($\chi^2=9.2$, <0.01).

Table III presents the 12-month rates for accidental pregnancy. The rates of Cu 380A users were consistently lower at all four centers than for users of the respective comparative device. The difference was statistically significant for Center A ($p<0.05$). Since the differences in all centers are of the same direction, we pooled the dataset. The combined accidental pregnancy

Table II: Selected patient characteristics at four centers: FHI comparative clinical trials of the TCu 380A and selected IUDs, 1984-1987

Characteristic	Centers							
	A		B		C		D	
	TCu380A (N=150)	TCu200 (N=147)	TCu380A (N=143)	TCu220 (N=154)	TCu380A (N=150)	MLCu250 (N=150)	TCu380A (N=146)	LLD (N=141)
Age								
≤24 years	44.0	52.3	25.2	31.8	34.7	36.0	42.4	41.1
25+ years	56.0	47.7	74.8	68.2	65.3	64.0	57.6	58.9
Parity								
≤1 births	30.0	30.6	37.1	42.8	37.4	38.0	34.3	34.8
2+ births	70.0	69.4	62.9	57.2	65.3	62.0	65.7	65.2
Education								
≤6 years	48.7	44.9	16.8	18.1	na*	na	29.4	37.6
7+ years	51.3	55.1	83.2	81.9	na	na	70.6	62.4
Wants more children								
Yes	55.8	61.2	55.9	57.8	58.0	62.0	51.4	45.4
No	44.2	38.8	44.1	42.2	42.0	38.0	48.6	54.6
Contraceptive used in the previous month								
None	48.0	49.0	33.6	30.5	40.0	50.7	72.6	76.6
Orals	37.3	38.8	35.7	46.1	12.7	8.7	10.3	7.1
Condoms	8.7	8.8	3.5	1.3	13.3	10.7	2.7	3.4
IUDs	2.0	1.3	15.4	12.3	17.3	17.3	9.5	7.7
Injectables	1.3	0.7	4.0	4.5	7.4	6.6	2.1	1.4
Withdrawal/rhythm and others	2.7	1.4	7.8	5.3	9.3	6.0	2.8	2.8
Induced abortions								
Yes	2.0	2.7	12.6	16.2	2.0	2.0	17.1**	4.3**
No	98.0	93.7	87.4	83.8	98.0	98.0	82.9	94.3

*No information available.

**Difference at p <0.01 level, 2 women in the LLD group who did not report data on induced abortions were excluded.

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Table III: Gross cumulative 12-month life-table accidental pregnancy rates (per 100 women) at four centers: FHI comparative clinical trials of the TCU 380A and selected IUDs, 1984-1987

	<u>Center</u>			
	A	B	C	D
TCu 380A	0.8 ± 0.8*	0.7 ± 0.7	0.7 ± 0.7	1.5 ± 1.0
TCu 200	6.2 ± 2.1*			
TCu 220		2.2 ± 1.3		
MLCu 250			2.1 ± 1.2	
LLD				1.8 ± 1.2

*Difference at $p < 0.05$ level.

rate at one year post-insertion was significantly lower ($p < 0.05$) among TCU 380A users than among users of the other devices combined (0.9 vs. 3.0 per 100 women, respectively).

Table IV shows that the 12-month expulsion rates were comparable between TCU 380A users and users of the respective comparative IUD at Center A (the TCU 200) and Center C (the MLCu 250). At Center B, one expulsion occurred among TCU 380A users compared to none among users of the TCU 220C. At Center D, TCU 380A users experienced a lower expulsion rate than users of the Lippes Loop D; the difference, however, was not statistically significant ($p > 0.1$).

The 12-month removal rate due to bleeding and/or pain among TCU 380A users was higher than among TCU 200 users at Center A, but lower than those for their counterparts at the other three centers (Table V). None of the above differences were statistically significant.

