

## One year experience using quinacrine pellets for non-surgical female sterilization

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**Tujuan:** Untuk mengevaluasi kemanjuran, keamanan dan penerimaan penggunaan transservikal dua kali pellet quinacrine 250 mg dan ibuproven 55,5 mg sebagai sterilisasi wanita non-bedah.

**Rancangan/rumusan data:** Kajian klinis dikerjakan dengan mengambil ibu-ibu yang menginginkan sterilisasi sebagai suatu cara keluarga berencana. Setiap wanita menerima quinacrine hydrochloride dengan dosis 250 mg dalam bentuk pellet silindris 7 buah diikuti dengan ibuproven 55.5 mg transservikal. Pellet dimasukkan dua kali dalam periode dua bulan selama fase proliferasi dari siklus menstruasi. Pengamatan lanjut dikerjakan dalam 6, 12, 24 dan 48 bulan setelah pemberian pellet terakhir. Data dikumpulkan menggunakan formulir buku yang dikembangkan oleh The International Federation for Family Health (IFFH).

**Tempat:** Klinik Keluarga Berencana, Bagian Obstetri dan Ginekologi KSU Wonosobo, Propinsi Jawa Tengah, Indonesia.

**Subjek, pasien, peserta:** 200 wanita diteliti selama periode Agustus 1992 sampai Oktober 1993. Semua memenuhi kriteria penerimaan dan penolakan.

**Ukuran luaran utama:** Komplikasi, keluhan, angka kehamilan dan angka kelangsungan.

**Hasil:** Umur dan anak hidup rata-rata adalah  $33,2 \pm 9,75$  (SD) dan  $3,5 \pm 0,50$  (SD). Efek samping utama setelah insersi pertama adalah sakit perut bawah pada 116 kasus (60,1%). Dua kasus mengalami sakit perut bawah berat yang memerlukan pengobatan antibiotika dan analgetika. Keluhan lain yang dilaporkan antara lain panas menggigil (13,5%) dan leukorea (7,8%) yang hilang tanpa pengobatan khusus. angka kelangsungan kumulatif per 100 wanita dalam 12 bulan setelah insersi terakhir pellet quinacrine adalah  $0,97 \pm 0,01$  (SE). Angka kehamilan adalah 0,01.

**Kesimpulan:** Hasil penelitian ini menunjukkan bahwa penggunaan pellet quinacrine perlu dikembangkan lebih lanjut sebagai metoda yang memberikan harapan, aman dan efektif pada sterilisasi wanita non-bedah dengan pertimbangan kemudahan dari metodenya.

[Maj Obstet Ginekol Indones 1996; 20: 39-43]

**Kata kunci:** Pellet quinacrine transservikal, kemanjuran, keamanan, angka kelangsungan, cara sterilisasi non-bedah.

**Objective:** To evaluate the safety and acceptability of two transcervical application of 250 mg of quinacrine and 55.5 mg ibuproven pellets in non-surgical female sterilization.

**Design/data identification:** A descriptive study was done by recruiting women seeking sterilization for family planning reason. Each woman received a 250 mg dose of quinacrine hydrochloride in the form of seven cylindrical pellets. The pellets were inserted twice with the period of two months during the proliferative phase of menstrual cycle. Follow-up was conducted in 6, 12, 24 and 48 months after the last administration. Data were collected using standardized forms developed by the International Federation for Family Health (IFFH).

**Setting:** Family planning clinic, Department of Obstetrics and Gynecology Wonosobo Regency Hospital. Central Java Province, Indonesia.

**Subject, patients, participants:** Two hundred women were studied during the period of from August 1992 to October 1993. All of them fulfilled the inclusion and exclusion criteria.

**Main outcome measures:** Complications, complains, pregnancy rate and continuation rate.

**Results:** Mean age and number of live births of women was  $33.2 \pm 9.75$  (SD) and  $3.5 \pm 0.50$  (SD). The main side effects after the first insertion were lower abdominal pain in 116 cases (60.1%), there were two cases who experienced severe lower abdominal pain and required antibiotic and analgesic treatment. Other complications reported were chilling (13.5%) and leucorrhea (7.8%) which subsided without any specific treatment. The cumulative continuation rates per 100 women at 12 months after the last quinacrine pellet insertions was  $0.97 \pm 0.01$  (SE). The pregnancy rate was 0.01.

