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Side effects from the copper IUD: do they decrease over time?

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Abstract

Background—The copper intrauterine device (IUD) can cause side effects in some women; increased uterine bleeding and pain may cause early removal. Because of simplified reporting from previous research, little is known about how side effects might change over time.

Study Design—This is a secondary analysis of a prospective study of 1,947 first-time copper IUD users. Over a one year period, we collected detailed information on side effects and looked for trends using generalized mixed effects regression modeling.

Results—During menses, most bleeding and pain side effects were found to decrease over time ($p < 0.05$). During intermenstrual intervals, overall spotting and pain complaints remained unchanged, but number of days with these problems increased ($p < 0.05$). Serious side effects that prompted either a clinic visit or IUD removal had a varied pattern over time, depending on the type of problem.

Conclusion—Side effects from the copper IUD can be troubling for both user and clinician. Some problems improve over time while others do not. This information may be helpful to counsel women who are considering an IUD and to current users who are contemplating removal due to side effects.

Keywords

copper IUD; intrauterine device; side effects; longitudinal analysis

1. Introduction

Copper intrauterine devices (IUDs), first marketed in the early 1970s, represent an important contraceptive option for 150 million women worldwide. The method is safe, rapidly reversible, inexpensive, highly effective, long-acting (up to 20 years for some products [1]), and non-hormonal; these attributes make it unique and desirable for many users. However, increased bleeding and pain cause up to 15% of users to have the device removed within the first year [2]; still higher percentages tolerate some level of these side effects yet retain use of the method. In one study, 67% of women using the TCu380A complained about menstrual side effects within the first year of use [3]. Anecdotal information accumulated from clinicians and some published information suggests that side effects from the copper IUD decrease over time [4, 5].

Perceptions of how side effects may change over time can be important factors in method acceptability and continued use. IUD users who perceive the device as a cause of intolerable

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side effects may have it removed. Those who perceive the IUD to cause nuisance side effects (or no side effects) or decreased side effects may use the IUD for long periods of time if still in need of contraception. Over time, IUD users may grow accustomed to the method and develop a more acceptable attitude toward minor side effects. These perceptions may be influenced by how attractive or feasible the alternatives are (e.g., adopting a different contraceptive method, risking unintended pregnancy) or by other forms of rationalization. If side effects tend to decrease over time, clinicians should discuss this finding with potential IUD users and with continuing users who return to the clinic seeking removal.

Serial measurements over time provide the only means of assessing whether side effects change. In a small study of 62 women using a copper IUD (NovaT), researchers used standardized definitions [6] to discover that episodes of frequent and prolonged bleeding at 3 months had changed from 19% and 24%, respectively, to 0% at 12 months for both problems [5]. A large study of 2,700 copper IUD users in India found that complaints of abdominal pain and bleeding decreased over a 24-month period [7]. In a study of 609 CuT380A users, participants were asked to summarize their experiences over a 12-month period; 60% reported increases in flow and 50% reported increases in number of bleeding days, while between 63% and 85% reported no changes or decreases in other menstrual events [8]. Pizarro et al. [9] reported a reduction in pain over a 12-month period with the Copper 7 IUD, however, the authors also cited limitations that have implications even today when we attempt to understand patterns of side effects.

Two factors severely limit our understanding of whether side effects decrease over time: attrition and reporting/analysis techniques. In the aforementioned studies, attrition rates were between 15% [5] and 50% [7]; thus, many participants did not have a measure recorded at the end of the period, either because of loss-to-follow, early IUD removal, or other reasons. Early removal is an event that is often associated with intolerable side effects; thus, when only satisfied users are represented in the last period of analysis, the comparisons over time give a false sense that side effects may have improved. The second factor involves the way the information is reported; simply showing the prevalence of problems in the study population at different time points ignores changes and patterns that may exist at the individual level. Thus, in combination with the problem of attrition, the prevalence approach to summarizing changes is inadequate for assessing trends.

Because of the aforementioned uncertainties regarding IUD-related side effects, appropriate statistical techniques are needed to examine the issue; to our knowledge, this has not been done. Furthermore, some consideration should be given toward severity of side effects; those cited as a reason for making a clinic visit or as a reason for removal are arguably the most pressing problems.