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Table IV: Gross cumulative 12-month life-table expulsion rates (per 100 women) at four centers: FHI comparative clinical trials of the TCu 380A and selected IUDs, 1984-1987

	<u>Center</u>			
	A	B	C	D
TCu 380A	4.8 ± 1.8	1.4 ± 1.0	3.4 ± 1.5	1.6 ± 1.1
TCu 200	4.3 ± 1.7			
TCu 220		0.0 ± 0.0		
MLCu 250			3.5 ± 1.5	
LLD				5.0 ± 2.0

Table V: Gross cumulative 12-month life-table removal rates for bleeding/pain (per 100 women) at four centers: FHI comparative clinical trials of the TCu 380A and selected IUDs, 1984-1987

	<u>Center</u>			
	A	B	C	D
TCu 380A	6.6 ± 2.1	0.9 ± 0.9	1.5 ± 1.0	3.1 ± 1.5
TCu 200	3.2 ± 1.6			
TCu 220		1.5 ± 1.1		
MLCu 250			2.0 ± 1.1	
LLD				4.9 ± 2.0

When data on TCU 380A users only were pooled for the four centers and controlled for age (≤ 24 vs $25+$) or parity (≤ 1 vs $2+$) of the women, the removal rate for bleeding and/or pain was found to be higher among the better-educated (7+ years) women than among the less-educated women ($p=0.08$). Women who received the IUDs for spacing purposes had a slightly higher rate than did limiters ($p=0.83$) (Table VI).

Table VI: Crude and adjusted gross cumulative 12-month life-table removal rates (per 100 women) for bleeding and pain for selected variables, TCU 380A only: pooled FHI comparative clinical trials of the TCU 380A and selected IUDs, 1984-1987

	Crude	Adjusted for Age*	Adjusted for Parity*	N
Education**				
≤ 6 years	1.53 \pm 0.76	1.56 \pm 0.77	1.63 \pm 0.82	140***
7+ years	4.42 \pm 1.25	4.40 \pm 1.25	4.59 \pm 1.31	299
Want more Children				
Yes	3.58 \pm 1.12	3.43 \pm 1.12	3.68 \pm 1.22	307****
No	2.36 \pm 0.95	2.88 \pm 1.22	1.79 \pm 0.72	263

*Adjusted by age (≤ 24 years vs $25+$ years) or parity (≤ 1 live births vs $2+$ live births).

** $P=0.08$ for the difference between women with ≤ 6 years of education and those with 7+ years of education for crude rates and rates adjusted by age or parity.

***Rates were calculated from pooled data for Centers A, B and D only. Information on education was not available for Center C.

****Nineteen women were excluded because of unspecified answer.

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Discussion

Because of randomization, characteristics of the women are comparable between those who were inserted with the TCU 380A and those with the comparative device at each of the four centers studied (Table II). Selection bias for the TCU 380A or the comparative IUD type was avoided and the validity of our findings enhanced. The only difference detected was the reported higher incidence of previous induced abortion in the comparative IUD group at Center D. This may be an artifact due to multiple comparisons.

The greater contraceptive efficacy of the TCU 380A reported by other researchers is replicated in this analysis (Table III).

The expulsion rates were not significantly different between the TCU 380A and the comparative IUD groups at any of the study centers and no consistent patterns in direction of differences were found among the four centers (Table IV). This also is commensurate with findings from previous studies. The higher incidence of expulsion among Lippes Loop users than among TCU 380A users in Center D, although not statistically significant ($p > 0.1$), may be real. The randomized comparative thirteen-country multi-center study conducted by the World Health Organization also revealed higher expulsion rates and lower continuation rates with the Lippes Loop D than with the T-shaped (the Copper T 220C) devices (17).

Of special interest here is the removal for bleeding and/or pain. It is usually the most frequent discontinuation event for the use of any IUDs at the one year or at shorter follow-ups. As stated above, a number of previous studies have reported a higher removal rate due to this reason for this otherwise very effective device. We did not find a consistently higher removal rate for bleeding and/or pain with the use of the TCU-380A, compared to its counterpart comparative devices (Table V). The complexity of this event is reflected in the wider fluctuation of its rate for TCU 380A users among the four centers than that of the other two termination rates studied (Tables III-V). Our finding also suggests that this rate varied according to the women's education level (Table VI). As with use of other IUDs, besides the actual incidence of bleeding and pain, perception and tolerance of the women toward these side effects and the availability of, and accessibility to, alternative contraceptive methods, are important determinants surrounding the decision of the women (and the service providers) for this type of removal.

The above findings did not substantially change when we excluded the 31 nulligravid women from our analysis.

