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A Comparative Study of the TCu 380A Versus TCu 200 IUDs in Nepal

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The cost-effectiveness and proven contraceptive efficacy of the TCu 380A should be considered when selecting a long-term, safe and effective, but reversible method

The intrauterine device (IUD) is a popular and highly tested method of contraception. Approximately 85 million women worldwide use IUDs, with the highest concentration of users being in China. In Viet Nam also, the IUD has the highest prevalence of use among reversible contraceptive methods.

The current generation of IUDs is safe for most women and about 99 per cent effective over one year of use (Chi, 1992; Farr and Amatya, 1994a and 1994b; Diaz and others, 1992; Mauldin and Segal, 1992; Sastrawinata and others, 1991; Sivin and Tatum, 1981; Sivin and Schmidt, 1987; Sivin and others, 1993; Sung and others, 1984; Tatum and others, 1989; Treiman and Kiskin, 1989; WHO, 1988 and 1990). The IUD is one of the more convenient methods of birth control because it does not require daily attention from the woman and it does not interfere with sexual activity. There are a variety of modern IUDs in many shapes and sizes available to women in developing countries. Copper was added to IUDs in the 1970s to improve their efficacy. The most effective copper IUD used today is the Copper T 380A (TCu 380A), which is being used in 70 countries around the world.

From 1985 through 1989, Family Health International (FHI) conducted a randomized clinical trial on IUDs in 23 developing countries. The trial focused primarily on the use of copper-bearing IUDs and was designed to establish the one-year efficacy of the then newly introduced TCu 380A IUD as compared with the IUD most commonly used at each study size. Additional study end-points included establishing one-year expulsion and removal rates. Safety data, such as insertion-related complaints and/or complications as well as post-insertion IUD-related complaints and adverse experiences, were also documented. Six IUDs were compared with the TCu 380A IUD in this series of studies. Five were copper-bearing: the Multiload Cu 250 IUD (MLCu 250), the Multiload Cu 375 IUD (MLCu 375), the Nova-T IUD, the Copper T 200 IUD (TCu 200) and the Copper T220 IUD (TCu 220). The sixth IUD was the non-medicated Lippes Loop IUD, a device that remains popular in some countries. This project was conducted from 1985 to 1989 and involved approximately 10,000 subjects.

As part of this multinational trial, a study to compare the safety and efficacy of the TCu 380A IUD with the locally used TCu 200 IUD was conducted at the Maternity Hospital in Thapathali, Kathmandu, Nepal. This clinical trial originally had been intended to continue through 36 months of subject follow-up; however, it was ended after the completion of 24 months of subject follow-up and before the completion of 36 months of subject follow-up on every active subject. This article reports the results of that study.

Materials and methods

Study design

FHI's Protection of Human Subjects Committee (PHSC) approved the protocol, fact sheet and informed-consent form used in the study before its initiation and served as the Institutional Review Board (IRB) in lieu of a local IRB.

TCu 380A or TCu 200 IUDs were randomly assigned to volunteer participants according to computer-generated sealed random allocation envelopes which were preprinted at FHI. At the time of each woman's admission to the study, the envelope corresponding to her assigned patient order number (PON) was opened, indicating which IUD was to be inserted. If a woman was admitted and was subsequently discovered to have an exclusion condition during the admission process, she was discontinued from the study and the PON was not reused. The next available PON was assigned to the next woman being admitted, using the appropriate random allocation envelope. The subjects agreed to use the IUD assigned to them as their sole method of contraception during the study period and were followed up for a minimum of 24 months post-insertion.

All study subjects fit the following profile: they were healthy women who had no contraindications for IUD use, gave informed consent to participate in the study, were sexually active and between 18 and 40 years of age. IUD insertions were to be performed during the interval period (last pregnancy was to have ended at least 40 days prior to IUD insertion). Subjects were to return for follow-up at 1, 3, 6, 12, 24 and 36 months after insertion and at any other time if complications occurred.

