Advances in Contraception 1998; 14: 69-77
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Advances in Contraception, 1998; 14: 69-77.

Four-year clinical evaluation of quinacrine pellets for non-surgical female sterilization

A. SUHADI (I), M. ANWAR (2) AND A. SOEJOENOES (3)

(I) Department of Obstetrics and Gynecology, Regency Hospital, Wonosobo 56311. Central Java, Indonesia
(2) Department of Obstetrics and Gynecology, Gadjah Mada University Faculty of Medicine, Dr Sardjito Hospital, Yogyakarta, Indonesia
(3) Department of Obstetrics and Gynecology, Diponegoro University Faculty of Medicine. Dr Kariadi Hospital, Semarang, Indonesia

Abstract

The aim of this study was to evaluate the efficacy, safety and acceptability of two monthly transcervical applications of quinacrine 252 mg and ibuprofen 55.5 mg as pellets for non-surgical female sterilization. From August 1992 through October 1996, a prospective clinical study was conducted on 200 normal women seeking surgical sterilization voluntarily in the Family Planning Clinic of the Department of Obstetrics and Gynecology, Regency Hospital, Wonosobo, Central Java, Indonesia. Quinacrine 252 mg and ibuprofen 55.5 mg were inserted transcervically, as pellets, using a Copper T IUD insertor in the proliferative phase of two consecutive menstrual cycles. The women were followed up 6, 12, 24 and 48 months after insertion. There were no major complications during the insertion procedures, and side-effects which occurred during the use of the methods were transient. Cumulative life-table continuation rate per 100 women at four years was 0.91 LO.02 (SE). The pregnancy failure rate was 0.04 or 4.3%. The results of this study indicate that intrauterine insertion ofquinacrine pellets is a safe, acceptable and effective method of non-surgical female sterilization.

Introduction

Surgical female sterilization, the most effective method of contraception for women who desire no additional children, is a procedure which requires trained personnel, adequate medical care facilities and acquisition and maintenance of sophisticated equipment [1].

Advances in Contraception 1998; 14: 69-77
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

For about three decades. investigators around the world have been trying to develop methods of surgical sterilization which arc safe and effective to meet with the unmet demand for voluntary sterilization, since it has been projected that around 180 million people will be seeking sterilization over the next 10 years [2,3].

Various chemical sterilants to produce tubal occlusion have been tried by many investigators. Ethanol. formaldehyde and silver nitrate can no longer be used because of their toxicity. Methyl cyanoacrylate (MCA) is an adhesive that solidifies very rapidly on contact with tissues, causing tissue adhesiveness. Phenol atebrine (Quinacrine- Biligraphin Paste, PAP), an occluding agent, has been extensively used in China since 1970. Phenol (carbolic acid) is a highly caustic chemical that. when injected into the fallopian tubes, rapidly causes extensive damage to the tubal mucosa, resulting in eventual occlusion by fibrosis. These chemicals arc highly effective but the process of application has not yet been established. The Erb method uses liquid silicon rubber to plug the oviducts, but its application requires a skilled surgeon and complex equipment [2,4–10].

Since 1968, Zipper and associates in Santiago, Chile, have evaluated various doses, concentrations, and solvents for suspension and instillation schedules of quinacrine that caused a high pregnancy rate and occasional transient toxic psychosis [1, 11,12].

In an effort to overcome these difficulties, quinacrine hydrochloride pellets have been developed to produce a delivery system that brings the chemical into prolonged contact with the tubal ostia through delayed uterine retention, and this increases the probability of successful occlusion. Because the quinacrine pellet dissolves relatively slowly within the uterine cavity, the risk of rapid intravascular absorption may be reduced [1].

The aim of this study was to evaluate the efficacy, safety and acceptability of two monthly transcervical applications of quinacrine 252 mg and ibuprofen 55.5 mg as pellets for non-surgical female sterilization.

Materials and methods

A prospective clinical study of quinacrine non-surgical female sterilization was conducted at Wonosobo Regency Hospital, Central Java, Indonesia. From August 1992 through October 1996, two hundred women, who gave informed consent, received 252 mg of quinacrine hydrochloride in the form of seven cylindrical pellets (Sipharm, Sissein, Switzerland) followed by 55.5 mg ibuprofen in three pellets transcervically during the proliferative phase of two consecutive menstrual cycles. Insertion is accomplished by placing seven quinacrine pellets followed by ibuprofen in three pellets in a plastic tube with a push rod positioned behind them. The tube was then passed through the cervical canal until the fundus was reached. The push rod was then held stationary, and the tube was pulled back, expelling the pellets into the upper segment of the uterine cavity. After the pellets had been discharged, the insertor was removed. The procedure is essentially the same as inserting a Copper T IUD (Kimia Farma, Bandung, Indonesia).