**Conclusions:** The result of the study indicated that the use of quinacrine pellets deserves to be further developed as a promising, safe and effective method of non-surgical female sterilization, considering the ease of the method.

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**Keywords:** Transcervical Quinacrine pellet, efficacy, safety, continuation rate, non-surgical sterilization method.

### INTRODUCTION

The estimated number of couples controlling their fertility through sterilization has increased dramati-

cally over the past two decades, from 15 million in 1970 to 100 million in 1980. In developing countries, the demand for sterilization far exceeds the supply of services. The approximated half of the fe-

**cund** women want no more children, but fewer than half of these women use effective methods of fertility control, due to among them the **lack** of funds, professional personal and the organization to mount such programs in the crowded urban or scattered rural areas. This is an estimate of unmet need for sterilization. Many of the women **continue** to use effective reversible methods of contraception for long periods after the desire of **no-more-children**.<sup>2,3</sup>

Extensive research has been performed to develop a simple method of non surgical female sterilization. Zipper and associates identified quinacrine **hydrochloride** as a drug likely to produce tubal occlusion when placed into the uterus.<sup>4</sup> Several clinical trials have been done to evaluate various doses, concentrations, solvents for the suspensions and instillation schedules of quinacrine. Zipper's quinacrine solution schedule of three instillations of a solution of 1.5 mg of quinacrine powder suspended in 5 ml of 2 % **xylocaine** has a high pregnancy rate **and produced** occasional transient toxic **psychosis**.<sup>5,6</sup>

In an effort to overcome these difficulties, **quinacrine hydrochloride pellets** have been developed to produce a delivery system that would bring the chemical into prolonged contact with the tubal ostia through delayed uterine retention, and this increase the probability of successful occlusion. Because the quinacrine pellet dissolves relatively slow within the uterine cavity, the risk of rapid intravascular absorption presented with the solution may be reduced.<sup>7</sup>

The aim of the study was to evaluate the efficacy, safety and acceptability of two transcervical applications of 250 mg quinacrine and 55.5 mg ibuprofen pellets as non-surgical female sterilization.

## MATERIALS AND METHODS

A descriptive study was conducted at the **Wonosobo Regency Hospital**, Central Java Province, Indonesia. From August 1992 through October 1993 two hundred women who gave informed consent received a 250 mg dose of quinacrine hydrochloride on the form of seven **cylindrical pellets** followed by 55.5 mg ibuprofen transcervically. The pellets was inserted with the period of two months during the proliferative phase of menstrual cycle. Insertion is accomplished by placing seven quinacrine pellets followed by 55.5 mg ibuprofen pellets in a plastic tube with a push rod positioned behind them. The tube is then passed through the cervical canal until the **fundus** is reached. Dilatation is infrequent. The push rod is then held stationary, and the tube is pulled back after it expelled the pellets into the upper segment of

the uterine cavity. After the pellets have been discharged, the inserter is removed.

The procedure is essentially the same as inserting an IUD. Insertions were performed during the proliferative phase of two consecutive menstrual cycles.<sup>7</sup>

Follow-up was scheduled at six, 12, 24 and 48 months after the last administration and at any time when complications or complaints **occurred**. Women were admitted to the study if they requested sterilization for family planning reason and if they did not have a history of medical or psychiatric problems. Excluded were women who had pathologic pelvic conditions (except cervicitis) or those 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 using standardized forms developed by the International Federation for Family Health (IFFH). Descriptive and life table analysis using Kaplan Meier Survival curve to draw the continuation rate conducted in this study.\*

## RESULTS

All 200 women completed the first insertions the report analysis, include 197 of the cases: three cases were excluded from the analysis due to discontinuing the second insertion.