2. Materials and methods

The data for this secondary analysis are from a previously described placebo-controlled randomized trial that examined the effect of prophylactic ibuprofen on IUD continuation rates; in that study, women were instructed to take 1200mg daily during menses for the first six months of IUD use [10]. Briefly, 1,962 women aged 18–49 years received a TCu380A device for the first time in their lives and enrolled in the study conducted from 2002 to 2003 in 42 public health facilities in Santiago, Chile. The mean age of the study population was 25 years. Five percent of participants were nulliparous, 65% had one previous live birth, and the remainder had at least two live births. Participants were asked to return for scheduled follow-up visits at 6, 13, 26 and 52 weeks after insertion. Twenty-five percent of the participants had the IUD removed within the first year. Of the 1,962 participants, only 15 women failed to provide any follow-up information; thus, this report contains information on side effects from

1,947 copper IUD users with and without ibuprofen. Informed consent was obtained from all volunteers and the research was approved by an institutional review board.

In the present analysis, we used different types of information on side effects to best identify any changes over time. For example, at each follow-up visit, we asked participants to compare the amount of menstrual blood loss and the level of menstrual pain during the last menses to that typically experienced before getting the IUD; the pre-coded responses to these questions were less, the same, or more pain/bleeding in both ibuprofen users and placebo controls (Table 1). For intermenstrual events, we asked participants whether pain and/or spotting occurred. For both menstrual bleeding and intermenstrual spotting/pain, we analyzed the number of days these events occurred. Participants also recorded events on a menstrual diary for the first six months; we analyzed these data to complement the information from the follow-up forms. Finally, we created three variables which we referred to as serious problems: these were spontaneously cited as a reason for the visit or as the reason for IUD removal. As described in our previous report [10], all IUD removals were attributed to a particular reason. If the participant mentioned bleeding and/or pain as the reasons for removal, then these reasons would prevail, unless the IUD was removed by the clinician because of partial expulsion.

To show data on prevalence of side effects over time, we grouped the reports into four time periods: 0 to 9 weeks, 9.1 to 19 weeks, 19.1 to 39 weeks, and > 39 weeks. This grouping captures the four scheduled follow-up times and the periods surrounding those times when unscheduled visits occurred. In addition, because of the varying lengths of time within each observation period, we calculated an incidence density measure, anticipating that lengthier time segments would naturally tally a higher number of events. We defined the incidence density in this way: number of events in a period ÷ number of person-weeks in that period. This measure was computed only for serious problems, since most of the other outcomes were not amenable to this type of analysis.

To assess side effect patterns over time, we used generalized linear mixed effects models [11,12] to analyze repeated measures from longitudinal data. As applied to our data, this approach used follow-up reports as the units of analysis (but took into account that multiple reports came from the same subject) to best characterize any pattern of change. Due to possible informative censoring (*viz*., when the side effect led to IUD removal), we did the modeling on four different analysis groups to better understand the possible impact (Table 2). The primary analysis was defined as all reports from all subjects; a total of 6,655 reports contributed to this analysis. This set of forms provided the single most important source of information to answer the question of whether side effects decrease if there is no informative censoring. In addition, a total of 5,961 menstrual diaries were analyzed.

Complementary information was provided by the subset of forms from women who completed at least one year of IUD use (completers, n=5,297 forms) and the subset of forms from women who had their IUD removed within the first year (incompleters, n=1,358 forms). Data from completers (also referred to as complete case analysis) were used to interpret patterns among women who were overall content with their method, either because of low/absence of side effects or decreasing problems. Incompleters offered just the opposite perspective: an opportunity to see if side effects got worse or remained intolerable. A final analysis group used all reports and imputation techniques referred to as “last observation carried forward” (LOCF, n=7,148 forms). This technique assumed that women who had their IUD removed early (prior to a year) would have experienced their last reported level of side effects for future scheduled visits, had they continued using the method. In summary, each analysis set and the statistics generated from the analysis has unique biases and strengths. Together, the different approaches to analyze the data can provide a more comprehensive picture to detect changes in side effects.

We used SAS version 9.13 (Cary, North Carolina) and the GLIMMIX procedure with variance components covariance structure [13]. We did separate modeling procedures for each side effect and analysis group noted above and reported the results in one of three ways: decreasing, increasing, or no change. We classified the side effect as decreasing or increasing if the p value on the test statistic was <0.05. To simplify the presentation, we did not report intercepts, coefficients, degrees of freedom, or t scores, though this information is available upon request.

After completing the above analyses, we conducted several ancillary analyses for serious problems. First, because the data for this secondary analysis were from a randomized trial of prophylactic ibuprofen, we accounted for the use of this medication and other types of analgesics used by participants during the study. We repeated the analyses, controlling for the use of such medications to determine how and if our main results changed. The second type of ancillary analysis involved examining participant characteristics; we focused on parity and age to determine whether particular subgroups had similar patterns of side effect changes over time.