Follow-up was scheduled at 6, 12, 24 and 48 months after the last insertion and any

Advances in Contraception 1998; 14: 69-77
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

time when complications or complaints occurred. Women were admitted to the study if they requested sterilization for family planning reasons and preferred this method over surgical sterilization. Excluded were women who had pathologic pelvic conditions (except cervicitis), such as upper tract infection, or gross distortion of the uterine cavity or who appeared unusually nervous. Those women who had to be excluded were offered a choice of surgical sterilization or other methods of contraception.

Data were collected on standardized forms developed by the International Federation for Family Health (IFFH). Life-table analysis using the Kaplan Meier Survival Curve to calculate the continuation rates was conducted in this study [13].

Results

All 200 women completed the first insertion but three did not have a second insertion and were offered an alternative contraceptive method. The long-term analysis was based on the 197 subjects completing two insertions and the 195 followed for four years, two women being lost-to-follow-up when they moved from the area.

Most of the women – 178 (89.0%) – came from rural areas, whereas 22 (11.0%) were urban dwellers. The mean age was 33.2 ± 9.75 (SD), ranging from 24 to 40 years. The mean number of live births for the population was 3.5 ± 0.50 (SD), with a range of 2–8 live births. Contraceptive use reported for the three months prior to first insertion is shown in Figure 1; the largest group of women, 69 (34.5%), had never

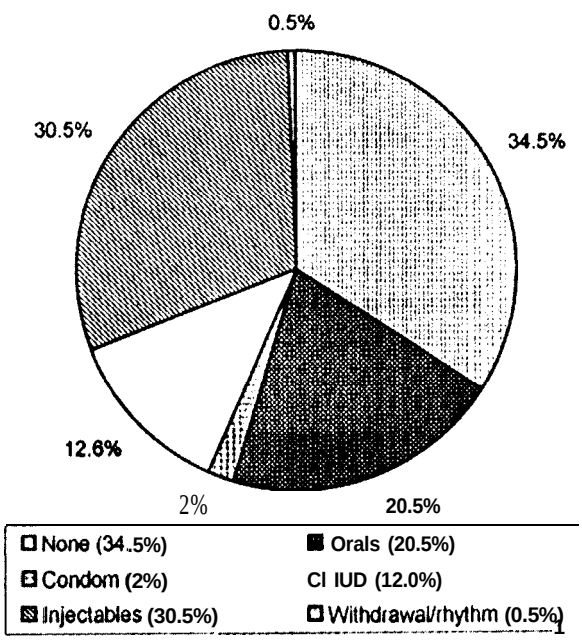

Figure 1. Distribution of contraceptive methods before quinacrine pellet insertion

Advances in Contraception 1998; 14: 69-77
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

Table 1. Complications aud complaints reported four years after second administration of quinacrine pellets

Complications/complaints[a]	*n*	*%*
Amenorrhea	2	1.1
Menorrhagia	1	0.5
Leukorrhea	1	0.5
Pain in lower abdomen	2	1.1
Fever	–	

[a]More than one complication/complaint may occur for each woman

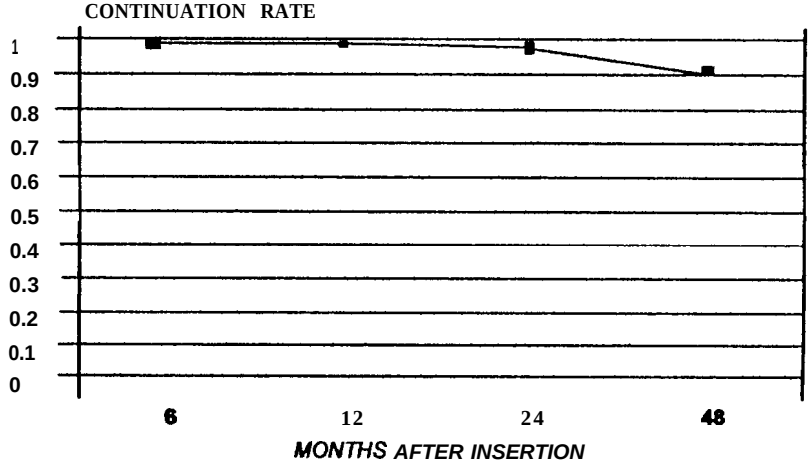

Figure 2. Cumulative life-table continuation rate at 48 months after second insertion (n = 195)