**Table 1** Number of quinacrine pellet insertions

Quinacrine pellets	n	%
First insertion	200	100.0
Second insertion	197	98.5

**Table 2** Area of origin for women

Area of origin	n	%
Urban	22	11.0
Rural	178	89.0
Total	200	100.0

The majority of the women 178 (89.0 %) came from rural areas, whereas 22 (11.0 %) were urban people. Areas of origin for these women are shown in Table 2.

Mean age and number of live births of women entering the study are provided in Table 3. The mean age was  $33.2 \pm 9.75$  (SD), ranging from 24 to 40 years. The mean number of live births for the popu-

lution was  $3.5 \pm 0.50$  (SD), with a range of 2 to 8 live births.

**Table 3** Age and live births for women entering quinacrine pellets study

Quinacrine pellets	
Mean Age (years)	$33.2 \pm 9.75$
Mean number of live births	$3.5 \pm 0.50$

**Table 4** Distribution of contraceptive methods before quinacrine pellet insertions

Contraceptive methods	n	%
None	69	34.5
IUD	25	12.5
Orals	40	20.0
Injectable	61	30.5
Condom	4	2.0
Withdrawl/rythm	1	0.5
Total	200	100.0

Most women 69 (34.5 %) had never used a contraceptive, while 43 % had used an effective method 3 months prior to this procedure (Table 4).

Complications and complaints reported are shown in Table 5. The main side effects after the first insertion were lower abdominal pain in 116 cases (60.1 %). Two women reported severe abdominal pain and required antibiotic and analgesic treatment. Chilling in 26 cases ( 13.5 %), leukorrhea in 15 cases (7.8 %). These symptoms lasted a few hours to a few days. Symptoms were generally milder after the second insertion. Temporary amenorrhea occurred in two women (1.0 %), that lasted to 4 months but required no treatment.

The cumulative continuation rates in this study per

100 women at one year were  $0.97 \pm 0.01$  (SE) (Table 6). Pregnancies occurred within one and two months after the second insertion. The pregnancy rate was 0.01 or 1%.

**Table 6** Cumulative continuation rate at 12 months after the second administrations

Months after administration	Continuation rate	S E
6	0.97	0.01
12	0.97	0.01

The diagnosis of pregnancy was made by pelvic examination or a combination of pregnancy test and pelvic examination. One of the pregnancies was terminated by menstrual regulation and the other pregnancy ended in a spontaneous delivery with term a female baby, and no major malformation was noted.

## DISCUSSIONS

Surgical female sterilization, the most effective method of contraception for women who desire no additional children, requires trained personal, adequate medical care facilities and the acquisition and maintenance of sophisticated equipment.<sup>7</sup>

For about three decades investigators around the world have been trying to develop a safe, 95 percent effective method of non-surgical female sterilization that could be performed under local anesthesia or on an outpatient basis by non physicians, preferably after only a brief training period. Such a method has been called vital for meeting the worldwide demand for voluntary sterilization, since it is projected that around 180 million peoples will be seeking sterilization over the next 10 years.<sup>9</sup>

Researchers have experimented with various

**Table 5** Complications and complaints reported within one year after second administration of quinacrine pellets

Complications/Complaints	First insertion (n = 200)		Second Insertion (n = 197)	
	n	%	n	%
Amenorrhea	2	1.0	2	1.0
Menorrhagia	7	3.6	3	1.5
Leukorrhea	15	7.8	4	2.0
Pain in lower abdomen	116	60.1	1	0.5
Chilling	26	13.5	4	2.0

\* More than one complication/complaint may occur for each women

chemical sterilants to produce tubal occlusion. Drugs such as **ethanol**, formaldehyde and silver nitrate **cause** tubal occlusion but cannot be used because of their toxicity. Methylcyanoacrylate (MCA), phenol **atebrine (Quinacrine)-biligraphin** paste (PAP) act by causing tissue adhesiveness. They are highly effective but the process of application has not so far been established for these chemicals, The Erb method used liquid silicon rubber to plug the oviducts, but its application required both a skilled surgeon and complex **equipment**.<sup>1,3,9,10,t1,12,13,14</sup>