Physical and pelvic examinations were to be performed during each clinical contact with the subjects.

Information on selected socio-demographic characteristics, reproductive and contraceptive histories, and pre-existing medical conditions was obtained at the time of admission into the study. Events related to IUD insertion were recorded on the admission form, and the occurrence of subsequent pertinent events, such as accidental pregnancy, expulsion, removal, complications and complaints, were recorded on the case report forms (CRFs) during follow-up visits.

Subjects were discontinued from the study if pregnancy occurred, if their IUD was partially or totally expelled, or if their IUD was removed for any reason. IUDs that were expelled, displaced or removed after insertion were not reused. Depending upon the investigator's judgement, a subject's IUD could be left in place at the end of the study period in accordance with the approved life-span for the IUD. Subjects who elected to continue using their study IUDs would be subsequently followed up according to standard medical practices at the hospital.

Study products

The TCu 380A IUD is T-shaped and made of polyethylene with barium sulphate added for x-ray detectability. It has a solid copper sleeve on each of its two transverse arms (33 mm2 surface area each) and copper wire of 314 mm2 surface area wound tightly around its vertical stem. The device is 32 mm wide and 36 mm long with a plastic ball at the bottom of the vertical stem to guard against cervical penetration. A clear or colourless polyethylene filament is tied in a knot through the ball to provide two marker threads.

The copper surface area on the TCu 380A IUD is the largest of any commercially available copper IUD; this increased surface area has been demonstrated to improve the contraceptive efficacy of the TCu 380A IUD over that of the standard TCu 200 IUD (Sivin and others, 1993). At the time of this study, the life-span of the TCu 380A IUD as approved by the United States Food and Drug Administration (FDA) was four years. However, subsequent studies conducted by the Population Council demonstrated a life-span of 10 years or more; in 1994 the United States FDA extended the life-span to 10 years.

The TCu 200 IUD, which is also T-shaped, made of polyethylene and contains barium sulphate for x-ray detectability, is likewise 32 mm wide and 36 mm long. The vertical stem is wound with copper wire to provide a total surface area of 200 mm2 of copper; this IUD also has two clear or colourless polyethylene marker threads attached at its end. This IUD was approved for use by the FDA in 1976; at the time of this study, it had an approved life-span of four years (Treiman and Liskin, 1988).

Data analysis

Clinical information on the safety and efficacy of the IUDs was recorded on CRFs by study staff and sent to FHI headquarters for processing and analysis. Comparisons between the two groups were made on the basis of discontinuation for one of the following reasons: accidental pregnancy, IUD expulsion/displacement, IUD removal because of bleeding or pain, other medical reasons, personal reasons, or because the woman was planning to become pregnant. IUD removals for other medical reasons were based on decisions made by either the investigator or the subject; some medical removals may not have been related to use of the IUD. Removals for other personal reasons were based on the request of the subject (e.g. moving her place of residence, being no longer sexually active, disapproval of spouse); an exception was requests for removal for the purpose of becoming pregnant.

A discontinuing subject was permitted to state only one reason for discontinuing participation in the study; competing reasons for discontinuation could not be entered into the database. If both an accidental pregnancy and an IUD expulsion were reported for the same subject, that woman was categorized by the investigator as having discontinued from the study for only one of these two reasons. The estimated date of discontinuation for unnoticed IUD expulsions, whether complete or partial, was calculated as the midpoint date between the dates of the last follow-up clinic visit at which the IUD was in situ and the visit at which the IUD expulsion was reported.

At 12 and 24 months, subject status was classified as (a) discontinued, (b) continuing, or (c) lost to follow-up. To assess a participant's status, she was considered as "discontinued" if she became pregnant, her IUD was expelled or displaced, or her IUD was removed for any reason. In the calculation of gross cumulative life-table discontinuation event rates, subjects classified as lost to follow-up contributed to the study until the date of their last clinic visit (Teitze and Lewit, 1970).