3. Results

A total of 6,440 follow-up forms containing information on the last cycle were analyzed. In the first nine-week period, 38% of participants reported more menstrual pain with the IUD compared to before using the IUD (Table 3). In the subsequent periods, roughly a third of participants reported more menstrual pain with the IUD than without the IUD. Interestingly, about a quarter of participants reported less pain with the IUD than prior to the IUD insertion. In the first nine weeks, two-thirds of participants reported increased menstrual blood loss; this percentage dropped gradually over subsequent weeks (to 48% in the last period). Intermenstrual problems varied slightly over the four time periods.

Of the 1,947 participants with some follow-up data, 177 (9%) experienced serious pain in the first nine weeks of use (Table 4). In the second, third, and fourth periods, lower percentages of women experienced severe pain, after accounting for attrition (IUD removal) in the denominator. When length of the observation period was taken into account with an incidence density measure, the prevalence of pain appeared to decrease consistently over the four time periods, from 1.1 to 0.5 to 0.4 to 0.3 events per 100 women-weeks. Serious problems with increased menstrual bleeding also appeared to decrease over time. Intermenstrual spotting did not change much over time.

Forty-two separate mixed effects regression models were constructed to examine various side effect trends over time, using the four different analysis groups (Table 5). Most results showed that menstrual side effects of pain and bleeding decreased over the different time periods compared with the levels before using IUD. The subset of women who had the IUD removed prematurely (incompleters) showed either no change in the different parameters or the problem was found to be increasing (in the case of number of days of menstrual bleeding). Even under the most conservative approach to interpreting changes in side effects (LOCF), the results showed that both menstrual pain and bleeding decreased.

For intermenstrual problems, most analyses showed that the side effects did not change over the follow-up period. The exceptions were found in the analysis of number of days with problems; number of pain days and number of spotting days increased in several key subgroup analyses.

For serious problems, the trends varied by type of side effect. For example, pain appeared to decrease over the follow-up period. Menstrual bleeding did not change; however, among incompleters and the LOCF subgroup, the problem was found to get worse. Intermenstrual spotting tended to get worse over time.

After controlling for the use of analgesics in the analysis of serious problems, the patterns described above did not change (data not shown). We created control variables to distinguish young age (≤24 yr) from all other ages and another control variable to indicate nulliparous women (n=91 in our study). We found some evidence that older women may fare better over time than younger women in terms of pain and complaints of increased menstrual blood loss. Nulliparous women showed a tendency to get worse over time in these same side effects, compared to parous women (data not shown).

4. Discussion

In this report, we provided a comprehensive picture of side effects from the copper IUD over a 12-month period. In addition to the standard approach of reporting prevalence of problems over time, we used more sophisticated techniques to assess trends. With mixed effects regression modeling techniques, we found substantial evidence that many types of bleeding and pain side effects decrease over time. The majority of improvement was found in problems that occur during menses, while most intermenstrual problems did not decrease over time. In separate analyses involving serious problems, pain (menstrual and/or intermenstrual) was found to decrease while bleeding problems did not improve. The results of the mixed effects regression modeling also varied by analysis group (all, completers, incompleters, and LOCF). For example, evidence of increasing problems was more common among incompleters and absent in women who completed a year with the IUD in situ. This pattern is commonsensical and validates two inter-related aspects of our work: 1) the important relationship between side effects and IUD removal events, and 2) our choice of statistical techniques to look at trends. For example, in the analyses using imputed data and LOCF, most outcomes either stayed the same or became worse over time. This finding is due in part to the LOCF assumption that side effects resulting in early removal would have persisted. Thus, as applied to our question, it would be difficult to observe and claim that side effects decrease over time using LOCF, unless there was overwhelming evidence of improvement in the available data. In this sense, the approach is conservative; as such, LOCF is often preferred by the U.S. Food and Drug Administration for regulatory submissions [14].

Despite the conservative nature of the LOCF approach, general bleeding and pain problems during menses were found to decrease over time in the LOCF subgroup analysis; this finding adds more weight to the overall conclusion that such side effects, in fact, decrease over time. Given the model's assumption that missing data are randomly distributed and censoring is non-informative, we chose a cautious way to interpret the overall findings: the truth about changing side effects may lie between results from the completers and the LOCF analyses.

We did this work because of concerns over the validity of claims that IUD side effects decrease over time. To reach such conclusions, most previously published material on this topic examined the prevalence of side effects at different time periods, without accounting for the possible impact of attrition. Like other reports, our display of prevalence over time (Tables 3 and 4) showed a decreasing trend in many side effects. Interestingly, our more sophisticated approach using longitudinal analyses corroborated many of these findings, despite 25% attrition from early IUD removal. This internal consistency in our dataset, however, cannot be extended to assume that secondary, longitudinal analyses on existing IUD databases from other studies would yield similar results.