One variable for which we could not control in this study is the insertors' experience. Although training was given in the insertion of

the TCu 380A before the initiation of this randomized trial, the investigators may have been more experienced in inserting the comparative device (which has been hitherto used in their centers for some time) than in inserting the TCu 380A. However, if experience did confound our results, we could anticipate two possible effects. First, the effect should be more apparent at Center C (the comparative device was the MLCu 250) and Center D (Lippes Loop D), than at Centers A and B where the similarly shaped devices (TCu 200 and TCu 220C, respectively) were used for comparison. We did not find this to be the case. Secondly, the removal rate for bleeding and/or pain of the TCu 380A, after the insertors have mastered the insertion technique with this newer device, would be lower than what we have detected here.

In summary, results from these four randomized clinical trials have provided additional evidence of the inherent superior efficacy of the TCu 380A. The risks of expulsion with the TCu 380A are comparable to other copper devices, but may be lower than for the inert Lippes Loop D. Lastly, we did not find a significant difference in removal rates for bleeding and/or pain between the TCu 380A and the comparative device users.

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REFERENCES

1. Roy S, Casagrande J, Cooper DL and Mishell DR Jr: Comparison of three different models of the copper T intrauterine contraceptive device. *Am J Obstet Gynecol* 134:568-574, 1979.
2. Sivin I and Stern J: Long-acting, more effective copper IUDs: A summary of U.S. experience, 1970-1975. *Stud Fam Plann* 10: 263-281, 1979.
3. Diaz J, Diaz MM, Pastene L et al.: Randomized clinical study of the TCu-380A and the Lippes Loop C, in Campinas, Brazil. *Contraception* 26:221-228, 1982.
4. Sivin I and Schmidt F: Effectiveness of IUDs: A review. *Contraception* 36:55-84, 1987.

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5. Champion BC, Behlilovic B, Arosemena JM et al.: A three-year evaluation of TCu 380Ag and Multiload Cu 375 intrauterine devices. *Contraception* 38:6310-639, 1988.
6. Sivin I and Tatum HJ: Four years of experience with the TCu 380A intrauterine contraceptive device. *Fertil Steril* 36:159-163, 1981.
7. Sung S, Qian L-J and Liu X: Two-year comparative clinical experience with three IUDs in China. In: Zatučni GI., Goldsmith, A., Sciarra, JJ and Osborn, CK, eds. *Intrauterine Contraception: Advances and Future Prospects*. Philadelphia: Harper & Row, 1985:109-114.
8. Sivin I: Copper T: Effectiveness and Risks. In: Sciarra, JJ, Zatučni, GT and Speidel, JJ eds. *Risks, Benefits and Controversies in Fertility Control*. Program for Applied Research on Fertility Regulation. Northwestern University, 1977:467-477.
9. Tatum HJ: Advances in intrauterine contraception. In: Zatučni GI and Osborn CK eds. *New Methods of Fertility Regulation*. Proceedings of an International Workshop on New Methods of Fertility Regulation. Dec. 18-19, 1980, Surabaya, Indonesia. Program for Applied Research on Fertility Regulation, Chicago, Illinois: Northwestern University, 1980:1-45.
10. Tatum HJ: Comparative experience with newer models of the Copper T in the United States. In: Hefnawi F and Segal SJ eds. *Analysis of Intrauterine Contraception*. Proceedings of the 3rd International Conference on Intrauterine Contraception, Cairo, Egypt. Dec. 12-14, 1974, Amsterdam: North-Holland, 1975:155-163.
11. Cole LP, Potts DM, Aranda C et al.: An evaluation of the TCu 380Ag and the Multiload Cu375. *Fertil and Steril* 43:214-217, 1985.
12. Apelo RA, Ramos RM, Bernardo E et al.: A 3-year evaluation of the TCu 380Ag and the Cu-7. *Int J Gynaecol Obstetrics* 28, 269-273, 1989.
13. Tatum H, Connell-Tatum EC, Waldman SN and Greenslade FC: The new Paragard Copper T 380A intrauterine device. *Medical Digest* 9:1-7, 1989.
14. Potter KG: Use-effectiveness of intrauterine contraception as a problem in competing risks. In: R. Freeman and J Takeshita, eds. *Family Planning in Taiwan*, Princeton, NJ: Princeton University Press, 1969:458-484.
15. Azen SP, Roy S, Pike MC et al.: A new procedure for the statistical evaluation of intrauterine contraception. *Am J Obstet Gynecol* 128, 329-335, 1977.

16. Kerson J: Standardization of cumulative failure rates. Demography 12:467-470, 1975.
17. World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction, "An Assessment of the Lippes Loop and the Copper T 220C", Report HRP/79.1 Rev. 1, Geneva, 1979.