used contraception, while 43% had used effective methods of contraception for three months prior to this study. Complications and complaints are shown in Table 1, which indicates that amenorrhea and lower abdominal pain occurred in two cases (1.1%) each. Menorrhagia and leukorrhea occurred in one case (0.5%) each. The cumulative life-table continuation rate in this study per 100 women at four years was 0.91 $\pm$ 0.02 (SE) (Figure 2). The pregnancy rate was 0.04 or 4.3% (Figure 3). The diagnosis of pregnancy was made by pelvic examination and proved by pregnancy test. Eight women became pregnant after the last insertion during the four-year follow-up period. Two of these pregnancies were terminated by vacuum aspiration; one pregnancy aborted spontaneously. The other five ended in spontaneous delivery of a term baby. No major malformations were noted, although one case was complicated by postpartum bleeding due to retained placenta.

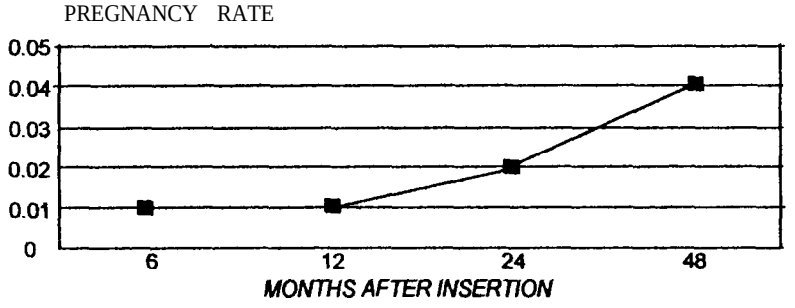

Figure 3. Pregnancy rate at 48 months after insertion ($n = 195$)

Discussion

Most of the women (89.0%) in this study were from rural areas, while, in a similar study conducted in Baroda, India, most of the clients (77.4%) were from urban areas [7].

The mean age and numbers of live births of the women were 33.2 $\pm$ 9.75 years (SD) and 3.5 $\pm$ 0.05 (SD), respectively. These figures are very similar to the characteristics of the clients from two previous studies [7,14]. There were no major complications or complaints during the four year follow-up in this study. Amenorrhea and pain of the lower abdomen occurred in a small number of patients and required no treatment. Other follow-up complaints included menorrhagia and leukorrhea. None of these side-effects appeared to be related to the sterilization procedure itself. Suhadi and Soejoenoes reported in 1996 [15] that the main side-effect after first insertions of pellets was lower abdominal pain in 116 cases (60.1%). Two women reported severe abdominal pain and required antibiotic and analgesic treatment. Fever occurred in 26 cases (13.5%) and leukorrhea in 15 (7.8%) after the first insertion [15]. Zipper et *al.* reported that one case in their series was treated with penicillin due to suspected infection [16]. Hieu et *al.* in Namha, Vietnam showed that the symptoms lasted from a few hours to a few days [17]. Symptoms were generally milder after the second insertion [15,17].

The life-table continuation rate per 100 women at 48 months after the last insertion of quinacrine pellets was significantly higher while the pregnancy rate was low. Pregnancy could occur at any time after insertion. The pregnancy rate for this study was comparable with that of another similar study in Baroda, India. The pregnancy rate in the study of Bhatt and Wdszak in Baroda, India was 3.7 $\pm$ 2.1 [17]. The study of Hieu in Vietnam showed that the failure rate (pregnancies) was strongly affected by the skill of the operator; the amount of experience the operator had was of little importance compared with his or her skill [17].

Data from several studies suggest that giving more than one insertion, one month apart, improves the efficacy of quinacrine pellet sterilization. Data from Zipper's

Advances in Contraception 1998; 14: 69-77
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

work [12] with slurries and pellet data from Mullick [25], El Kady *et al.* [26] and Hieu *et al.* [17] suggest that three insertions are more effective than one or two, and that two insertions are better than one. However, preliminary analysis of long-term pregnancy data from the Chile cohort shows no difference between two and three insertions, although this preliminary analysis did not control for dosage or use of adjuvants [18].