Our work has numerous strengths linked to the quality of the dataset: high number of participants, very little loss to follow-up, precise information necessary for correctly recording the outcomes, and ample follow-up period to measure how/if side effects change over time. Another strength of this work is our use of a mixed effects model to address the issue of whether side effects decrease. Other approaches, such as comparing prevalence of side effects over time

are possibly biased because of attrition (early removal of the IUD); a higher prevalence of problems is expected in earlier periods, while just the opposite is expected in latter periods predominantly composed of satisfied users. In the only sophisticated approach we could find in the field of contraception [15], researchers examined some of these issues among users of depot medroxyprogesterone acetate (injectable). Lastly, we defined an outcome denoting serious problems and looked at how those changed over time, to complement the analyses on any/all types of side effects.

Though we found substantial evidence that participants believed menstrual blood loss decreased over the time period, objective measures of blood loss from other studies show otherwise. For example, in research involving used sanitary products, copper IUDs have been shown to increase menstrual blood loss by about 50% over pre-insertion levels [16,17] and the increase appears constant, at least in the first 12 months. Thus, it is important to remember that our work is based on subjective impressions of change as reported by the participants.

For clinician-client interactions, the results from our analysis may be helpful in numerous ways. First, the detailed way in which we reported side effects can help potential IUD users (or current users) anticipate the overall prevalence of problems based on data from a population of first-time users. Second, the results showing that many side effects decrease over time can be reassuring to patients and help avoid premature removal. If problems persist, however, non-steroidal anti-inflammatory drugs are a proven treatment for alleviating IUD-related bleeding and pain side effects [18].

Approximately 2% of the data used in this analysis were from interviews conducted more than 13.5 months after IUD insertion. Excluding these data would have truncated longitudinal information on side effect patterns for approximately 8% of the participants. We did a sensitivity analysis to exclude such data and found that the results did not change our interpretation on whether side effects decrease over time.

Of all intrauterine devices being inserted today, the copper T is the oldest; the basic design and technology was established in the late 1960s. Modest improvements a few years later led to the TCu380A, which has been shown to be the best copper device being used in the world today [19]. Women’s overall satisfaction with the TCu380A remains high, as evidenced by the average first-year continuation rate of 78% [20].

Though we found some evidence that side effects from the TCu380A decrease over time, the product still causes problems that often lead to premature removal, as reported earlier [10]. Other countries such as China and Mexico have newer products (different shapes/sizes, analgesic-releasing, composite materials) that may offer comparable efficacy, yet fewer side effects, particularly for young and/or nulliparous women. New research is needed to better determine whether these products are superior to the TCu380A.

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Table 1

Definition of variables

Type and variable name	Concept
Last menses	
Level of pain*	Compared to before using the IUD: less, the same, or more
Amount of blood loss*	Compared to before using the IUD: less, the same, or more
Days of bleeding	Analysis of number of days
Last intermenstrual interval	
Any pain event	Dichotomous
Number of pain days	Analysis of number of days
Any spotting	Dichotomous
Number of spotting days	Analysis of number of days
Serious problems	
Pain (menstrual or intermenstrual)	Specific problem spontaneously mentioned as the reason for the clinic visit or as the reason for IUD removal
Increases in menstrual bleeding	
Intermenstrual spotting	

*Two sources of data analyzed separately: follow-up form for 12 months and menstrual diary for first six months.

Table 2

Groups for analysis and number of reports (forms) on which the mixed effects modeling is based

Analysis group	N	Definition	Notes/uses
All	6655 5961*	All subjects and all available data on the date of occurrence	Unadulterated view of data used to provide perhaps the best overall interpretation
Completers	5297	Only subjects who used the IUD for at least one year	Provides complementary information
Incompleters	1358	Only subjects who had the IUD removed prior to one year	Provides complementary information
All, LOCF (last observation carried forward)	7148	All subjects and all available data; however, in case of removal prior to one year, the data values at time of removal are carried forward and imputed for the remaining scheduled visits	Provides most conservative approach to interpreting data

* Number of menstrual diaries analyzed.

