

# A potential single insertion protocol for quinacrine pellet non-surgical female sterilization

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## Abstract

Two preliminary single-insertion clinical trials of the quinacrine pellet method of non-surgical female sterilization were compared. Both trials used trans cervical application of quinacrine, 252 mg, and diclofenac, 75 mg, as pellets. In the first trial (21 April 1992 to 17 February 1993), 58 women received oral contraceptives for three months. In the second trial (19 February 1993 to 25 May 1994), 229 women received medroxyprogesterone acetate, 150 mg IM, at the time of quinacrine insertion. At 18 months, the life-table pregnancy failure rate per 100 women of the first trial was 8.6 (SE 3.7), whereas the failure rate for the medroxyprogesterone acetate group was 0.5 (SE 0.5),  $p < 0.05$ . There were no serious complications or side-effects in either group.

Larger confirming trials with random allocation and long-term systematic follow-up are needed to determine whether a single injection of medroxyprogesterone improves the efficacy of quinacrine.

## Introduction

The quinacrine pellet method of non-surgical female sterilization as developed by Zipper et al. [1] involves transcervical insertion of quinacrine pellets, each containing 36 mg quinacrine, utilizing a modified intrauterine device (IUD) inserter. Seven pellets or 252 mg of quinacrine is the usual dose. Quinacrine causes inflammation and fibrosis, resulting in closure of the intramural tube [2]. Efficacy is influenced by dose of quinacrine [3], number of insertions [4,5], presence of blood in the uterine

cavity [5], the addition of adjuvants [6] and, possibly, supplemental contraception for 3 months post-insertion [3]. Finally, and probably an over-riding factor suggested in a large field trial [4], is insertion technique. Consistent insertion of pellets at the fundus is probably the proper technique.

The most desirable protocol for a non-surgical female sterilization method should be one that is safe, effective, inexpensive, acceptable and can be provided by paramedical personnel during a single visit [7]. The Vietnam field trial [4] provides evidence for all of these desirable qualities except the single visit. We report on a protocol that may provide this last quality.

### Materials and methods

The study was approved by the Ethics Committee of the Indian Rural Medical Association and was carried out at the Association's main training center in Calcutta. All procedures were performed by the senior author (BCM). Women requesting a permanent method of contraception were offered the following protocol: Single insertion of quinacrine, 252 mg (7 pellets), with diclofenac, 75 mg (3 pellets), inserted transcervically using a modified Copper T IUD inserter. Medroxyprogesterone acetate, 150 mg IM, was given in the deltoid muscle immediately after insertion in one group. This procedure was accepted by 229 women between 19 February 1993 and 25 May 1994. In a previous group, the same procedure was used except that oral contraceptives were prescribed for 3 months instead of medroxyprogesterone IM; 58 women accepted this procedure between 21 April 1992 and 17 February 1993. The cut-off date for the collection of data was 30 November 1994.

Insertions were made with a cold-sterilized inserter that was made perfectly dry by a spirit wash. Pellets were kept clean but not sterilized before loading in the inserter as quinacrine itself is strongly bacteriocidal [8]. The quinacrine pellets (Sipharm, Switzerland) had a dissolution time of 30 min and the diclofenac pellets of 10 min.

Aseptic precautions, similar to those for IUD insertion were used. A vaginal speculum was introduced to expose the cervix. The uterocervical length was measured using a 4-mm plastic cannula. If the uterine length was more than 8 cm, pregnancy was first excluded. The inserter was gently introduced to the area of the fundus and the plunger advanced to release the pellets.

Several weeks into the recruitment of the medroxyprogesterone acetate group, BCM learned of the importance of the consistent placement of all pellets at the fundus from the work of Hieu and co-workers and immediately began using the insertion technique advised by them [4]: the inserter was advanced to the fundus and then withdrawn 0.5 cm before advancing the plunger.

Our resources did not permit systematic follow-up visits but subjects were encouraged to return to the clinic for any complaints. This clinic is widely known in the community as the main abortion facility in the area. Subjects were informed that, in the event of failure of the method, first-trimester abortion would be provided upon request without charge.

### Results

There were no serious complications reported in this series. Side-effects were similar to those reported by others [1,4,5] except that we rarely saw pruritus. The life-table failure rates are shown in Table 1. The difference in failure rates between the two groups is not statistically significant at 6 or 12 months but is at 18 months.

**Table 1. Cumulative life-table failure rates for 100 women for a single intrauterine insertion of quinacrine, 252 mg, plus diclofenac, 75 mg, comparing additional contraception of three months' oral contraception ( $n=58$ )<sup>a</sup> or with medroxyprogesterone acetate, 150 mg IM ( $n=229$ )<sup>b</sup>**

Contraception	Months	Failures	At risk	Rate	SE
Oral	6	2	56	3.45	2.40
	12	1	55	5.17	2.91
	18	2	53	8.62 <sup>c</sup>	3.69
Medroxyprogesterone	6	0	225	0.00	0.00
	12	1	151	0.55	0.55
	18	0	54	0.55 <sup>c</sup>	0.55

<sup>a</sup>Insertions 21 April 1992 to 17 February 1993; <sup>b</sup>Insertions 19 February 1993 to 25 May 1994; <sup>c</sup> $p < 0.05$

### Discussion

This study has a number of serious shortcomings. Random or other systematic sampling is absent, introducing the potential for one or more biases when one group is compared with the other. For example, the change in the insertion technique during the medroxyprogesterone phase of the study may have contributed to its lower failure rate. When this study was initiated in April 1992, medroxyprogesterone was not available to us in India and it remained unavailable to us until February 1993. During the oral contraceptive phase of this study, we were troubled by the frequency of pregnancy with this single insertion method, suspecting, even before this phase was terminated, that the failure rate would be unacceptably high. When medroxyprogesterone was made available to us, the switch was made immediately.