Data from prehysterectomy studies by Merchant [27] of single insertions in 40 women suggest that the reason for different efficacy rates by number of insertions may be more complex than originally thought. Merchant's data suggest that the inflammatory and fibrotic process takes six weeks to complete. Thus. it is possible that two insertions or even one insertion might be just as effective as three after a sufficient interval. These studies recommended a supplementary form of contraception for six weeks following quinacrine insertions. If this hypothesis is correct. then the early failure rate after one or two insertion regimens is likely to be high. hut the longer term failure rate might be similar to that with three insertions.

Data from a recent study by Bashir are consistent with this hypothesis. Bashir [28,29] has been performing single insertions of quinacrine in Pakistan for several years with surprisingly low failure rates. Recent work in Pakistan by Bashir [29] suggests that ibuprofen given either orally or by the intrauterine route, in conjunction with quinacrine pellet insertion, may reduce pregnancy rates. The dose of quinacrine to be used in single insertion should probably be not less than 216 mg or more than 324 mg. Merchant's prehysterectomy data suggest that a 100-mg dose of quinacrine is too low, and that more than 324 mg would be superfluous. Recent data from Bairngi show low failure rates with a dose of 2 16 mg quinacrine plus ibuprofen or declofenac and three cycles of oral contraceptives [18]. Sokal and co-workers have documented improved efficacy for women 35 years of age and over, as is expected for all contraceptive methods [19].

A recent report by Mullick and co-workers provides evidence for acceptable efficacy with a single insertion and medroxyprogesterone (150 mg im) given at the time of insertion of pellets [20]. This improved efficacy may be due to the ability of medroxyprogesterone to relax uterine musculature, including the tubal ostia, with more consistent delivery of quinacrine to the tubes. It might be also due to its antiestrogenic effect. Zipper and co-workers have demonstrated that estrogen promotes recovery of quinacrine-induced tubal inflammation in the rat [21].

Concerns have been expressed regarding possible carcinogenicity of intrauterine administration of quinacrine because it is a known mutagen. However, there are no reports of cancer with use of quinacrine for treatment or prophylaxis for malaria at much higher doses orally (36 000 to 52 000 mg per year) than needed for sterilization by intrauterine application). Also, a recent 2–14-year follow-up study in Chile showed no evidence of increased risk of cancer by intrauterine administration of quinacrine [19].

There were no deaths over the four years of these studies. In over 100000 quinacrine sterilizations to date, there has been no reported case fatality, and serious complications are rare [22].

The main advantage of this method for a developing country is the possibility of

Advances in Contraception 1998; 14: 69-77
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

increasing contraceptive use among women who want no more children, while providing more effective contraception than temporary methods and thereby slowing rapid population growth and decreasing maternal mortality by preventing unwanted pregnancy, especially for high-parity women. At this time, Indonesia has a very low prevalence of female sterilization 2.9% [23] and an unacceptably high maternal mortality rate of 390 per 100000 live births [24]. Quinacrine pellets are a safe, acceptable and effective method of non-surgical female sterilization. Any health care provider trained in IUD insertion could deliver this sterilization method.

Conclusions

The use of quinacrine pellets is a promising method of non-surgical female sterilization because of its safety, acceptability and effectiveness. More data are needed on the long-term safety of the method and on other factors, including the insertion technique, the number of insertions, and whether antiprostaglandin or medroxyprogesterone increases efficacy.

Acknowledgements

We are grateful to Elton Kessel, MD, Secretary General of the International Federation for Family Health, Leasburg, North Carolina, USA, for his guidance. The quinucrine and ibuprofen pellets were provided by the Center for Research on Population and Security, Research Triangle Park, North Carolina.