Fisher's Exact Test was used to compare the incidence of complications and complaints ever reported during the 24-month follow-up period. The gross cumulative life-table method was used to calculate all discontinuation event rates. The Z Test was used to make comparisons of the gross cumulative life-table rates at 24 months. Statistical significance was set at $p>0.05$ for comparing complications and complaints and discontinuation event rates.

Results

Study population

Two hundred subjects were enrolled in the study over a seven-month enrolment period beginning in November 1987. By

random allocation, 100 subjects received the TCu 380A IUD and 100 subjects received the TCu 200 IUD. All subjects had their IUDs inserted six weeks or more after the end of their last pregnancy. There was one protocol violation in which one subject in the TCu 200 IUD group was over 40 years old; the specific violation was not considered clinically relevant and therefore she was permitted to continue in the study.

Baseline characteristics

Table 1 summarizes subject characteristics and reproductive history at admission. The mean age was 23.1 years for the TCu 380A IUD group and 23.5 years for the TCu 200 IUD group. All subjects in each IUD study group had at least one live birth prior to admission into the study and the overall mean was similar for both study groups. Less than 10 per cent of the subjects in each IUD study group reported having used a contraceptive method in the month prior to study enrolment. At least 88 per cent of the subjects in each study group were breast-feeding, with over one half of the women in both study groups breast-feeding with no supplementation. These measures were found to be similar between the two IUD study groups.

Table 1: Baseline characteristics of women using the TCu 380A or the TCu 200 IUD

Characteristic	TCu 380A IUD (N=100)	TCu 200 IUD (N=100)
Mean age (years)	23.1	23.5
Mean live births (number)	1.7	1.9
Breast-feeding status		
No lactation (%)	8.0	12.0
Full lactation (%)	59.0	54.0
Partial lactation (%)	33.0	34.0
Contraceptive method used in month prior to IUD insertion		
Yes (%)	5.0	7.0

Insertion status

Complications or complaints reported at the time of IUD insertion were few in number (data not shown). One subject in the TCu 200 IUD group reported having had intermenstrual pain prior to IUD insertion; this event did not interfere with the insertion. The only insertion-related complaint reported was mild pelvic pain: e.g. in 16.0 per cent of the women receiving the TCu 380A and 19.0 per cent of those receiving the TCu 200; this difference was not statistically significant.

Adverse experiences reported during follow-up

Table 2 summarizes complications and complaints ever reported during follow-up visits. Since the number of subjects in each IUD study group was 100, the percentage of subjects ever reporting any complications or complaints is equal to the number of subjects in that group.

No hospitalizations were reported during this study. Reports of menstrual complaints during follow-up were few in number. There were no reports of dysmenorrhoea; however, menorrhagia was reported by some subjects in both the TCu 380A and TCu 200 IUD groups (3 per cent and 5 per cent, respectively). Intermenstrual pelvic pain, spotting and bleeding were also reported, although the proportion of subjects in either study group experiencing these complaints did not exceed 7 per cent. None of these differences was statistically significant.

Table 2 also summarizes the occurrence of inflammations or infections during follow-up. One case of pelvic inflammatory disease (PID), i.e. endometritis, in a TCu 200 IUD user was reported, but no cases were reported among TCu 380A users. One case of a mucoid vaginal discharge was reported in each IUD study group. No uterine perforations were reported during follow-up.

Table 2: Women ever reporting complications or complaints during follow-up * (per cent)

Complications/complaints	TCu 380A IUD (N=100)	TCu 200 IUD (N=100)
Menstrual problems		
Intermenstrual pelvic pain	5.0	7.0
Intermenstrual bleeding	4.0	7.0

Intermenstrual spotting	4.0	1.0
Menorrhagia	3.0	5.0
Unspecified menstrual complaint	0.0	1.0
Pelvic inflammatory disease (PID)		
Confined to uterus	0.0	1.0
Inflammations/infections		
Mucoid vaginal discharge	1.0	1.0
Other IUD-related findings		
Unspecified IUD problems	1.0	2.0

* Note: None of the complications/complaints was significantly different (Fisher's Exact Test: p<0.05).