The lack of systematic follow-up (which stems from our lack of resources) makes it impossible to completely rule out under-reporting of significant events. However, we have good reason to believe that all or most significant events are reported to us. This clinic is well known in the community and it is also well known that all treatment for complications and side-effects of all abortion and contraceptive services is free.

We have learned from previous studies in this center that women do return if they have problems. For example, in one study where tetracycline was used as the

sclerosing agent rather than quinacrine, 32 of 55 women (58%) treated returned to the clinic pregnant and in another, 35 of 102 women (34%) returned to the clinic pregnant [9]. Furthermore, in one postabortion protocol using quinacrine, 15 of 50 women returned pregnant (30%) and, in another one, 12 of 50 returned pregnant (24%) [9]. (These two studies provided important evidence that blood in the uterus, for any reason, including procedure trauma, interferes with the action of the quinacrine.)

We believe that virtually all significant events are recorded. However, without a high rate of systematic follow-up, there are no assurances that all failures and serious complications are recorded. Some women, though they had declared that they wanted no more children before having the quinacrine procedure, and fully knowing that abortion is legal and safe at this clinic, may have chosen to continue their pregnancy without reporting it.

Lastly, as shown in Table 1, at 18-months follow-up, when the differences are shown to be statistically significant, the numbers of women at risk in the two study groups are 53 and 54. In life-table analyses, as a rule of thumb, 50 individuals at risk is considered to be the minimum number necessary for reliable calculations, placing the usefulness of our calculations at 18-months follow-up close to the borderline.

The important finding of this study is that the use of intrauterine application of pellets of quinacrine, 252 mg, and diclofenac, 75 mg, with a single injection of medroxyprogesterone, 150 mg IM, does apparently provide safe effective contraception at least through the first 18 months of use. Other studies [10] indicate that the risk of pregnancy failure declines over time. If this proves so with this protocol, it will provide an attractive option as a permanent contraceptive method. The short-term complications of this method [4,10] indicate that it is safer than surgical sterilization. The main long-term concern is the possibility of an increased risk of cancer of the uterus, which is probably remote [11,12]. However, as with IUDs and oral contraceptives, this increased risk, if any, can only be known after extensive and long-term use [13].

Besides providing additional contraceptive protection while fibrosis is underway, the action of medroxyprogesterone, if any, is not known. One hypothesis is that this drug may prevent spasm of the tubal ostia, resulting in a more consistent exposure of quinacrine to the intramural tube. The need for postinsertion contraception is not yet well demonstrated, although there is some evidence supporting its use [3]. The potentiating action of diclofenac [6] needs confirmation in larger studies. At this time, our protocol provides the most attractive single-insertion non-surgical female sterilization method. However, this study needs confirmation in a larger series with longer and systematic follow-up which will only come when adequate resources are made available.

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#### Resumé

On a comparé les expériences de deux essais cliniques d'une insertion unique préliminaire de pellets de quinacrine dans la méthode de stérilisation féminine non chirurgicale. Dans ces deux essais, les pellets de 252 mg de quinacrine et 75 mg de diclofenac ont été appliqués par la voie transcervicale. Dans le premier (du 21 avril 1992 au 17 février 1993), on a administré 58 femmes des contraceptifs oraux pendant 3 mois. Dans le second (du 19 février 1993 au 25 mai 1994), 229 femmes ont reçu par voie intra-musculaire 150 mg d'acétate de medroxyprogesterone au moment de l'insertion de quinacrine. A 18 mois, le taux d'échecs par grossesse du premier essai, d'après la table de survie pour 100 femmes, était de 8,6 (norme 3,7), alors qu'il était de 0,5 (norme 0,5) dans le groupe de l'acétate de medroxyprogesterone, soit  $p < 0,05$ . Aucune complication ou effet secondaire grave n'est survenu ni dans un groupe ni dans l'autre.

Il est nécessaire de procéder à des essais de plus grande envergure privant des administrations au hasard et un suivi systématique à long terme pour déterminer si une seule injection de médroxyprogesterone rend la quinacrine plus efficace.

#### Resumen

Se comparó la experiencia de dos ensayos clínicos preliminares de una sola colocación por el método de esterilización femenina no quirúrgica de bolita de quinacrina. En los dos ensayos se utilizó la aplicación transcervical de 252 mg de quinacrina y 75 mg de diclofenac en bolitas. En el primer ensayo (21 de abril de 1992 a 17 de febrero de 1993), 58 mujeres recibieron anticonceptivos orales durante tres meses. En el Segundo ensayo (19 de febrero de 1993 a 25 de mayo de 1994), 229 mujeres recibieron 150 mg de acetato de medroxiprogesterona IM en el momento de la colocación de quinacrina. A los 18 meses, la tasa de no embarazo con tablas de vida por cada 100 mujeres en el primer ensayo fue 8,6 (S.E. 3,7) y la tasa de no embarazo en el grupo de acetato de medroxiprogesterona fue 0,5 (S.E. 0,5),  $p < 0,05$ . No hubo complicaciones graves ni efectos secundarios en ninguno de los grupos.

Se necesitan ensayos **más** amplios de confirmación con **asignación** aleatoria y seguimiento **sistemático** a largo plazo **para** determinar si **una sola inyección** de medroxiprogesterona mejora la eficacia de la quinacrina.

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