References

1. Zipper J, Cole LP, Goldsmith A, Wheeler R, Rivera M. Quinacrine hydrochloride pellets: preliminary data on a nonsurgical method of female sterilization. Int J Gynaecol Obstet. 1980;18:275-9.
2. Kcsscl E, Mumford SD. Potential demand for voluntary female sterilization in the 1980s: The compelling need for a nonsurgical method. Fertil Steril. 1982;37:725-33.
3. Kessel E. Prospects for nonsurgical female stcrilizntion. Int J Gynaecol Obstet. 1989;29:1-4.
4. Kessel II. Zipper J, Mumford SD. Introduction. The quinacrinc pellet method for nonsurgical female sterilization, a collection of background materials. Center for Research on Population and Security, Research Triangle Park, North Carolina, USA. 1990: 1-11.
5. Klitsch M. Sterilization without surgery. Int Fam Perspect. 1982;8:101-4.
6. Kang XP, Wan HZ, Wang P, Wang SX, Chow LP. Effectiveness of phenol atebrine-paste (PAP) instillation for nonsurgical female sterilization. Int J Gynaecol Obstet. 1990;33:49-57.
7. Bhatt R, Waszak CS. Four year follow-up insertion of quinacrinc hydrochloride pellets as a means of nonsurgical female sterilization. Fertil Steril. 1985;44:49-57.
8. Zipper J, Medel R, Goldsmith A, Edelman D, Pastene L, Rivcra M. The clinical efficacy of the repeated transcervical instillation ofquinacrine for female sterilization. Int J Gynaecol Obstet. 1976;14:499-502.
9. Laufe LE, Cole LP. Nonsurgical female sterilization. Int J Gynaecol Obstet. 1980;18:333-9.
10. Mehtaji S, Jadwani K, Goyal V. Chemical sterilization with quinacrine. In: Pachauri S, ed. Fourth Transaction of Scientific Papers of the India FRP Contributors Conference, India Fertility Research Programme. 1977: 167-70.
11. Zipper J. Stacchetti E, Medel M. Human fertility control by transvaginal chemical sterilization: clinical use of quinacrine on the fallopian tube. Fertil Steril. 1970;21:581-9.

Advances in Contraception 1998; 14: 69-77
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

12. Zipper J. Stacchetti Ii. Medel M. Transvaginal chemical sterilization: clinical use of quinacrine plus potentiating adjuvants. Contraception. 1975; 12:111 21.
13. Mathews DE. Farewell VT. Kaplan-Meier Actuarial Survival Curves. In: Using and Understanding Medical Statistics. Basel, New York: Karger; 1985:67 75.
I.I. Zipper J. Rivera M. Cole LP. Brown E. Wheeler KG. Efficacy of two insertions of 100 minute releasing quinacrinc hydrochloride pellets for nonsurgical female sterilization. Adv Contracept. 1987; 3:255 61.
15. Suhadi A. Soejoenoes A. One year experience using quinacrinc pellets for nonsurgical female sterilization. Indonesian J Obstet Gynecol. 1996;20(1):39 43.
16. Zipper J. Edelman D. Cole LP. Rivera M. Overview of quinacrine pellets for nonsurgical female sterilization. In: Zatuchni GI, Shelton JD, Goldsmith A. Sciarra JJ. eds. Female Transcervical Sterilization. Philadelphia: Harper and Row: 1983:172.
17. Hieu DT, Tan TT, Tan DN. Nguyet PT. Vinh DQ. 31781 cases of nonsurgical female sterilization with quinacrinc pellets in Vietnam. Lancet. 1983;342:21317.
IX. Sokal DC. Zipper J. King T. Quinacrine: Clinical Experience. Background paper for the World Health Organization Consultation on the development of new technologies for female sterilization. Geneva: WHO; 1994:25-7.
19. Sokal DC. Zipper J. King T. Transcervical quinacrine sterilization: clinical experience. Int J Gynecol Obstet. 1995;51(Suppl):556-69.
20. Mullick BC, Kessel E, Mumford SD. A potential single insertion protocol for quinacrine pellet non-surgical female sterilization. Adv Contracept. 1995;11:239-44.
21. Zipper J. Prager R. Medel M. Biologic changes induced hy unilateral intrauterine instillation of quinacrinc in the rat and their reversal by either estradiol or progesterone. Fertil Steril. 1973;24:4852.
22. Kessel E. 100000 quinacrine sterilizations. Adv Contracept. 1996;12:69 -76.
23. Central Bureau of Statistics (CBS) [Indonesia] and State Ministry of Population/National Family Planning Coordinating Board (NFPCB) and Ministry of Health (MOH) and Macro International Inc. (MI). Indonesian Demographic and Health Survey 1994. Calverton, Maryland: CBS and MI: 1995:73.
24. Central Bureau of Statistics (CBS) [Indonesia] and State Ministry of Population/National Family Planning Coordinating Board (NFPCB) and Ministry of Health (MOH) and Macro International Inc. (MI). Indonesian Demographic and Health Survey IYY4. Calverton, Maryland: CBS and MI: 1995:211.
25. Mullick B. Mumford SD. Kessel E. Studies of quinacrine and of tetracycline for nonsurgical female sterilization. Adv Contracept. 1987;3:245 254.
26. El Kady AA. Nagih HS, Kessel E. Efficacy and safety of repeated transcervical quinacrine pellet insertions for female sterilization. Fertil Steril. 1993;59:301-304.
27. Merchant RN. Doctor VM. Thaku SS et al. Clinico pathological study of fallopian tube after transcervical insertion of quinacrine hydrochloride pellets. Adv Contracept. 1986;2:79 90.
28. Bashir A. Quinacrine nonsurgical female sterilization. Adv Contracept Dcliv Syst. 1993;9:37 42.
29. Bashir A. Muhammad M. Muhammad AC. Muhammad YC. Non-surgical female sterilization: 3 years expcricncc with quinacrinc. Seminar on Quinacrine for Non-surgical Female Sterilization. Karachi, 1994.