Continuation status at 24 months

Gross cumulative life-table discontinuation event rates are presented in table 3. Significantly more TCu 200 IUD users (p=0.02) experienced removal of their IUD during the 24-month follow-up period for personal reasons than did TCu 380A IUD users (6.7 and 1.2 per 100 women, respectively; p=0.02). Other 24-month discontinuation rates were statistically similar for both IUD groups, including those for accidental pregnancy, the primary outcome variable of interest. The overall continuation rate at 24 months was higher for TCu 380A IUD users than for TCu 200 IUD users (82.8 and 74.9 per 100 women, respectively), although this difference was not statistically significant (p=0.18). Owing to use of "motivators" who conducted home visits during the course of the study, loss to follow-up was low.

Table 3: Gross cumulative 12-month and 24-month life-table event ratesa

	TCu 380A IUD (N=100)		TCu 200 IUD (N=100)		
Event and time period	Rate	S.E.	Rate	S.E.	p value[b]
Accidental pregnancy					
12 months	0.0	0.0	0.0	0.0	
24 months	0.0	0.0	2.5	1.7	0.14
IUD expulsion					
12 months	8.2	2.8	10.3	3.1	
24 months	8.2	2.8	11.4	3.2	0.45
Bleeding/pain					
12 months	3.2	1.8	0.0	0.0	
24 months	3.2	1.8	0.0	0.0	0.08
Other medical reason					
12 months	1.0	1.0	0.0	0.0	
24 months	1.0	1.0	0.0	0.0	0.32
Planning pregnancy					
12 months	1.0	1.0	2.2	1.5	
24 months	4.6	2.3	7.1	2.8	0.48
Personal reasons					
12 months	0.0	0.0	4.3	2.1	
24 months	1.2	1.2	6.7	2.7	0.02
Continuation rate[c]					
12 months	87.0	3.4	84.0	3.7	
24 months	82.8	3.8	74.9	4.3	0.18

Notes: a per 100 women; b The Z-test was used to assess comparisons between gross cumulative life-table rates at a fixed point in time (24 months); and c Continuation rate is calculated by subtracting the total

discontinuation rate (for all reasons) from 100.

Discussion

The major objective of this trial was to compare and evaluate the use of the TCu 380A IUD and the TCu 200 IUD among a population of women recruited at the Maternity Hospital in Thapathali. Study participants used one of the two IUDs for a period of 24 months as their sole means of contraception.

Mild pelvic pain was the only complication during IUD insertion reported among both study groups. There were few reports of complications and complaints during follow-up (less than 7 per cent of the subjects in either IUD study group reported any one complication or complaint), and most of those were related to menstrual disturbances. Such complaints are not uncommon among IUD users in the first months following insertion; generally they did not lead to IUD removals (only three TCu 380A IUD and no TCu 200 IUD removals were due to bleeding/pain).

An overwhelming majority (88 per cent or more) of the women in both study groups were actively breast-feeding and many were not using contraception at the time of admission into the study. Data were not collected as to the timing when breast-feeding ceased among these women. Although it is possible that the very high number of breast-feeding subjects may have contributed to the fact that there were no accidental pregnancies reported during the first 12 months post-insertion (owing to lactational amenorrhoea), we do not have the data to determine if this was indeed the case. Overall, only two accidental pregnancies were reported during the study, both occurring among TCu 200 IUD users during the second 12 months of IUD use.