Since 1968, Zipper and associates in Santiago, Chile, evaluated various doses, concentrations, solvents for the suspension and instillation schedules of quinacrine and caused 69-94 % tubal **occlusion**.<sup>1,7</sup>

Zipper has also found that two transcervical applications of 250 mg quinacrine pellets followed by intramuscular or intrauterine administration of **antiprostaglandins** both lowers the incidence of mild side effects and the failure **rates**.<sup>3,4,14</sup>

Since August 1992 through October 1993 Non-surgical female sterilization using two transcervical applications of quinacrine pellets were conducted on **200** females in the Family Planning Clinic, **Wonosobo** Regency Hospital, Central Java Province, Indonesia. Three cases were excluded due to discontinuing the second insertion. The majority of the women (89.0 %) in the study was from rural areas. Bhatt and Waszak in Baroda, India reported the majority of the study (77.4 %) was from urban **areas**.<sup>11</sup>

The mean age of the women was  $33.2 \pm 9.75$  (SD), the youngest was 24 years and the oldest was 40 years, whereas the mean number of live births was  $3.5 \pm 0.50$  (SD), ranging from 2 to 8. These figures were 31.3 years for the mean age and 3.5 for the mean number of live births in the study of Bhatt and Waszak in Baroda, India (1985).<sup>11</sup> The figures in the studies of Zipper and associates in Santiago, Chile, were 3 1.4 years and 3.6.4

About 34.5 percent of women used no contraception before quinacrine insertion and this was comparable with another similar study in Baroda, **India**.<sup>11</sup>

There were no major complication during the procedure. There were two **cases** who experienced severe lower abdominal pain and, required antibiotic and analgesic treatment. Zipper reported that one case in his study was treated with **penicillin**.<sup>15</sup> Other complications reported were chilling (13.5 %) and leukorrhea (7.8 %) which subsided without any specific treatment. Hieu and associates in Namha, Vietnam, showed that these symptoms lasted for a few hours to a few days. Symptoms were generally milder after the second insertion.<sup>16</sup>

The **cumulative** continuation rate per 100 women at

12 months after the last quinacrine pellets insertions was  $0.97 \pm 0.01$  (SE). Pregnancies **occured** in one and two months after the second insertion resulting the pregnancy rate of 0.01 or **1%** due to incomplete tubal occlusion. The one year pregnancy failure rate in the Vietnam trial was 2.63 per 100 women for those receiving two monthly transcervical insertions of 252 mg quinacrine as pellets and 5.15 for those receiving single insertion. 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**.<sup>16</sup> There are other possibilities for lowering the failure rate. For example, pre hysterectomy studies showed that completion of tubal occlusion takes at least 6 weeks in some women. The use of contraception for during this period would be advisable.<sup>16</sup> The dose of quinacrine to be used in a single insertion should probably not **be** less than 2 16 mg or more than 324 mg. Merchant's pre hysterectomy data suggest that a 100 mg dose of quinacrine is too low, and that more than 324 mg would be superfluous. Recent data from **Bairagi** showed low failure rates with a dose of 2 16 mg of quinacrine plus ibuprofen or diclofenac and three cycles of oral contraceptives.<sup>17</sup>

There were no deaths in this study. Up till now, no death have been reported using this method anywhere in the world. The 'use of quinacrine pellets appears to have reduced the incidence of transient toxic psychosis or cortical excitation, a side effect that has been observed in studies using intrauterine solution. No women in the Indonesia studies developed transient psychosis. But in the Zipper studies using solution 2 % developed transient **psychosis**.<sup>15</sup>

Eventhough mortality related to surgical sterilization is low, there are still some risks associated with the surgical procedure. These risks as well as the unmet demand for sterilization, are reason for the urgent need for development of non-surgical female sterilization procedures.

## CONCLUSIONS

1. The use of **quinacrine** pellets is a promising method because of its safe, acceptability and effectiveness for non-surgical female sterilization.
2. The use of quinacrine pellets should be extended to the general practitioner and midwifery personnel, seen from the ease of the method.
3. 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 antiprostaglandins increase efficacy.

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