Manuscript received 20 July 1997.
Accepted for publication 20 Aug. 1997.

Resumé

Cette étude avait pour but d'évaluer l'efficacité, l'innocuité et l'acceptabilité de deux applications transcervicales mensuelles de pellets contenant 252 mg de quinacrine et 55.5 mg d'ibuprofen pour une stérilisation féminine non chirurgicale. Depuis août 1992 jusqu'à octobre 1996, une étude cliniquc prospective a été menée chez 200 femmes normales se présentant volontairement pour unc stérilisation chirurgicale à la Clinique de planning familial du Service d'obstétrique et gynécologie du Rcgcncy Hospital de Wonosoho (Java centrale, Indonésie). Des pellets contenant 252 mg dc quinacrine cl 55,5mg d'ibuprofen ont été insérés transcervicalement à l'aide d'un instrument d'insertion intra-utérine Coppet T au cours de la phase proliférative de deux cycles menstruels consécutifs. Les visites de suivi ont cu lieu aux sixième, douzième et vingt-quatrième mois après l'insertion au cours dc la période dc quatre ans. Aucune complication niajeure n'est survenue pendant l'inserlion proprement dite et les effets secondaires observés avec cette méthode étaient passagers. Le taux de poursuite cumulé de la table de survie pour 100 patientes sur la période de quatre ans était de 0.9 ± 0.02 (SE). Le taux de grossesse par échec de la méthode s'est élevé

Advances in Contraception 1998; 14: 69-77
(CREATED FROM SCANNED DOCUMENT, PLEASE REFER TO ORIGINAL)

à 0,04, soit 4,3%. Les résultats de cette étude indiquent que l'insertion intra-utérine de pellets de quinacrine est une méthode de sttrilisation feminine non chirurgicale sans danger, acceptable et efhcace.

Hesumen

El objetivo de este estudio consistió en evaluar la eficacia, seguridad y aceptabilidad de la aplicación transcervical bimestral de 252 mg de quinacrina y 55,5 mg de ibuprofen en forma de *pellets* para la esterilizacion femenina no quirúrgica. Desde agosto de 1992 hasta octubre de 1996 se hizo un estudio clinic0 prospectivo con 200 mujeres normales que solicitaron voluntariamente esterilizacion quirúrgica en la Clínica de Planificación Familiar del Departamento de Obstetricia y Ginecologia del Regency Hospital, Wonosobo, Region Central de Java, Indonesia. Los 252 mg de quinacrina y 55.5 mg de ibuprofen se insertaron transcervicalmente, como *pellets*, utilizando un dispositivo de inserción DIU Copper Ten la fase proliferativa de dos ciclos mensuales consecutivos. El seguimiento se hizo a los 6, 12 y 24 meses de la inserción y en un período de cuatro años. No hubo complicaciones graves durdnte los procedimientos de inserción y los efectos secundarios ocurridos durante el uso del método fueron pasajeros. La tasa acumulativa de continuación de tablas de vida por cada 100 mujeres a los cuatro años fue $0,9 \pm 0,02$ (SE). Las tasas de fracaso por embarazo fueron 00,4 6 4,3%. El resultado de este estudio indicó que la insercibn intrauterina de *pellets* de quinacrina es un método seguro, aceptable y eficaz de esterilizacion femenina no quirúrgica.