While the difference in the IUD removal rates for bleeding and/or pain was not statistically significant, there were no IUD removals for this reason in the TCu 200 IUD group (life-table rate of 0.0 per 100 women) compared with a removal rate of 3.2 per 100 women in the TCu 380A IUD group. This finding was somewhat unexpected since there was no statistically significant post-insertion increase in the incidence of menstrual complaints among TCu 380A IUD users compared with TCu 200 IUD users. Since the TCu 380A IUD was being introduced in Nepal at the time this study was conducted, it is possible that some TCu 380A IUD users complaining of menstrual problems had the IUD removed as a precaution: this group of women comprised the first ones with whom the physicians and paramedical staff performing the insertions had experience in dealing with this device. However, this cannot be determined with certainty given these data. No additional removals for bleeding and/or pain occurred in the TCu 380A IUD group from months 12 to 24.

IUD removal rates for personal reasons were significantly higher among users of the TCu 200 IUD than among users of the TCu 380A. This is in contrast with removal rates for personal reasons in a pooled analysis for similar study sites (Farr and Amatya, 1994a). Most of the removals during the study were a result of the spouse's disapproval; however, a satisfactory explanation of why there should be a difference in the incidence of removals for this reason cannot be determined.

It is important to note that expulsion rates and removal rates for bleeding and pain or for other medical reasons were low for both study groups, and are similar to those reported from other regions of the world. Concern with unsubstantiated evidence that women in the Asia-Pacific region may not be ideal candidates for currently available standard T-shaped IUDs, particularly the TCu 380A device, has contributed to lower than expected prevalence rates. Some physicians and family planning providers in Asian countries have expressed concern that these devices may be too large for most Asian women, thereby resulting in a higher rate of morbidity and a correspondingly higher rate of removal if inserted. However, the results from this study indicate that the Nepalese women in this clinic population had a good experience using these IUDs over a two-year period. While attending physicians must ensure that a woman is an appropriate candidate for an IUD, these data suggest that Asian women can use the TCu 380A and other T-shaped copper-releasing devices without major complications.

Although this study population was not large enough to have high power in detecting differences between the two IUD groups, a pooled analysis of data from six other FHI-sponsored clinical trails comparing the TCu 380A IUD to the TCu 200 IUD over 12 months of use in five countries (Cameroon, Chile, El Salvador, Mexico and Pakistan; N=1,631) using a similar protocol had considerably higher power (Farr and Amatya, 1994). In that pooled analysis, the TCu 380A IUD was found to be significantly more effective in preventing pregnancy than the TCu 200 IUD (12-month gross cumulative life-table pregnancy rates were 0.5 and 2.6 per 100 women, respectively; $p<0.01$). That study also showed that IUD discontinuation rates, i.e. IUD expulsions or displacements and removals due to bleeding/ pain, personal reasons, medical reasons or planning pregnancy, were similar for both types of IUD. The incidence of other clinical events, such as intermenstrual bleeding and/or pain, inflammations/infections and insertion-related problems, did not differ between TCu 380A and TCu 200 IUD users, although TCu 200 IUD users had fewer reports of dysmenorrhoea. Taking the findings from the larger study into perspective, the trend in the discontinuation rates reported in the Nepal study are slightly lower, but in the same direction between the two IUD user groups. This suggests that the TCu 380A is possibly more effective in preventing accidental pregnancy, which is among the many aspects of this contraceptive device holding implications for large-scale family planning and birth-spacing programmes.

There are several other policy and programme implications. The extended life-span of the TCu 380A IUD allows for longer contraceptive protection, a reduction in risks associated with insertion of a new IUD, a reduction in the number of abortions due to contraceptive failure of many compliance-based methods. Further, it is potentially more cost-effective on a national scale owing to a reduced need for more frequent re-insertions associated with IUDs having shorter effective life-spans. The non-abortifacient effect of the TCu 380A and other copper-bearing devices is another important factor. These are clinically and programmatically important considerations when costs of providing family planning on a national basis continue

to rise in the developing world, especially in those countries where other long-term reversible options are limited. Therefore, the cost-effectiveness and proven contraceptive efficacy of the TCu 380A IUD should be considered by family planning practitioners when selecting an IUD for women who want a long-term, safe and effective, but reversible, method of contraception.

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