Table 3

Perceptions of last cycle using the IUD, as recorded during the follow-up interview*

Timing and type of problem	Time period			
	1st period 0–9 weeks	2nd period 9–19 weeks	3rd period 19–39 weeks	4th period >39 weeks
Last menses				
Level of menstrual pain compared to before the IUD				
Less	398 (25.3)	468 (29.3)	456 (27.1)	441 (27.7)
Same	571 (36.4)	640 (40.1)	677 (40.3)	629 (39.5)
More	601 (38.3)	488 (30.6)	547 (32.6)	524 (32.9)
Amount of blood loss compared to before the IUD				
Less	181 (11.5)	229 (14.3)	220 (13.1)	189 (11.9)
Same	324 (20.6)	469 (29.4)	554 (33.0)	632 (39.6)
More	1065 (67.8)	898 (56.3)	906 (53.9)	773 (48.5)
Days of bleeding				
Mean (s.d)	6 (2.7)	5.9 (2.9)	6.1 (3.4)	5.6 (2.6)
Median	5	5	5	5
Last intermenstrual interval				
Any pain	341 (21.7)	299 (18.7)	363 (21.6)	387 (24.3)
Number of pain days				
Mean (s.d)	0.81 (2.5)	0.68 (2.4)	0.99 (3.3)	0.94 (2.7)
Median	0	0	0	0
Any spotting	376 (24.0)	320 (20.0)	418 (24.9)	451 (28.3)
Number of spotting days				
Mean (s.d)	1 (3)	1 (3.7)	1.3 (4.2)	1 (2.5)
Median	0	0	0	0
Total number of follow-up reports	1570	1596	1680	1594

* From follow-up forms over a 12-month period.

Note: This analysis is based on 6,440 follow-up reports; of the 6,655 total reports, 215 were excluded from this analysis because the participant had not experienced a full cycle with the IUD in situ.

Table 4

Incidence of serious problems over time

Type of problem cited spontaneously as the reason for the visit or reason for IUD removal	Time periods			
	1st period 0–9 weeks	2nd period 9–19 weeks	3rd period 19–39 weeks	4th period >39 weeks
Any pain				
N (%)*	177 (9.1)	78 (4.4)	108 (6.6)	68 (4.7)
n	182	83	117	72
Incidence density**	1.1	0.5	0.4	0.3
Increases in menstrual bleeding				
N (%)*	106 (5.4)	82 (4.7)	106 (6.5)	44 (3.1)
n	107	89	114	45
Incidence density**	0.6	0.5	0.4	0.2
Intermenstrual spotting				
N (%)*	37 (1.9)	26 (1.5)	51 (3.1)	22 (1.5)
n	40	26	52	22
Incidence density**	0.2	0.2	0.2	0.1
Total number of women still using the IUD at the start of the period	1947	1757	1632	1441
Total number of women making at least one follow-up visit in period	1574	1476	1454	1441
Total number of women-weeks (in hundreds)	166.9	169.0	304.3	228.7

Note: This analysis is based on 6,655 follow-up reports involving 1,947 different women.

N=number of different women experiencing the problem in the given period.

n=total number of events experienced by all participants in the given period.

* Percentage based on total number of women entering period.

** Uses total number of events in the numerator (n) and women-weeks in the denominator, expressed as number of events per 100 women-weeks.

Table 5

Results of mixed effects regression modeling to examine changes in problems over time * by type of side effect and population used in the analysis

	Analysis groups			
Type of problem	**All**	**Completers**	**Incompleters**	**LOCF**
Last menses				
Level of menstrual pain compared to before the IUD				
Follow-up form	Decreasing	Decreasing	No change	Decreasing
Menstrual diary **	Decreasing	--	--	--
Amount of blood loss compared to before the IUD				
Follow-up form	Decreasing	Decreasing	No change	Decreasing
Menstrual diary **	Decreasing	--	--	--
Days of bleeding	No change	No change	Increasing	No change
Last intermenstrual interval				
Any pain	No change	No change	No change	No change
Number of pain days	Increasing	No change	Increasing	Increasing
Any spotting	No change	No change	No change	No change
Number of spotting days	Increasing	No change	Increasing	No change
Serious problems				
Any pain	Decreasing	Decreasing	No change	No change
Menstrual bleeding	No change	No change	Increasing	Increasing
Intermenstrual spotting	Increasing	No change	Increasing	Increasing

* Labeled as decreasing or increasing trend if p value < 0.05. Otherwise, labeled as "no change."

** Available for first six months only. Subgroup analyses not performed due to concerns over validity.

All=all available data. Completers=only women who used the IUD for one full year. Incompleters=only women who had the IUD removed before one year.

LOCF (last observation carried forward) = all available data and imputation for data points after an IUD removal event; the data points were imputed using the technique of last observation carried forward for only subsequent scheduled visits.